Clinical Study Protocol

Protocol Title:

A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee

Date of Protocol:

15-Feb-2023

NCT Number:

NCT04683627

Appendix 16.1.1 Protocol and Protocol Amendments

HP-5000-US-07 - Protocol Version 1.0 – 29 September 2020
HP-5000-US-07 - Protocol Amendment #1 (Version 2.0) - 07 January 2021

PROTOCOL

PRODUCT NAME/NUMBER:	HP-5000 (diclofenac sodium) topical system
PROTOCOL NUMBER:	HP-5000-US-07
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee
PROTOCOL DATE:	Protocol Version 1.0: September 29, 2020
SPONSORED BY:	Noven Pharmaceuticals, Inc. 100 Town Square Place, 5th Floor Jersey City, New Jersey 07310 USA 1 (551) 233- 2700
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Independent Ethics Committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Noven Pharmaceuticals, Inc.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	HP-5000-US-07
VERSION:	1.0
PROTOCOL TITLE:	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted]

[redacted]

Date

2. SYNOPSIS

Product Name/Number	HP-5000 (diclofenac sodium) topical system
Protocol Number	HP-5000-US-07
Development Phase	Phase 3
Name of Active Ingredient	Diclofenac sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt)
Protocol Title	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee
Indication	Treatment of the pain of osteoarthritis of the knee(s)
Investigator(s)	Approximately [redacted] investigators in the US
Study Center(s)	Approximately [redacted] centers in the US
Study Duration	Approximately 17 weeks (4 weeks Screening/Washout + 12 weeks Treatment + 1 week Follow-up)
Objective(s)	Primary Objectives • To evaluate the effect of HP-5000 on pain among subjects with osteoarthritis (OA) of the knees at Week 12. Key Secondary Objectives • To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Week 12. • To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Week 12. Other Secondary Objectives • To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on pain intensity as measured by numeric rating scale (NRS) scores on a daily diary. • To evaluate the onset of effect of HP-5000 on pain among subjects with OA of the knees. • To evaluate the pattern of use of rescue medication in the study. • To evaluate skin irritation, discomfort, and adhesion following administration of HP-5000. • To evaluate the safety and tolerability of HP-5000. • To evaluate the effect of HP-5000 treatment on Quality of Life (QOL).
Planned Number of Subjects	Sufficient number of subjects will be screened in order to enroll and randomize a total of approximately [redacted]ects to the study.
Inclusion Criteria	Subjects who fulfill the following inclusion criteria will be eligible to participate: 1. Provides written informed consent, prior to entering the study or undergoing any study procedures; 2. Male or female aged 40 to 85 years with a clinical diagnosis of OA of the target knee according to the American College of Rheumatology (ACR) criteria, including: a. Symptoms for at least 6 months prior to Screening; b. Pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to any other conditions such as bursitis, tendonitis, etc.); c. The pain in the target knee required the use of nonsteroidal anti-inflammatory drugs (NSAIDs) either over the counter (OTC)

	per recommendation of a physician or by prescription (documented history is required) d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed or recommended by a clinician for 30 consecutive days prior to the Screening Visit. 3. Has an X-ray of the target knee, taken no more than 1 year before Baseline, showing evidence of OA with Kellgren-Lawrence grade 1 to 3 disease (as assessed by a radiologist). 4. Has pain of OA in the designated/target study knee: a. [redacted] 6. Has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline Visit (V2). 7. Able to swallow and tolerate rescue medication, acetaminophen (APAP) (moderately sized tablets). 8. Female subjects of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year [no menses for 12 consecutive months]), or if of childbearing potential must be non-pregnant at the time of Screening Visit and on the morning of Baseline Visit, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or a vasectomized partner during their study participation and for 90 days following the last dose administration. Transdermal contraceptives are not allowed. All female subjects must agree not donate blood during the study and for 90 days after completion of the study. Male subjects who have not had a vasectomy must agree to use a barrier method of birth control example, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during their study participation and for 90 days following the last dose administration, and all male subjects must also not donate sperm or blood during the study and for 90 days after completion of the study. 9. Be reliable, willing, and able to cooperate with all study procedures including, but not limited to, the following: a. Accurately fill out the eDiary on a daily basis. b. Return for study visits on the required dates. c. Accurately and reliably report adverse symptoms (including treatment-emergent signs and symptoms) that he/she develops while participating in study. d. Use the patch as specified by the protocol.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria will not be allowed to participate in the study 1. Body mass index (BMI) > 40kg/m^2 at Screening (Visit 1). 2. The non-target knee pain severity score is [redacted] at Screening (Visit 1) and Baseline (Day 0).

	3. Any subject who did not follow the restriction of prohibited therapies during Washout period. 4. Arthritis of the target knee that is not caused by OA but caused by diseases such as rheumatoid arthritis, gout, psoriasis, syphilitic arthropathy, ochronosis, metabolic or other primary bone disease, or acute traumatic injury. 5. Any subject diagnosed with fibromyalgia. 6. Any other painful or disabling conditions affecting the target knee or leg. 7. Clinically significant elevation of serum creatinine (2:2 mg/dL), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (at 3 x upper limit of normal [ULN]) at the Screening Visit. 8. Known allergy or hypersensitivity to diclofenac, APAP, acetylsalicylic acid (aspirin [ASA]), or any other NSAID, [redacted] glycerin, propylene glycol, or ethanol. 9. Severe uncontrolled cardiovascular, renal, hepatic, or other systemic illness/disease. 10. A documented gastroduodenal ulcer (by upper gastrointestinal [GI] series or endoscopy), GI perforation or any GI bleeding (except hemorrhoidal bleeding) within 6 months prior to Screening Visit. 11. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline. 12. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups. 13. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments). 14. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment. 15. Treatment with oral or intra-muscular corticosteroids within 90 days of Screening Visit, treatment of the target knee with topical or intra-articular corticosteroids within 90 days of Screening Visit, or topical or intra-articular corticosteroid treatment of any other joint within 30 days of Screening Visit. 16. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit. 17. Any subject who had received the following intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy and amniotic fluid injection in the target knee 6 months prior to Screening Visit. 18. Any opioid use 7 days prior to the Screening Visit. 19. Any subject who had previous exposure to HP-5000. 20. Any subject who needs to use cyclosporine, lithium, or methotrexate. 21. Use of another investigational drug or device within 30 days (or 90 days for biologics) prior to study entry. 22. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause. 23. Any skin abnormality present at the potential patch application site (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion or significant skin disorder such as atrophy, psoriasis, or vitiligo). 24. Any of the following skin conditions present at the potential patch application site; presence of tattoo, excessive hair or open sores, or scar tissue. 25. Any subject expecting to have knee replacement surgery within 6 months on the target knee or the non-target knee. 26. Any subject with a psychiatric condition that in the investigator's opinion may interfere with his/her participation in the study.

	27. The subject is an employee, or family member of an employee, of the study center, the contract research organization (CRO) or the sponsor involved in this study. 28. Subjects who test positive for severe acute respiratory syndrome coronavirus 2 infection within 2 weeks prior to screening.
Investigational Drug(s)	HP-5000 topical system [redacted] diclofenac sodium/[redacted]
Reference Product	Placebo patch (0 mg diclofenac sodium/ [redacted] Placebo patches are identical in appearance to HP-5000 patch but without the active ingredient diclofenac sodium
Study Treatment(s)	The following are the treatment arms of the study: Treatment Arm — Treatment Regimen HP-5000 — One patch applied [redacted] to alternate side (inner or outer) of the target knee. Placebo — One patch applied [redacted] to alternate side (inner or outer) of the target knee.
Rescue Medication	If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of any other aches they might experience during the trial, such as headache, reduction of fever and the target knee pain of OA (not for the non-target knee) except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to for all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8).
Study Endpoints	Primary Efficacy Endpoint • WOMAC Likert (LK)3.1 OA (pain) change from Baseline at Week 12 Key Secondary Efficacy Endpoints • WOMAC LK3.1 OA (physical function) change from Baseline at Week 12 • WOMAC LK3.1 OA (stiffness) change from Baseline at Week 12 Secondary Efficacy Endpoints • WOMAC LK3.1 OA (pain) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (physical function) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (stiffness) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (composite score) change from Baseline at Weeks 1, 2, 4, 8, and 12 • Change from Baseline in pain intensity assessed on an 11-point NRS at Weeks 1, 2, 4, 8, and 12 • Change from Baseline in pain intensity assessed on an 11-point NRS of a weekly average of all available daily pain scores at each week from Week 1 through 12 • Change from Baseline in Patient Global Assessment at Weeks 1, 2, 4, 8, and 12 • Patient Global Impression of Change (PGIC) at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (pain) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (physical function) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (stiffness) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12 • Proportion of subjects, the number of days, and the total number of rescue medication tablets used during the treatment phase • The onset of the effect: Pain intensity assessed on an 11-point NRS change from Baseline

	• Mini-OA Knee and Hip QOL (Mini-OAKHQOL) scores change from Baseline at Weeks 4 and 12 • Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) impairment scores change from Baseline at Weeks 4 and 12. Safety Endpoints • The incidence of treatment-emergent adverse events (AEs), AEs leading to discontinuation of the study drug, serious adverse events (SAEs), and other significant AEs. • Change from Baseline in clinical laboratory tests, electrocardiogram (ECG) findings, body weight, physical examination findings and vital signs. • Dermal assessments: irritation, discomfort, and adhesion.
Randomization	Subjects will be randomly assigned using a 1:1 ratio to 1 of 2 treatment arms: HP-5000 or placebo.
Analysis Populations:	Intent-to-Treat (ITT): All consented and randomized subjects regardless of any protocol deviations. Analyses performed on the ITT set will be based on the randomized treatment assignment and all available data. The ITT will be used as the primary set for analysis of efficacy endpoints. Safety Analysis Set (SAF): All subjects who have had at least 1 patch of double-blind study drug applied and who have at least 1 post-dose safety measurement during the Double-blind Treatment Phase. The SAF will be used for the analysis of dermal evaluations and safety endpoints.
Efficacy Analyses	Efficacy Outcome Analyses: Primary Efficacy Outcome Analysis The fixed-sequence procedure will be applied for primary and key secondary endpoints of this study, where the order in which the hypotheses are tested is pre-specified as following: (1) WOMAC pain, (2) WOMAC physical function, and (3) WOMAC stiffness. Testing begins with the first hypothesis (H_1) about WOMAC pain, and each test is carried out as long as significant results with level of significance a=0.05 are observed in all preceding tests. The fixed-sequence procedure controls the family-wise error rate because, for each hypothesis, testing is conditional upon rejecting all hypotheses earlier in the sequence. All statistical tests of hypotheses in this trial will be 2-sided with a Type I Error rate of 0.05. The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-5000 *vs*. placebo) in the change from Baseline to Week 12 in WOMAC pain score in all randomized subjects. Outliers are defined *a priori* as (i) WOMAC scores obtained more than 24 hours after removal/detachment of double-blind study drug; or (ii) WOMAC scores obtained within 24 hours after the subject using rescue medication. WOMAC scores obtained 24 hours after removal/detachment of the study drug or WOMAC scores obtained within 24 hours after the subject using rescue medication will be excluded as outliers. The primary efficacy variable, change from Baseline to Week 12 in the WOMAC pain score, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in WOMAC pain score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC pain score as covariates. An unstructured covariance matrix will be assumed. Because the primary analysis assumes missing at random primary endpoint, suitable supplementary/sensitivity analyses will be performed to challenge the assumptions of

	the prespecified primary analysis by incorporating reasons for missingness in the analysis. Key Secondary Outcome Analyses: The MMRM model will be used the same way as for primary variable only include change from Baseline in WOMAC physical function (or stiffness) score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC physical function (or stiffness) score as covariates. Other secondary efficacy endpoints will be analyzed but will not be included into the fixed-sequence procedure. Further details will be provided in the Statistical Analysis Plan.

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4. LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
APAP	acetaminophen
ARB	angiotensin receptor blocker
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
COX	cyclooxygenase
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
[redacted]	[redacted]
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LK	Likert
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MNAR	missing not at random
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OAKHQOL	OA Knee and Hip QOL
OTC	over the counter
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PMM	Pattern Mixture Model
PRP	platelet rich plasma
QOL	Quality of Life
QTcF	QT interval corrected for heart rate (Fridericia's correction)

SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization Drug Dictionary
WOMAC	West Ontario and McMasters Universities Osteoarthritis Index

5. INTRODUCTION

5.1. Background and Rationale

An estimated 52.5 million adults (22.7% of the population)[1] in the United States (US) have physician-diagnosed osteoarthritis (OA); 22.7 million (9.8% of all adults) have arthritis and arthritis-attributable activity limitations. Based on these data, it is projected that 78 million (26%) adults aged 18 years or older will have physician-diagnosed arthritis by the year 2040.[2] Patients with arthritis are encouraged to be active, since it has been shown that exercise and activity help to decrease pain associated with OA, improve function, and delay disability. However, activity and exercise are often limited by the pain associated with arthritis, and this pain may become part of a cycle of inactivity and weight gain that tends to perpetuate the stiffness and disability associated with OA. Additionally, oral nonsteroidal anti-inflammatory drug (NSAID) medications used over time may cause gastrointestinal (GI) distress and interfere with the blood-clotting cycle. Opioid medications often lose their effectiveness with chronic use and require increasing dosages; patients may also become dependent on the opioid pain relievers, thereby introducing additional health problems and increasing disease and healthcare system burden. There is an unmet need for safer, reliable, and effective pain medications without the safety risk and limited efficacy associated with those currently available.

Diclofenac sodium belongs to the phenylacetic acid class of NSAIDs developed by Ciba Geigy Co., Ltd., Switzerland, in 1965. In the US, diclofenac sodium is available in various dosage forms, including tablet, eye drop, extended-release tablet, gel, patch, capsule, and solution. The mechanism of action of NSAIDs is not completely understood but thought to be related to prostaglandin synthetase (cyclooxygenase [COX]-1 and COX-2) inhibition.

Noven Pharmaceuticals, Inc. is developing a formulation of diclofenac sodium for topical administration, the HP-5000 topical system (patch) for the treatment of pain of OA of the knee(s). The topical HP-5000 patch will provide patients with OA with another treatment option that may have potential benefits compared with the existing formulations, as follows:

- Delivery of drug into the treatment target area resulting in lower systemic and GI exposure when compared with orally administered diclofenac sodium and a possible reduction of systemic side effects including GI ulcers/lesions and adverse reactions such as nausea, vomiting, dyspepsia, and stomach pain.
- Improvement of compliance with [redacted] compared with existing topical formulations and use by patients who have difficulty swallowing oral preparations.

5.2. Clinical Experience

To date, the HP-5000 development program includes [redacted] These studies have been completed [redacted] evaluating the pharmacokinetics (PK) and tolerability in [redacted] healthy volunteers and efficacy and safety in [redacted] subjects with OA pain of the knee. The lead formulation for this program, HP-5000[redacted], which contains [redacted] mg diclofenac sodium [redacted] with a patch size of [redacted] was selected based on the efficacy, safety, PK profile, and patch performance characteristics.

The HP-5000[redacted] formulation is being developed [redacted] by Noven's parent c[redacted] for different [redacted] indications [redacted] and is referred to as the [redacted]

The Phase 1 study that evaluated PK and safety for the current formulation (HP-5000 [redacted] in healthy volunteers was as follows:

- [redacted]

[redacted]

[redacted]

Data across these studies demonstrated an acceptable performance, safety and tolerability profile for HP-5000[redacted]

Hereinafter, HP-5000[redacted] is referred as HP-5000 in this protocol. Further details about HP-5000 development and detailed information are available in the Investigator's Brochure (IB).

5.3. Summary of Potential Risks and Benefits

The HP-5000 formulations have been studied in a number of PK studies and most recently in a large randomized, placebo-controlled Phase 2 efficacy and safety study in the US among subjects with pain of OA of the knee [redacted]. The PK studies revealed a PK profile supportive of topical use via transdermal route. The Phase 2 study demonstrated significant reduction in pain by Week 4 compared with placebo with a favorable systemic safety profile and good dermal tolerability with HP-5000 formulation. The potential benefits for subjects of study participation are the following: (1) may experience a reduction in pain and inflammation as a result of treatment with the HP-5000 patch, (2) may experience improvement in their physical function and stiffness, and (3) will contribute to the scientific knowledge and therapeutic advancement in OA disease state that may lead to expansion of future treatment options for subjects with OA.

The potential risks for subjects for participating in study include those associated with exposure to the HP-5000 patch and the risks inherent in medical evaluation, including venipunctures at various times in study.

A summary of the pharmaceutical properties and known potential risks of the HP-5000 patch are provided in the current version of the IB.[3] The investigator(s) must become familiar with all sections of the HP-5000 IB.

6. OBJECTIVES

6.1. Primary Objectives

- To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Week 12.

6.2. Key Secondary Objectives

- To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Week 12.
- To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Week 12.

6.3. Other Secondary Objectives

- To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on pain intensity as measured by numeric rating scale (NRS) scores on a daily diary.
- To evaluate the onset of effect of HP-5000 on pain among subjects with OA of the knees.
- To evaluate the pattern of use of rescue medication in the study.
- To evaluate skin irritation, discomfort, and adhesion following administration of HP-5000.
- To evaluate the safety and tolerability of HP-5000.
- To evaluate the effect of HP-5000 treatment on Quality of Life (QOL).

7. STUDY DESIGN

Note: Pandemic-related restrictions may result in difficulties regarding the conduct of the study. If circumstances require it, a protocol amendment may be created to document changes to some aspects of the study, such as inclusion/exclusion criteria, visit windows, visit schedules, the possibility of remote (rather than on site) visits, and distribution of study drug.

7.1. Overall Study Design and Plan - Description

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study in the US evaluating the efficacy and safety of HP-5000 in subjects with OA pain of the knees.

The study will consist of up to a 28-day Screening Phase that will include a Washout Period of current prescription and over the counter (OTC) analgesics; a 12-week Double-blind Treatment Phase, and a 1-week safety Follow-up Phase.

- **Screening Phase**: Subjects will be seen in the clinic where the study will be described to them and will be asked to sign the informed consent form (ICF). No screening procedures may begin prior to obtaining informed consent. After obtaining a written informed consent, subjects will be screened for participation in the study. The target knee for the purpose of the study will be defined as the one which causes the subject more pain than the other knee and will be identified at Screening visit using the NRS score. During the Screening Phase, subjects will complete a daily electronic diary (eDiary) to record pain severity of their target knee. Subjects who satisfy the entry criteria at Screening and Washout visit will be instructed to begin the Washout Period for 7 to 14 days, or at least 5 half-lives, whichever is longer, prior to the Baseline Visit (Day 0).

  During the Washout Period, current prescription and OTC analgesics will be discontinued. However, rescue medication (acetaminophen [APAP]) for the treatment of any other aches the subject might experience during the trial, such as headache, reduction of fever, and the target knee pain of OA (not for the non-target knee) will be permitted (a maximum of 2 g/day) except within 3 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited for 2 days until clinic visit on Day 0), on the day of Baseline Visit (V3). During the Washout Period, subjects will complete a daily eDiary to record rescue medication usage in addition to pain severity of their target knee. Following completion of the Washout Period, subjects will return to the clinic for their Baseline Visit (Day 0). Eligible subjects will be randomized to either HP-5000 or placebo in a 1:1 ratio.

- **Double-blind Treatment Phase**: Subjects will apply a single patch to the target knee [redacted] After the removal of the patch [redacted]

[redacted] a new patch will be applied to a different site on the target knee. Subjects will be instructed to rotate the patch application site [redacted] to alternate sides (inner and outer) of the target knee. During the Double-blind Treatment Phase, subjects will also complete a [redacted] eDiary to record patch application and removal time, adhesion, irritation, discomfort, and pain assessments; and amount of rescue medication (APAP) taken daily, if applicable. A maximum of 2 g/day of APAP will be allowed as rescue medication except from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8).

NOTE: Subjects are NOT allowed to apply HP-5000 on the non-target knee at any time during the study.

- **Follow-up Phase**: Subjects will have a safety visit approximately 7 days after the Week 12 End-of-Treatment Visit. The investigator or qualified study staff will contact all subjects by phone for continued safety monitoring of adverse events (AEs). At the discretion of the investigator, subjects may have to return to the clinic for their Follow-up Visit.

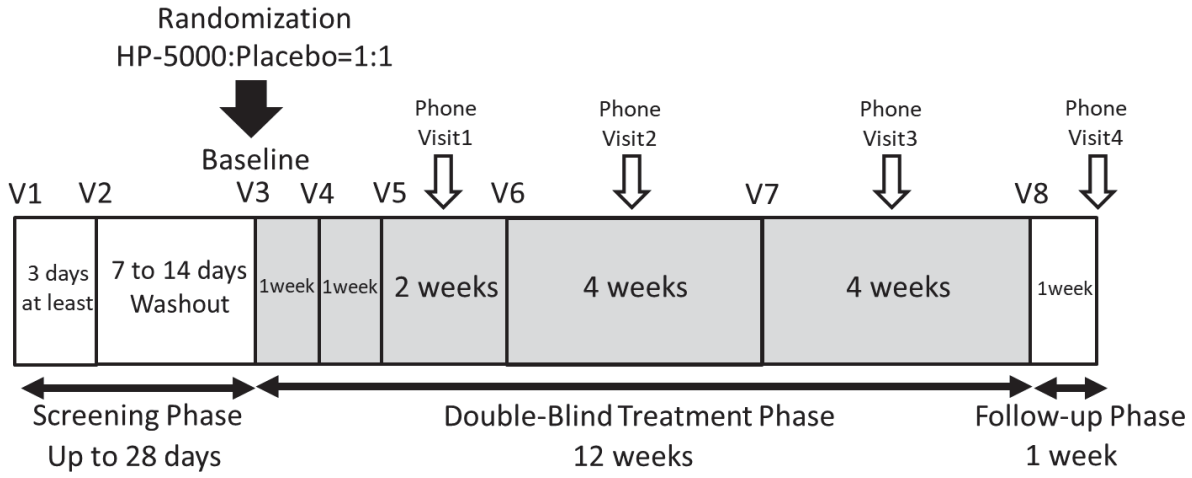


Figure 1 A Schematic of the Study Design

7.2. Discussion of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of HP-5000 in subjects with OA pain of the knees. Such a design is well accepted and considered standard in drug development when evaluating new therapeutic modalities across different disease areas.

A parallel-group design was selected because it is free of the assumptions underlying competing designs (for example, crossover). A parallel-group approach is considered the optimal study design to evaluate efficacy in pivotal registration clinical trials.

The use of a randomized double-blind design will minimize bias by randomly assigning the subjects to treatment arms, and ensuring that the subjects, investigators and site personnel, and the Sponsor/designee are blinded to the treatment allocations.

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. The comparison with placebo is justified as subjects will be closely monitored and study treatment will be discontinued and the subject will be returned to standard of care (SOC) treatment if their status deteriorates.

The rationale for dose selection is described in **Section 9.6**.

The 12-week duration is considered to be sufficient to evaluate the effect on chronic pain of OA. This time period is also sufficient to evaluate changes in the primary and secondary outcome measures.

The use of rescue medication is prohibited within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8), thus ensuring the integrity of the pain assessments and safeguarding against confounding due to rescue medications.

7.3. Study Sites

The study will take place at approximately [redacted] sites in the US that are qualified by background and experience and manage patients with OA. Each site is anticipated to screen a sufficient number of subjects to be able to randomize approximately [redacted] subjects, as detailed in the **Section 13.2**.

8. SUBJECT POPULATION

8.1. Selection of Study Population

The study will enroll up to [redacted] subjects with pain of OA of the knee in a 1:1 ratio (HP-5000:Placebo). The pain should have been stable over the previous 6 months prior to Screening (Visit 1).

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site, including reasons for screen failure.

8.2. Study Entry Criteria

All subjects being considered for participation in this clinical study must meet all the inclusion criteria and none of the exclusion criteria.

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Provides written informed consent, prior to entering the study or undergoing any study procedures;
2. Male or female aged 40 to 85 years with a clinical diagnosis of OA of the target knee according to the American College of Rheumatology (ACR) criteria, including:
    a. Symptoms for at least 6 months prior to Screening;
    b. Pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to any other conditions such as bursitis, tendonitis, etc.);
    c. The pain in the target knee required the use of NSAIDs either OTC per recommendation of a physician or by prescription (documented history is required).
    d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed or recommended by a clinician for 30 consecutive days prior to the Screening Visit.
3. Has an X-ray of the target knee, taken no more than 1 year before Baseline, showing evidence of OA with Kellgren-Lawrence grade 1 to 3 disease (as assessed by a radiologist).
4. Has pain of OA in the designated/target study knee:
    [redacted]

[redacted]

6. Has a WOMAC pain score of [redacted] at the Baseline Visit (V2).
7. Able to swallow and tolerate rescue medication, APAP (moderately sized tablets).
8. Female subjects of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year [no menses for 12 consecutive months]), or if of childbearing potential must be non-pregnant at the time of Screening Visit and on the morning of Baseline Visit, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or a vasectomized partner during their study participation and for 90 days following the last dose administration. Transdermal contraceptives are not allowed. All female subjects must agree not donate blood during the study and for 90 days after completion of the study.

   Male subjects who have not had a vasectomy must agree to use a barrier method of birth control example, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during their study participation and for 90 days following the last dose administration, and all male subjects must also not donate sperm or blood during the study and for 90 days after completion of the study.
9. Be reliable, willing, and able to cooperate with all study procedures including, but not limited to, the following:
   a. Accurately fill out the eDiary on a daily basis.
   b. Return for study visits on the required dates.
   c. Accurately and reliably report adverse symptoms (including treatment-emergent signs and symptoms) that he/she develops while participating in study.
   d. Use the patch as specified by the protocol.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if the he or she meets any of the following criteria:

1. Body mass index (BMI) > 40 kg/m^2 at Screening (Visit 1).
2. The non-target knee pain severity score is [redacted] at Screening (Visit 1) and Baseline (Day 0).
3. Any subject who did not follow the restriction of prohibited therapies during Washout period.

4. Arthritis of the target knee that is not caused by OA but caused by diseases such as rheumatoid arthritis, gout, psoriasis, syphilitic arthropathy, ochronosis, metabolic or other primary bone disease, or acute traumatic injury.
5. Any subject diagnosed with fibromyalgia.
6. Any other painful or disabling conditions affecting the target knee or leg.
7. Clinically significant elevation of serum creatinine (2:2 mg/dL), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (at 3 × upper limit of normal [ULN]) at the Screening Visit.
8. Known allergy or hypersensitivity to diclofenac, APAP, acetylsalicylic acid (aspirin [ASA]), or any other NSAID, [redacted] glycerin, propylene glycol, or ethanol.
9. Severe uncontrolled cardiovascular, renal, hepatic, or other systemic illness/disease.
10. A documented gastroduodenal ulcer (by upper GI series or endoscopy), GI perforation or any GI bleeding (except hemorrhoidal bleeding) within 6 months prior to Screening Visit.
11. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
12. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
13. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
14. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment.
15. Treatment with oral or intra-muscular corticosteroids within 90 days of Screening Visit, treatment of the target knee with topical or intra-articular corticosteroids within 90 days of Screening Visit, or topical or intra-articular corticosteroid treatment of any other joint within 30 days of Screening Visit.
16. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
17. Any subject who had received the following intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy and amniotic fluid injection in the target knee 6 months prior to Screening Visit.
18. Any opioid use 7 days prior to the Screening Visit.
19. Any subject who had previous exposure to HP-5000.
20. Any subject who needs to use cyclosporine, lithium, or methotrexate.
21. Use of another investigational drug or device within 30 days (or 90 days for biologics) prior to study entry.

22. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause.
23. Any skin abnormality present at the potential patch application site (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion or significant skin disorder such as atrophy, psoriasis, or vitiligo).
24. Any of the following skin conditions present at the potential patch application site; presence of tattoo, excessive hair or open sores, or scar tissue.
25. Any subject expecting to have knee replacement surgery within 6 months on the target knee or the non-target knee.
26. Any subject with a psychiatric condition that in the investigator's opinion may interfere with his/her participation in the study.
27. The subject is an employee, or family member of an employee, of the study center, the contract research organization (CRO) or the sponsor involved in this study.
28. Subjects who test positive for severe acute respiratory syndrome coronavirus 2 infection within 2 weeks prior to screening.

