Clinical Study Protocol

Protocol Title:

A 4-Week, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee

Date of Protocol:

31-Oct-2016

NCT Number:

NCT03277066

16.1.1 Protocol and Protocol Amendments

Final Amendment #2.0, dated 12-Jan-2018

Final Amendment #1.0, dated 22-May-2017

Final Protocol, Version 1.0, dated 31-Oct-2016

PROTOCOL

PRODUCT NAME/NUMBER:	HP-5000 Topical Patch
PROTOCOL NUMBER:	HP-5000-US-05
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee
PROTOCOL DATE:	Original Protocol: 31 October 2016 Final Amendment #1: 22 May 2017 Final Amendment #2: 12 January 2018
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-05

VERSION: Amendment #2

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) 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] Date

[redacted] Date

[redacted]

2. SYNOPSIS

PRODUCT NAME/NUMBER	HP-5000 Topical Patch
PROTOCOL NUMBER	HP-5000-US-05
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A 4-week, randomized, double-blind, multicenter, placebo-controlled phase 2 study to evaluate the efficacy and safety of HP-5000 in subjects with osteoarthritis (OA) of the knee.
INDICATION	Osteoarthritis pain of the knee
OBJECTIVES	**Primary:** • To evaluate the efficacy of HP-5000 in subjects with osteoarthritis of the knee compared to placebo. **Secondary:** • To evaluate the skin irritation, discomfort, adhesion, and adhesive residue following administration of HP-5000. • To evaluate the safety and tolerability of HP-5000. • To determine the plasma concentrations of diclofenac following administration of HP-5000.
STUDY DESIGN	This is a multicenter, randomized, double-blind, and placebo-controlled phase 2 study evaluating 2 active formulations of HP-5000 in subjects with OA of the knee. 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 4-week Double-blind Treatment Phase, and a 1-week safety Follow-up Period. Subjects will be seen in the clinic at the Screening Visit, Baseline Visit (Day 0), Day 7, Day 14, Day 28 (end of study), and Day 35 (safety Follow-up Visit). A ± 2 days window will be allowed for all clinic visits during the Double-blind Treatment Phase and safety Follow-up visit. Site personnel will also contact the subjects by phone after the Screening Visit in order to instruct subjects on when to begin the Washout Period. **Screening Phase/Washout Period:** Subjects will be seen in the clinic, and the study will be described to them. Subjects will be asked to sign the informed consent form. 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. Subjects whose **preliminary** entry criteria have been met will be contacted by the site via telephone starting from Day -25 and 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, rescue medication (acetaminophen [APAP]) will be permitted (a maximum of 2 g/day) except within 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited for 2 days until clinic visit on Day 0). During the Washout Period, subjects will complete daily electronic diaries (eDiaries) to record pain severity of their target knee and rescue medication usage from the day of Screening Visit to the day of the Baseline Visit. **Double-blind Treatment Phase:** Following completion of the Screening/Washout Period, subjects will return to the clinic for their Baseline Visit (Day 0 or V2). Eligible subjects will be randomized to either HP-5000[redacted], HP-5000[redacted], or placebo in a 1:1:2 ratio. Subjects will apply a single patch to the target knee once [redacted] starting from Day 1 of the Double-blind Treatment Phase [redacted]. The patch will be removed [redacted] after application, and a

	new patch will be applied to a different site on the target knee. Subjects will be instructed to rotate the patch application [redacted] to alternate sides of the target knee (between inner and outer). During the Double-blind Treatment Phase, subjects will also complete daily eDiaries to record patch application and removal times, adhesion and pain assessments; and amount of rescue medication (acetaminophen) taken daily, if applicable. A maximum of 2 g/day of acetaminophen, also known as APAP, will be allowed as rescue medication for the treatment of both target knee and non-target knee pain except within the 1 calendar day prior to each clinic visit (e.g., rescue medication is prohibited from Day 6 until clinic visit on Day 7 if subject will visit the study site on Day 7). **NOTE:** Subjects are **NOT** allowed to apply HP-5000 on the non-target knee at any time during the study treatment period. Blood samples will be collected on Day 14 and 28 (or at the Early Termination Visit [EOT]) where plasma will be analyzed for diclofenac concentrations. Actual blood sampling times will be recorded. **Follow-up Period:** Subjects will have a safety visit approximately 7 days after the End-of-Treatment Visit (Week 4). 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 Safety Visit.
PLANNED NUMBER OF SUBJECTS	The total number of subjects randomized in the study and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY ENTRY CRITERIA	The following inclusion and exclusion criteria must be met by subjects to participate in this study: **Inclusion criteria**: 1. Provide 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. Knee 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 prescribed. 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 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. 4. Has mild to moderate pain in the designated/target study knee: [redacted] 5. Has a Western Ontario and McMaster Universities Osteoarthritis Index

(WOMAC) pain score of [redacted] at the Baseline Visit (V2).