8.2.3 Premature Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly and if a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor or CRO must be notified.

Subjects may be withdrawn if continuing in the study is not in the subject's best interest, their clinical condition worsens during the study or for safety reasons, as determined by the investigator, as follows:

- Adverse events: If the reason for removal of a subject from the study is an AE, the principal specific event and any related clinical/diagnostic test results will be recorded on the electronic case report form (eCRF). If a subject withdraws because of an AE along with another reason and/or subjects are unwilling to continue in the study because of an AE, the withdrawal will be considered due to the AE and the eCRF will be completed to reflect this reason for withdrawal. A narrative description will be required for all early withdrawals due to AEs.
- The subject is unwilling to continue in the study.
- Subject requires treatment with a prohibited concomitant medication.
- Lack of compliance with protocol by subject.

- Pregnancy. If the subject becomes pregnant during the clinical study, the study drug should be discontinued immediately and the subject will be withdrawn from the study and followed until the time of delivery.
- The investigator or the Sponsor terminates the study for any reason.

In all cases, the reason for study withdrawal must be recorded in the eCRF and if the reason is not known, the investigator must make every effort to establish whether withdrawal was due to was an AE. Subjects for whom the study drug is discontinued will be encouraged to continue in order to complete all the scheduled procedures.

If a subject is withdrawn early from the study, the following procedures will be performed:

- Subjects will have Early Termination (ET) procedures performed as shown in the Schedule of Events (see **Section 10.2**).
- All ET procedures should be completed and recorded on the ET eCRF page. If withdrawal occurs at a regular scheduled visit, the Early Withdrawal eCRF page should be used instead of the regular visit eCRF page to record any information related to the visit.

It is important to evaluate these subjects at the study center as soon as possible. Investigators must make at least 3 documented attempts to contact subjects who fail to attend scheduled visits by telephone or any other means and document the attempts. After 3 documented unsuccessful contact attempts the subject can be considered lost to follow-up.

8.3. Subject Replacement Criteria

Subjects who withdraw after randomization and the application of the first treatment patch will not be replaced.

9. TREATMENTS

9.1. Identification of Investigational Product

The following is a description of study drug:

- HP-5000 [redacted] patch
  Each patch contains [redacted] diclofenac sodium.

HP-5000 will be supplied as diclofenac sodium in a patch manufactured by [redacted]

9.1.1 Labeling

Labels will be computer-generated for all investigational products (IPs) with the following information (other information may also be included as needed):

- Protocol number
- Subject number (record at the time of dispensing)
- Package contents (quantity)
- Storage instructions
- Caution: "New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"
- Sponsor name and address

9.1.2 Packaging

In the Double-blind Treatment Phase, HP-5000 and placebo patches will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

Sites and subjects will be instructed to save all empty packaging or packaging containing unused patches for final disposition by the Sponsor or its designee.

The Drug Dispensing Log must be available for monitoring, auditing, or inspection. **Section 9.8** details the accountability of clinical supplies through the use of a Drug Dispensing Log.

9.2. Treatments Administered

HP-5000 will be administered [redacted] for 12 weeks.

The treatment arms for this study are the following:

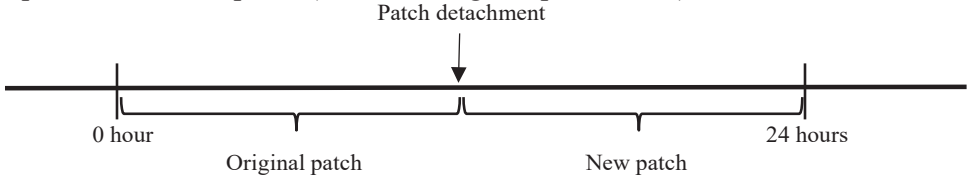
Table 1 Treatment Arms

Treatment Arm	[redacted] Treatment
HP-5000	HP-5000 [redacted] patch Each patch contains [redacted] diclofenac sodium.
Placebo	HP-5000 [redacted] Placebo patch Each patch contains [redacted] diclofenac sodium.

One patch [redacted] will be applied [redacted] (approximately [redacted] to alternate sides (inner and outer knee) of the target knee after showering/bathing.

Note:

- Subjects will be instructed not to bathe or shower while wearing the patch.
- In case the patch completely detaches within 24 hours of application, the detached patch will be applied again on the same site. If the detached patch does not re-adhere, a replacement patch (new patch) will be applied on the same site until the next scheduled replacement of the patch (see following sample scheme).



  Even if the applied replacement patch completely detaches by accident again, an additional application of another new patch will not be allowed and the subject will wait to apply a patch until the next scheduled replacement.
- Subjects will not be allowed to apply any patches to the non-target knee at any time during the study.
- Even if there is a day when subjects do not take a shower or bath, they need to replace a patch approximately every [redacted].

Detailed application instructions for subjects will be provided in a separate manual/guide.

9.3. Dispensing and Storage

Study drug supplied by [redacted] is to be used exclusively according to this protocol. The investigator is responsible for dispensing study drug according to the dosage and administration scheme and for ensuring proper storage of study drug.

The investigator, or designee, must confirm the receipt of study drug with his/her signature. A copy of this receipt must be kept by the investigator. Until study drug is dispensed to the subjects, it must be stored between 15°C to 30°C (59°F to 86°F) and in a dry place in a securely locked area that is not generally accessible.

All study drug supplies must be stored in a secure locked area with access limited to the investigator or those persons authorized by the investigator to dispense the study drug to subjects. Study drug should be stored as per the label.

9.4. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who will meet study entry criteria will be randomly assigned in a 1:1 ratio to receive HP-5000 or placebo patches. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects who met eligibility criteria are enrolled into the study. The study center will not be a blocking factor in the randomization schedule. At each visit, subjects will be given a kit containing sufficient study drug to last until the next scheduled study visit.

The randomization schedule will be prepared before the start of the study. No one involved in the clinical conduct will have access to the randomization schedule before the official unblinding of treatment assignment. No subject will be randomized into this study more than once.

9.5. Blinding and Unblinding Treatment Assignment

To protect the blind, placebo patches will be identical in appearance to the HP-5000 patches.

All subjects, investigators, and study personnel involved in the conduct of the study, including the project study team and data management, will be blinded to study drug treatment assignment with the exception of a prespecified unblinded statistician/programmer, who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study related personnel. If an interim

analysis is to be conducted, unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the clinical study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be only permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

In the case of a medical emergency, to appropriately treat the subject, study drug will need to be unblinded. Instructions for breaking the blind will be included in the IWRS manual. The investigator may break the randomization code for an individual subject. However, the investigator should make every effort to discuss the unblinding of the subject with the Medical Monitor prior to unblinding.

If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the Medical Monitor immediately of the blind breaking incident without revealing the subject's treatment assignment.

In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified, explained by a comment on the appropriate eCRF page along with the date and reason for study discontinuation; and captured on the SAE Form (see **Section 11.2.6.1** for SAE reporting to sponsor).

The investigator or designee must record the date and reason for unblinding or study discontinuation on the appropriate eCRF for that subject.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the Medical Monitor.

9.6. Selection of Doses and Administration in the Study

The dosing regimen of diclofenac [redacted] in a patch size of [redacted] applied [redacted] and rotated between 2 sites on the target knee, inner and outer sides, is based on the following considerations and rationale:

- A dose that targets diclofenac exposure after HP-5000 patch application that is similar to that of registered topical diclofenac products and considerably lower than that of oral diclofenac tablets.
- Previously completed clinical studies using the same size patch showed no issue on efficacy, safety (including dermal safety) and patch performance using the selected dose and administration.
- Patch size was developed that allows for rotation at a minimum of 2 sites to minimize local irritation at the application site of the knee.

9.7. Dose Adjustment Criteria

Dose adjustment is **NOT** allowed in this study.

9.8. Drug Accountability

The investigator or pharmacist, as appropriate, must maintain adequate records of the receipt and conditions of all study drugs, dispensing, return, or other disposition of study drug including the date, quantity dispensed to each subject, batch or code number, identification of subjects (subject number) who received study drug and any reasons for departure from the protocol-dispensing instructions. Receipt of study drug must also be confirmed within IWRS. The drug accountability records, along with dispensed and unused packaging must be available for monitoring, auditing, or inspection as deemed necessary.

The investigator will not supply study drug to any person except those named as sub-investigators (on the Form FDA 1572), designated study personnel, and subjects in this study. The investigator will not dispense study drug from any study sites other than those listed (on the Form FDA 1572).

Study drug may not be relabeled or reassigned for use by other subjects. If any of the study drug is not dispensed, is lost, stolen, unusable, or is received in a damaged container, this information must be documented and reported to Noven and appropriate regulatory agencies, as required.

At the completion of the study, a final reconciliation of all study drugs (dispensed, returned, used, and unused) must be performed by the site and only unused patches must be returned to the sponsor

(or designated location). The unused study drug must be left in the original packaging and returned to the Sponsor (or designee) for destruction.

9.9. Treatment Compliance

Treatment compliance with study drug regimens will be assessed by study personnel via the counting of returned unused patches, patch application, removal and by questioning the subject, if necessary, at every post-randomization visit. Treatment compliance will also be calculated as the number of patches applied divided by the prescribed number of patches over a given period, expressed as a percentage.

At Visits 4 through 8 or any Early Termination Visit, the study drug (patches) from the previous visit will be returned to the investigator. The study drug will be inventoried and non-compliance assessed as follows: use of less than 80% or more than 120% of study drug during any evaluation period (visit to visit). If the subject is non-compliant, and if there is a medically related need to do so, then the Medical Monitor should be contacted to discuss the subject's eligibility to continue in the study.

The subject must be counseled if compliance is not satisfactory (fail to apply the study drug on 2 or more consecutive days and/or miss any eDiary entries for 2 or more consecutive days). The subject must be contacted by a site personnel and re-instructed on how to apply the study drug and complete the eDiary. The re-instruction will be documented in the subject's chart (progress notes or clinical notes).

Subjects will be asked to record their daily intake/use of rescue medication/study drug in the eDiary. Deviations from the planned doses (overdose, missed dose or timing) will be recorded on the subjects' eCRF. The eDiaries will be constantly reviewed by study personnel.

9.10. Concomitant/Prior Therapies

All medications used prior or during treatment (including OTC medications, herbal supplements, non-pharmacological activities [Exercise, Weight Loss, Tai Chi, etc.] and rescue medication) will be recorded in the source document and on the appropriate eCRF page. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.10.1 Permitted Therapies

Glucosamine, chondroitin, and antidepressants (used for any indication other than pain) will be allowed if used as stable therapy for at least 90 days prior to Screening Visit. However, if used for less than 90 days, these drugs will be considered prohibited concomitant medications and will

require a Washout Period. Subjects will be allowed to continue stable ASA therapy not for OA pain (up to 81 mg/day).

Other concomitant medications for treatment of ongoing medical conditions are allowed, but should be limited to those medications considered necessary in the opinion of the investigator.

9.10.2 Prohibited Therapies

Prohibited medications/therapies are presented in **Table 2**.

Table 2 Prohibited Medications/Therapies

Prohibited Medications/Therapies	Conditions
Any nonsteroidal anti-inflammatory drugs (NSAIDs) (selective or nonselective [Topical drug not for knees will be allowed]), acetaminophen (APAP) (>2 g/day), aspirin (ASA) (>81 mg/day), anticonvulsants (i.e., pregabalin and gabapentin etc.), muscle relaxants, other oral analgesics (prescription and/or over the counter [OTC]), antidepressants prescribed for the control of chronic pain syndromes, antihistamine with a sedative effect, sedatives for insomnia, topical products on the knee including methyl salicylate, camphor, menthol, methylsulfonylmethane, [redacted] capsaicin, any nonpharmaceutical therapy to relieve knee pain (physiotherapy, massage therapy, hot wax therapy, ice pack, acupuncture, thermal modalities, radiofrequency ablation, transcutaneous electrical nerve stimulation [TENS], pulsed vibration therapy, etc.), device to relieve knee pain (biofemoral bracing, kinesiotaping, modified shoes, wedged insoles etc.), hydroxychloroquine.	Prohibited during the study starting at Washout Visit
Any opioids, cannabinoids (prescribed or used recreationally), corticosteroids including oral, intra-muscular and intra-articular, topical, inhalation (a stable dose by inhalation for seasonal allergies and/or topical use for dermatologic allergies are allowed [Not allowed on the knees]), intra-articular viscosupplementation (e.g., Synvisc®), intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection, cyclosporine, lithium, or methotrexate	Prohibited during the study starting at Screening Visit
MAJOR SURGERY: Surgery to the target knee (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments). MINOR SURGERY: Surgery to the target knee defined as anything other than major surgery (as defined above)	Prohibited during the study starting at Screening Visit

Note: The investigator should contact the Medical Monitor with any concerns about the acceptability of any medication.

9.10.3 Concomitant Medication Cautions

Investigator's clinical judgment will be used in the following situations (the Medical Monitor for the study may be contacted if necessary);

- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or beta-blockers: Concomitant use with HP-5000 may diminish the antihypertensive effect of these drugs. Monitor blood pressure.
- ACE Inhibitors and ARBs: Concomitant use with HP-5000 in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk subjects, monitor for signs of worsening renal function.
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor subjects to assure diuretic efficacy including antihypertensive effects.
- Digoxin: Concomitant use with HP-5000 can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.

9.11. Rescue Medication

If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of any other aches they might experience during the trial, such as headache, reduction of fever and the target knee pain of OA (not for the non-target knee) except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Information regarding the use of rescue medication, such as the number of tablets taken, the time when it was taken, and the reason of use, will be recorded on the eDiary. Subjects should not use OTC APAP as rescue medication, i.e., they should only use the APAP provided by the Sponsor or designee. Rescue medication will be labeled appropriately for the study to ensure visual difference from similar OTC medications and to ensure proper understanding the rescue medication should be used for this study. NSAIDs or any other analgesics except study drug and rescue medication provided will not be permitted from the time that informed consent form is signed until study completion or early termination. Stable low doses of ASA up to 81 mg/day will be allowed.

Subjects are **NOT** allowed to apply study treatment drug (HP-5000/Placebo) on the non-target knee at any time during the Double-blind Treatment Phase.

9.12. Treatment after End of Study

After completing the study, each subject will follow up with their primary care physician to be treated and followed according to standard clinical practice.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited therapy they are taking.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (see **Section 10.2**). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a clinical study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Periods and Visits

10.1.1 Screening Phase

10.1.1.1 Screening (Visit 1)

Screening visit will be completed 28 to 14 days prior to the Baseline Visit. The subject must be screened before entering the Washout Period of the study (V2). The following procedures will be performed at Screening Visit (V1):

1. Obtain written informed consent and assign a subject number.
2. Register the subject in IWRS.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information including the onset of OA.
5. Record medical history including prior and current therapies (e.g., prescription and nonprescription medications). Any prior use of medications used to treat OA and OA pain and prior 30-day use for all other medications should also be collected. If the subject has any psychiatric condition and his/her participation is considered appropriate, a documented rationale is required in the source document and eCRF.
6. Perform a complete physical examination, which will include assessment of the head, eyes, ears, nose, and throat, cardiovascular, respiratory, gastrointestinal/abdominal, musculoskeletal, dermatological, neurological, and psychiatric/psychological body systems.
7. Weight (kg), height (cm), and vital signs (heart rate, respiratory rate, temperature, and supine blood pressure) will be measured.
8. Instruct the subject on how to use NRS and WOMAC before performing first assessments.
9. Perform NRS evaluation of average and worst pain **for a left knee and a right knee, respectively,** and record them in the Electronic Clinical Outcome Assessment (eCOA).

10. Identify the target knee. The target knee is defined as the one which causes the subject more pain than the other knee and will be identified using NRS score. The subject will be instructed to refer to this specific (target) knee throughout their participation in the study when responding to WOMAC questionnaire and NRS evaluation.
    If the pain of both knees is identical (i.e. both knees have NRS score of 2), the investigator will define the target knee based on other difficulties (physical function, stiffness, etc.) and discussion with the subject. The discussion will be documented in the source document. The change of the target knee will not be allowed for any reason.
11. Administer the WOMAC questionnaire for the target knee.
12. Review the X-ray of the target knee (by a radiologist). If subject does NOT have any X-ray of the target knee taken within the past year, a mandatory new X-ray to confirm the disease will have to be taken prior to starting the Washout Period. The X-ray should be reviewed by the completion of Baseline Visit.
13. Perform 12-lead electrocardiogram (ECG) and laboratory tests.
14. Perform urine drug, alcohol and pregnancy tests.
15. Record the eligibility of the subject in IWRS. If the subject screen fails, the date and the reason will be recorded in IWRS.
16. Ensure that the subject has access to, and understands how to use, the eDiary.
17. Instruct the subject to continue to assess and record their target knee pain at home daily, using the NRS 11-point pain scale in the eDiary during the Screening Phase.

At home, subjects are required to conduct the following assessments/procedures:

Perform the following assessments and record in the eDiary on daily basis:

Assess and record the pain of the target knee using the NRS 11-point pain scale when subjects take a shower or bath during the Screening Phase (Approximately every 24 hours. Even if subjects do not take a shower or bath, the assessment is necessary every 24 hours).

Note: If subjects withdraw or discontinue after signing the informed consent and prior to the registration in IWRS, the date and reason will be recorded in IWRS. Detailed information will be provided in a separate Manual.

10.1.1.2 Washout Visit (Visit 2)

The following procedures will be performed at the Washout Visit (V2):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Review eDiary NRS 11-point pain scores. [redacted]

[redacted] will be entered to the eCOA system and the mean NRS scores will be calculated.

3. Record the eligibility of the subject in IWRS. If the subject screen fail, the date and the reason will be recorded in IWRS.
4. Placebo training will be performed to educate subjects. The aim is to minimize the placebo response and increase their awareness for the purpose of the trial to determine a new drug is effective and safe.
5. Subjects whose eligibility has been preliminarily confirmed will be asked to washout of their current medications for at least 7 days to a maximum of 14 days (or at least 5 half-lives, whichever is longer).
6. Subjects will be instructed by the site to stop taking all prescription and physician recommended OTC analgesic medications, but will be informed that rescue medication (i.e., APAP) may be used (a maximum of 2 g/day) as needed except **within 3 calendar days prior to the Baseline Visit (V3) and the day of Baseline Visit (V3).**
7. Dispense rescue medication.
8. Ensure that the subjects have access to, and understands how to access and use, the eDiary.
9. Instruct the subject to continue to assess and record their target knee pain at home daily, using the NRS 11-point pain scale in the eDiary during the Washout Period.
10. Subjects will be instructed to record the number of tablets of rescue medication used, the time and the reason in the eDiary.

At home, subjects are required to conduct the following assessments/procedures:

Perform the following assessments and record in the eDiary on daily basis:

1. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when the subjects take a shower or bath during the Screening Phase (Approximately every 24 hours. Even if subjects do not take a shower or bath, the assessment is necessary every 24 hours). The time of NRS assessment will be recorded in the eDiary. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
2. Record the number of tablets of rescue medication used, if any, the date taken and the reason.

Note: If subjects withdraw or discontinue prior to Visit 2, the date and the reason will be recorded in IWRS.

10.1.2 Baseline Visit (Visit 3, Day 0)

The subject must be screened and the Washout Visit performed prior to the Baseline Visit. The following will take place during the Baseline Visit (Visit 3, Day 0):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Review subject's use of prior/concomitant medications.
3. Obtain vital signs measurements.
4. Perform an NRS 11-point pain assessment **for the non-target knee pain.**
5. Administer the WOMAC questionnaire for the target knee.
6. Perform Patient Global Assessment (PGA).
7. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
8. eDiary NRS 11-point pain scores will be reviewed by the investigator or the study coordinator. The 11-point NRS scores [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated. If the score of the 1 day before of Baseline Visit is missing, the subject will be excluded from the study.
9. Perform a 12-lead ECG.
10. Obtain blood and urine samples for laboratory testing.
11. Perform a urine drug, alcohol and pregnancy tests.
12. Perform Baseline dermal safety assessment (irritation only).
13. Record the eligibility of the subject in IWRS. If the subject screen fail, the date and the reason will be recorded in IWRS.
14. Randomly assign the subject to a treatment group using IWRS.
15. Perform a QOL Questionnaire.
16. Placebo training will be performed to educate subjects. The aim is to minimize the placebo response and increase their awareness for the purpose of the trial to determine a new drug is effective and safe.
17. Collection of unused rescue medication.
    Note: Do not dispense rescue medication. Rescue medication is prohibited from Visit 3 until Visit 4.
18. Perform rescue medication accountability/reconciliation.
19. Instruct the subject concerning the patch application and removal method including how to rotate the patches by using a video and a separate manual/guide.

20. Dispense the double-blind study drug and instruct subjects on proper patch application. The first patch will be applied on the target knee at sites. Subjects will be instructed to replace the patch [redacted] after showering/bathing. The first patch applied at sites may be replaced within 24 hours if subjects bathe or shower. Subjects will be instructed not to bathe or shower while wearing the study drug.
21. Subject will be instructed to report to the site and record unscheduled patch detachment, incidences of irritation and discomfort in their eDiary and not to participate in strenuous activities or other activities that cause heavy perspiration during the double-blind treatment phase.
22. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee after showering/bathing;
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug on non-target knee at all times.

Note: If subjects withdraw or discontinue prior to Visit 3 or randomization, the date and the reason will be recorded in IWRS.

10.1.3 Double-blind Treatment Phase

During the 12-week Double-blind Treatment Phase, the following procedures will take place:

<u>At home, subjects are required to conduct the following assessments/procedures</u>:

1. Remove the patch before showering/bathing and apply a new patch on the target knee (inner or outer by [redacted] rotation) [redacted]
2. Perform the following assessments and record in the eDiary on daily basis:

a. Record patient eDiary information [redacted] when subjects replace the patch and before they sleep.
b. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace the patch. The time of NRS assessment will be recorded in the eDiary. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
c. Record the time of patch application and removal when subjects replace the patch.
d. Record the time of unscheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
e. Record the number of tablets of rescue medication used, the time and the reason (if applicable) when subjects take a tablet or before they sleep.
f. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

At the clinical sites visits, investigators (or site personnel as appropriate) will conduct the following:

Visit 4 and Visit 5 (Week 1 and Week 2)

1. Obtain vital signs measurements.
2. Administer the WOMAC questionnaire for the target knee.
3. Perform PGA.
4. Perform Patient Global Impression of Change (PGIC).
5. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
6. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
7. Collection of unused study drug and rescue medication.
8. Review subject's use of rescue medication/concomitant medication.
9. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
10. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
11. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.

12. Re-instruct the subject concerning the patch application and removal method.
13. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] (approximately every [redacted] to the target knee after showering/bathing;
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take any rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 1 (midway between Week 2-4)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.
    e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.
3. Answer the questionnaires related to adhesion, skin irritation and discomfort. Record any issues with adhesion, skin irritation and discomfort.
4. Re-instruct the subject concerning the patch application and removal method.

5. Ensure that the subject's scheduled dose is administered and daily NRS pain scores and the application are recorded correctly.
6. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
7. Review subject's use of concomitant medication.
8. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
9. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Visit 6 (Week 4)

1. Obtain vital signs measurements.
2. Obtain blood and urine samples for laboratory testing.
3. Perform a pregnancy test.
4. Administer the WOMAC questionnaire for the target knee.
5. Perform PGA.
6. Perform PGIC.
7. Perform a QOL Questionnaire.
8. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
9. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
10. Collection of unused study drug and rescue medication.
11. Review subject's use of rescue medication/concomitant medication.

12. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
13. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
14. Re-instruct the subject concerning the patch application and removal method.
15. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
16. **Patient Education**: At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] (approximately every [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 2 (midway between Week 4-8)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.

e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

3. Re-instruct the subject concerning the patch application and removal method.
4. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
5. Review subject's use of concomitant medication.
6. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
7. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] (approximately every [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Visit 7 (Week 8)

1. Obtain vital signs measurements.
2. Perform a pregnancy test.
3. Administer the WOMAC questionnaire for the target knee.
4. Perform PGA.
5. Perform PGIC.
6. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
7. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
8. Collection of unused study drug and rescue medication.
9. Review subject's use of rescue medication/concomitant medication.

10. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
11. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
12. Re-instruct the subject concerning the patch application and removal method.
13. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
14. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] (approximately every [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 3 (midway between Week 8-12)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.

e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

3. Re-instruct the subject concerning the patch application and removal method.
4. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
5. Review subject's use of concomitant medication.
6. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
7. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
   a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
   b. keep the patch attached [redacted] including while sleeping;
   c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
   d. accurately reporting pain;
   e. accurately reporting rescue medication use;
   f. understanding when to return for their next visit and the importance of returning on schedule;
   g. adhering to the overall research plan; and
   h. Do NOT apply study drug to non-target knee at any time.

Visit 8 (Week 12)

1. Perform physical examination.
2. Obtain vital signs measurements.
3. Obtain subject's weight.
4. Obtain blood and urine samples for laboratory testing.
5. Perform a 12-lead ECG.
6. Perform a pregnancy test.
7. Administer the WOMAC questionnaire for the target knee.
8. Perform PGA.
9. Perform PGIC.
10. Perform a QOL Questionnaire.
11. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.

12. Remove the patch on a skin.
13. Instruct a subject to perform the following assessments in the eDiary when they remove the patch at the site:
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale
    b. Record the time of patch removal.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable).
    d. Record the number of tablets of rescue medication used, the time and the reason.
    e. Answer the questionnaires related to adhesion, skin irritation and discomfort. Record any issues with adhesion, skin irritation and discomfort.
14. Review the subjects' eDiary entries.
15. Collection of unused study drug and rescue medication.
16. Review subject's use of rescue medication/concomitant medication.
17. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
18. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.

Note: After Visit 8, subjects may resume their standard of care treatment.

10.1.4 Follow-up Phase

A follow-up phone Visit will take place approximately 7 days after Visit 8 (or Early Termination Visit), and will include the following assessment and procedures:

1. Review subject's use of concomitant medications.
2. Review AEs.
3. Record the findings in the eCRF.

10.1.5 Early Termination Visit (if applicable)

Subjects who are discontinued prematurely from study for any reason after Baseline (Visit 3) must complete the Early Termination Visit. If the subject comes for an Unscheduled Visit and a decision to withdraw the subject is made, then the Early Termination Visit procedures will be performed and the Early Termination Visit eCRF will be completed (and not the Unscheduled Visit eCRF). During this visit the following assessments and procedures will be performed:

1. Perform physical examination.
2. Obtain vital signs measurements.

3. Obtain subject's weight.
4. Obtain blood and urine samples for laboratory testing.
5. Perform a urine pregnancy test.
6. Perform a 12-lead ECG.
7. Administer the WOMAC questionnaire for the target knee.
8. Perform PGA.
9. Perform PGIC.
10. Perform a QOL Questionnaire.
11. Remove the patch on a skin.
12. Instruct a subject to perform the following assessments in the eDiary when they remove the patch at the site:
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale
    b. Record the time of patch removal.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable).
    d. Record the number of tablets of rescue medication used, the time and the reason.
13. Review the subjects' eDiary entries.
14. Collection of unused study drug and rescue medication.
15. Review subject's use of rescue and concomitant medications.
16. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
17. Perform dermal safety assessment (irritation, discomfort, and adhesion).
18. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
19. Record the date and the reason of early termination in the eCRF.

10.2. The Schedule of Events

Phase	Screening Phase				Double-blind Treatment Phase										Follow-up	ET
	Screening[k]	Washout[k]		Baseline												
Week				**0**		**1**		**2**		**4**		**8**		**12**	**13**	
Clinic visit	**1**	**2**		**3**		**4**		**5**		**6**		**7**		**8**		
Phone Visit[a]									**1**		**2**		**3**		**4**	
Day	**-28 to -14**	**-25 to -7**	**-6 to -1**	**0**	**1-6**	**7**	**8-13**	**14**	**15-27**	**28**	**29-55**	**56**	**57-83**	**84**	**91**	
Visit Window (Days)						**±2**		**±2**	**21±3**	**±2**	**35±3**	**±7**	**70±3**	**±7**	**±7**	
Informed Consent	X															
Demographics	X															
Medical History	X															
Inclusion/Exclusion criteria	X	X		X												
Randomization				X												
Physical Examination	X													X		X
Vital signs	X			X		X		X		X		X		X		X
Height	X															
Weight	X													X		X
Clinical Laboratory test[b]	X			X						X				X		X
Urine Pregnancy Test	X			X						X		X		X		X
Drug Screen/ Alcohol Test	X			X												
12-lead ECG	X			X										X		X
X-Ray[c]	X															
Dispense Rescue Medication		X				X		X		X		X				
Use of Rescue Medication[d]		X	X				X		X		X		X			X
Study Drug Application[e]				X	X	X	X	X	X	X	X	X	X	X		
Collection of Unused Study Drug and Rescue Medication				X[l]		X		X		X		X		X		X
Drug Accountability				X[l]		X		X		X		X		X		X
Patient eDiary[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pain Intensity 11-Point NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Dermal Evaluations[g]				X		X		X		X		X		X		X
WOMAC[h]	X			X		X		X		X		X		X		X
PGA				X		X		X		X		X		X		X
PGIC						X		X		X		X		X		X
QOL Questionnaire[i]				X						X				X		X
Placebo training		X		X												
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[j]				X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; eDiary = electronic diary; ET = early termination; ECG = electrocardiogram; NRS = numeric rating scale; PGA= Patient Global Assessment; PGIC=Patient Global Impression of Change; WOMAC = Western Ontario and McMaster Universities Arthritis Index; QOL = quality of life.

a Principal Investigator or designee contacts subjects approximately midway between Weeks 2-4, 4-8, and 8-12.
b Clinical laboratory testing includes hematology, biochemistry, urinalysis, and fasting glucose and lipids. Fasting glucose and lipids should be performed after 8 to 10 hours of fasting (no food or drink, except for water). Fasting glucose and lipids should be done at the Baseline Visit, if not done at the Screening Visit.
c Historical X-rays done within 1 year prior to the Baseline Visit are acceptable. If subject does NOT have any target knee X-ray done within the past year, a mandatory new X-ray to confirm the disease will have to be performed prior to starting the Washout Period and the X-ray should be reviewed by the completion of Baseline Visit.
d If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral acetaminophen per day as rescue medication for the treatment of any other aches they might experience during the trial, such as headache, reduction of fever and the target knee pain of osteoarthritis (not for the non-target knee) except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to for all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8).
e Study treatment will be applied on Day 0 at sites. Instructions for application and removal of study drug patches will be provided to the subject at Baseline visit.
f Subjects will be instructed on how to use the eDiary at the Screening Visit. For Screening Phase, subjects will be asked to record their NRS pain scores of the target knee and the number of tablets of rescue medication used, the time and the reason in the eDiary. For 12-week administration period, subjects will be asked to record their NRS pain scores of the target knee, and the number of tablets of rescue medication used, the time and the reason, unscheduled detachment of study drug and the reason and answer the questionnaire related to adhesion, skin irritation and discomfort, record any issues with adhesion, skin irritation and discomfort in the eDiary.
g Dermal evaluations will assess irritation, discomfort, and adhesion (At Visit 3, irritation only).
h WOMAC will include WOMAC pain intensity, WOMAC stiffness, and WOMAC physical function.
i QOL Questionnaire is Mini-OA Knee and Hip QOL (Mini-OAKHQOL) and Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA).
j AEs will be collected starting from the first administered dose.
k Screening visit will be completed -28 to -14 days prior to Baseline Visit. Screening Phase should be up to 28 days. Washout Period will be initiated from the Washout Visit. Washout period is for 7 to 14 days.
l Only for rescue medication.

10.3. Assessments

Note: For the various questionnaires that are used during this study, at each time point where a questionnaire is being completed there must be no reference back to previous questionnaires that have been completed by that subject during the study.

10.3.1 Efficacy

10.3.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC LK version 3.1 is the most recent version of this instrument for the assessment of hip and knee OA. The WOMAC Osteoarthritis Index is widely used to measure pain, stiffness, and physical function in subjects with OA pain. It is considered to be a reliable and valid instrument for this indication.[4,5,6]

Subjects will rate each of scales for Pain, Stiffness, and Physical Function over the past 24 hours. The WOMAC questionnaire will be completed for the target knee. The scores will be recorded in the eCRF.

The **WOMAC Pain** scale evaluates the following 5 items:

[redacted]

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4).

The **WOMAC Stiffness** scale assesses 2 items:

[redacted]

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4).

The **WOMAC Physical Function** assesses the following 17 categories using the 0 to 4 scale (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4) described previously:

[redacted]

The **WOMAC Composite score** is most commonly calculated by summing the items for all 3 subscales. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. The total score is calculated as follows: Total score=_/96= __%

10.3.1.2 Patient Global Assessment

The PGA is a self-administered instrument that measures the subject's overall impression of their OA pain in their target knee on a 5-point scale where 0 = "Very Good" and 4 = "Very Poor". The scores will be recorded in the eCRF.

Subjects will be asked the complete the following statement:

"How would you rate your osteoarthritis condition over the last 24 hours?"

The response options include the following:

Very Good	0
Good	1
Moderate	2
Poor	3
Very Poor	4

10.3.1.3 Patient Global Impression of Change

The PGIC is a self-administered instrument that measures change in subjects' overall improvement with treatment on a scale where 1 = "very much improved" and 7 = "very much worse." The scores will be recorded in the eCRF. Subjects will be asked the following question: "How would

you rate your overall improvement with treatment during the clinical trial?" The response options include the following:

Very Much Improved	1
Much Improved	2
Minimally Improved	3
No Change	4
Minimally Worse	5
Much Worse	6
Very Much Worse	7

10.3.1.4 Numeric Rating Scale

The NRS is an 11-point scale from 0 to 10. On this scale, 0 = no pain and 10 = the worst pain imaginable. NRS 11-point scale will be assessed in 2 ways. One is the average pain condition over the last 24 hours, and the other is the worst painful condition over the last 24 hours.

The subject will rate his or her target knee average and worst pain intensity when they replace a patch and before taking any rescue medication on the day using the following question: "On a scale from 0 to 10, where "zero" represents "no pain" and "10" represents "the worst possible pain," how would you rate the average / worst pain that you have been feeling in your knee over the last 24 hours?"

Note:

1. The average pain scale (not worst) will be used for the eligibility confirmation of inclusion criteria and identifying the target knee.
2. The NRS pain assessment must be performed daily by the subject at home between Screening (V1) and the start of the Washout Period. [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated for subjects to be considered eligible for study participation.
3. The subject will continue assessing and recording the NRS pain score daily at home during the Washout Period. [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated for subjects to be considered eligible for study participation.

10.3.1.5 Use of Rescue Medication

If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of any other aches they might experience during the trial, such as headache, reduction of fever and the target knee pain of OA (not for the non-target knee) except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Information regarding the use of rescue medication, such as the number of tablets, the time and the reason of use, will be recorded on the appropriate concomitant medication eCRF. Subjects should not use OTC APAP as rescue medication.

10.3.2 Safety

Safety assessments will include the evaluation of laboratory assessments, vital signs, 12-lead ECGs, physical examinations, dermal safety assessments and AEs.

10.3.2.1 Laboratory Safety Assessments

10.3.2.1.1 Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (see **Section 10.2**).

Hematology:	Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential.
Serum chemistry:	Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, y-glutamyltransferase, blood urea nitrogen, creatinine, fasting glucose and total lipids (8 to 10 hours after fasting is required for these laboratory testing), cholesterol, triglycerides, high density lipoprotein, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid.
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leukocyte esterase, nitrite, total bilirubin, urobilinogen.
Pregnancy test (urine):	For women of childbearing potential only.
Urine drug screen:	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, methamphetamine, methadone, phencyclidine, and tetrahydrocannabinol.
Alcohol test (urine):	Ethanol.

A central laboratory will be used to process all hematology, clinical chemistry, and urinalysis samples. Urine drug screens, alcohol tests, and pregnancy tests will be conducted at the study sites. Details on sampling, handling, and storage of samples will be given in a separate laboratory manual.

10.3.2.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of biological samples are outlined in the HP-5000-US-07 laboratory manual. The investigator is

responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

10.3.2.2 Clinical Examinations

10.3.2.2.1 Vital Signs, Weight and Height

Vital signs, including heart rate, respiratory rate, temperature, and supine blood pressure will be measured at designated time points. Blood pressure will be measured with the subject in the supine position only. The supine blood pressure should be measured after the subject has been lying down for 5 minutes. Weight (kg) and height (cm) will also be measured.

10.3.2.2.2 Electrocardiogram

The 12-lead ECG will be a complete, standardized recording and will be performed at designated time points after the subject has been in a supine position for at least 5 minutes before the 12-lead ECG is obtained. All ECG recordings will be identified with the subject number, initials, date, and time of the recording and will be attached to the subject's eCRF. ECG parameter values and interpretation of results will be captured in the eCRF.

10.3.2.2.3 Physical Examination

The following physical examination will be performed at designated time points before potential exposure to study drug and at the completion of exposure.

- General Appearance
- Head/ Face
- Eyes/ Fundoscopy
- Ears/Hearing
- Nose
- Mouth, Teeth and Throat
- Neck & Thyroid
- Chest/Lungs
- Abdomen
- Skin, Hair, and Nails
- Musculoskeletal: Extremities, Spine
- Vascular/Circulatory
- Lymphatic
- Psychiatric/Behavior
- Brief neurologic

10.3.2.3 Adverse Events

The definitions and management of and special considerations for AEs are provided in **Section 11**.

10.3.2.4 Evaluations of Patch and Dermal Assessment

Safety dermal characteristics will be assessed using a 5-point numerical scale of adhesion, Berger and Bowman scale of Irritation, 5-point numerical scale of Discomfort.[7]

10.3.2.4.1 Patch Adhesion

Patch adhesion will be assessed in 2 ways: in-clinic and at-home. At each clinic visit, patch adhesion will be assessed by the investigator or a designee (who will be a trained medical professional such as a nurse practitioner or physician assistant) using the following 5-point numerical scale:

- 0 = 2:90% adhered (essentially no lift off the skin).
- 1 = 2:75% to <90% adhered (some edges only lifting off of the skin).
- 2 = 2:50% to <75% adhered (less than half of the system lifting off of the skin).
- 3 = <50% adhered but not detached (more than half the system lifting off of the skin without falling off).
- 4 = patch detached (patch completely off the skin).

During the Double-blind Treatment Phase at home, subjects will report on any incidence of unscheduled patch detachment, the time and the reason and record in the eDiary. When subjects replace the patch, subjects will complete a questionnaire about adhesion and residue in the eDiary to confirm the following:

- Is the patch 100% attached to the skin? If No, is more than half of the patch still attached?
- Is there any residue on your skin after removing the patch?

10.3.2.4.2 Irritation

At each clinic visit, the application site where the previous patch was applied will be examined for signs of skin irritation. All subjects will be evaluated by a trained investigator or designee using the Berger and Bowman scale[7] as described below.

Half grades will not be assigned if reactions fall between the unit grades, rather, the more severe of the 2 grades will be assigned.

Dermal response score will be rated on a 0 to 7 scale, whereby 0 is rated as “No evidence of irritation” and 7 is rated as “Strong reaction spreading beyond test (application) site.”

Dermal Response

- 0 = no evidence of irritation
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible; minimal edema or minimal papular response
- 3 = erythema and papules

- 4 = definite edema
- 5 = erythema, edema, and papules
- 6 = vesicular eruption
- 7 = strong reaction spreading beyond the application site

Other effects will be scored via a letter scale and a corresponding numeric scale, whereby N (0) is rated as "No effects" and H (3) is rated as "Small petechial erosions and/or scabs."

Other Effects

- A = slightly glazed appearance
- B = marked glazed appearance
- C = glazing with peeling and cracking
- F = glazing with fissures
- G = film of dried serous exudates covering all or part of the patch site
- H = small petechial erosions and/or scabs
- N = no other observations

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about skin irritation in the eDiary. Subjects will be asked to report any skin irritation to the site staff. Skin irritation reported by the subjects will be recorded as AEs. The investigator will assess any irritation observed at the patch application site at clinic visits. If the score of the dermal response and other effects are not 0 or N (0), it will be evaluated as AEs.

The subjects will be instructed to contact to their site and arrange for an unscheduled visit (i.e., site visit or virtual visit using remote video systems if available) when they experience any significant or intolerable irritation at home to manage the dermal reaction and evaluate it using the above scale.

10.3.2.4.3 Discomfort

Discomfort will be assessed by the investigator or a designee using a predefined discomfort rating scale. The evaluator will ask the subject, "Are you experiencing any discomfort related to the patch?" If the answer is no, the overall level of discomfort will be rated as 0. If the answer is yes, the evaluator will then ask the subject to rate the discomfort as mild, moderate, or severe along with the description of the discomfort (e.g., itching, burning, pain, stinging, soreness, dryness, and other). Any discomfort mentioned should be recorded as AEs and rated as follows:

- 0 = No discomfort
- 1 = Mild discomfort
- 2 = Moderate but tolerable discomfort
- 3 = Severe, intolerable discomfort
- 4 = Patch not present

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about discomfort in the eDiary. If there is any discomfort, the description (e.g., itching, burning, pain, stinging, soreness, dryness, and other) will be recorded in the eDiary.

Discomfort reported by the subjects will be recorded as AEs.

The subjects will be instructed to contact to their site and arrange for an unscheduled visit (i.e., site visit or virtual visit using remote video systems if available) when they experience any significant or intolerable discomfort at home to manage the dermal reaction and evaluate it using the above scale.

10.3.3 QOL

10.3.3.1 Mini-OA Knee and Hip QOL (Mini-OAKHQOL)

The 20-item Mini-OA Knee and Hip QOL (Mini-OAKHQOL) has good psychometric properties and can be used for the measurement of QOL in subjects with OA of the lower limbs (see **Section 18.3**).

Subjects will complete a questionnaire about QOL at clinical visits.

10.3.3.2 Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA)

The Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) Knee or Hip is a 6-item validated questionnaire that assesses the impact of OA on absenteeism, presenteeism, work productivity, and activity impairment. Each subscale score is expressed as an impairment percentage (0-100) where higher numbers indicate greater impairment and less productivity. The WPAI: OA is self-administered by the subject and takes less than 5 minutes to complete (see **Section 18.4**).

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

Per the International Council for Harmonisation (ICH), an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will NOT be considered AEs unless there is an increase in the frequency or severity, or a change in the nature of the disease or condition during the Double-blind Treatment Phase (worsening of a pre-existing condition is considered an AE). AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

Any medical condition or clinically significant laboratory abnormality with an onset date after signing the Informed Consent and before the time of dosing is considered to be pre-existing, and should be documented as Medical History (and not as an AE). Any new medical condition or clinically significant laboratory abnormality or an exacerbation of a pre-existing condition with an onset date after signing of Informed Consent and after the time of first dosing should be recorded as an AE. Events occurring in subjects treated with placebo will also be considered AEs. However, AEs reported during treatment-free periods before study drug has been administered are not considered AEs; these events are captured on the eCRF as updates to the subject's medical history.

- All AEs encountered during the clinical study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from after the start of the study drug. AEs in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. It is up to the investigator to determine whether an abnormal laboratory value constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g., if new onset viral

hepatitis is causing elevated ALT, hepatitis should be captured as the AE and not the elevated ALT).

- Examples of laboratory abnormalities, which should be considered as AEs include those which result in withdrawal of the study treatment, withholding study treatment pending some investigational outcome, reduction of dose of the study treatment, or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be reported on the appropriate AE page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.
- Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a study drug, the known information is contained in the IB which includes the HP-5000 Developmental Core Safety Information.

An unexpected AE is one for which the specificity or severity is not consistent with the current IB and Developmental Core Safety Information.

Furthermore, reports that add significant information on specificity or severity of a known, already documented AE constitute unexpected events.

11.1.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death

NOTE: Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should usually be reported as the outcome of a specific SAE.

- is life-threatening.

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does NOT qualify the condition or event as an SAE.

- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly in the offspring/fetus.

NOTE: A congenital anomaly in an infant born to a mother who was exposed to study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received a study drug is NOT considered an SAE but an AE.

- Is an important medical event.

NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency or drug abuse.*

11.2. Management of Adverse Events

Adverse events will be collected from the time of first dose administration through the Follow-up Visit or Early Termination Visit, whichever occurs first.

Subjects who complete the Double-blind Treatment Phase or terminate early will continue to be monitored for AEs for 30 days from last day for study treatment, unless resolution, they withdraw consent or are lost to follow-up.

11.2.1 Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in **Section 11.1.3**.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in **Section 11.1.3**.

11.2.2.3 Action Taken

Action taken may consist of:

Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Dose interrupted	Patch temporarily removed
Dose not changed	No action taken with study drug
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as follows:

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

- Fatal*
- Unknown

***NOTE**: Only select fatal as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to study drug. The categories for classifying the investigator's opinion of the relationship are listed below.

Not related	An AE with sufficient evidence to accept that there is no causal relationship to study drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven).
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable, and in which other drugs, events or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Definitely Related	An AE occurring in a plausible time relationship to study drug administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

Note: AEs at patch application site will be collected and marked with the flag in the eCRF to be able review and analyze them separately.

11.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information; where appropriate (The period of observation for the study is described in **Section 11.2**):

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to study drug

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, as necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject should be withdrawn from the study and the reason and date of withdrawal must be documented in the eCRF. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or Medical Monitor.

If a subject experiences an intolerable AE , the investigator must decide whether to withdraw the subject from the study and/or treat the subject. Special procedures may be recommended for the specific study drug, such as the collection of a serum sample for determining blood concentrations of study drug, or treatment regimens, as appropriate.

It is **NOT** necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see **Section 9.5** for a description of the unblinding procedures.

11.2.5 Follow-up

All ongoing SAEs at the time of discontinuation will be followed (up to a maximum of 30 days after the last dose of study drug) to a satisfactory resolution, or until it becomes stable, or until it can be explained by another known causes (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All ongoing AEs at the time of discontinuation will be followed for up to 7 days. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting of Adverse Events

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Noven Pharmacovigilance within 24 hours of first becoming aware of the event by completing, signing and dating the SAE Form (within the eCRF), verifying the accuracy of the information recorded in the form with the source documents.

All SAEs, irrespective of relationship to study treatment, must be reported to Noven as soon as possible but no later than 24 hours using the appropriate SAE form within the eCRF.

It is very important that the SAE form (within the eCRF) be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality. All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization. Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form (within the eCRF). If eCRF system is down or not accessible for the site, the "Noven Serious Adverse Event Reporting Form (Noven SAE form)" must be used for reporting to Noven Pharmacovigilance. The site should use the eCRF system as the primary means to notify of the SAE (initial or follow-up). The Noven SAE "paper" form should only be used as the back-up option for notification if the eCRF system is down.

If the situation where the Noven SAE "paper" form is to be used, **all SAEs, irrespective of relationship to study treatment, must be reported to Noven as soon as possible but no later than 24 hours to:**

Email: [redacted]

SAEs, regardless of causality assessment, must be collected through the Termination Visit and for 30 days following study drug discontinuation, whichever is longer.

Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The written report should be submitted on the SAE form (within the eCRF) provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Subject's study number
- Subject's age
- Subject's gender
- Date of first dose of study drug
- Date of last dose of study drug, if applicable
- Adverse event term
- The seriousness criteria that were met
- Date of occurrence of the event
- A brief description of the event and outcome to date
- Any actions taken in response to the SAE
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to study drug ("Is there a reasonable possibility that the study drug caused the SAE?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Preliminary SAE reports and/or any missing or additional relevant information concerning the SAE should be provided to the recipients of the initial information as soon as possible on a follow-up SAE form (within the eCRF), together with the following information (AE, date of occurrence, subject number, study ID, study drug, and site number) including copies of hospital case reports, autopsy reports and other documents requested by the sponsor; this will allow the follow-up information to be linked to the initial SAE report.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his/her health authorities, institutional review board (IRB), principal and coordinating investigators, study investigators, and institutions.

11.2.6.2 Nonserious Adverse Events

All non-serious AEs will be reported to the Sponsor on an ongoing basis and will be captured in the eCRF.

11.2.7 Pregnancy Reporting

All females of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Females should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Male study participants will be instructed to practice birth control measures to prevent a partner's pregnancy during the subject's study participation and for 90 days following the last dose administration.

Pregnancy testing will be conducted prior to administration of study drug on every female of childbearing potential. A female who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A female who becomes pregnant during study drug treatment will be immediately withdrawn from the study. Any female who becomes pregnant during treatment and within 30 days of discontinuing study drug will be followed by the investigator until birth or termination of pregnancy. Any pregnancy for which the estimated date of conception occurred prior to the Termination Visit of the study and for 30 days following study drug discontinuation, whichever is longer, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

An induced abortion or a spontaneous abortion is considered to be a SAE and should be reported in the same timeframe and in the same manner as all other SAEs (see **Section 11.2.6.1**).

The investigator must report the pregnancy to Noven using the **Noven Pregnancy Notification Report form** via the same email address as for SAE reporting. The investigator should contact the designated individuals who receive SAE notification and record information related to the pregnancy on a **Noven Pregnancy Notification Report form** provided by the sponsor or its designee.

Pregnancies must be reported to Noven as soon as possible, but no later than 24 hours to:

Email: [redacted]

ET Visit assessments are required as soon as possible after learning of the pregnancy. The Clinical Site should record and maintain all relevant information on the appropriate study form and eCRF, including the follow-up and outcome of the pregnancy.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed-up and documented even if the subject was discontinued from the study (with the subject's consent). The Clinical Site must report all pregnancy follow-up information to the Sponsor using the Noven Pregnancy Follow-up Report form via email to [redacted] within 24 hours of receiving the pregnancy follow-up information. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. The Clinical Site must report all congenital abnormalities/birth defects and spontaneous miscarriages using the SAE form (within the eCRF) via email to [redacted] within 24 hours of receiving the information. Elective abortions without complications should not be handled as AEs.

12. DATA SAFETY MONITORING BOARD

There will be no Data Safety Monitoring Board for this study.

13. STATISTICAL METHODS

13.1. Study Endpoints

13.1.1 Primary Efficacy Endpoint

- WOMAC LK3.1 OA (pain) change from Baseline at Week 12

13.1.2 Key Secondary Efficacy endpoints

- WOMAC LK3.1 OA (physical function) change from Baseline at Week 12
- WOMAC LK3.1 OA (stiffness) change from Baseline at Week 12

13.1.3 Secondary Efficacy Endpoints

- WOMAC LK3.1 OA (pain) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (physical function) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (stiffness) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (composite score) change from Baseline at Weeks 1, 2, 4, 8, and 12
- Change from Baseline in pain intensity assessed on an 11-point NRS at Weeks 1, 2, 4, 8, and 12
- Change from Baseline in pain intensity assessed on an 11-point NRS of a weekly average of all available daily pain scores at each week from Week 1 through 12
- Change from Baseline in Patient Global Assessment at Weeks 1, 2, 4, 8, and 12
- Patient Global Impression of Change (PGIC) at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (pain) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (physical function) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (stiffness) of 2:30%, 2:50%, 2:70% and 2:90% at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects, the number of days, and the total number of rescue medication tablets used during the treatment phase
- The onset of the effect: Pain intensity assessed on an 11-point NRS change from Baseline
- Mini-OA Knee and Hip QOL (Mini-OAKHQOL) scores change from Baseline at Weeks 4 and 12
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) impairment scores change from Baseline at Weeks 4 and 12.

13.1.4. Safety Endpoints

- The incidence of treatment-emergent AEs, AEs leading to discontinuation of the study drug, SAEs, and other significant AEs.
- Change from Baseline in clinical laboratory tests, ECG findings, body weight, physical examination findings, and vital signs.
- Dermal assessments: irritation, discomfort, and adhesion.

13.2. Sample Size Determination

Based on the HP-5000 Phase 2 study results, the assumed [redacted] of the test product in the pivotal study will be about [redacted] The sample size of [redacted] subjects per treatment arm (or total of about [redacted] subjects) will be included in order to have 80% power to demonstrate statistically significant difference versus placebo using a 2-sided overall Type I Error rate of 0.05.

A sufficient number of subjects will be screened to randomize the proposed sample size.

13.3. Analysis Populations

The following analysis populations are planned for this study:

- Intent-to-Treat (ITT): Includes all consented and randomized subjects. Regardless of any protocol deviations, analyses performed on the ITT set will be based on the randomized treatment assignment and all available data. The ITT will be used as the primary set for analysis of efficacy endpoints.
- Safety Analysis Set (SAF): Includes all subjects who have had at least 1 patch of double-blind study drug applied and who have at least 1 post-dose safety measurement during the Double-blind Treatment Phase. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the SAF will be based on treatment actually received. The SAF will be used for the analysis of dermal evaluations and safety endpoints.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect study drug, analyses of the ITT population will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

13.4. Statistical Analyses

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock. Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a *P* value of <0.05 will be considered statistically significant. For analyses involving study site, if the number of subjects per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Summary statistics will be provided for the variables described below. For continuous variables, these statistical analyses will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

13.4.1 Study Subjects and Demographics

13.4.1.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, and withdrawing, along with reasons for withdrawal will be tabulated overall and by treatment group. The number of subjects and patches in each analysis population will be reported.

13.4.1.2 Protocol Deviations

A by-subject listing of all protocol deviations and violations will be reported in the clinical study report (CSR).

13.4.1.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations. Demographic variables will include age, gender, height, weight, BMI, target knee (left or right), duration of OA of the knee and age at the onset of the disease. Information on race and ethnicity will be collected for any eventual analysis of differences in response to study drug, in accordance with local regulatory requirements. Baseline subject characteristics will include medical history, physical examination findings, and previous OA treatment modalities.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.4.2 Exposure and Compliance

Investigational product administration will be summarized in terms of the number of patches applied and removed, the number of patches removed earlier along with the summary of reasons for early removal. For each subject mean in terms of duration of exposure will be calculated. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

13.4.3 Efficacy Analyses

Efficacy variables will be summarized and analyzed using the ITT population as primary, unless otherwise specified.

13.4.3.1 Primary Analysis

The primary efficacy endpoint of this study is the change from Baseline to Week 12 in the WOMAC pain score, and key secondary endpoints are the change from Baseline to Week 12 in the WOMAC physical function and WOMAC stiffness. The primary analysis set is the ITT. The comparison of interest is: HP-5000 versus placebo.

The fixed-sequence procedure will be applied for primary and key secondary endpoints of this study, where the order in which the hypotheses are tested is pre-specified as following: (1) WOMAC pain, (2) WOMAC physical function, and (3) WOMAC stiffness. Testing begins with the first hypothesis (H_1) about WOMAC pain, and each test is carried out as long as significant results with level of significance a=0.05 are observed in all preceding tests. The fixed-sequence procedure controls the family-wise error rate because, for each hypothesis, testing is conditional upon rejecting all hypotheses earlier in the sequence.

All statistical tests of hypotheses in this trial will be 2-sided with a Type I Error rate of 0.05.

The estimand in the primary analysis for efficacy is the difference between treatments groups (HP-5000 *vs*. placebo) in the change from Baseline to Week 12 in WOMAC pain score in all randomized subjects. Outliers are defined *a priori* as (i) WOMAC scores obtained more than 24 hours after removal/detachment of double-blind study drug; or (ii) WOMAC scores obtained within 24 hours after the subject using rescue medication. WOMAC scores obtained 24 hours after removal/detachment of the study drug or WOMAC scores obtained within 24 hours after the subject using rescue medication will be excluded as outliers.

The primary efficacy variable, change from Baseline to Week 12 in the WOMAC pain score, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in WOMAC pain score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC pain score as covariates. An unstructured covariance matrix will be assumed. If the unstructured covariance matrix fails to converge, a series of other covariance structures will be tested for use.

Other sensitivity analyses will be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis as described below.

The use of MMRM inherently implies that the treatment effect on the change from baseline in the WOMAC score will be similar for the patients who withdraw and for those who complete the study in their respective treatment groups, conditional on the outcomes observed prior to withdrawal (MAR [Missing at random] assumption). To assess the robustness of the MAR assumption, sensitivity analyses which utilize multiple imputations and a different assumption about unobserved outcomes will be performed, as detailed below.

A number of sensitivity analyses of the primary efficacy endpoint will be performed to assess the impact of assumptions about unobserved missing data patterns on the primary inferences in the trial.