6. If female:
   a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the Screening Visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile).
   b. Subject could not become pregnant because she is surgically sterile (hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months), or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the Screening Visit.
7. Able to swallow and tolerate rescue medication, APAP (moderately sized tablets).
8. Be reliable, willing, and able to cooperate with all study procedures including 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 symptoms (including treatment-emergent signs and symptoms).
   d. Use the patch as required by protocol.

Exclusion criteria:

1. Body mass index (BMI) > 40.
2. The non-target knee pain severity score is [redacted] at Screening and Baseline (Day 0).
3. Any subject who disobeyed the restriction of prohibited therapies (i.e., use rescue medication) during Screening prior to the start of the Washout Period and 2 days prior to the Baseline Visit (V2).
4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma).
5. Clinically significant elevation of serum creatinine (176.8 µmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN]) at the Screening Visit.
6. Known allergy or hypersensitivity to the use of diclofenac, [redacted], [redacted], ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID.
7. Severe uncontrolled cardiac, renal, hepatic or other systemic disease.
8. A documented gastroduodenal ulcer (upper GI series or endoscopy) or any GI bleeding (except hemorrhoidal) within 6 months prior to Screening Visit.
9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
11. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
12. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment.
13. 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 (see **Section 9.10.2**).
14. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
15. Any subject who had used opioids 7 days prior to the Screening Visit.
16. Any subject who had previous exposure to HP-5000.
17. Any subject whose participation would conflict with contraindications, warnings

	or precautions as stated in the prescribing information for oral or topical diclofenac (e.g., any subject taking ACE inhibitors, cyclosporine, diuretics, lithium, or methotrexate – refer Section 3.1.5 of the Investigator Brochure (IB) for prescribing information). 18. Use of another investigational drug within 30 days prior to study entry. 19. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause. 20. Any subject with fibromyalgia. 21. Any other painful or disabling conditions affecting the knee or leg. 22. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo. 23. Any subject expecting to have knee replacement surgery within 6 months. 24. Any subject with a psychiatric condition in the investigator's opinion may interfere with subject's participation in the study. 25. 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.
INVESTIGATIONAL PRODUCTS	HP-5000 [redacted] topical patch HP-5000 [redacted] topical patch Each formulation contains [redacted] diclofenac sodium.
REFERENCE PRODUCT	Placebo [redacted]: Patches identical in appearance to both HP-5000 [redacted] patch and HP-5000 [redacted] patch but without the active ingredient diclofenac sodium.
TREATMENT REGIMENS	The following are the different treatment arms: **Treatment Arm** — [redacted] **Treatment** HP-5000 [redacted] — One patch applied [redacted] to alternate side of the target knee (inner or outer). HP-5000 [redacted] — One patch applied [redacted] to alternate side of the target knee (inner or outer). Placebo — One patch applied [redacted] to alternate side of the target knee (inner or outer).
PLANNED STUDY SITES	Approximately [redacted] study sites in the United States.
CRITERIA FOR EVALUATION OF STUDY OBJECTIVES	**Primary efficacy endpoint**: The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score between Baseline and Week 4. **Secondary efficacy endpoints**: • WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1, and Week 2 • WOMAC LK3.1 OA Index (stiffness) between Baseline and Week 1, Week 2, and Week 4 • WOMAC LK3.1 OA Index (physical function) between Baseline and Week 1, Week 2, and Week 4 • WOMAC LK3.1 OA Index (composite score) between Baseline and Week 1, Week 2, and Week 4 • Patient Global Assessment between Baseline and Week 4 • Patient Global Impression of Change between Week 1 and Week 4 • Pain intensity assessed on an 11-point NRS between Baseline and Week 1, Week 2, and Week 4 • Use of rescue medication between Baseline and Week 1, Week 2, and Week 4

	Safety endpoints: • Adverse events, AEs leading to discontinuation from the study drug, SAEs, and deaths. • Change from Baseline in clinical laboratory results (including fasting glucose and total lipids [8 to 10 hours of fasting is required for these laboratory testing]), ECG results, body weight, and vital signs. • Dermal safety: adhesion, irritation, discomfort, and adhesive residue. **Pharmacokinetic endpoint:** • Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] on Day 14 and 28 (or at the Early Termination Visit).
STATISTICAL METHODS	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. 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 statistics 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. **Analysis Populations** • Intent-to-Treat (ITT): Will include all 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. • Full Analysis Set (FAS): Will include all randomized subjects who have had at least 1 patch of Double-blind study drug applied and who have a Baseline WOMAC pain score and at least 1 post-baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment. • Safety Analysis Set (SAF): Will include all subjects who have had at least 1 patch of double-blind study medication 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 both the analysis of dermal evaluations and safety endpoints. • Pharmacokinetic Analysis Set (PAS): Will include all subjects who have received at least 1 dose of study drug during the Double-blind Treatment Phase and have at least 1 blood sample for pharmacokinetic (PK) assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the