Pattern-Mixture Model and Copy Reference Sensitivity Analyses of MMRM Approach:

Robustness of the primary results under MNAR (Missing not at random) mechanisms will be assessed using pattern-mixture modeling and copy reference imputation approaches. All sensitivity analyses will be based on the pattern mixture model using multiple imputation technique for the dropout reasons and their assumed pattern of missing data as follows:

- Lack of efficacy (LOE) as MNAR with other missing data as MAR
- LOE, rescue medication and adverse events (AE) as MNAR with other missing data as MAR
- Any reason (all dropout) as MNAR

a. Multiple Imputation: Pattern Mixture Model (PMM)

The missing data due to early discontinuations will be imputed assuming MNAR following the approach described in Permutt (2016)[8]. That approach will be implemented by imputing missing data first under the MAR assumption in each treatment group using multiple imputation and then adding a pre-defined L1 to each imputed value in the placebo group and adding a different pre-defined L2 to each imputed value in the active treatment group, then varying L1 and L2 over an enclosure of a plausible range of values. As noted in the article by Permutt (2016)[8], this is considered the most appropriate kind of sensitivity analysis for the missing data problem. Also, this imputation approach was documented on Page 89 of the NRC report (2010)[9].

b. Multiple Imputation: Copy Reference (Placebo) Approach

This is placebo-based imputation for missing data which will be implemented assuming missing data from the placebo group as MAR and also as MNAR. This will be performed by first implementing placebo-based imputation (copying the distribution of WOMAC scores in the placebo group) for missing data in the active treatment group and the placebo group (as MAR). Then, an adjustment for MNAR in both treatment groups will be implemented by adding a common shift (L) to the imputed data, worsening the imputed data further, in both the placebo and the active treatment groups as described in Koch and Wienner (2016)[10]. This step is necessary because it is possible to have a lower treatment discontinuation rate in the active treatment group than in the placebo group and it is important to consider a MNAR approach in the placebo group in such a case. Using a similar argument as in the previous paragraph, the shift L will assume similar values to those of L1, that is L=1,2,4,8,12 (while the case of L=0 represents the common copy placebo method, where missing data from placebo are considered as MAR).

Sensitivity analysis using different methods of handling missing data will provide useful information about effectiveness of the study drug and confidence in the reliability of the conclusions drawn. Programming details including SAS code will be provided in the SAP.

13.4.3.2 Analyses for Key Secondary Endpoints

The MMRM model will be used the same way as for primary variable only include change from Baseline in WOMAC physical function (or stiffness) score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC physical function (or stiffness) score as covariates.

The fixed-sequence procedure will be applied for primary and key secondary endpoints as described in **Section 13.4.3.1**. Other secondary efficacy endpoints will not be included into the fixed-sequence procedure.

Other sensitivity analyses may be performed on the key secondary endpoints to assess the robustness of the results based on the model used for primary analysis. Details will be provided in the Statistical Analysis Plan.

13.4.3.3 Analyses for Secondary Endpoints

All WOMAC LK3.1 OA Indices, PGA, PGIC, and NRS secondary efficacy endpoints will be analyzed similar to the primary analyses. An MMRM model will be used with change from

baseline as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the baseline assessment score as covariates.

The observed value and change from baseline each assessment score will also be summarized descriptively by visit using summary statistics in addition to the above noted model.

The proportion of responders and non-responders for WOMAC pain, WOMAC physical function or users of rescue medication will be summarized by visit. Treatment comparisons will be made using a logit model with treatment effect as the only term in the model.

The pain intensity assessed on an 11-point NRS average and worst score between Baseline and each day will be tabulated by day and presented graphically.

A weekly average of all available pain scores will be calculated using the 11-point NRS average and worst score. MMRM model will be used to address the secondary objective to compare for change from baseline between treatment arms by weeks; and data will be presented graphically. The all available scores of daily NRS scores evaluated when the subjects replace the patch and the NRS scores evaluated before any rescue medication use will be analyzed.

The NRS pain score for assessment at Weeks 1, 2, 4, 8, and 12 is a mean of the NRS pain scores reported for pain [redacted] using the 11-point NRS average and worst score. MMRM model will be used to address the secondary objective to compare the change from baseline between treatment arms by weeks; and data will be presented graphically.

To address the objective for rescue medication, the proportion of subjects, the number of days using rescue and total rescue use during the entire treatment period will be summarized by treatment arms.

13.4.4 Safety Analyses

All safety summaries will be descriptive; statistical significance tests may be performed on safety data that will be described in the SAP.

Safety analyses will be conducted using data from the SAF population (as defined in **Section 13.3**). Safety variables include AEs, clinical laboratory values, body weight, vital signs, ECG readings,

physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.4.4.1 Adverse Events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term. Summaries of AEs by severity and relationship to study drug will also be provided. Serious adverse events and AEs resulting in discontinuation of study drug will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of study drug will be produced.

13.4.4.2 Dermal Performance

The frequency and percentage of subjects and number of patches with findings related to dermal performance including irritation, discomfort, and adhesion will be summarized.

13.4.4.2.1 Irritation

The frequency and percentage of subjects with patches in each combined and concatenated category will be summarized from the above scales at each visit and overall. The Concatenated Irritation score consists of numerical “Dermal Response” score + the “Other Effects” lettered score; for example: 2N, 2A, 3G, etc. The Combined irritation score will be calculated as a numerical total; i.e., numerical “Dermal Response” score + numeric equivalent for the “Other Effects” lettered score (note that the “Other Notations” do not have numeric equivalents and do not contribute to the numeric Combined irritation score); e.g., 2N, 2A, and 3G will be reported as 2, 2, and 6 combined irritations scores respectively.
In addition to the above, the frequency and percentage of subjects with a combined score of 3 or more will be tabulated.

The information from eDiary data will be included in the summary table and listings.

13.4.4.2.2 Discomfort

The information from eDiary data will be included in the summary table and listings.

13.4.4.2.3 Adhesion

The frequency and percentage of patches in each category will be summarized from the above scale at each visit and overall. The number of subjects with the worst score will be summarized and presented. The information from eDiary data will be included in summary table and the listing.

13.4.4.2.4 Dermal Evaluations at Home

At home, subjects will complete a questionnaire about skin irritation, discomfort, and adhesion in the eDiary. A by-subject listing of this data will be presented in addition to summary tables for each dermal assessment.

13.4.4.3 Concomitant Medications

Prior and concomitant therapies will be summarized for the Safety population. All prior and concomitant medications recorded in the eCRF will be coded to generic term and all matching ATC codes using the current version of WHO-DD. Summaries will be prepared using the coded generic term. All prior and concomitant medications recorded in the eCRF will be listed.

13.4.4.4 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from Baseline values will be presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from Baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit. Pre- and post-treatment values will also be presented with an analysis of mean changes from Baseline.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.4.4.5 Vital Signs and Body Weight

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for body weight, BMI, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate.

The number of subjects with vital signs values categorized as below, within, or above normal ranges, will be tabulated showing change from Baseline (shift tables) for each parameter by

treatment group and by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from Baseline.

13.4.4.6 Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected for heart rate (Fridericia's correction [QTcF]), and heart rate for each treatment group at each time point.

13.4.4.7 Physical Examination Findings

The abnormal findings in the complete physical examination will be captured and analyzed as AEs.

13.4.4.8 Dermal Safety

The number and percentage of subjects with findings related to dermal safety including adhesion, irritation, and discomfort will be summarized. A by-subject listing of individual dermal safety findings will also be provided.

13.4.5 Interim Analysis

No interim analyses are planned.

13.5. Database

The final database will be compliant with Food and Drug Administration (FDA) Data Standard catalog from Electronic Common Technical Document/eCTD (May 2015) and Providing Regulatory Submissions in Electronic Format - Standardized Study Data (July 2016).

14. STUDY CONDUCT

The study will be conducted in accordance with all applicable regulatory requirements, including ICH Good Clinical Practice (GCP) guidelines, subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (see **Section 15**). The sponsor reserves the right to withdraw a subject from the study (see **Section 8.2.3**), to terminate participation of a study site at any time, and/or to discontinue the study.

Noven agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (see **Section 17**), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the April 1996 ICH Guidance for Industry E6 Good Clinical Practice (GCP), and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing Noven with

documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Site Initiation

Study personnel may not screen or enroll subjects into the study until after the initiation visit has been conducted, including all required training is complete, and all study supplies are on-site. The investigator and the full study site staff must be available at this visit. All staff must have an initiation visit before they conduct any study specific procedures.

The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All required regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

Following the initiation visit, the study will be monitored as per clinical monitoring plan, or additional visit may occur when deemed necessary, while subjects are actively randomized into the study.

14.2. Screen Failures

Subjects who fail any of the inclusion and/or exclusion criteria may not be rescreened for the study. Retesting of clinical laboratory evaluations within the screening window is permitted (i.e., retesting of central clinical laboratory analytes can be done only once).

14.3. Study Documents

All documentation and material provided by Noven or designee for this study are to be retained in a secure location and treated as confidential material.

14.3.1 Investigator's Regulatory Documents

The regulatory documents are listed in the HP-5000-US-07 Study Manual. All required regulatory documents must be received from the investigator and reviewed and approved by Noven or its designee before the study site can initiate the study and before Noven will authorize shipment of study drug to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendments, the HP-5000 topical patch IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.3.2 Case Report Forms

By signing the Investigator's Agreement (see **Section 17**), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF and are enrolled/randomized.

Case report forms are considered confidential property of Noven and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit in a neat, legible manner to ensure accurate interpretation of data. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee. The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.3.3 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. All source documents must be accessible for verification by the site monitor, auditor, and IRB for inspections and by the regulatory authority(ies). Direct access to source documents must be guaranteed by the

investigator, sub-investigator, or study coordinator, who must provide support at all times for these activities. Subject confidentiality will be protected at all times. Remote source data verification may be used; this should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory, to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.4. Data Quality Control

Noven and its designees will perform quality control checks on this clinical study.

14.4.1 Monitoring Procedures

Noven and/or its designee will monitor the study to ensure study is conducted in accordance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associates (CRAs) will visit the investigator and study site at periodic intervals and maintain periodic communication. Alternatively, centralized monitoring of data acquired by electronic data capture systems (e.g., eCRFs, central laboratory data, ECG data etc) will occur in an ongoing and/or cumulative manner.

Additional off-site monitoring activities may include phone calls, video visits, e-mails, or other online tools in order to discuss the trial with the investigator and site staff. These activities may be used to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, and trial participant status.

It will be the CRA's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The investigator agrees to allow the CRAs and other authorized Noven personnel access (either in person or electronically). The CRAs will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The CRAs will review:

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures

- laboratory test reports
- other patient records and study documents
- AE procedures, storage and accountability of study drug and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (see **Section 17**), the investigator agrees:

- to meet with the CRAs during study site visits;
- to ensure that study staff is available to the CRAs as needed;
- to provide the CRAs access to all study documentation, to the clinical supplies dispensing and storage area; and
- to assist the monitors in their activities, if requested

Further, the investigator agrees to allow Noven or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in a separate manual.

14.4.2 Data Management

Noven or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and standard operating procedures. A comprehensive data management plan will be developed including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.4.3 Quality Assurance/Audit

Study sites, study database and study documentation may be subject to quality assurance audits during the course of the study by Noven or its designee. Audits may be undertaken to check compliance with GCP guidelines, and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or CSR)

Noven or its designee may conduct additional audits on a selection of study sites, which will require access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities clinical inspection according to GCP guidelines. The investigator should agree to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other study files necessary to conduct that audit or inspection. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct a clinical inspection, the investigator shall notify Noven immediately.

14.5. Premature Termination of the Study

The study may be prematurely terminated at Noven's discretion at any time and for any reason. If the study is terminated or suspended, Noven will promptly inform the investigators/sites and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The ethics committee will also be promptly informed and provided with the reason(s) for the termination or suspension by Noven or by the investigator/institution, as specified by the applicable regulatory requirement(s).

Study Site Closure:

At the end of the study, all study sites will be closed, typically after database lock. Noven may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Non-compliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.5.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the study drug has been approved or the sponsor has discontinued its research with study drug, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of study drug

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense. The final database will be archived by Noven according to the regulatory requirements.

14.6. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion with and agreement by Noven and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s), etc.).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

14.7. Clinical Study Report

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports.

14.8. Use of Information and Publication

All information concerning study drug, Noven's operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by Noven or its designee to the investigator and not previously published, is considered confidential and remains the sole property of Noven. Case report forms also remain the property of Noven. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Noven in connection with the continued development of study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Noven. Publication or other public presentation of study drug data resulting from this study requires prior review and written approval of Noven. Abstracts, manuscripts, and presentation materials should be provided to Noven for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Noven has reviewed and commented on such a presentation or manuscript for publication.

14.9. Subject Insurance and Indemnity

Noven will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of insurance will be kept in the study files.

14.10. Data Protection

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of Noven and/or submitted to one or more sponsor offices worldwide, the ethics committee, and regulatory authorities.

Prior to the subject's enrollment in the study, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes.

The subject must be assured that their identity will be protected. To facilitate this, a unique identification code will be assigned by the investigator to each study subject. This will be used

instead of the subject's name and cross-referenced with the subject's date of birth when reporting AEs and/or other study-related data.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Ethical Conduct of the study

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (64th General Assembly, Fortaleza, Brazil, October 2013), the April 1996 ICH guidelines (E6) of GCP (including archiving of essential study documents), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities of participating country(ies) before sites are initiated.

15.2. Subject Information and Informed Consent

The investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

The investigator will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the ICF. After completion, ICFs will be kept and archived by the investigator in the investigator's study file. A copy of the ICF(s) must be provided to the participant. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

15.3. Approval by Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations. Prior to initiation of the study at each study site, the protocol, the ICF(s), the subject information sheet(s), details of the subject

recruitment procedures, and any other relevant study documentation will be submitted to the responsible local and/or national IRB and approved.

Written notification of approval is to be provided by the investigator to the sponsor's monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Noven form, IRB Approval Form, or written documentation from the IRB containing the same information.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by Noven before implementation. This written approval will consist of a completed IRB approval form or written documentation from the IRB containing the same information.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. Upon completion of the study, the investigator will provide the IRB with a brief report of the outcome of the study, if required.

15.4. Subject Insurance and Finance

Noven will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCE

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3. Investigational Brochure, Diclofenac Sodium Transdermal Drug Delivery System, HP-5000 Transdermal Patch. Noven Pharmaceuticals, Inc. [redacted] Edition No. 03, September 9, 2014.
4. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833-1840.
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6. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal anti-inflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578-1587.
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17. ATTACHMENTS

Investigator's Agreement

PROTOCOL NUMBER: HP-5000-US-07

PROTOCOL TITLE: A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee

FINAL PROTOCOL: September 29, 2020 Version 1.0

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Noven during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an IP during and after study completion.

Principal Investigator:

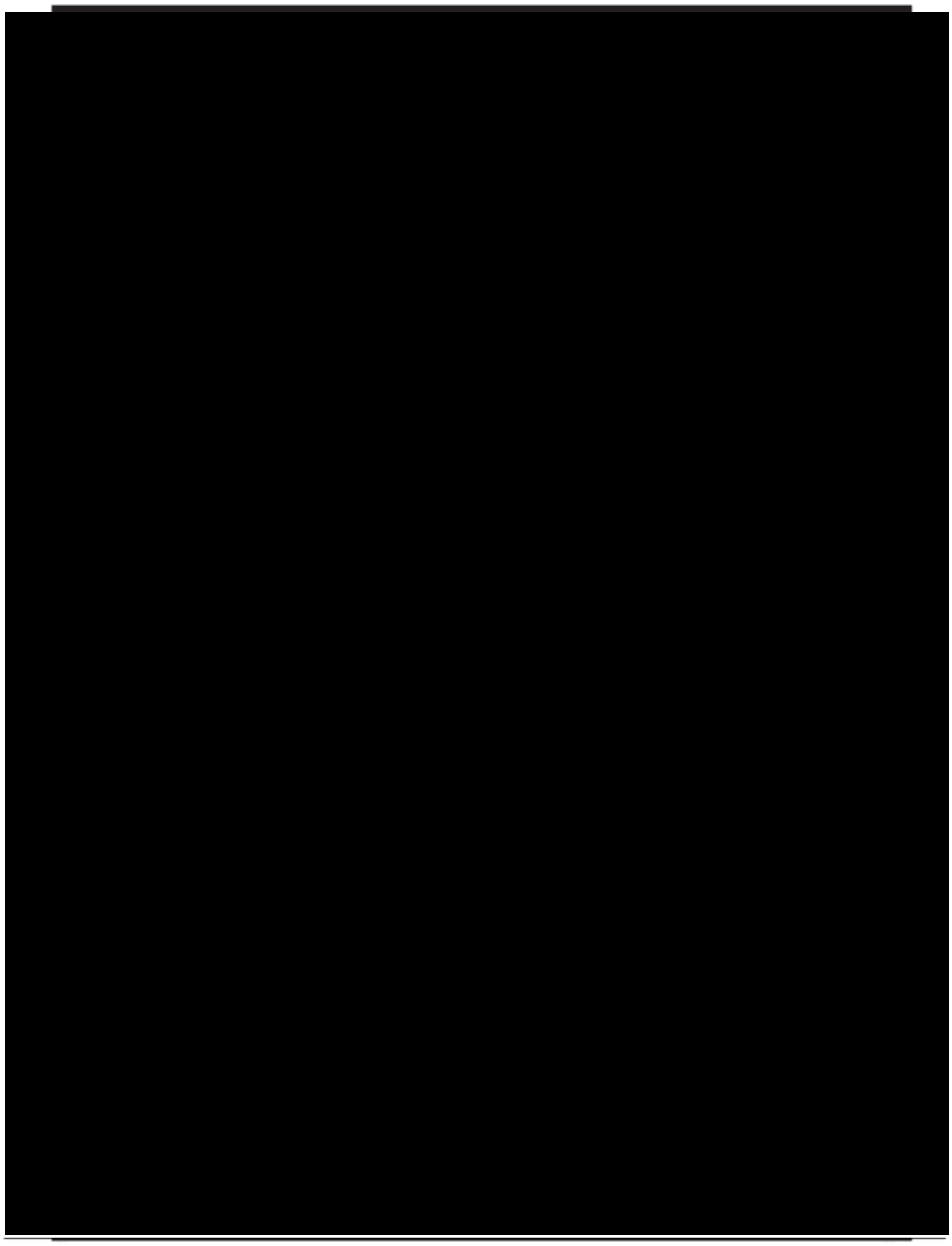
Printed Name: _____

Signature: _____

Date: _____

18. APPENDICES

18.1. Western Ontario and McMaster Universities Osteoarthritis (WOMAC) LK3.1 Index



English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE WOMA

Section A

PAIN

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM$_B$**

Section B

STIFFNESS

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM$_{C1-3}$**

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE WOMc2-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOMC3-3**

DIFFICULTY PERFORMING DAILY ACTIVITIES

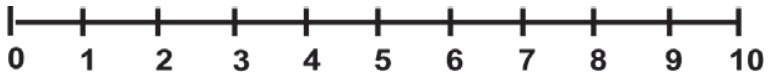
[redacted]

English for USA - V2

18.2. 11-Point Numeric Rating Scale (NRS)

This is a sample of the Numerical Rating Scale. Please use the rating scale provided in the study reference manual.

Instructions: Show the pain scale to the subject and explain that on the 0 to 10 pain rating scale, 0 means no pain and 10 means the worst possible pain. A value in the middle of the scale (around 5) would be moderate pain; a value of 2 or 3 would be mild pain and a value of 7 or higher is considered severe pain.



No Pain **Worst Possible Pain**

Adapted from: Farrar JT, Young JP, La Moreaux L, Werth JL, and Poole MR: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.

18.3. Mini-OA Knee and Hip QOL (Mini-OAKHQOL)

Quality of life in osteoarthritis of lower limbs

Mini-OAKHQoL

Quality of Life in Rheumatology Group© 2012

Please read the following instructions carefully:

The following statements refer to the impact your knee and/or hip osteoarthritis has had on your quality of life. This information allows us to better understand how you are living on a daily basis with your osteoarthritis.

☞ Check the response that best describes your situation,

between "**not at all**" and "**absolutely**" ,
between "**not at all**" and "**a great deal**",
between "**never**" and "**all the time**"
according to each of the proposed statements.

There is no right or wrong answer.

☞ For each statement check only one response (☑)

Example:

	Not at all										A great deal
I have difficulty climbing stairs.	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☐
	0	1	2	3	4	5	6	7	8	9	10

Date completed: |__|__| |__|__| |__|__|__|__|

THIS QUESTIONNAIRE CONSISTS OF THREE PAGES (INCLUDING THIS ONE).

Quality of Life in Rheumatology Group© 2012
Version 1.1

Read these questions one by one paying attention to your quality of life OVER THE PAST FOUR WEEKS.
Check the response that corresponds best to the way you are living with your osteoarthritis.

	Not at all										A great deal
1. I have difficulty walking	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
2. I have difficulty bending down or getting up	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
3. I have difficulty climbing up stairs	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
4. I have difficulty dressing myself (socks, shoes, tights/pantyhose)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
5. I have difficulty getting in or out of a car	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
6. I have difficulty performing my tasks at work	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Not applicable	☐										
7. It takes me longer to do things	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
8. I feel unhappy because of my pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
9. I worry about having to depend on others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
10. I am limited in my sexual activities	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No sexual activity in the past 4 weeks	☐										

	Never										Always
11. I have difficulty staying in the same position for a long time, (sitting, standing, being still)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
12. I have pain (how often)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

	Not at all										Unbearable
13. I have pain (intensity)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Read these questions one by one paying attention to your quality of life
OVER THE PAST FOUR WEEKS.
Check the response that corresponds best to the way you are living with your osteoarthritis.

	Not at all										Absolutely
14. I am able to plan long term projects	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
15. I get out of the house as much as I would like	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Never										**All the time**
16. I wake up because of my pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
17. I wonder about what I will become in the future	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
18. I am irritable, grouchy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Not at all										**A great deal**
19. I feel that others understand the difficulties I have related to my osteoarthritis	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
20. I feel supported by those close to me (partner, family,…)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Please make sure that you have checked one box and only one
for each of the 20 statements.

Thank you for answering this questionnaire

18.4. Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA)

Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

The following questions ask about the effect of your osteoarthritis of the knee or hip on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your osteoarthritis of the knee or hip? *Include hours you missed on sick days, times you went in late, left early, etc., because of your* osteoarthritis of the knee or hip. *Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

1

5. During the past seven days, how much did your osteoarthritis of the knee or hip affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee or hip affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your work a great deal.

Consider only how much osteoarthritis of the knee or hip affected productivity while you were working.

Osteoarthritis of the knee or hip had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Osteoarthritis of the knee or hip completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your osteoarthritis of the knee or hip affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee or hip affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your activities a great deal.

Consider only how much osteoarthritis of the knee or hip affected your ability to do your regular daily activities, other than work at a job.

Osteoarthritis of the knee or hip had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Osteoarthritis of the knee or hip completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:OA V2.0 (US English)

2

18.5. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

18.6. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

PROTOCOL

PRODUCT NAME/NUMBER:	HP-5000 (diclofenac sodium) topical system
PROTOCOL NUMBER:	HP-5000-US-07
DEVELOPMENT PHASE:	3
PROTOCOL TITLE:	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee
PROTOCOL DATE:	Protocol Version 1.0: September 29, 2020 Amendment #1 Version 2.0: January 7, 2021
SPONSORED BY:	Noven Pharmaceuticals, Inc. 100 Town Square Place, 5th Floor Jersey City, New Jersey 07310 USA 1 (551) 233- 2700
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents. Information contained in this protocol is confidential in nature, and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Independent Ethics Committee, or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Noven Pharmaceuticals, Inc.

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	HP-5000-US-07
VERSION:	2.0
PROTOCOL TITLE:	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted]

[redacted]
Date

2. SYNOPSIS

Product Name/Number	HP-5000 (diclofenac sodium) topical system
Protocol Number	HP-5000-US-07
Development Phase	Phase 3
Name of Active Ingredient	Diclofenac sodium (2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt)
Protocol Title	A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee
Indication	Treatment of the pain of osteoarthritis of the knee(s)
Investigator(s)	Approximately [redacted] investigators in the US
Study Center(s)	Approximately [redacted] centers in the US
Study Duration	Approximately 17 weeks (4 weeks Screening/Washout + 12 weeks Treatment + 1 week Follow-up)
Objective(s)	Primary Objectives • To evaluate the effect of HP-5000 on pain among subjects with osteoarthritis (OA) of the knees at Week 12. Key Secondary Objectives • To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Week 12. • To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Week 12. Other Secondary Objectives • To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Weeks 1, 2, 4, and 8. • To evaluate the effect of HP-5000 on pain intensity as measured by numeric rating scale (NRS) scores on a daily diary. • To evaluate the onset of effect of HP-5000 on pain among subjects with OA of the knees. • To evaluate the pattern of use of rescue medication in the study. • To evaluate skin irritation, discomfort, and adhesion following administration of HP-5000. • To evaluate the safety and tolerability of HP-5000. • To evaluate the effect of HP-5000 treatment on Quality of Life (QOL).
Planned Number of Subjects	Sufficient number of subjects will be screened in order to enroll and randomize a total of approximately [redacted]ects to the study.
Inclusion Criteria	Subjects who fulfill the following inclusion criteria will be eligible to participate: 1. Provides written informed consent, prior to entering the study or undergoing any study procedures; 2. Male or female aged 40 to 85 years with a clinical diagnosis of OA of the target knee according to the American College of Rheumatology (ACR) criteria, including: a. Symptoms for at least 6 months prior to Screening; b. Pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to any other conditions such as bursitis, tendonitis, etc.); c. The pain in the target knee required the use of nonsteroidal anti-inflammatory drugs (NSAIDs) either over the counter (OTC)

	per recommendation of a physician or by prescription (documented history is required) d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed or recommended by a clinician for 30 consecutive days prior to the Screening Visit. 3. Has an X-ray of the target knee, taken no more than 1 year before Baseline, showing evidence of OA with Kellgren-Lawrence grade 1 to 3 disease (as assessed by a radiologist). 4. Has pain of OA in the designated/target study knee: [redacted] 6. Has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] the Baseline Visit (V3). 7. Able to swallow and tolerate rescue medication, acetaminophen (APAP) (moderately sized tablets). 8. Female subjects of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year [no menses for 12 consecutive months]), or if of childbearing potential must be non-pregnant at the time of Screening Visit and on the morning of Baseline Visit, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or a vasectomized partner during their study participation and for 90 days following the last dose administration. Transdermal contraceptives are not allowed. All female subjects must agree not donate blood during the study and for 90 days after completion of the study. Male subjects who have not had a vasectomy must agree to use a barrier method of birth control example, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during their study participation and for 90 days following the last dose administration, and all male subjects must also not donate sperm or blood during the study and for 90 days after completion of the study. 9. Be reliable, willing, and able to cooperate with all study procedures including, but not limited to, the following: a. Accurately fill out the eDiary on a daily basis. b. Return for study visits on the required dates. c. Accurately and reliably report adverse symptoms (including treatment-emergent signs and symptoms) that he/she develops while participating in study. d. Use the patch as specified by the protocol.
Exclusion Criteria	Subjects who meet any of the following exclusion criteria will not be allowed to participate in the study 1. Body mass index (BMI) > 40kg/m^2 at Screening (Visit 1). 2. The non-target knee pain severity score is [redacted] at Screening (Visit 1) and Baseline (Day 0).

	3. Any subject who did not follow the restriction of prohibited therapies during Washout period (including use of rescue medication within 3 calendar days prior to the Baseline Visit). 4. Arthritis of the target knee that is not caused by OA but caused by diseases such as rheumatoid arthritis, gout, psoriasis, syphilitic arthropathy, ochronosis, metabolic or other primary bone disease, or acute traumatic injury. 5. Any subject diagnosed with fibromyalgia. 6. Any other painful or disabling conditions affecting the target knee or leg. 7. Clinically significant elevation of serum creatinine (≥2 mg/dL), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (at 3 x upper limit of normal [ULN]) at the Screening Visit. 8. Known allergy or hypersensitivity to diclofenac, APAP, acetylsalicylic acid (aspirin [ASA]), or any other NSAID, [redacted] glycerin, propylene glycol, or ethanol. 9. Severe uncontrolled cardiovascular, renal, hepatic, or other systemic illness/disease. 10. A documented gastroduodenal ulcer (by upper gastrointestinal [GI] series or endoscopy), GI perforation or any GI bleeding (except hemorrhoidal bleeding) within 6 months prior to Screening Visit. 11. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline. 12. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups. 13. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments). 14. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment. 15. Treatment with oral or intra-muscular corticosteroids within 90 days of Screening Visit, treatment of the target knee with topical or intra-articular corticosteroids within 90 days of Screening Visit, or topical or intra-articular corticosteroid treatment of any other joint within 30 days of Screening Visit. 16. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit. 17. Any subject who had received the following intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy and amniotic fluid injection in the target knee 6 months prior to Screening Visit. 18. Any opioid use 7 days prior to the Screening Visit. 19. Any subject who had previous exposure to HP-5000. 20. Any subject who needs to use cyclosporine, lithium, or methotrexate. 21. Use of another investigational drug or device within 30 days (or 90 days for biologics) prior to study entry. 22. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause. 23. Any skin abnormality present at the potential patch application site (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion or significant skin disorder such as atrophy, psoriasis, or vitiligo). 24. Any of the following skin conditions present at the potential patch application site; presence of tattoo, excessive hair or open sores, or scar tissue. 25. Any subject expecting to have knee replacement surgery within 6 months on the target knee or the non-target knee. 26. Any subject with a psychiatric condition that in the investigator's opinion may interfere with his/her participation in the study.

	27. The subject is an employee, or family member of an employee, of the study center, the contract research organization (CRO) or the sponsor involved in this study. 28. Subjects who test positive for severe acute respiratory syndrome coronavirus 2 infection within 2 weeks prior to screening.
Investigational Drug(s)	HP-5000 topical system [redacted] iclofenac sodium/[redacted]
Reference Product	Placebo patch (0 mg diclofenac sodium/ [redacted] Placebo patches are identical in appearance to HP-5000 patch but without the active ingredient diclofenac sodium
Study Treatment(s)	The following are the treatment arms of the study: Treatment Arm — Treatment Regimen HP-5000 — One patch applied [redacted] to alternate side (inner or outer) of the target knee. Placebo — One patch applied [redacted] to alternate side (inner or outer) of the target knee.
Rescue Medication	If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of the target knee pain of OA because of lack of efficacy of study drug (not for the non-target knee) if the subject does not feel enough pain relief by the study drug, any other aches they might experience during the trial such as headache and reduction of fever except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to for all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Subjects should not use OTC APAP as rescue medication, i.e., they should only use the APAP provided by the Sponsor or designee.
Study Endpoints	Primary Efficacy Endpoint • WOMAC Likert (LK)3.1 OA (pain) change from Baseline at Week 12 Key Secondary Efficacy Endpoints • WOMAC LK3.1 OA (physical function) change from Baseline at Week 12 • WOMAC LK3.1 OA (stiffness) change from Baseline at Week 12 Secondary Efficacy Endpoints • WOMAC LK3.1 OA (pain) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (physical function) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (stiffness) change from Baseline at Weeks 1, 2, 4, and 8 • WOMAC LK3.1 OA (composite score) change from Baseline at Weeks 1, 2, 4, 8, and 12 • Change from Baseline in pain intensity assessed on an 11-point NRS at Weeks 1, 2, 4, 8, and 12 • Change from Baseline in pain intensity assessed on an 11-point NRS of a weekly average of all available daily pain scores at each week from Week 1 through 12 • Change from Baseline in Patient Global Assessment at Weeks 1, 2, 4, 8, and 12 • Patient Global Impression of Change (PGIC) at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (pain) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (physical function) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12 • Treatment Response: Reduction in the WOMAC LK3.1 OA Index (stiffness) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12 • Proportion of subjects, the number of days, and the total number of rescue medication tablets used during the treatment phase

	• The onset of the effect: Pain intensity assessed on an 11-point NRS change from Baseline • Mini-OA Knee and Hip QOL (Mini-OAKHQOL) scores change from Baseline at Weeks 4 and 12 • Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) impairment scores change from Baseline at Weeks 4 and 12. Safety Endpoints • The incidence of treatment-emergent adverse events (AEs), AEs leading to discontinuation of the study drug, serious adverse events (SAEs), and other significant AEs. • Change from Baseline in clinical laboratory tests, electrocardiogram (ECG) findings, body weight, physical examination findings and vital signs. • Dermal assessments: irritation, discomfort, and adhesion.
Randomization	Subjects will be randomly assigned using a 1:1 ratio to 1 of 2 treatment arms: HP-5000 or placebo.
Analysis Populations:	Intent-to-Treat (ITT): All consented and randomized subjects regardless of any protocol deviations. Analyses performed on the ITT set will be based on the randomized treatment assignment and all available data. The ITT will be used as the primary set for analysis of efficacy endpoints. Safety Analysis Set (SAF): All subjects who have had at least 1 patch of double-blind study drug applied and who have at least 1 post-dose safety measurement during the Double-blind Treatment Phase. The SAF will be used for the analysis of dermal evaluations and safety endpoints.
Efficacy Analyses	Efficacy Outcome Analyses: Primary Efficacy Outcome Analysis The fixed-sequence procedure will be applied for primary and key secondary endpoints of this study, where the order in which the hypotheses are tested is pre-specified as following: (1) WOMAC pain, (2) WOMAC physical function, and (3) WOMAC stiffness. Testing begins with the first hypothesis (H_1) about WOMAC pain, and each test is carried out as long as significant results with level of significance α=0.05 are observed in all preceding tests. The fixed-sequence procedure controls the family-wise error rate because, for each hypothesis, testing is conditional upon rejecting all hypotheses earlier in the sequence. All statistical tests of hypotheses in this trial will be 2-sided with a Type I Error rate of 0.05. The estimand in the primary analysis for efficacy is the difference between treatment groups (HP-5000 *vs*. placebo) in the change from Baseline to Week 12 in WOMAC pain score in all randomized subjects from the ITT population and taking into account intercurrent events using the composite strategy. The study treatment discontinuation due to reasons related to study treatment (e.g. adverse events (AE), lack of efficacy (LOE), etc.), rescue medicationdrug use within 24 hours of WOMAC pain assessment, removal/detachment of the patch for more than 24 hours before WOMAC pain assement are defined as intercurrent events. Composite strategy will be applied to the stratum of subjects experiencing intercurrent events. For the intercurrent events of study treatment discontinuation due to reasons related to study treatment (e.g. adverse events (AE), lack of efficacy (LOE), etc.), the obtained WOMAC pain score will be addressed in the analysis by expecting the long-term benefit from the treatment for that patient to be zero from the time of intercurrent event. For the other intercurrent events including rescue medication drug use within 24 hours of WOMAC assessment, removal/detachment of study patch for more than 24 hours before WOMAC assement, the obtained WOMAC pain score will not be included in the analysis.

	The primary efficacy variable, change from Baseline to Week 12 in the WOMAC pain score, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in WOMAC pain score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC pain score as covariates. An unstructured covariance matrix will be assumed. Because the primary analysis assumes missing at random primary endpoint, suitable supplementary/sensitivity analyses will be performed to challenge the assumptions of the prespecified primary analysis by incorporating reasons for missingness in the analysis. <u>Key Secondary Outcome Analyses:</u> The MMRM model will be used the same way as for primary variable only include change from Baseline in WOMAC physical function (or stiffness) score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC physical function (or stiffness) score as covariates. Other secondary efficacy endpoints will be analyzed but will not be included into the fixed-sequence procedure. Further details will be provided in the Statistical Analysis Plan.

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4. LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
APAP	acetaminophen
ARB	angiotensin receptor blocker
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
COX	cyclooxygenase
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
[redacted]	[redacted]
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IWRS	interactive web response system
LK	Likert
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MNAR	missing not at random
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OAKHQOL	OA Knee and Hip QOL
OTC	over the counter
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PMM	Pattern Mixture Model
PRP	platelet rich plasma
QOL	Quality of Life
QTcF	QT interval corrected for heart rate (Fridericia's correction)

SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization Drug Dictionary
WOMAC	West Ontario and McMasters Universities Osteoarthritis Index

5. INTRODUCTION

5.1. Background and Rationale

An estimated 52.5 million adults (22.7% of the population)[1] in the United States (US) have physician-diagnosed osteoarthritis (OA); 22.7 million (9.8% of all adults) have arthritis and arthritis-attributable activity limitations. Based on these data, it is projected that 78 million (26%) adults aged 18 years or older will have physician-diagnosed arthritis by the year 2040.[2] Patients with arthritis are encouraged to be active, since it has been shown that exercise and activity help to decrease pain associated with OA, improve function, and delay disability. However, activity and exercise are often limited by the pain associated with arthritis, and this pain may become part of a cycle of inactivity and weight gain that tends to perpetuate the stiffness and disability associated with OA. Additionally, oral nonsteroidal anti-inflammatory drug (NSAID) medications used over time may cause gastrointestinal (GI) distress and interfere with the blood-clotting cycle. Opioid medications often lose their effectiveness with chronic use and require increasing dosages; patients may also become dependent on the opioid pain relievers, thereby introducing additional health problems and increasing disease and healthcare system burden. There is an unmet need for safer, reliable, and effective pain medications without the safety risk and limited efficacy associated with those currently available.

Diclofenac sodium belongs to the phenylacetic acid class of NSAIDs developed by Ciba Geigy Co., Ltd., Switzerland, in 1965. In the US, diclofenac sodium is available in various dosage forms, including tablet, eye drop, extended-release tablet, gel, patch, capsule, and solution. The mechanism of action of NSAIDs is not completely understood but thought to be related to prostaglandin synthetase (cyclooxygenase [COX]-1 and COX-2) inhibition.

Noven Pharmaceuticals, Inc. is developing a formulation of diclofenac sodium for topical administration, the HP-5000 topical system (patch) for the treatment of pain of OA of the knee(s). The topical HP-5000 patch will provide patients with OA with another treatment option that may have potential benefits compared with the existing formulations, as follows:

- Delivery of drug into the treatment target area resulting in lower systemic and GI exposure when compared with orally administered diclofenac sodium and a possible reduction of systemic side effects including GI ulcers/lesions and adverse reactions such as nausea, vomiting, dyspepsia, and stomach pain.
- Improvement of compliance with [redacted] compared with existing topical formulations and use by patients who have difficulty swallowing oral preparations.

5.2. Clinical Experience

To date, the HP-5000 development program includes [redacted] These studies have been completed with various formulations of HP-5000, evaluating the pharmacokinetics (PK) and tolerability in healthy volunteers and efficacy and safety in subjects with OA pain of the knee. The lead formulation for this program, HP-5000 , which contains mg diclofenac sodium with a patch size of cm^2 was selected based on the efficacy, safety, PK profile, and patch performance characteristics.

The HP-5000 formulation is being developed in Japan by Noven's parent company, [redacted] for different indications [redacted] and is referred to as the [redacted]

The Phase 1 study that evaluated PK and safety for the current formulation (HP-5000) in healthy volunteers was as follows:

- [redacted]

The Phase 2 efficacy and safety study performed in the US on patients with OA pain of the knee is as follows:

- [redacted]

[redacted]

Data across these studies demonstrated an acceptable performance, safety and tolerability profile for HP-5000[redacted].

Hereinafter, HP-5000[redacted] is referred as HP-5000 in this protocol. Further details about HP-5000 development and detailed information are available in the Investigator's Brochure (IB).

5.3. Summary of Potential Risks and Benefits

The HP-5000 formulations have been studied in a number of PK studies and most recently in a large randomized, placebo-controlled Phase 2 efficacy and safety study in the US among subjects with pain of OA of the knee [redacted]. The PK studies revealed a PK profile supportive of topical use via transdermal route. The Phase 2 study demonstrated significant reduction in pain by Week 4 compared with placebo with a favorable systemic safety profile and good dermal tolerability with HP-5000 formulation. The potential benefits for subjects of study participation are the following: (1) may experience a reduction in pain and inflammation as a result of treatment with the HP-5000 patch, (2) may experience improvement in their physical function and stiffness, and (3) will contribute to the scientific knowledge and therapeutic advancement in OA disease state that may lead to expansion of future treatment options for subjects with OA.

The potential risks for subjects for participating in study include those associated with exposure to the HP-5000 patch and the risks inherent in medical evaluation, including venipunctures at various times in study.

A summary of the pharmaceutical properties and known potential risks of the HP-5000 patch are provided in the current version of the IB.[3] The investigator(s) must become familiar with all sections of the HP-5000 IB.

6. OBJECTIVES

6.1. Primary Objectives

- To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Week 12.

6.2. Key Secondary Objectives

- To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Week 12.
- To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Week 12.

6.3. Other Secondary Objectives

- To evaluate the effect of HP-5000 on pain among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on physical function among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on stiffness among subjects with OA of the knees at Weeks 1, 2, 4, and 8.
- To evaluate the effect of HP-5000 on pain intensity as measured by numeric rating scale (NRS) scores on a daily diary.
- To evaluate the onset of effect of HP-5000 on pain among subjects with OA of the knees.
- To evaluate the pattern of use of rescue medication in the study.
- To evaluate skin irritation, discomfort, and adhesion following administration of HP-5000.
- To evaluate the safety and tolerability of HP-5000.
- To evaluate the effect of HP-5000 treatment on Quality of Life (QOL).

7. STUDY DESIGN

Note: Pandemic-related restrictions may result in difficulties regarding the conduct of the study. If circumstances require it, a protocol amendment may be created to document changes to some aspects of the study, such as inclusion/exclusion criteria, visit windows, visit schedules, the possibility of remote (rather than on site) visits, and distribution of study drug.

7.1. Overall Study Design and Plan - Description

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study in the US evaluating the efficacy and safety of HP-5000 in subjects with OA pain of the knees.

The study will consist of up to a 28-day Screening Phase that will include a Washout Period of current prescription and over the counter (OTC) analgesics; a 12-week Double-blind Treatment Phase, and a 1-week safety Follow-up Phase.

- **Screening Phase**: Subjects will be seen in the clinic where the study will be described to them and will be asked to sign the informed consent form (ICF). No screening procedures may begin prior to obtaining informed consent. After obtaining a written informed consent, subjects will be screened for participation in the study. The target knee for the purpose of the study will be defined as the one which causes the subject more pain than the other knee and will be identified at Screening visit using the NRS score. During the Screening Phase, subjects will complete a daily electronic diary (eDiary) to record pain severity of their target knee. Subjects who satisfy the entry criteria at Screening and Washout visit will be instructed to begin the Washout Period for 7 to 14 days, or at least 5 half-lives, whichever is longer, prior to the Baseline Visit (Day 0).

  During the Washout Period, current prescription and OTC analgesics will be discontinued. However, rescue medication (acetaminophen [APAP]) for the treatment of the target knee pain of OA because of lack of efficacy of study drug (not for the non-target knee) if the subject does not feel enough pain relief by the study drug, any other aches the subject might experience during the trial, such as headache and reduction of fever will be permitted (a maximum of 2 g/day) except within 3 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited for 2 days until clinic visit on Day 0 and on the day of Baseline Visit [V3]). Subjects should not use OTC APAP as rescue medication, i.e., they should only use the APAP provided by the Sponsor or designee. During the Washout Period, subjects will complete a daily eDiary to record rescue medication usage in addition to pain severity of their target knee. Following completion of the Washout Period, subjects will return to the clinic for their Baseline Visit (Day 0). Eligible subjects will be randomized to either HP-5000 or placebo in a 1:1 ratio.

- **Double-blind Treatment Phase**: Subjects will apply a single patch to the target knee [redacted] After the removal of the patch [redacted] a new patch will be applied to a different site on the target knee. Subjects will be instructed to rotate the patch application site [redacted] to alternate sides (inner and outer) of the target knee. During the Double-blind Treatment Phase, subjects will also complete a [redacted] eDiary to record patch application and removal time, adhesion, irritation, discomfort, and pain assessments; and amount of rescue medication (APAP) taken daily, if applicable. A maximum of 2 g/day of APAP will be allowed as rescue medication except from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Subjects should not use OTC APAP as rescue medication, i.e., they should only use the APAP provided by the Sponsor or designee.

  NOTE: Subjects are NOT allowed to apply HP-5000 on the non-target knee at any time during the study.

- **Follow-up Phase**: Subjects will have a safety visit approximately 7 days after the Week 12 End-of-Treatment Visit. The investigator or qualified study staff will contact all subjects by phone for continued safety monitoring of adverse events (AEs). At the discretion of the investigator, subjects may have to return to the clinic for their Follow-up Visit.

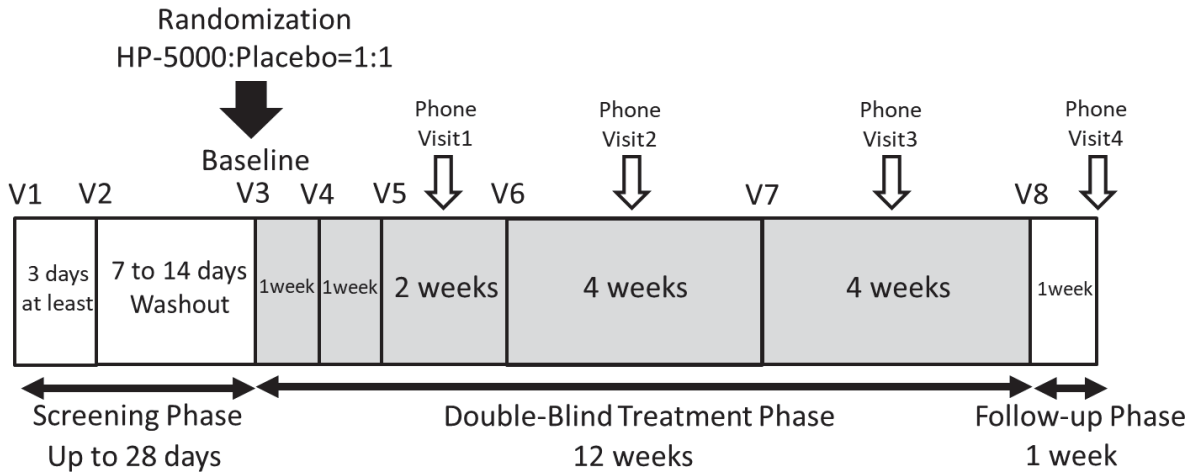


Figure 1 A Schematic of the Study Design

7.2. Discussion of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled Phase 3 study evaluating the efficacy and safety of HP-5000 in subjects with OA pain of the knees. Such a design is well accepted and considered standard in drug development when evaluating new therapeutic modalities across different disease areas.

A parallel-group design was selected because it is free of the assumptions underlying competing designs (for example, crossover). A parallel-group approach is considered the optimal study design to evaluate efficacy in pivotal registration clinical trials.

The use of a randomized double-blind design will minimize bias by randomly assigning the subjects to treatment arms, and ensuring that the subjects, investigators and site personnel, and the Sponsor/designee are blinded to the treatment allocations.

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. The comparison with placebo is justified as subjects will be closely monitored and study treatment will be discontinued and the subject will be returned to standard of care (SOC) treatment if their status deteriorates.

The rationale for dose selection is described in **Section 9.6**.

The 12-week duration is considered to be sufficient to evaluate the effect on chronic pain of OA. This time period is also sufficient to evaluate changes in the primary and secondary outcome measures.

The use of rescue medication is prohibited within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8), thus ensuring the integrity of the pain assessments and safeguarding against confounding due to rescue medications.

7.3. Study Sites

The study will take place at approximately [redacted] sites in the US that are qualified by background and experience and manage patients with OA. Each site is anticipated to screen a sufficient number of subjects to be able to randomize approximately [redacted] subjects, as detailed in the **Section 13.2**.

8. SUBJECT POPULATION

8.1. Selection of Study Population

The study will enroll up to [redacted] subjects with pain of OA of the knee in a 1:1 ratio (HP-5000:Placebo). The pain should have been stable over the previous 6 months prior to Screening (Visit 1).

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site, including reasons for screen failure.

8.2. Study Entry Criteria

All subjects being considered for participation in this clinical study must meet all the inclusion criteria and none of the exclusion criteria.

8.2.1 Inclusion Criteria

A subject will be eligible for study participation if he or she meets all of the following criteria:

1. Provides written informed consent, prior to entering the study or undergoing any study procedures;
2. Male or female aged 40 to 85 years with a clinical diagnosis of OA of the target knee according to the American College of Rheumatology (ACR) criteria, including:
    a. Symptoms for at least 6 months prior to Screening;
    b. Pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to any other conditions such as bursitis, tendonitis, etc.);
    c. The pain in the target knee required the use of NSAIDs either OTC per recommendation of a physician or by prescription (documented history is required).
    d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed or recommended by a clinician for 30 consecutive days prior to the Screening Visit.
3. Has an X-ray of the target knee, taken no more than 1 year before Baseline, showing evidence of OA with Kellgren-Lawrence grade 1 to 3 disease (as assessed by a radiologist).
4. Has pain of OA in the designated/target study knee:
    [redacted]

[redacted]

6. Has a WOMAC pain score of [redacted] at the Baseline Visit (V3).
7. Able to swallow and tolerate rescue medication, APAP (moderately sized tablets).
8. Female subjects of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year [no menses for 12 consecutive months]), or if of childbearing potential must be non-pregnant at the time of Screening Visit and on the morning of Baseline Visit, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or a vasectomized partner during their study participation and for 90 days following the last dose administration. Transdermal contraceptives are not allowed. All female subjects must agree not donate blood during the study and for 90 days after completion of the study.

   Male subjects who have not had a vasectomy must agree to use a barrier method of birth control example, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during their study participation and for 90 days following the last dose administration, and all male subjects must also not donate sperm or blood during the study and for 90 days after completion of the study.
9. Be reliable, willing, and able to cooperate with all study procedures including, but not limited to, the following:
   a. Accurately fill out the eDiary on a daily basis.
   b. Return for study visits on the required dates.
   c. Accurately and reliably report adverse symptoms (including treatment-emergent signs and symptoms) that he/she develops while participating in study.
   d. Use the patch as specified by the protocol.

8.2.2 Exclusion Criteria

A subject will be excluded from the study if the he or she meets any of the following criteria:

1. Body mass index (BMI) > 40 kg/m^2 at Screening (Visit 1).
2. The non-target knee pain severity score is [redacted] at Screening (Visit 1) and Baseline (Day 0).
3. Any subject who did not follow the restriction of prohibited therapies during Washout period (including use of rescue medication within 3 calendar days prior to the Baseline Visit).

4. Arthritis of the target knee that is not caused by OA but caused by diseases such as rheumatoid arthritis, gout, psoriasis, syphilitic arthropathy, ochronosis, metabolic or other primary bone disease, or acute traumatic injury.
5. Any subject diagnosed with fibromyalgia.
6. Any other painful or disabling conditions affecting the target knee or leg.
7. Clinically significant elevation of serum creatinine (≥2 mg/dL), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (at 3 × upper limit of normal [ULN]) at the Screening Visit.
8. Known allergy or hypersensitivity to diclofenac, APAP, acetylsalicylic acid (aspirin [ASA]), or any other NSAID, [redacted], glycerin, propylene glycol, or ethanol.
9. Severe uncontrolled cardiovascular, renal, hepatic, or other systemic illness/disease.
10. A documented gastroduodenal ulcer (by upper GI series or endoscopy), GI perforation or any GI bleeding (except hemorrhoidal bleeding) within 6 months prior to Screening Visit.
11. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
12. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
13. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
14. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment.
15. Treatment with oral or intra-muscular corticosteroids within 90 days of Screening Visit, treatment of the target knee with topical or intra-articular corticosteroids within 90 days of Screening Visit, or topical or intra-articular corticosteroid treatment of any other joint within 30 days of Screening Visit.
16. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
17. Any subject who had received the following intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy and amniotic fluid injection in the target knee 6 months prior to Screening Visit.
18. Any opioid use 7 days prior to the Screening Visit.
19. Any subject who had previous exposure to HP-5000.
20. Any subject who needs to use cyclosporine, lithium, or methotrexate.
21. Use of another investigational drug or device within 30 days (or 90 days for biologics) prior to study entry.

22. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause.
23. Any skin abnormality present at the potential patch application site (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion or significant skin disorder such as atrophy, psoriasis, or vitiligo).
24. Any of the following skin conditions present at the potential patch application site; presence of tattoo, excessive hair or open sores, or scar tissue.
25. Any subject expecting to have knee replacement surgery within 6 months on the target knee or the non-target knee.
26. Any subject with a psychiatric condition that in the investigator's opinion may interfere with his/her participation in the study.
27. The subject is an employee, or family member of an employee, of the study center, the contract research organization (CRO) or the sponsor involved in this study.
28. Subjects who test positive for severe acute respiratory syndrome coronavirus 2 infection within 2 weeks prior to screening.

8.2.3 Premature Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly and if a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor or CRO must be notified.

Subjects should not be asked to withdraw from the study because of experiencing AE, lack of efficacy, pregnancy, or lack of compliance to the clinical study protocol, etc. Those patients can stop their study treatments (for subjects who do not comply the protocol specified instructions and procedures, every effort will be made to keep them in the study after stopping treatment unless there is an adverse impact on subject safety). Discontinuation from study treatment does not automatically lead to a complete withdrawal from the study. Subjects discontinuing from study treatment are strongly encouraged to continue in the study up to the study completion (Follow-up Phone Visit, Week 13).

Subjects who decide they do not wish to remain in the study should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Subjects are encouraged to return to all scheduled site and telephone visits, perform all procedures (including eDiary completion and blood draws) and follow the all requirements of the protocol (including the prohibited therapies), but without study treatment administration, until the end of the study (Follow-up Phone Visit, Week 13).

The reason for study treatment discontinuation and withdrawal from the study will be separately recorded. When the subject discontinues study treatment and/or withdraw from the study, the reason will be recorded in the medical records and eCRF using the below categories for discontinuation of study treatment and withdrawal from the study respectively.
The reasons will be grouped into three main categories: “study treatment related”, “not study treatment related”, and “uncertain” and more specific sub-categories will be described under each of the three main categories.

- Study treatment related
  - Lack of efficacy
  - Adverse events
  - Deviation from protocol (Please specify the deviation)
  - Other
- Not study treatment related
  - Adverse events
  - Prohibited Medication Use
  - Pregnancy
  - Deviation from protocol (Please specify the deviation)
  - COVID-19
  - Subject does not meet enrollment criteria and inadvertently enrolled
  - Other
- Uncertain
  - Lost to follow up
  - Withdrawal of informed consent by subject without reason
  - Other

In all cases, the reason for discontinuation of study treatment or withdrawal from the study must be recorded in the eCRF and if the reason is not known, the investigator must make every effort to confirm the reason.
If a subject is withdrawn early from the study, the following procedures will be performed:

- Subjects will have Early Termination (ET) procedures performed as shown in the Schedule of Events (see **Section 10.2**).
- All ET procedures should be completed and recorded on the ET eCRF page. If withdrawal occurs at a regular scheduled visit, the Early Withdrawal eCRF page should be used instead of the regular visit eCRF page to record any information related to the visit.

It is important to evaluate these subjects at the study center as soon as possible. Investigators must make at least 3 documented attempts to contact subjects who fail to attend scheduled visits by telephone or any other means and document the attempts. After 3 documented unsuccessful contact attempts the subject can be considered lost to follow-up.

8.3. Subject Replacement Criteria

Subjects who withdraw after randomization and the application of the first treatment patch will not be replaced.

9. TREATMENTS

9.1. Identification of Investigational Product

The following is a description of study drug:

- HP-5000 [redacted] patch
  Each patch contains [redacted] diclofenac sodium.

HP-5000 will be supplied as diclofenac sodium in a patch manufactured by [redacted]

9.1.1 Labeling

Labels will be computer-generated for all investigational products (IPs) with the following information (other information may also be included as needed):

- Protocol number
- Subject number (record at the time of dispensing)
- Package contents (quantity)
- Storage instructions
- Caution: "New Drug – Limited by United States Law to Investigational Use" and "Keep out of reach of children"
- Sponsor name and address

9.1.2 Packaging

In the Double-blind Treatment Phase, HP-5000 and placebo patches will be packaged so as to be blinded to the investigator, the study clinic personnel, and the subjects.