	study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion. **Primary Efficacy Analysis**: The primary efficacy endpoint of this study is the change from Baseline to Week 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are: • HP-5000 [redacted] versus placebo • HP-5000 [redacted] versus placebo The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-5000 dose group *vs*. placebo) in the change from Baseline to Week 4 in WOMAC pain score in all subjects as randomized, under the assumption that all randomized subjects remain on their randomized treatment throughout the study. WOMAC scores obtained more than 24 hours after discontinuation of double-blind study drug will be excluded as a-priori defined outliers. The primary efficacy variable, the change from Baseline to Week 4 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 [redacted], HP-5000 [redacted], and placebo), 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. The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed. Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. These analyses may include multiple imputation and pattern-mixture models for handling of missing data. Details will be provided in the SAP. The analyses will be performed according to the National Academy of Sciences (2010) guidelines. **Analysis of Secondary Efficacy Endpoints**: Other secondary efficacy endpoints will be analyzed using the change in mean as appropriate. • WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1, and Week 2. • WOMAC LK3.1 OA Index (stiffness) between Baseline and Week 1, Week 2 and Week 4. • WOMAC LK3.1 OA Index (physical function) between Baseline and Week 1, Week 2 and Week 4. • WOMAC LK3.1 OA Index (composite score) between Baseline and Week 1, Week 2 and Week 4. • Patient Global Assessment between Baseline and Week 4. • Patient Global Impression of Change between Week 1 and Week 4. • Pain intensity assessed on an 11-point NRS between Baseline, Week 1, Week 2, and Week 4. • Use of rescue medication between Baseline and Week 1, Week 2 and Week 4.

	Additional categorical response analyses may be performed; additional details will be provided in the SAP. Additional categorical response analyses may be performed; additional details will be provided in the SAP. **Analysis of Safety and Dermal Assessments:** All safety summaries will be descriptive; statistical significance tests may be performed on safety data that will be described in the SAP. Safety variables include AEs, clinical laboratory values, vital signs, ECG readings, physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted. **Analysis of PK:** Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] will be evaluated and summarized as descriptive statistics by treatment.
SAMPLE SIZE DETERMINATION	Assuming an effect size of [redacted] on the change in WOMAC pain score from Baseline to Week 4 between active HP-5000[redacted] and HP-5000[redacted] treatments *vs*. placebo, the probability for detecting the clinically meaningful effect size [redacted] or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the study and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY TREATMENT DURATION	The maximum treatment duration for each subject is 4 weeks. The total duration of study participation for each subject is approximately 9 weeks.

3. TABLE OF CONTENTS

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APAP	acetaminophen
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	institutional review board
ITT	intent-to-treat
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	over the counter
PK	Pharmacokinetics
PAS	pharmacokinetic analysis set
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
TDDS	transdermal drug delivery system
ULN	upper limit of normal
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 doctor-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 doctor-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 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 their opioid pain reliever, thereby introducing additional health problems into the equation. There is an unmet need for a safe, reliable, and effective pain medication without the risk and lack of efficacy associated with those currently available.

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

Noven Pharmaceuticals, Inc. has started the development of a formulation of diclofenac sodium for topical administration via a transdermal patch system, the HP-5000 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:

- Transfer of drug into the treatment target area resulting in lower systemic and GI exposure when compared to 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 PK and tolerability in [redacted] healthy volunteers. The lead formulations for this program, HP 5000 [redacted] and HP 5000 [redacted], both of which contain [redacted] diclofenac sodium [redacted] with a patch size of [redacted], were selected based on the diclofenac pharmacokinetic profile and patch performance characteristics, such as irritation and adhesion on the mobile knee joint application site.

It should be noted that the HP 5000 [redacted] formulation is also being developed [redacted] by Noven's parent company, [redacted] for different [redacted] indications (i.e., [redacted] and [redacted] and is referred to as the [redacted] (also known as [redacted]. Study [redacted] has been included in the development program to provide additional safety data. [redacted]

[redacted]

[redacted]

[redacted]

Further details about HP-5000 are found in the Investigator's Brochure.

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with OA (1) may experience a reduction in pain and inflammation as a result of treatment with the HP-5000 patch and (2) will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for subjects with OA.

The potential risks of study participation include those associated with exposure to the HP-5000 patch and the risks of medical evaluation, including venipuncture.

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

6. OBJECTIVES

6.1. Primary Objectives

- To evaluate the efficacy of HP-5000 in subjects with osteoarthritis of the knee compared to placebo.