Sites and subjects will be instructed to save all empty packaging or packaging containing unused patches for final disposition by the Sponsor or its designee.

The Drug Dispensing Log must be available for monitoring, auditing, or inspection. **Section 9.8** details the accountability of clinical supplies through the use of a Drug Dispensing Log.

9.2. Treatments Administered

HP-5000 will be administered [redacted] for 12 weeks.
The treatment arms for this study are the following:

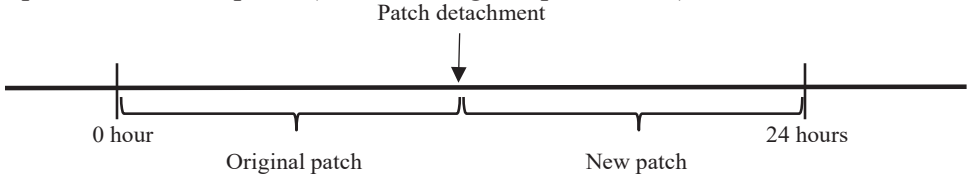
Table 1 Treatment Arms

Treatment Arm	[redacted] Treatment
HP-5000	HP-5000 [redacted] patch Each patch contains [redacted] diclofenac sodium.
Placebo	HP-5000 [redacted] Placebo patch Each patch contains 0% [redacted] diclofenac sodium.

One patch (100 cm^2) will be applied [redacted] to alternate sides (inner and outer knee) of the target knee after showering/bathing.

Note:

- Subjects will be instructed not to bathe or shower while wearing the patch.
- In case the patch completely detaches within 24 hours of application, the detached patch will be applied again on the same site. If the detached patch does not re-adhere, a replacement patch (new patch) will be applied on the same site until the next scheduled replacement of the patch (see following sample scheme).



  Even if the applied replacement patch completely detaches by accident again, an additional application of another new patch will not be allowed and the subject will wait to apply a patch until the next scheduled replacement.
- Subjects will not be allowed to apply any patches to the non-target knee at any time during the study.
- Even if there is a day when subjects do not take a shower or bath, they need to replace a patch [redacted]

Detailed application instructions for subjects will be provided in a separate manual/guide.

9.3. Dispensing and Storage

Study drug supplied by [redacted] is to be used exclusively according to this protocol. The investigator is responsible for dispensing study drug according to the dosage and administration scheme and for ensuring proper storage of study drug.

The investigator, or designee, must confirm the receipt of study drug with his/her signature. A copy of this receipt must be kept by the investigator. Until study drug is dispensed to the subjects, it must be stored between 15°C to 30°C (59°F to 86°F) and in a dry place in a securely locked area that is not generally accessible.

All study drug supplies must be stored in a secure locked area with access limited to the investigator or those persons authorized by the investigator to dispense the study drug to subjects. Study drug should be stored as per the label.

9.4. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who will meet study entry criteria will be randomly assigned in a 1:1 ratio to receive HP-5000 or placebo patches. The randomization numbers will be assigned sequentially through a central interactive web response system (IWRS) as subjects who met eligibility criteria are enrolled into the study. The study center will not be a blocking factor in the randomization schedule. At each visit, subjects will be given a kit containing sufficient study drug to last until the next scheduled study visit.

The randomization schedule will be prepared before the start of the study. No one involved in the clinical conduct will have access to the randomization schedule before the official unblinding of treatment assignment. No subject will be randomized into this study more than once.

9.5. Blinding and Unblinding Treatment Assignment

To protect the blind, placebo patches will be identical in appearance to the HP-5000 patches.

All subjects, investigators, and study personnel involved in the conduct of the study, including the project study team and data management, will be blinded to study drug treatment assignment with the exception of a prespecified unblinded statistician/programmer, who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study related personnel. If an interim analysis is to be conducted, unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the clinical study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be only permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

In the case of a medical emergency, to appropriately treat the subject, study drug will need to be unblinded. Instructions for breaking the blind will be included in the IWRS manual. The investigator may break the randomization code for an individual subject. However, the investigator should make every effort to discuss the unblinding of the subject with the Medical Monitor prior to unblinding.

If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the Medical Monitor immediately of the blind breaking incident without revealing the subject's treatment assignment.

In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified, explained by a comment on the appropriate eCRF page along with the date and reason for study discontinuation; and captured on the SAE Form (see **Section 11.2.6.1** for SAE reporting to sponsor).

The investigator or designee must record the date and reason for unblinding or study discontinuation on the appropriate eCRF for that subject.

If treatment assignment is unblinded for an individual subject, study personnel will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study. Thus, the overall study blind will not be compromised. If a subject's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the Medical Monitor.

9.6. Selection of Doses and Administration in the Study

The dosing regimen of diclofenac [redacted] mg in a patch size of [redacted] applied [redacted] and rotated between 2 sites on the target knee, inner and outer sides, is based on the following considerations and rationale:

- A dose that targets diclofenac exposure after HP-5000 patch application that is similar to that of registered topical diclofenac products and considerably lower than that of oral diclofenac tablets.
- Previously completed clinical studies using the same size patch showed no issue on efficacy, safety (including dermal safety) and patch performance using the selected dose and administration.
- Patch size was developed that allows for rotation at a minimum of 2 sites to minimize local irritation at the application site of the knee.

9.7. Dose Adjustment Criteria

Dose adjustment is **NOT** allowed in this study.

9.8. Drug Accountability

The investigator or pharmacist, as appropriate, must maintain adequate records of the receipt and conditions of all study drugs, dispensing, return, or other disposition of study drug including the date, quantity dispensed to each subject, batch or code number, identification of subjects (subject number) who received study drug and any reasons for departure from the protocol-dispensing instructions. Receipt of study drug must also be confirmed within IWRS. The drug accountability records, along with dispensed and unused packaging must be available for monitoring, auditing, or inspection as deemed necessary.

The investigator will not supply study drug to any person except those named as sub-investigators (on the Form FDA 1572), designated study personnel, and subjects in this study. The investigator will not dispense study drug from any study sites other than those listed (on the Form FDA 1572).

Study drug may not be relabeled or reassigned for use by other subjects. If any of the study drug is not dispensed, is lost, stolen, unusable, or is received in a damaged container, this information must be documented and reported to Noven and appropriate regulatory agencies, as required.

At the completion of the study, a final reconciliation of all study drugs (dispensed, returned, used, and unused) must be performed by the site and only unused patches must be returned to the sponsor (or designated location). The unused study drug must be left in the original packaging and returned to the Sponsor (or designee) for destruction.

9.9. Treatment Compliance

Treatment compliance with study drug regimens will be assessed by study personnel via the counting of returned unused patches, patch application, removal and by questioning the subject, if necessary, at every post-randomization visit. Treatment compliance will also be calculated as the number of patches applied divided by the prescribed number of patches over a given period, expressed as a percentage.

At Visits 4 through 8 or any Early Termination Visit, the study drug (patches) from the previous visit will be returned to the investigator. The study drug will be inventoried and non-compliance assessed as follows: use of less than 80% or more than 120% of study drug during any evaluation period (visit to visit). If the subject is non-compliant, and if there is a medically related need to do so, then the Medical Monitor should be contacted.

The subject must be counseled if compliance is not satisfactory (fail to apply the study drug on 2 or more consecutive days and/or miss any eDiary entries for 2 or more consecutive days). The subject must be contacted by a site personnel and re-instructed on how to apply the study drug and complete the eDiary. The re-instruction will be documented in the subject's chart (progress notes or clinical notes).

Subjects will be asked to record their daily intake/use of rescue medication/study drug in the eDiary. Deviations from the planned doses (overdose, missed dose or timing) will be recorded on the subjects' eCRF. The eDiaries will be constantly reviewed by study personnel.

9.10. Concomitant/Prior Therapies

All medications used prior or during treatment (including OTC medications, herbal supplements, non-pharmacological activities [Exercise, Weight Loss, Tai Chi, etc.] and rescue medication) will be recorded in the source document and on the appropriate eCRF page. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.10.1 Permitted Therapies

Glucosamine, chondroitin, and antidepressants (used for any indication other than pain) will be allowed if used as stable therapy for at least 90 days prior to Screening Visit. However, if used for less than 90 days, these drugs will be considered prohibited concomitant medications and will require a Washout Period. Subjects will be allowed to continue stable ASA therapy not for OA pain (up to 81 mg/day).

Other concomitant medications for treatment of ongoing medical conditions are allowed, but should be limited to those medications considered necessary in the opinion of the investigator.

9.10.2 Prohibited Therapies

Prohibited medications/therapies are presented in **Table 2**.

Table 2 Prohibited Medications/Therapies

Prohibited Medications/Therapies	Conditions
Any nonsteroidal anti-inflammatory drugs (NSAIDs) (selective or nonselective [Topical drug not for knees will be allowed]), acetaminophen (APAP) (>2 g/day), aspirin (ASA) (>81 mg/day), anticonvulsants (i.e., pregabalin and gabapentin etc.), muscle relaxants, other oral analgesics (prescription and/or over the counter [OTC]), antidepressants prescribed for the control of chronic pain syndromes, antihistamine with a sedative effect, sedatives for insomnia, topical products on the knee including methyl salicylate, camphor, menthol, methylsulfonylmethane, [redacted] capsaicin, any nonpharmaceutical therapy to relieve knee pain (physiotherapy, massage therapy, hot wax therapy, ice pack, acupuncture, thermal modalities, radiofrequency ablation, transcutaneous electrical nerve stimulation [TENS], pulsed vibration therapy, etc.), device to relieve knee pain (biofemoral bracing, kinesiotaping, modified shoes, wedged insoles etc.), hydroxychloroquine.	Prohibited during the study starting at Washout Visit
Any opioids, cannabinoids (prescribed or used recreationally), corticosteroids including oral, intra-muscular and intra-articular, topical, inhalation (a stable dose by inhalation for seasonal allergies and/or topical use for dermatologic allergies are allowed [Not allowed on the knees]), intra-articular viscosupplementation (e.g., Synvisc®), intra-articular drugs/biologics; anti-nerve growth factor agents, platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection, cyclosporine, lithium, or methotrexate	Prohibited during the study starting at Screening Visit
MAJOR SURGERY: Surgery to the target knee (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments). MINOR SURGERY: Surgery to the target knee defined as anything other than major surgery (as defined above)	Prohibited during the study starting at Screening Visit

Note: The investigator should contact the Medical Monitor with any concerns about the acceptability of any medication.

9.10.3 Concomitant Medication Cautions

Investigator's clinical judgment will be used in the following situations (the Medical Monitor for the study may be contacted if necessary);

- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or beta-blockers: Concomitant use with HP-5000 may diminish the antihypertensive effect of these drugs. Monitor blood pressure.
- ACE Inhibitors and ARBs: Concomitant use with HP-5000 in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk subjects, monitor for signs of worsening renal function.
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor subjects to assure diuretic efficacy including antihypertensive effects.
- Digoxin: Concomitant use with HP-5000 can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.

9.11. Rescue Medication

If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of the target knee pain of OA because of lack of efficacy of study drug (not for the non-target knee) if the subject does not feel enough pain relief by the study drug and any other aches they might experience during the trial such as headache and reduction of fever except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Information regarding the use of rescue medication, such as the number of tablets taken, the time when it was taken, and the reason of use, will be recorded on the eDiary. Subjects should not use OTC APAP as rescue medication, i.e., they should only use the APAP provided by the Sponsor or designee. Rescue medication will be labeled appropriately for the study to ensure visual difference from similar OTC medications and to ensure proper understanding the rescue medication should be used for this study. NSAIDs or any other analgesics except study drug and rescue medication provided will not be permitted from the time that informed consent form is signed until study completion or early termination. Stable low doses of ASA up to 81 mg/day will be allowed.

Subjects are **NOT** allowed to apply study treatment drug (HP-5000/Placebo) on the non-target knee at any time during the Double-blind Treatment Phase.

9.12. Treatment after End of Study

After completing the study, each subject will follow up with their primary care physician to be treated and followed according to standard clinical practice.

10. STUDY PROCEDURES

Subjects must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited therapy they are taking.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (see **Section 10.2**). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. If a subject misses a clinical study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Periods and Visits

10.1.1 Screening Phase

10.1.1.1 Screening (Visit 1)

Screening visit (V1) will be completed 28 to 10 days prior to the Baseline Visit. The subject must be screened before entering the Washout Period of the study (V2). The following procedures will be performed at Screening Visit (V1):

1. Obtain written informed consent and assign a subject number.
2. Register the subject in IWRS.
3. Assess inclusion/exclusion criteria.
4. Collect demographic information including the onset of OA.
5. Record medical history including prior and current therapies (e.g., prescription and nonprescription medications). Any prior use of medications used to treat OA and OA pain and prior 30-day use for all other medications should also be collected. If the subject has any psychiatric condition and his/her participation is considered appropriate, a documented rationale is required in the source document and eCRF.
6. Perform a complete physical examination, which will include assessment of the head, eyes, ears, nose, and throat, cardiovascular, respiratory, gastrointestinal/abdominal, musculoskeletal, dermatological, neurological, and psychiatric/psychological body systems.
7. Weight (kg), height (cm), and vital signs (heart rate, respiratory rate, temperature, and supine blood pressure) will be measured.
8. Instruct the subject on how to use NRS and WOMAC before performing first assessments.
9. Perform NRS evaluation of average and worst pain **for a left knee and a right knee, respectively,** and record them in the Electronic Clinical Outcome Assessment (eCOA).

10. Identify the target knee. The target knee is defined as the one which causes the subject more pain than the other knee and will be identified using NRS average pain score. The subject will be instructed to refer to this specific (target) knee throughout their participation in the study when responding to WOMAC questionnaire and NRS evaluation.
    If the pain of both knees is identical (i.e. both knees have NRS average pain score of 2), the investigator will define the target knee based on other difficulties (physical function, stiffness, etc.) and discussion with the subject. The discussion will be documented in the source document. The change of the target knee will not be allowed for any reason.
11. Administer the WOMAC questionnaire for the target knee.
12. Review the X-ray of the target knee (by a radiologist). If subject does NOT have any X-ray of the target knee taken within the past year, a mandatory new X-ray to confirm the disease will have to be taken prior to starting the Washout Period. The X-ray should be reviewed by the completion of Baseline Visit.
13. Perform 12-lead electrocardiogram (ECG) and laboratory tests.
14. Perform drug (urine), alcohol (breathalyzer) and pregnancy (urine) tests.
15. Record the eligibility of the subject in IWRS. If the subject screen fails, the date and the reason will be recorded in IWRS.
16. Ensure that the subject has access to, and understands how to use, the eDiary.
17. Instruct the subject to continue to assess and record their target knee pain at home daily, using the NRS 11-point pain scale in the eDiary during the Screening Phase.

At home, subjects are required to conduct the following assessments/procedures:

Perform the following assessments and record in the eDiary on daily basis:

Assess and record the pain of the target knee using the NRS 11-point pain scale when subjects take a shower or bath during the Screening Phase (Approximately every 24 hours. Even if subjects do not take a shower or bath, the assessment is necessary every 24 hours).

Note: If subjects withdraw or discontinue after signing the informed consent and prior to the registration in IWRS, the date and reason will be recorded in IWRS. Detailed information will be provided in a separate Manual.

10.1.1.2 Washout Visit (Visit 2)

The following procedures will be performed at the Washout Visit (V2):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Review eDiary NRS 11-point pain scores. [redacted]

[redacted] will be entered to the eCOA system and the mean NRS scores will be calculated.

3. Record the eligibility of the subject in IWRS. If the subject screen fail, the date and the reason will be recorded in IWRS.
4. Placebo training will be performed to educate subjects. The aim is to minimize the placebo response and increase their awareness for the purpose of the trial to determine a new drug is effective and safe.
5. Subjects whose eligibility has been preliminarily confirmed will be asked to washout of their current medications for at least 7 days to a maximum of 14 days (or at least 5 half-lives, whichever is longer).
6. Subjects will be instructed by the site to stop taking all prescription and physician recommended OTC analgesic medications, but will be informed that rescue medication (i.e., APAP) may be used (a maximum of 2 g/day) as needed except **within 3 calendar days prior to the Baseline Visit (V3) and the day of Baseline Visit (V3).**
7. Dispense rescue medication.
8. Ensure that the subjects have access to, and understands how to access and use, the eDiary.
9. Instruct the subject to continue to assess and record their target knee pain at home daily, using the NRS 11-point pain scale in the eDiary during the Washout Period.
10. Subjects will be instructed to record the number of tablets of rescue medication used, the time and the reason in the eDiary.

At home, subjects are required to conduct the following assessments/procedures:

Perform the following assessments and record in the eDiary on daily basis:

1. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when the subjects take a shower or bath during the Screening Phase (Approximately every 24 hours. Even if subjects do not take a shower or bath, the assessment is necessary every 24 hours). The time of NRS assessment will be recorded in the eDiary. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
2. Record the number of tablets of rescue medication used, if any, the date taken and the reason.

Note: If subjects withdraw or discontinue prior to Visit 2, the date and the reason will be recorded in IWRS.

10.1.2 Baseline Visit (Visit 3, Day 0)

The subject must be screened and the Washout Visit performed prior to the Baseline Visit. The following will take place during the Baseline Visit (Visit 3, Day 0):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Review subject's use of prior/concomitant medications.
3. Obtain vital signs measurements.
4. Perform an NRS 11-point pain assessment **for the non-target knee pain**.
5. Administer the WOMAC questionnaire for the target knee.
6. Perform Patient Global Assessment (PGA).
7. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
8. eDiary NRS 11-point pain scores will be reviewed by the investigator or the study coordinator. [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated. If the score of the 1 day before of Baseline Visit is missing, the subject will be excluded from the study.
9. Perform a 12-lead ECG.
10. Obtain blood and urine samples for laboratory testing.
11. Perform a drug (urine), alcohol (breathalyzer) and pregnancy (urine) tests.
12. Perform Baseline dermal safety assessment (irritation only).
13. Record the eligibility of the subject in IWRS. If the subject screen fail, the date and the reason will be recorded in IWRS.
14. Randomly assign the subject to a treatment group using IWRS.
15. Perform a QOL Questionnaire.
16. Placebo training will be performed to educate subjects. The aim is to minimize the placebo response and increase their awareness for the purpose of the trial to determine a new drug is effective and safe.
17. Collection of unused rescue medication. Note: Do not dispense rescue medication. Rescue medication is prohibited from Visit 3 until Visit 4.
18. Perform rescue medication accountability/reconciliation.
19. Instruct the subject concerning the patch application and removal method including how to rotate the patches by using a video and a separate manual/guide.
20. Dispense the double-blind study drug and instruct subjects on proper patch application. The first patch will be applied on the target knee at sites. Subjects will be instructed to

replace the patch [redacted] after showering/bathing. [redacted] Subjects will be instructed not to bathe or shower while wearing the study drug.

21. Subject will be instructed to report to the site and record unscheduled patch detachment, incidences of irritation and discomfort in their eDiary and not to participate in strenuous activities or other activities that cause heavy perspiration during the double-blind treatment phase.
22. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee after showering/bathing;
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug on non-target knee at all times.

Note: If subjects withdraw or discontinue prior to Visit 3 or randomization, the date and the reason will be recorded in IWRS.

10.1.3 Double-blind Treatment Phase

During the 12-week Double-blind Treatment Phase, the following procedures will take place:

<u>At home, subjects are required to conduct the following assessments/procedures</u>:

1. Remove the patch before showering/bathing and apply a new patch on the target knee (inner or outer by [redacted] rotation) approximately every [redacted]
2. Perform the following assessments and record in the eDiary on daily basis:
    a. Record patient eDiary information [redacted] when subjects replace the patch and before they sleep.

b. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace the patch. The time of NRS assessment will be recorded in the eDiary. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
c. Record the time of patch application and removal when subjects replace the patch.
d. Record the time of unscheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
e. Record the number of tablets of rescue medication used, the time and the reason (if applicable) when subjects take a tablet or before they sleep.
f. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

At the clinical sites visits, investigators (or site personnel as appropriate) will conduct the following:

Visit 4 and Visit 5 (Week 1 and Week 2)

1. Obtain vital signs measurements.
2. Administer the WOMAC questionnaire for the target knee.
3. Perform PGA.
4. Perform Patient Global Impression of Change (PGIC).
5. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
6. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
7. Collection of unused study drug and rescue medication (Note: At Visit 4, there will be no collection of rescue medication since the rescue medication is collected and not dispensed at Visit 3.).
8. Review subject's use of rescue medication/concomitant medication.
9. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
10. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
11. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.

12. Re-instruct the subject concerning the patch application and removal method.
13. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee after showering/bathing;
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take any rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 1 (midway between Week 2-4)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.
    e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.
3. Answer the questionnaires related to adhesion, skin irritation and discomfort. Record any issues with adhesion, skin irritation and discomfort.
4. Re-instruct the subject concerning the patch application and removal method.

5. Ensure that the subject's scheduled dose is administered and daily NRS pain scores and the application are recorded correctly.
6. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
7. Review subject's use of concomitant medication.
8. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
9. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Visit 6 (Week 4)

1. Obtain vital signs measurements.
2. Obtain blood and urine samples for laboratory testing.
3. Perform a pregnancy test.
4. Administer the WOMAC questionnaire for the target knee.
5. Perform PGA.
6. Perform PGIC.
7. Perform a QOL Questionnaire.
8. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
9. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
10. Collection of unused study drug and rescue medication.
11. Review subject's use of rescue medication/concomitant medication.

12. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
13. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
14. Re-instruct the subject concerning the patch application and removal method.
15. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
16. **Patient Education**: At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 2 (midway between Week 4-8)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.

e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

3. Re-instruct the subject concerning the patch application and removal method.
4. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
5. Review subject's use of concomitant medication.
6. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
7. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
   a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
   b. keep the patch attached [redacted] including while sleeping;
   c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
   d. accurately reporting pain;
   e. accurately reporting rescue medication use;
   f. understanding when to return for their next visit and the importance of returning on schedule;
   g. adhering to the overall research plan; and
   h. Do NOT apply study drug to non-target knee at any time.

Visit 7 (Week 8)

1. Obtain vital signs measurements.
2. Perform a pregnancy test.
3. Administer the WOMAC questionnaire for the target knee.
4. Perform PGA.
5. Perform PGIC.
6. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.
7. Review the subjects' eDiary entries. If there is any missing entry, re-instruct the subject to record the eDiary daily.
8. Collection of unused study drug and rescue medication.
9. Review subject's use of rescue medication/concomitant medication.

10. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
11. Dispense study drug and rescue medication and ensure subject has continued access to the eDiary.
12. Re-instruct the subject concerning the patch application and removal method.
13. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
14. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
    a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
    b. keep the patch attached [redacted] including while sleeping;
    c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
    d. accurately reporting pain;
    e. accurately reporting rescue medication use;
    f. understanding when to return for their next visit and the importance of returning on schedule;
    g. adhering to the overall research plan; and
    h. Do NOT apply study drug to non-target knee at any time.

Phone Visit 3 (midway between Week 8-12)

During the time interval between visits, the site coordinator contact (via telephone) the subjects.

1. Review subject's eDiary. If there is any missing entry, re-instruct the subject to record the eDiary daily.
2. Ensure to record the eDiary correctly.
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale when subjects replace a patch. In addition to the regular assessment of NRS, the NRS assessment will be performed immediately before the subject takes any rescue medication on the day (if applicable).
    b. Record the time of patch application and removal when subjects replace a patch.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable) at the time of unscheduled detachment or before they sleep.
    d. Record the number of tablets of rescue medication used, the time and the reason when subjects take a tablet or before they sleep.

e. Answer the questionnaires related to adhesion, skin irritation and discomfort when subjects replace a patch and record any issues with adhesion, skin irritation and discomfort.

3. Re-instruct the subject concerning the patch application and removal method.
4. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
5. Review subject's use of concomitant medication.
6. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.
7. **Patient Education:** At all clinical study visits, the investigator (or designee) will explain the importance of the following:
   a. applying study drug [redacted] to the target knee (where required, showering/bathing should be done prior to patch application);
   b. keep the patch attached [redacted] including while sleeping;
   c. recording patient eDiary information [redacted] when subjects replace the patch, take the rescue medication and before they sleep;
   d. accurately reporting pain;
   e. accurately reporting rescue medication use;
   f. understanding when to return for their next visit and the importance of returning on schedule;
   g. adhering to the overall research plan; and
   h. Do NOT apply study drug to non-target knee at any time.

Visit 8 (Week 12)

1. Perform physical examination.
2. Obtain vital signs measurements.
3. Obtain subject's weight.
4. Obtain blood and urine samples for laboratory testing.
5. Perform a 12-lead ECG.
6. Perform a pregnancy test.
7. Administer the WOMAC questionnaire for the target knee.
8. Perform PGA.
9. Perform PGIC.
10. Perform a QOL Questionnaire.
11. Perform dermal safety assessment (irritation, discomfort, and adhesion) and record the time of the evaluation for each assessment in the eCOA.

12. Remove the patch on a skin.
13. Instruct a subject to perform the following assessments in the eDiary when they remove the patch at the site:
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale
    b. Record the time of patch removal.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable).
    d. Record the number of tablets of rescue medication used, the time and the reason.
    e. Answer the questionnaires related to adhesion, skin irritation and discomfort. Record any issues with adhesion, skin irritation and discomfort.
14. Review the subjects' eDiary entries.
15. Collection of unused study drug and rescue medication.
16. Review subject's use of rescue medication/concomitant medication.
17. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
18. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.

Note: After Visit 8, subjects may resume their standard of care treatment.

10.1.4 Follow-up Phase

A follow-up phone Visit will take place approximately 7 days after Visit 8 (or Early Termination Visit), and will include the following assessment and procedures:

1. Review subject's use of concomitant medications.
2. Review AEs.
3. Record the findings in the eCRF.

10.1.5 Early Termination Visit (if applicable)

Subjects who are discontinued prematurely from study for any reason after Baseline (Visit 3) must complete the Early Termination Visit. If the subject comes for an Unscheduled Visit and a decision to withdraw the subject is made, then the Early Termination Visit procedures will be performed and the Early Termination Visit eCRF will be completed (and not the Unscheduled Visit eCRF). During this visit the following assessments and procedures will be performed:

1. Perform physical examination.
2. Obtain vital signs measurements.

3. Obtain subject's weight.
4. Obtain blood and urine samples for laboratory testing.
5. Perform a urine pregnancy test.
6. Perform a 12-lead ECG.
7. Administer the WOMAC questionnaire for the target knee.
8. Perform PGA.
9. Perform PGIC.
10. Perform a QOL Questionnaire.
11. Remove the patch on a skin.
12. Instruct a subject to perform the following assessments in the eDiary when they remove the patch at the site:
    a. Perform and record scoring of the pain of the target knee using the NRS 11-point pain scale
    b. Record the time of patch removal.
    c. Record the time of not scheduled complete patch detachment and the reason (if applicable).
    d. Record the number of tablets of rescue medication used, the time and the reason.
13. Review the subjects' eDiary entries.
14. Collection of unused study drug and rescue medication.
15. Review subject's use of rescue and concomitant medications.
16. Perform drug accountability/reconciliation of study drug and rescue medication. The reconciliation (missing patch, failure of application, unscheduled detachment and application, etc.) will be recorded in the eCRF.
17. Perform dermal safety assessment (irritation, discomfort, and adhesion).
18. Review AEs. The irritation and discomfort reported in the eDiary will be treated as AEs.
19. Record the date and the reason of early termination in the eCRF.

10.2. The Schedule of Events

Phase	Screening Phase				Double-blind Treatment Phase										Follow-up	ET
	Screening[k]	Washout[k]		Baseline												
Week				0		1		2		4		8		12	13	
Clinic visit	1	2		3		4		5		6		7		8		
Phone Visit[a]									1		2		3		4	
Day	-28 to -10	-14 to -7		0	1-6	7	8-13	14	15-27	28	29-55	56	57-83	84	91	
Visit Window (Days)						±2		±2	21±3	±2	42±3	±7	70±3	±7	±2	
Informed Consent	X															
Demographics	X															
Medical History	X															
Inclusion/Exclusion criteria	X	X		X												
Randomization				X												
Physical Examination	X													X		X
Vital signs	X			X		X		X		X		X		X		X
Height	X															
Weight	X													X		X
Clinical Laboratory test[b]	X			X						X				X		X
Urine Pregnancy Test	X			X						X		X		X		X
Drug Screen/ Alcohol Test	X			X												
12-lead ECG	X			X										X		X
X-Ray[c]	X															
Dispense Rescue Medication		X				X		X		X		X				
Use of Rescue Medication[d]		X	X				X		X		X		X			X
Study Drug Application[e]				X	X	X	X	X	X	X	X	X	X	X		
Collection of Unused Study Drug and Rescue Medication				X[l]		X		X		X		X		X		X
Drug Accountability				X[l]		X		X		X		X		X		X
Patient eDiary[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pain Intensity 11-Point NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Dermal Evaluations[g]				X		X		X		X		X		X		X
WOMAC[h]	X			X		X		X		X		X		X		X
PGA				X		X		X		X		X		X		X
PGIC						X		X		X		X		X		X
QOL Questionnaire[i]				X						X				X		X
Placebo training		X		X												
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[j]				X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; eDiary = electronic diary; ET = early termination; ECG = electrocardiogram; NRS = numeric rating scale; PGA= Patient Global Assessment; PGIC=Patient Global Impression of Change; WOMAC = Western Ontario and McMaster Universities Arthritis Index; QOL = quality of life.

a Principal Investigator or designee contacts subjects approximately midway between Weeks 2-4 (Day21±3), 4-8 (Day42±3), and 8-12 (Day70±3).
b Clinical laboratory testing includes hematology, biochemistry, urinalysis, and fasting glucose and lipids. Fasting glucose and lipids should be performed after 8 to 10 hours of fasting (no food or drink, except for water). Fasting is necessary for all labolatory tests. However, if the subject is not able to fast at Visit 1, at least fasting at Visit 3 should be done during Screening Phase.
c Historical X-rays done within 1 year prior to the Baseline Visit are acceptable. If subject does NOT have any target knee X-ray done within the past year, a mandatory new X-ray to confirm the disease will have to be performed prior to starting the Washout Period and the X-ray should be reviewed by the completion of Baseline Visit.
d If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral acetaminophen per day as rescue medication for the treatment of the target knee pain of OA because of lack of efficacy of study drug (not for the non-target knee) if the subject does not feel enough pain relief by the study drug, any other aches they might experience during the trial such as headache and reduction of fever except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to for all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8).
e Study treatment will be applied on Day 0 at sites. Instructions for application and removal of study drug patches will be provided to the subject at Baseline visit.
f Subjects will be instructed on how to use the eDiary at the Screening Visit. For Screening Phase, subjects will be asked to record their NRS pain scores of the target knee and the number of tablets of rescue medication used, the time and the reason in the eDiary. For 12-week administration period, subjects will be asked to record their NRS pain scores of the target knee, and the number of tablets of rescue medication used, the time and the reason, unscheduled detachment of study drug and the reason and answer the questionnaire related to adhesion, skin irritation and discomfort, record any issues with adhesion, skin irritation and discomfort in the eDiary.
g Dermal evaluations will assess irritation, discomfort, and adhesion (At Visit 3, irritation only).
h WOMAC will include WOMAC pain intensity, WOMAC stiffness, and WOMAC physical function.
i QOL Questionnaire is Mini-OA Knee and Hip QOL (Mini-OAKHQOL) and Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA).
j AEs will be collected starting from the first administered dose.
k Screening visit (Visit 1) will be completed -28 to -10 days prior to Baseline Visit. Washout visit (Visit 2) is at least 3 days after Visit 1 (e.g. If Visit 1 is Day -10, Visit 2 can be scheduled on Day -7). Washout visit (Visit 2) will be completed -14 to -7 days prior to Baseline Visit. Washout Period will be initiated from the Washout Visit (Visit 2). Washout period is for 7 to 14 days.
l Only for rescue medication.

10.3. Assessments

Note: For the various questionnaires that are used during this study, at each time point where a questionnaire is being completed there must be no reference back to previous questionnaires that have been completed by that subject during the study.

10.3.1 Efficacy

10.3.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC LK version 3.1 is the most recent version of this instrument for the assessment of hip and knee OA. The WOMAC Osteoarthritis Index is widely used to measure pain, stiffness, and physical function in subjects with OA pain. It is considered to be a reliable and valid instrument for this indication.[4,5,6]

Subjects will rate each of scales for Pain, Stiffness, and Physical Function over the past 24 hours. The WOMAC questionnaire will be completed for the target knee. The scores will be recorded in the eCRF.

The **WOMAC Pain** scale evaluates the following 5 items:

[redacted]

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4).

The **WOMAC Stiffness** scale assesses 2 items:

[redacted]

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4).

The **WOMAC Physical Function** assesses the following 17 categories using the 0 to 4 scale (None = 0, Mild = 1, Moderate = 2, Severe = 3, Extreme = 4) described previously:

[redacted]

The **WOMAC Composite score** is most commonly calculated by summing the items for all 3 subscales. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. The total score is calculated as follows: Total score=_/96= __%

10.3.1.2 Patient Global Assessment

The PGA is a self-administered instrument that measures the subject's overall impression of their OA pain in their target knee on a 5-point scale where 0 = "Very Good" and 4 = "Very Poor". The scores will be recorded in the eCRF.

Subjects will be asked the complete the following statement:

"How would you rate your osteoarthritis condition over the last 24 hours?"

The response options include the following:

Very Good	0
Good	1
Moderate	2
Poor	3
Very Poor	4

10.3.1.3 Patient Global Impression of Change

The PGIC is a self-administered instrument that measures change in subjects' overall improvement with treatment on a scale where 1 = "very much improved" and 7 = "very much worse." The scores will be recorded in the eCRF. Subjects will be asked the following question: "How would

you rate your overall improvement with treatment during the clinical trial?" The response options include the following:

Very Much Improved	1
Much Improved	2
Minimally Improved	3
No Change	4
Minimally Worse	5
Much Worse	6
Very Much Worse	7

10.3.1.4 Numeric Rating Scale

The NRS is an 11-point scale from 0 to 10. On this scale, 0 = no pain and 10 = the worst pain imaginable. NRS 11-point scale will be assessed in 2 ways. One is the average pain condition over the last 24 hours, and the other is the worst painful condition over the last 24 hours.

The subject will rate his or her target knee average and worst pain intensity when they replace a patch and before taking any rescue medication on the day using the following question: "On a scale from 0 to 10, where "zero" represents "no pain" and "10" represents "the worst possible pain," how would you rate the average / worst pain that you have been feeling in your knee over the last 24 hours?"

Note:

1. The average pain scale (not worst) will be used for the eligibility confirmation of inclusion criteria and identifying the target knee.
2. The NRS pain assessment must be performed daily by the subject at home between Screening (V1) and the start of the Washout Period. [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated for subjects to be considered eligible for study participation.
3. The subject will continue assessing and recording the NRS pain score daily at home during the Washout Period. [redacted] will be entered to the eCOA system and the mean NRS scores will be calculated for subjects to be considered eligible for study participation.

10.3.1.5 Use of Rescue Medication

If needed, subjects will be allowed to take up to a maximum of 2 g (4 × 500 mg tablets) of oral APAP per day (as provided by the Sponsor or designee) as rescue medication for the treatment of of the target knee pain of OA because of lack of efficacy of study drug (not for the non-target knee) if the subject does not feel enough pain relief by the study drug, any other aches they might experience during the trial such as headache and reduction of fever except within 3 calendar days prior to the Baseline Visit, on the day of Baseline Visit (V3), from Baseline Visit until Visit 4, within 2 calendar days prior to all subsequent visits (V5, V6, V7, and V8), and on the day of the clinic visits (V4, V5, V6, V7, and V8). Information regarding the use of rescue medication, such as the number of tablets, the time and the reason of use, will be recorded on the appropriate concomitant medication eCRF. Subjects should not use OTC APAP as rescue medication.

10.3.2 Safety

Safety assessments will include the evaluation of laboratory assessments, vital signs, 12-lead ECGs, physical examinations, dermal safety assessments and AEs.

10.3.2.1 Laboratory Safety Assessments

10.3.2.1.1 Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (see **Section 10.2**).

Hematology:	Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), white blood cell count including differential.
Serum chemistry:	Albumin, total bilirubin, direct bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, blood urea nitrogen, creatinine, fasting glucose and total lipids (8 to 10 hours after fasting is required for these laboratory testing), cholesterol, triglycerides, high density lipoprotein, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid.
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones, leukocyte esterase, nitrite, total bilirubin, urobilinogen.
Pregnancy test (urine):	For women of childbearing potential only.
Urine drug screen:	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, methamphetamine, methadone, phencyclidine, and tetrahydrocannabinol.
Alcohol test (breathalyzer):	Ethanol.

A central laboratory will be used to process all hematology, clinical chemistry, and urinalysis samples. Drug screens, alcohol tests, and pregnancy tests will be conducted at the study sites. A breathalyzer alcohol test will be performed at Visit 1 and Visit 3. Details on sampling, handling, and storage of samples will be given in a separate laboratory manual.

10.3.2.1.2 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of biological samples are outlined in the HP-5000-US-07 laboratory manual. The investigator is

responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

10.3.2.2 Clinical Examinations

10.3.2.2.1 Vital Signs, Weight and Height

Vital signs, including heart rate, respiratory rate, temperature, and supine blood pressure will be measured at designated time points. Blood pressure will be measured with the subject in the supine position only. The supine blood pressure should be measured after the subject has been lying down for 5 minutes. Weight (kg) and height (cm) will also be measured.

10.3.2.2.2 Electrocardiogram

The 12-lead ECG will be a complete, standardized recording and will be performed at designated time points after the subject has been in a supine position for at least 5 minutes before the 12-lead ECG is obtained. All ECG recordings will be identified with the subject number, initials, date, and time of the recording and will be attached to the subject's eCRF. ECG parameter values and interpretation of results will be captured in the eCRF.

10.3.2.2.3 Physical Examination

The following physical examination will be performed at designated time points before potential exposure to study drug and at the completion of exposure.

- General Appearance
- Head/ Face
- Eyes/ Fundoscopy
- Ears/Hearing
- Nose
- Mouth, Teeth and Throat
- Neck & Thyroid
- Chest/Lungs
- Abdomen
- Skin, Hair, and Nails
- Musculoskeletal: Extremities, Spine
- Vascular/Circulatory
- Lymphatic
- Psychiatric/Behavior
- Brief neurologic

10.3.2.3 Adverse Events

The definitions and management of and special considerations for AEs are provided in **Section 11**.

10.3.2.4 Evaluations of Patch and Dermal Assessment

Safety dermal characteristics will be assessed using a 5-point numerical scale of adhesion, Berger and Bowman scale of Irritation, 5-point numerical scale of Discomfort.[7]

10.3.2.4.1 Patch Adhesion

Patch adhesion will be assessed in 2 ways: in-clinic and at-home. At each clinic visit, patch adhesion will be assessed by the investigator or a designee (who will be a trained medical professional such as a nurse practitioner or physician assistant) using the following 5-point numerical scale:

- 0 = ≥90% adhered (essentially no lift off the skin).
- 1 = ≥75% to <90% adhered (some edges only lifting off of the skin).
- 2 = ≥50% to <75% adhered (less than half of the system lifting off of the skin).
- 3 = <50% adhered but not detached (more than half the system lifting off of the skin without falling off).
- 4 = patch detached (patch completely off the skin).

During the Double-blind Treatment Phase at home, subjects will report on any incidence of unscheduled patch detachment, the time and the reason and record in the eDiary. When subjects replace the patch, subjects will complete a questionnaire about adhesion and residue in the eDiary to confirm the following:

- Is the patch 100% attached to the skin? If No, is more than half of the patch still attached?
- Is there any residue on your skin after removing the patch?

10.3.2.4.2 Irritation

At each clinic visit, the application site where the previous patch was applied will be examined for signs of skin irritation. All subjects will be evaluated by a trained investigator or designee using the Berger and Bowman scale[7] as described below.

Half grades will not be assigned if reactions fall between the unit grades, rather, the more severe of the 2 grades will be assigned.

Dermal response score will be rated on a 0 to 7 scale, whereby 0 is rated as “No evidence of irritation” and 7 is rated as “Strong reaction spreading beyond test (application) site.”

Dermal Response

- 0 = no evidence of irritation
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible; minimal edema or minimal papular response
- 3 = erythema and papules
- 4 = definite edema

- 5 = erythema, edema, and papules
- 6 = vesicular eruption
- 7 = strong reaction spreading beyond the application site

Other effects will be scored via a letter scale and a corresponding numeric scale, whereby N is rated as "No effects" and H is rated as "Small petechial erosions and/or scabs."

Other Effects

- A = slightly glazed appearance
- B = marked glazed appearance
- C = glazing with peeling and cracking
- F = glazing with fissures
- G = film of dried serous exudates covering all or part of the patch site
- H = small petechial erosions and/or scabs
- N = no other observations

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about skin irritation in the eDiary. Subjects will be asked to report any skin irritation to the site staff. Skin irritation reported by the subjects will be recorded as AEs. The investigator will assess any irritation observed at the patch application site at clinic visits. If the score of the dermal response and other effects are not 0 or N, it will be evaluated as AEs.

The subjects will be instructed to contact to their site and arrange for an unscheduled visit (i.e., site visit or virtual visit using remote video systems if available) when they experience any significant or intolerable irritation at home to manage the dermal reaction and evaluate it using the above scale.

10.3.2.4.3 Discomfort

Discomfort will be assessed by the investigator or a designee using a predefined discomfort rating scale. The evaluator will ask the subject, "Are you experiencing any discomfort related to the patch?" If the answer is no, the overall level of discomfort will be rated as 0. If the answer is yes, the evaluator will then ask the subject to rate the discomfort as mild, moderate, or severe along with the description of the discomfort (e.g., itching, burning, pain, stinging, soreness, dryness, and other). Any discomfort mentioned should be recorded as AEs and rated as follows:

- 0 = No discomfort
- 1 = Mild discomfort

- 2 = Moderate but tolerable discomfort
- 3 = Severe, intolerable discomfort
- 4 = Patch not present

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about discomfort in the eDiary. If there is any discomfort, the description (e.g., itching, burning, pain, stinging, soreness, dryness, and other) will be recorded in the eDiary.

Discomfort reported by the subjects will be recorded as AEs.

The subjects will be instructed to contact to their site and arrange for an unscheduled visit (i.e., site visit or virtual visit using remote video systems if available) when they experience any significant or intolerable discomfort at home to manage the dermal reaction and evaluate it using the above scale.

10.3.3 QOL

10.3.3.1 Mini-OA Knee and Hip QOL (Mini-OAKHQOL)

The 20-item Mini-OA Knee and Hip QOL (Mini-OAKHQOL) has good psychometric properties and can be used for the measurement of QOL in subjects with OA of the lower limbs (see **Section 18.3**).

Subjects will complete a questionnaire about QOL at clinical visits.

10.3.3.2 Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA)

The Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) Knee or Hip is a 6-item validated questionnaire that assesses the impact of OA on absenteeism, presenteeism, work productivity, and activity impairment. Each subscale score is expressed as an impairment percentage (0-100) where higher numbers indicate greater impairment and less productivity. The WPAI: OA is self-administered by the subject and takes less than 5 minutes to complete (see **Section 18.4**).

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

Per the International Council for Harmonisation (ICH), an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will NOT be considered AEs unless there is an increase in the frequency or severity, or a change in the nature of the disease or condition during the Double-blind Treatment Phase (worsening of a pre-existing condition is considered an AE). AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

Any medical condition or clinically significant laboratory abnormality with an onset date after signing the Informed Consent and before the time of dosing is considered to be pre-existing, and should be documented as Medical History (and not as an AE). Any new medical condition or clinically significant laboratory abnormality or an exacerbation of a pre-existing condition with an onset date after signing of Informed Consent and after the time of first dosing should be recorded as an AE. Events occurring in subjects treated with placebo will also be considered AEs. However, AEs reported during treatment-free periods before study drug has been administered are not considered AEs; these events are captured on the eCRF as updates to the subject's medical history.

- All AEs encountered during the clinical study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from after the start of the study drug. AEs in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. It is up to the investigator to determine whether an abnormal laboratory value constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g., if new onset viral

hepatitis is causing elevated ALT, hepatitis should be captured as the AE and not the elevated ALT).

- Examples of laboratory abnormalities, which should be considered as AEs include those which result in withdrawal of the study treatment, withholding study treatment pending some investigational outcome, reduction of dose of the study treatment, or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be reported on the appropriate AE page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.
- Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

11.1.2 Unexpected Adverse Event

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a study drug, the known information is contained in the IB which includes the HP-5000 Developmental Core Safety Information.

An unexpected AE is one for which the specificity or severity is not consistent with the current IB and Developmental Core Safety Information.

Furthermore, reports that add significant information on specificity or severity of a known, already documented AE constitute unexpected events.

11.1.3 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death

NOTE: Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should usually be reported as the outcome of a specific SAE.

- is life-threatening.

NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does NOT qualify the condition or event as an SAE.

- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly in the offspring/fetus.

NOTE: A congenital anomaly in an infant born to a mother who was exposed to study drug during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received a study drug is NOT considered an SAE but an AE.

- Is an important medical event.

NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, development of drug dependency or drug abuse.*

11.2. Management of Adverse Events

Adverse events will be collected from the time of first dose administration through the Follow-up Visit or Early Termination Visit, whichever occurs first.

Subjects who complete the Double-blind Treatment Phase or terminate early will continue to be monitored for AEs for 30 days from last day for study treatment, unless resolution, they withdraw consent or are lost to follow-up.

11.2.1 Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be classified as

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in **Section 11.1.3**.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in **Section 11.1.3**.

11.2.2.3 Action Taken

Action taken may consist of:

Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Dose interrupted	Patch temporarily removed
Dose not changed	No action taken with study drug
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as follows:

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

- Fatal*
- Unknown

***NOTE**: Only select fatal as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to study drug. The categories for classifying the investigator's opinion of the relationship are listed below.

Not related	An AE with sufficient evidence to accept that there is no causal relationship to study drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven).
Unlikely related	An AE, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable, and in which other drugs, events or underlying disease provide plausible explanations.
Possibly related	An AE with a reasonable time sequence to administration of the study drug, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Definitely Related	An AE occurring in a plausible time relationship to study drug administration, and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.

Note: AEs at patch application site will be collected and marked with the flag in the eCRF to be able review and analyze them separately.

11.2.3 Documentation

All AEs occurring within the period of observation for the study must be documented in the eCRF with the following information; where appropriate (The period of observation for the study is described in **Section 11.2**):

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to study drug

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, as necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the subject should be withdrawn from the study and the reason and date of withdrawal must be documented in the eCRF. The decision about whether the subject may continue in the study will be made by the sponsor after consultation with the investigator and/or Medical Monitor.

If a subject experiences an intolerable AE , the investigator must decide whether to withdraw the subject from the study and/or treat the subject. Special procedures may be recommended for the specific study drug, such as the collection of a serum sample for determining blood concentrations of study drug, or treatment regimens, as appropriate.

It is **NOT** necessary to unblind a subject's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see **Section 9.5** for a description of the unblinding procedures.

11.2.5 Follow-up

All ongoing SAEs at the time of discontinuation will be followed (up to a maximum of 30 days after the last dose of study drug) to a satisfactory resolution, or until it becomes stable, or until it can be explained by another known causes (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All ongoing AEs at the time of discontinuation will be followed for up to 7 days. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the eCRF page.

11.2.6 Reporting of Adverse Events

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to Noven Pharmacovigilance within 24 hours of first becoming aware of the event by completing, signing and dating the SAE Form (within the eCRF), verifying the accuracy of the information recorded in the form with the source documents.

All SAEs, irrespective of relationship to study treatment, must be reported to Noven as soon as possible but no later than 24 hours using the appropriate SAE form within the eCRF.

It is very important that the SAE form (within the eCRF) be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality. All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization. Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form (within the eCRF). If eCRF system is down or not accessible for the site, the "Noven Serious Adverse Event Reporting Form (Noven SAE form)" must be used for reporting to Noven Pharmacovigilance. The site should use the eCRF system as the primary means to notify of the SAE (initial or follow-up). The Noven SAE "paper" form should only be used as the back-up option for notification if the eCRF system is down.

If the situation where the Noven SAE "paper" form is to be used, **all SAEs, irrespective of relationship to study treatment, must be reported to Noven as soon as possible but no later than 24 hours to:**

Email: [redacted]

SAEs, regardless of causality assessment, must be collected through the Termination Visit and for 30 days following study drug discontinuation, whichever is longer.

Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The written report should be submitted on the SAE form (within the eCRF) provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Subject's study number
- Subject's age
- Subject's gender
- Date of first dose of study drug
- Date of last dose of study drug, if applicable
- Adverse event term
- The seriousness criteria that were met
- Date of occurrence of the event
- A brief description of the event and outcome to date
- Any actions taken in response to the SAE
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to study drug ("Is there a reasonable possibility that the study drug caused the SAE?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

Preliminary SAE reports and/or any missing or additional relevant information concerning the SAE should be provided to the recipients of the initial information as soon as possible on a follow-up SAE form (within the eCRF), together with the following information (AE, date of occurrence, subject number, study ID, study drug, and site number) including copies of hospital case reports, autopsy reports and other documents requested by the sponsor; this will allow the follow-up information to be linked to the initial SAE report.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his/her health authorities, institutional review board (IRB), principal and coordinating investigators, study investigators, and institutions.

11.2.6.2 Nonserious Adverse Events

All non-serious AEs will be reported to the Sponsor on an ongoing basis and will be captured in the eCRF.

11.2.7 Pregnancy Reporting

All females of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Females should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Male study participants will be instructed to practice birth control measures to prevent a partner's pregnancy during the subject's study participation and for 90 days following the last dose administration.

Pregnancy testing will be conducted prior to administration of study drug on every female of childbearing potential. A female who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A female who becomes pregnant during study will immediately discontinue the study treatment. The subject is encouraged to return to all scheduled site and telephone visits, perform all procedures (including eDiary completion and blood draws) and follow the all requirements of the protocol (including the prohibited therapies), but without study treatment administration, until the end of the study (Follow-up Phone Visit, Week 13). Any female who becomes pregnant during treatment and within 30 days of discontinuing study drug will be followed by the investigator after the completion of the study until birth or termination of pregnancy. Any pregnancy for which the estimated date of conception occurred prior to the Termination Visit of the study and for 30 days following study drug discontinuation, whichever is longer, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

An induced abortion or a spontaneous abortion is considered to be a SAE and should be reported in the same timeframe and in the same manner as all other SAEs (see **Section 11.2.6.1**).

The investigator must report the pregnancy to Noven using the **Noven Pregnancy Notification Report form** via the same email address as for SAE reporting. The investigator should contact the designated individuals who receive SAE notification and record information related to the pregnancy on a **Noven Pregnancy Notification Report form** provided by the sponsor or its designee.

Pregnancies must be reported to Noven as soon as possible, but no later than 24 hours to:

Email: [redacted]

The Clinical Site should record and maintain all relevant information on the appropriate study form and eCRF, including the follow-up and outcome of the pregnancy.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed-up and documented even if the subject was discontinued from the study (with the subject's consent). The Clinical Site must report all pregnancy follow-up information to the Sponsor using the Noven Pregnancy Follow-up Report form via email to [redacted] within 24 hours of receiving the pregnancy follow-up information. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. The Clinical Site must report all congenital abnormalities/birth defects and spontaneous miscarriages using the SAE form (within the eCRF) via email to [redacted] within 24 hours of receiving the information. Elective abortions without complications should not be handled as AEs.

12. DATA SAFETY MONITORING BOARD

There will be no Data Safety Monitoring Board for this study.

13. STATISTICAL METHODS

13.1. Study Endpoints

13.1.1 Primary Efficacy Endpoint

- WOMAC LK3.1 OA (pain) change from Baseline at Week 12

13.1.2 Key Secondary Efficacy endpoints

- WOMAC LK3.1 OA (physical function) change from Baseline at Week 12
- WOMAC LK3.1 OA (stiffness) change from Baseline at Week 12

13.1.3 Secondary Efficacy Endpoints

- WOMAC LK3.1 OA (pain) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (physical function) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (stiffness) change from Baseline at Weeks 1, 2, 4, and 8
- WOMAC LK3.1 OA (composite score) change from Baseline at Weeks 1, 2, 4, 8, and 12
- Change from Baseline in pain intensity assessed on an 11-point NRS at Weeks 1, 2, 4, 8, and 12
- Change from Baseline in pain intensity assessed on an 11-point NRS of a weekly average of all available daily pain scores at each week from Week 1 through 12
- Change from Baseline in Patient Global Assessment at Weeks 1, 2, 4, 8, and 12
- Patient Global Impression of Change (PGIC) at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (pain) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (physical function) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12
- Treatment Response: Reduction in the WOMAC LK3.1 OA Index (stiffness) of ≥30%, ≥50%, ≥70% and ≥90% at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects, the number of days, and the total number of rescue medication tablets used during the treatment phase
- The onset of the effect: Pain intensity assessed on an 11-point NRS change from Baseline
- Mini-OA Knee and Hip QOL (Mini-OAKHQOL) scores change from Baseline at Weeks 4 and 12
- Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA) impairment scores change from Baseline at Weeks 4 and 12.

13.1.4. Safety Endpoints

- The incidence of treatment-emergent AEs, AEs leading to discontinuation of the study drug, SAEs, and other significant AEs.
- Change from Baseline in clinical laboratory tests, ECG findings, body weight, physical examination findings, and vital signs.
- Dermal assessments: irritation, discomfort, and adhesion.

13.2. Sample Size Determination

Based on the HP-5000 Phase 2 study results, the assumed [redacted] of the test product in the pivotal study will be about [redacted] The sample size of [redacted] subjects per treatment arm (or total of about [redacted] subjects) will be included in order to have 80% power to demonstrate statistically significant difference versus placebo using a 2-sided overall Type I Error rate of 0.05.

A sufficient number of subjects will be screened to randomize the proposed sample size.

13.3. Analysis Populations

The following analysis populations are planned for this study:

- Intent-to-Treat (ITT): Includes all consented and randomized subjects. Regardless of any protocol deviations and/or treatment compliance, analyses performed on the ITT set will be based on the randomized treatment assignment and all available data. The ITT will be used as the primary set for analysis of efficacy endpoints.
- Safety Analysis Set (SAF): Includes all subjects who have had at least 1 patch of double-blind study drug applied and who have at least 1 post-dose safety measurement during the Double-blind Treatment Phase. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the SAF will be based on treatment actually received. The SAF will be used for the analysis of dermal evaluations and safety endpoints.

Inclusion in the analysis populations will be determined prior to database lock.

If a subject is randomized incorrectly or is administered the incorrect study drug, analyses of the ITT population will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

13.4. Statistical Analyses

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock. Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a *P* value of <0.05 will be considered statistically significant. For analyses involving study site, if the number of subjects per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Summary statistics will be provided for the variables described below. For continuous variables, these statistical analyses will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

13.4.1 Study Subjects and Demographics

13.4.1.1 Disposition and Withdrawals

The numbers of subjects randomized, completing, discontinuing from study treatment, and withdrawing from the study, along with reasons for withdrawal will be tabulated overall and by treatment group. The number of subjects and patches in each analysis population will be reported.

13.4.1.2 Protocol Deviations

A by-subject listing of all protocol deviations and violations will be reported in the clinical study report (CSR).

13.4.1.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for all analysis populations. Demographic variables will include age, gender, height, weight, BMI, target knee (left or right), duration of OA of the knee and age at the onset of the disease. Information on race and ethnicity will be collected for any eventual analysis of differences in response to study drug, in accordance with local regulatory requirements. Baseline subject characteristics will include medical history, physical examination findings, and previous OA treatment modalities.

Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

13.4.2 Exposure and Compliance

Investigational product administration will be summarized in terms of the number of patches applied and removed, the number of patches removed earlier along with the summary of reasons for early removal. For each subject mean in terms of duration of exposure will be calculated. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

13.4.3 Efficacy Analyses

Efficacy variables will be summarized and analyzed using the ITT population as primary, unless otherwise specified.

13.4.3.1 Primary Analysis

The primary efficacy endpoint of this study is the change from Baseline to Week 12 in the WOMAC pain score, and key secondary endpoints are the change from Baseline to Week 12 in the WOMAC physical function and WOMAC stiffness. The primary analysis set is the ITT. The comparison of interest is: HP-5000 versus placebo.