6.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the skin irritation, discomfort, adhesion, and adhesive residue following administration of HP-5000.
- To evaluate the safety and tolerability of HP-5000.
- To determine the plasma concentrations of diclofenac following administration of HP-5000.

7. STUDY DESIGN

7.1. Overall Study Design and Plan - Description

This is a 4-week, randomized, double-blind, multicenter, placebo-controlled phase 2 study to evaluate the efficacy, safety and tolerability of HP-5000 compared with that of placebo in the treatment of OA. The study will run for approximately 9 weeks comprised of up to a maximum of 28-day Screening Phase that will include a Washout Period of up to a maximum of 14 days, a 4-week Double-blind Treatment Phase, and a 1-week Follow-up Safety Period. Subjects will be randomly assigned to receive [redacted] one of the following 3 treatments in a 1:1:2 ratio: HP-5000 [redacted], HP-5000 [redacted] or placebo patch, respectively. The placebo patch will be identical in appearance to the 2 HP-5000 active patches. The total number of subjects randomized in the study and included in the primary analysis will be approximately 300.

The duration of double-blind treatment is expected to be 4 weeks and the total duration of the study for each individual subject will be approximately 9 weeks.

- **Screening/Washout Period**: Visit 1 (up to 28 Days): This is the period between Screening Visit (V1) and Baseline Visit (V2): After signing the informed consent, the Screening Phase will begin. Subjects whose **preliminary** entry criteria have been met on Visit 1 will be contacted by the site via telephone starting from Day -25 and will be instructed to begin the Washout Period for 7 to a maximum of 14 days (or at least 5 half-lives, whichever is longer) prior to start the Baseline Visit (V2).

  During Visit 1, subjects will receive instruction on how to use the patient eDiary. The first pain score will be performed at the site at the Screening Visit (V1). If eligible, subjects will have to record pain severity of their target knee score on the patient eDiary every day at home before the start of the Washout and during the Washout Period using the 11-point NRS Scale. Subjects may start rescue medication usage as needed from the start of the Washout Period (i.e., Day -25). Subjects will record rescue medication usage in their eDiary starting from the Washout Period. [redacted] If determined to be eligible, the subject will continue to record his/her pain score daily of the target knee during the Washout Period. The mean pain score, using the 11-point NRS scale, **of at least the last 2 consecutive days immediately prior to the Baseline Visit**

(Day 0) will be calculated for subjects to be considered eligible for study participation and be randomized for study treatment (See **Section 8.2.1**). During the Washout Period, rescue medication (acetaminophen [APAP]) will be permitted (a maximum of 2 g/day) except within 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited from Day-2 until clinic visit on Day 0).

- **Baseline Visit:** Visit 2 (Day 0): Subjects will be re-evaluated according to the inclusion and exclusion criteria and the mean patient eDiary pain score will be calculated. Subjects who continue to meet all of the inclusion criteria, none of the exclusion criteria, who have completed the patient eDiary for **at least 2 daily NRS scores of the last 3 consecutive days immediately prior to the Baseline Visit,** and whose mean pain score is at least 5 at Baseline (V2) for those subjects who had a mean pain score of 2 to < 3 at the start of the Washout Period or has increased by at least 2 worsening scores for those who had a mean pain score of 3 to 6 at the start of the Washout Period and, will be randomized to receive one of 2 active formulations of HP-5000 or placebo (see **Section 8.2.1**).

- **Double-blind Treatment Phase**: On Day 1 of the Double-blind Treatment Phase, subjects will start applying their assigned patch for 4 consecutive weeks (from approximately Week 5 through 8): Subjects will be randomized to receive either HP-5000[redacted] HP-5000[redacted] or placebo patch. Dose modifications will **NOT** be permitted. Subjects who cannot tolerate their designated study drug dose will be withdrawn from the study.

- **Follow-up Period:** Visit 6 (Week 9): After the 4-week of the Double-blind Treatment Phase, the study center will conduct a follow-up phone call for safety monitoring or based on the investigator's judgment, a subject may return to the study center for the safety Follow-up Visit.

Note: All subjects will be contacted by phone between clinical visits to assess AEs, general well-being, provide visit reminders, and reinforce eDiary record and treatment compliance. Dose modifications will **NOT** be permitted and study procedures will be reinforced.

At each clinical study visit, subjects will undergo efficacy and safety evaluations including dermal safety assessments. Efficacy evaluations will include the change from Baseline values in the Western Ontario and McMaster Universities (WOMAC) LK3.1 OA index for pain, stiffness, physical function, and composite score, the Patient Global Assessment (PGA), the Patient Global

Impression of Change (PGIC), and pain intensity assessed on an 11-point NRS and the subjects' use of rescue medication.

Note: NRS will be performed at home. WOMAC, PGA, and PGIC will be performed at the site during each clinic visit.