The fixed-sequence procedure will be applied for primary and key secondary endpoints of this study, where the order in which the hypotheses are tested is pre-specified as following: (1) WOMAC pain, (2) WOMAC physical function, and (3) WOMAC stiffness. Testing begins with the first hypothesis (H_1) about WOMAC pain, and each test is carried out as long as significant results with level of significance α=0.05 are observed in all preceding tests. The fixed-sequence procedure controls the family-wise error rate because, for each hypothesis, testing is conditional upon rejecting all hypotheses earlier in the sequence.

All statistical tests of hypotheses in this trial will be 2-sided with a Type I Error rate of 0.05.

The estimand in the primary analysis for efficacy is the difference between treatment groups (HP-5000 *vs*. placebo) in the change from Baseline to Week 12 in WOMAC pain score in all randomized subjects from the ITT population and taking into account intercurrent events using the composite strategy. The study treatment discontinuation due to reasons related to study treatment (e.g. adverse events (AE), lack of efficacy (LOE), etc.), rescue medication use within 24 hours of WOMAC pain assessment, removal/detachment of the patch for more than 24 hours before WOMAC pain assessment are defined as intercurrent events.
Composite strategy will be applied to the stratum of subjects experiencing intercurrent events.

For the intercurrent events of study treatment discontinuation due to reasons related to study treatment (e.g. adverse events (AE), lack of efficacy (LOE), etc.), the obtained WOMAC pain score will be addressed in the analysis by expecting the long-term benefit from the treatment for that patient to be zero from the time of intercurrent event. For the other intercurrent events including rescue medication use within 24 hours of WOMAC assessment and removal/detachment of study patch for more than 24 hours before WOMAC assement, the obtained WOMAC pain score will not be included in the analysis.

The primary efficacy variable, change from Baseline to Week 12 in the WOMAC pain score, will be analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM model will include change from Baseline in WOMAC pain score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC pain score as covariates. An unstructured covariance matrix will be assumed. If the unstructured covariance matrix fails to converge, a series of other covariance structures will be tested for use.

Other sensitivity analyses will be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis as described below.
The use of MMRM inherently implies that the treatment effect on the change from baseline in the WOMAC score will be similar for the patients who withdraw and for those who complete the study in their respective treatment groups, conditional on the outcomes observed prior to withdrawal (MAR [Missing at random] assumption). To assess the robustness of the MAR assumption, sensitivity analyses which utilize multiple imputations and a different assumption about unobserved outcomes will be performed, as detailed below.
A number of sensitivity analyses of the primary efficacy endpoint will be performed to assess the impact of assumptions about unobserved missing data patterns on the primary inferences after intercurrent events in the trial.
Pattern-Mixture Model and Copy Reference Sensitivity Analyses of MMRM Approach:
Robustness of the primary results under MNAR (Missing not at random) mechanisms will be assessed using pattern-mixture model and copy reference imputation approaches. All sensitivity analyses will be based on the pattern mixture model using multiple imputation technique for the dropout reasons and their assumed pattern of missing data as follows:

- Not Study Treatment Related or Uncertain reason for withdrawn as MAR
- Study Treatment Related reason as MNAR

a. Multiple Imputation: Pattern Mixture Model (PMM)

The missing data due to early discontinuations will be imputed assuming MNAR following the approach described in Permutt (2016)[8]. That approach will be implemented by imputing missing

data first under the MAR assumption in each treatment group using multiple imputation and then adding a pre-defined Δ1 to each imputed value in the placebo group and adding a different pre-defined Δ2 to each imputed value in the active treatment group, then varying Δ1 and Δ2 over an enclosure of a plausible range of values. As noted in the article by Permutt (2016)[8], this is considered the most appropriate kind of sensitivity analysis for the missing data problem. Also, this imputation approach was documented on Page 89 of the NRC report (2010)[8].

b. Multiple Imputation: Copy Reference (Placebo) Approach

This is placebo-based imputation for missing data which will be implemented assuming missing data from the placebo group as MAR and also as MNAR. This will be performed by first implementing placebo-based imputation (copying the distribution of WOMAC scores in the placebo group) for missing data in the active treatment group and the placebo group (as MAR). Then, an adjustment for MNAR in both treatment groups will be implemented by adding a common shift (Δ) to the imputed data, worsening the imputed data further, in both the placebo and the active treatment groups as described in Koch and Wienner (2016)[10]. This step is necessary because it is possible to have a lower treatment discontinuation rate in the active treatment group than in the placebo group and it is important to consider a MNAR approach in the placebo group in such a case. Using a similar argument as in the previous paragraph, the shift Δ will assume similar values to those of Δ1, that is Δ=1,2,4,8,12 (while the case of Δ=0 represents the common copy placebo method, where missing data from placebo are considered as MAR).

Sensitivity analysis using different methods of handling missing data will provide useful information about effectiveness of the study drug and confidence in the reliability of the conclusions drawn. Programming details including SAS code will be provided in the SAP.

13.4.3.2 Analyses for Key Secondary Endpoints

The MMRM model will be used the same way as for primary variable only include change from Baseline in WOMAC physical function (or stiffness) score as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the Baseline WOMAC physical function (or stiffness) score as covariates.

The fixed-sequence procedure will be applied for primary and key secondary endpoints as described in **Section 13.4.3.1**. Other secondary efficacy endpoints will not be included into the fixed-sequence procedure.

Other sensitivity analyses may be performed on the key secondary endpoints to assess the robustness of the results based on the model used for primary analysis. Details will be provided in the Statistical Analysis Plan.

13.4.3.3 Analyses for Secondary Endpoints

All WOMAC LK3.1 OA Indices, PGA, PGIC, and NRS secondary efficacy endpoints will be analyzed similar to the primary analyses. An MMRM model will be used with change from baseline as the repeated dependent variable, with treatment (HP-5000 and placebo), visit, treatment-by-visit interaction, and the baseline assessment score as covariates.

The observed value and change from baseline each assessment score will also be summarized descriptively by visit using summary statistics in addition to the above noted model.

The proportion of responders and non-responders for WOMAC pain, WOMAC physical function or users of rescue medication will be summarized by visit. Treatment comparisons will be made using a logit model with treatment effect as the only term in the model.

The pain intensity assessed on an 11-point NRS average and worst score between Baseline and each day will be tabulated by day and presented graphically.

A weekly average of all available pain scores will be calculated using the 11-point NRS average and worst score. MMRM model will be used to address the secondary objective to compare for change from baseline between treatment arms by weeks; and data will be presented graphically. The all available scores of daily NRS scores evaluated when the subjects replace the patch and the NRS scores evaluated before any rescue medication use will be analyzed.

The NRS pain score for assessment at Weeks 1, 2, 4, 8, and 12 is a mean of the NRS pain scores reported for pain over the last 24 hours for the 3 days (the last 2 days prior to each clinic visit and the day of the clinical visit) using the 11-point NRS average and worst score. MMRM model will be used to address the secondary objective to compare the change from baseline between treatment arms by weeks; and data will be presented graphically.

To address the objective for rescue medication, the proportion of subjects, the number of days using rescue and total rescue use during the entire treatment period will be summarized by treatment arms.

13.4.4 Safety Analyses

All safety summaries will be descriptive; statistical significance tests may be performed on safety data that will be described in the SAP.

Safety analyses will be conducted using data from the SAF population (as defined in **Section 13.3**). Safety variables include AEs, clinical laboratory values, body weight, vital signs, ECG readings, physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.4.4.1 Adverse Events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with study drug through the Follow-up Visit or Early Termination Visit, whichever occurs first. The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term. Summaries of AEs by severity and relationship to study drug will also be provided. Serious adverse events and AEs resulting in discontinuation of study drug will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of study drug will be produced.

13.4.4.2 Dermal Performance

The frequency and percentage of subjects and number of patches with findings related to dermal performance including irritation, discomfort, and adhesion will be summarized.

13.4.4.2.1 Irritation

The frequency and percentage of subjects with patches in each combined and concatenated category will be summarized from the above scales at each visit and overall. The Concatenated Irritation score consists of numerical “Dermal Response” score + the “Other Effects” lettered score; for example: 2N, 2A, 3G, etc. The Combined irritation score will be calculated as a numerical total; i.e., numerical “Dermal Response” score + numeric equivalent for the “Other Effects” lettered score (note that the “Other Notations” do not have numeric equivalents and do not contribute to the numeric Combined irritation score); e.g., 2N, 2A, and 3G will be reported as 2, 2, and 6 combined irritations scores respectively.

Numeric equivalent for the "Other Effects" lettered score is A (0), B (1), C (2), F (3), G (3), H (3), N (0).

In addition to the above, the frequency and percentage of subjects with a combined score of 3 or more will be tabulated.

The information from eDiary data will be included in the summary table and listings.

13.4.4.2.2 Discomfort

The information from eDiary data will be included in the summary table and listings.

13.4.4.2.3 Adhesion

The frequency and percentage of patches in each category will be summarized from the above scale at each visit and overall. The number of subjects with the worst score will be summarized and presented. The information from eDiary data will be included in summary table and the listing.

13.4.4.2.4 Dermal Evaluations at Home

At home, subjects will complete a questionnaire about skin irritation, discomfort, and adhesion in the eDiary. A by-subject listing of this data will be presented in addition to summary tables for each dermal assessment.

13.4.4.3 Concomitant Medications

Prior and concomitant therapies will be summarized for the Safety population. All prior and concomitant medications recorded in the eCRF will be coded to generic term and all matching ATC codes using the current version of WHO-DD. Summaries will be prepared using the coded generic term. All prior and concomitant medications recorded in the eCRF will be listed.

13.4.4.4 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from Baseline values will be presented for clinical laboratory values for each treatment group at each time point.

The number of subjects with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from Baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit. Pre- and post-treatment values will also be presented with an analysis of mean changes from Baseline.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.4.4.5 Vital Signs and Body Weight

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for body weight, BMI, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate.

The number of subjects with vital signs values categorized as below, within, or above normal ranges, will be tabulated showing change from Baseline (shift tables) for each parameter by treatment group and by study visit. Pre- and post-treatment values may also be presented with an analysis of mean changes from Baseline.

13.4.4.6 Electrocardiograms

The number and percentage of subjects with normal and abnormal ECG findings will be summarized for each treatment group at each time point.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected for heart rate (Fridericia's correction [QTcF]), and heart rate for each treatment group at each time point.

13.4.4.7 Physical Examination Findings

The abnormal findings in the complete physical examination will be captured and analyzed as AEs.

13.4.4.8 Dermal Safety

The number and percentage of subjects with findings related to dermal safety including adhesion, irritation, and discomfort will be summarized. A by-subject listing of individual dermal safety findings will also be provided.

13.4.5 Interim Analysis

No interim analyses are planned.

13.5. Database

The final database will be compliant with Food and Drug Administration (FDA) Data Standard catalog from Electronic Common Technical Document/eCTD (May 2015) and Providing Regulatory Submissions in Electronic Format - Standardized Study Data (July 2016).

14. STUDY CONDUCT

The study will be conducted in accordance with all applicable regulatory requirements, including ICH Good Clinical Practice (GCP) guidelines, subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (see **Section 15**). The sponsor reserves the right to withdraw a subject from the study (see **Section 8.2.3**), to terminate participation of a study site at any time, and/or to discontinue the study.

Noven agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (see **Section 17**), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the April 1996 ICH Guidance for Industry E6 Good Clinical Practice (GCP), and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing Noven with

documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Site Initiation

Study personnel may not screen or enroll subjects into the study until after the initiation visit has been conducted, including all required training is complete, and all study supplies are on-site. The investigator and the full study site staff must be available at this visit. All staff must have an initiation visit before they conduct any study specific procedures.

The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate ICF.
2. All required regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

Following the initiation visit, the study will be monitored as per clinical monitoring plan, or additional visit may occur when deemed necessary, while subjects are actively randomized into the study.

14.2. Screen Failures

Subjects who fail any of the inclusion and/or exclusion criteria may not be rescreened for the study. Retesting of clinical laboratory evaluations within the screening window is permitted (i.e., retesting of central clinical laboratory analytes can be done only once).

14.3. Study Documents

All documentation and material provided by Noven or designee for this study are to be retained in a secure location and treated as confidential material.

14.3.1 Investigator's Regulatory Documents

The regulatory documents are listed in the HP-5000-US-07 Study Manual. All required regulatory documents must be received from the investigator and reviewed and approved by Noven or its designee before the study site can initiate the study and before Noven will authorize shipment of study drug to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendments, the HP-5000 topical patch IB, eCRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

14.3.2 Case Report Forms

By signing the Investigator's Agreement (see **Section 17**), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF and are enrolled/randomized.

Case report forms are considered confidential property of Noven and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit in a neat, legible manner to ensure accurate interpretation of data. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee. The eCRFs must be signed by the investigator or a sub-investigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.3.3 Source Documents

Information recorded in the EDC system should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. All source documents must be accessible for verification by the site monitor, auditor, and IRB for inspections and by the regulatory authority(ies). Direct access to source documents must be guaranteed by the

investigator, sub-investigator, or study coordinator, who must provide support at all times for these activities. Subject confidentiality will be protected at all times. Remote source data verification may be used; this should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff.

Clinical laboratory data required by the protocol will be electronically transferred from the central/local laboratory, to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

14.4. Data Quality Control

Noven and its designees will perform quality control checks on this clinical study.

14.4.1 Monitoring Procedures

Noven and/or its designee will monitor the study to ensure study is conducted in accordance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associates (CRAs) will visit the investigator and study site at periodic intervals and maintain periodic communication. Alternatively, centralized monitoring of data acquired by electronic data capture systems (e.g., eCRFs, central laboratory data, ECG data etc) will occur in an ongoing and/or cumulative manner.

Additional off-site monitoring activities may include phone calls, video visits, e-mails, or other online tools in order to discuss the trial with the investigator and site staff. These activities may be used to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, and trial participant status.

It will be the CRA's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The investigator agrees to allow the CRAs and other authorized Noven personnel access (either in person or electronically). The CRAs will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. The CRAs will review:

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures

- laboratory test reports
- other patient records and study documents
- AE procedures, storage and accountability of study drug and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRF are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (see **Section 17**), the investigator agrees:

- to meet with the CRAs during study site visits;
- to ensure that study staff is available to the CRAs as needed;
- to provide the CRAs access to all study documentation, to the clinical supplies dispensing and storage area; and
- to assist the monitors in their activities, if requested

Further, the investigator agrees to allow Noven or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in a separate manual.

14.4.2 Data Management

Noven or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures. A comprehensive data management plan will be developed including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

14.4.3 Quality Assurance/Audit

Study sites, study database and study documentation may be subject to quality assurance audits during the course of the study by Noven or its designee. Audits may be undertaken to check compliance with GCP guidelines, and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or CSR)

Noven or its designee may conduct additional audits on a selection of study sites, which will require access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities clinical inspection according to GCP guidelines. The investigator should agree to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other study files necessary to conduct that audit or inspection. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct a clinical inspection, the investigator shall notify Noven immediately.

14.5. Premature Termination of the Study

The study may be prematurely terminated at Noven's discretion at any time and for any reason. If the study is terminated or suspended, Noven will promptly inform the investigators/sites and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The ethics committee will also be promptly informed and provided with the reason(s) for the termination or suspension by Noven or by the investigator/institution, as specified by the applicable regulatory requirement(s).

Study Site Closure:

At the end of the study, all study sites will be closed, typically after database lock. Noven may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Non-compliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.5.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the study drug has been approved or the sponsor has discontinued its research with study drug, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of study drug

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense. The final database will be archived by Noven according to the regulatory requirements.

14.6. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion with and agreement by Noven and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s), etc.).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

14.7. Clinical Study Report

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports.

14.8. Use of Information and Publication

All information concerning study drug, Noven's operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by Noven or its designee to the investigator and not previously published, is considered confidential and remains the sole property of Noven. Case report forms also remain the property of Noven. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Noven in connection with the continued development of study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Noven. Publication or other public presentation of study drug data resulting from this study requires prior review and written approval of Noven. Abstracts, manuscripts, and presentation materials should be provided to Noven for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Noven has reviewed and commented on such a presentation or manuscript for publication.

14.9. Subject Insurance and Indemnity

Noven will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of insurance will be kept in the study files.

14.10. Data Protection

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of Noven and/or submitted to one or more sponsor offices worldwide, the ethics committee, and regulatory authorities.

Prior to the subject's enrollment in the study, the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes.

The subject must be assured that their identity will be protected. To facilitate this, a unique identification code will be assigned by the investigator to each study subject. This will be used

instead of the subject's name and cross-referenced with the subject's date of birth when reporting AEs and/or other study-related data.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Ethical Conduct of the study

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (64th General Assembly, Fortaleza, Brazil, October 2013), the April 1996 ICH guidelines (E6) of GCP (including archiving of essential study documents), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities of participating country(ies) before sites are initiated.

15.2. Subject Information and Informed Consent

The investigator is responsible for ensuring that no subject is subject to any study-related examination or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

The investigator will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the ICF. After completion, ICFs will be kept and archived by the investigator in the investigator's study file. A copy of the ICF(s) must be provided to the participant. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact on their subsequent care.

15.3. Approval by Institutional Review Board

For Investigational New Drug (IND) studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations. Prior to initiation of the study at each study site, the protocol, the ICF(s), the subject information sheet(s), details of the subject

recruitment procedures, and any other relevant study documentation will be submitted to the responsible local and/or national IRB and approved.

Written notification of approval is to be provided by the investigator to the sponsor's monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed Noven form, IRB Approval Form, or written documentation from the IRB containing the same information.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by Noven before implementation. This written approval will consist of a completed IRB approval form or written documentation from the IRB containing the same information.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the investigator will submit written summaries of the study status to the IRB annually, or more frequently if requested by the IRB. Upon completion of the study, the investigator will provide the IRB with a brief report of the outcome of the study, if required.

15.4. Subject Insurance and Finance

Noven will provide the insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCE

1. Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2010-2012. MMWR Morb Mortal Wkly Rep. 2013;62 (44):869-873.
2. Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. Arthritis Rheumatol. 2016;68(7):1582–1587
3. Investigational Brochure, Diclofenac Sodium Transdermal Drug Delivery System, HP-5000 Transdermal Patch. Noven Pharmaceuticals, Inc. and [redacted] Edition No. 03, September 9, 2014.
4. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833-1840.
5. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14-17.
6. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal anti-inflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578-1587.
7. Berger RS, Bowman JP. A Reappraisal of the 21-day Cumulative Irritation Test in Man. J Toxicol Cutaneous Ocular Toxicol. 1982;1(2):109-115.
8. Permutt T. Sensitivity analysis for missing data in regulatory submissions. Stat Med. 2016;35(17):2876–2879.
9. National Research Council. The prevention and treatment of missing data in clinical trials. Washington, DC: National Academies Press; 2010.
10. Koch GG, Wienner LE. Commentary for the Missing Data Working Group's Perspective for Regulatory Clinical Trials, Estimands, and Sensitivity analyses. Stat Med. 2016;35:2887–2893.

17. ATTACHMENTS

Investigator's Agreement

PROTOCOL NUMBER: HP-5000-US-07

PROTOCOL TITLE: A 12-Week, Randomized, Double-blind, Placebo-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of HP-5000 Topical System (Patch) in Subjects with Osteoarthritis Pain of the Knee

FINAL PROTOCOL: Amendment #1 January 7, 2021 Version 2.0

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Noven during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an IP during and after study completion.

Principal Investigator:

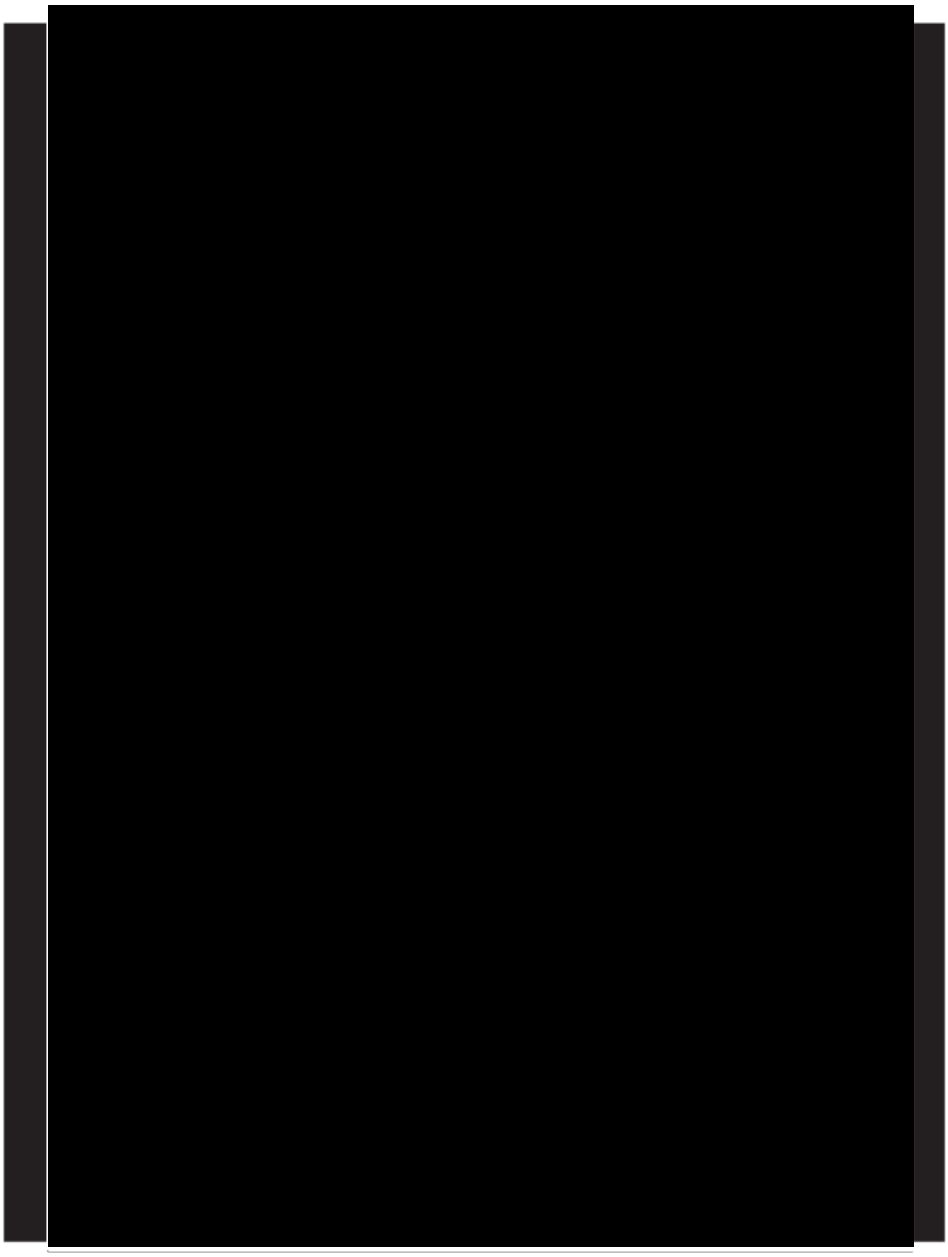
Printed Name: _____

Signature: _____

Date: _____

18. APPENDICES

18.1. Western Ontario and McMaster Universities Osteoarthritis (WOMAC) LK3.1 Index



English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE WOMA

Section A

PAIN

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOMs**

Section B

STIFFNESS

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM$_{C1-3}$**

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE WOMC2-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

[redacted]

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE WOMC3-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

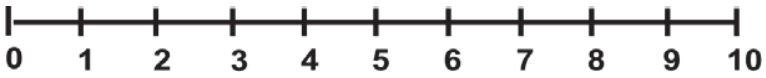
[redacted]

English for USA - V2

18.2. 11-Point Numeric Rating Scale (NRS)

This is a sample of the Numerical Rating Scale. Please use the rating scale provided in the study reference manual.

Instructions: Show the pain scale to the subject and explain that on the 0 to 10 pain rating scale, 0 means no pain and 10 means the worst possible pain. A value in the middle of the scale (around 5) would be moderate pain; a value of 2 or 3 would be mild pain and a value of 7 or higher is considered severe pain.



No Pain **Worst Possible Pain**

Adapted from: Farrar JT, Young JP, La Moreaux L, Werth JL, and Poole MR: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.

18.3. Mini-OA Knee and Hip QOL (Mini-OAKHQOL)

Quality of life in osteoarthritis of lower limbs

Mini-OAKHQoL

Quality of Life in Rheumatology Group© 2012

Please read the following instructions carefully:

The following statements refer to the impact your knee and/or hip osteoarthritis has had on your quality of life. This information allows us to better understand how you are living on a daily basis with your osteoarthritis.

☞ Check the response that best describes your situation,

between "**not at all**" and "**absolutely**" ,
between "**not at all**" and "**a great deal**",
between "**never**" and "**all the time**"
according to each of the proposed statements.

There is no right or wrong answer.

☞ For each statement check only one response (☑)

Example:

	Not at all										A great deal
I have difficulty climbing stairs.	☐	☐	☐	☐	☐	☑	☐	☐	☐	☐	☐
	0	1	2	3	4	5	6	7	8	9	10

Date completed: |__|__| |__|__| |__|__|__|__|

THIS QUESTIONNAIRE CONSISTS OF THREE PAGES (INCLUDING THIS ONE).

Quality of Life in Rheumatology Group© 2012
Version 1.1

Read these questions one by one paying attention to your quality of life OVER THE PAST FOUR WEEKS.
Check the response that corresponds best to the way you are living with your osteoarthritis.

	Not at all										A great deal
1. I have difficulty walking	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
2. I have difficulty bending down or getting up	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
3. I have difficulty climbing up stairs	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
4. I have difficulty dressing myself (socks, shoes, tights/pantyhose)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
5. I have difficulty getting in or out of a car	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
6. I have difficulty performing my tasks at work	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
Not applicable	☐										
7. It takes me longer to do things	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
8. I feel unhappy because of my pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
9. I worry about having to depend on others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
10. I am limited in my sexual activities	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No sexual activity in the past 4 weeks	☐										

	Never										Always
11. I have difficulty staying in the same position for a long time, (sitting, standing, being still)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
12. I have pain (how often)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

	Not at all										Unbearable
13. I have pain (intensity)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Read these questions one by one paying attention to your quality of life
OVER THE PAST FOUR WEEKS.
Check the response that corresponds best to the way you are living with your osteoarthritis.

	Not at all										Absolutely
14. I am able to plan long term projects	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
15. I get out of the house as much as I would like	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Never										All the time
16. I wake up because of my pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
17. I wonder about what I will become in the future	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
18. I am irritable, grouchy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Not at all										A great deal
19. I feel that others understand the difficulties I have related to my osteoarthritis	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
20. I feel supported by those close to me (partner, family,…)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10

Please make sure that you have checked one box and only one
for each of the 20 statements.

Thank you for answering this questionnaire

18.4. Work Productivity and Activity Impairment Questionnaire for Osteoarthritis (WPAI: OA)

Work Productivity and Activity Impairment Questionnaire: Osteoarthritis of the Knee or Hip V2.0 (WPAI:OA)

The following questions ask about the effect of your osteoarthritis of the knee or hip on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your osteoarthritis of the knee or hip? *Include hours you missed on sick days, times you went in late, left early, etc., because of your* osteoarthritis of the knee or hip. *Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

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5. During the past seven days, how much did your osteoarthritis of the knee or hip affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If osteoarthritis of the knee or hip affected your work only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your work a great deal.

Consider only how much osteoarthritis of the knee or hip affected productivity while you were working.

Osteoarthritis of the knee or hip had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Osteoarthritis of the knee or hip completely prevented me from working

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6. During the past seven days, how much did your osteoarthritis of the knee or hip affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If osteoarthritis of the knee or hip affected your activities only a little, choose a low number. Choose a high number if osteoarthritis of the knee or hip affected your activities a great deal.

Consider only how much osteoarthritis of the knee or hip affected your ability to do your regular daily activities, other than work at a job.

Osteoarthritis of the knee or hip had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Osteoarthritis of the knee or hip completely prevented me from doing my daily activities

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18.5. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

18.6. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf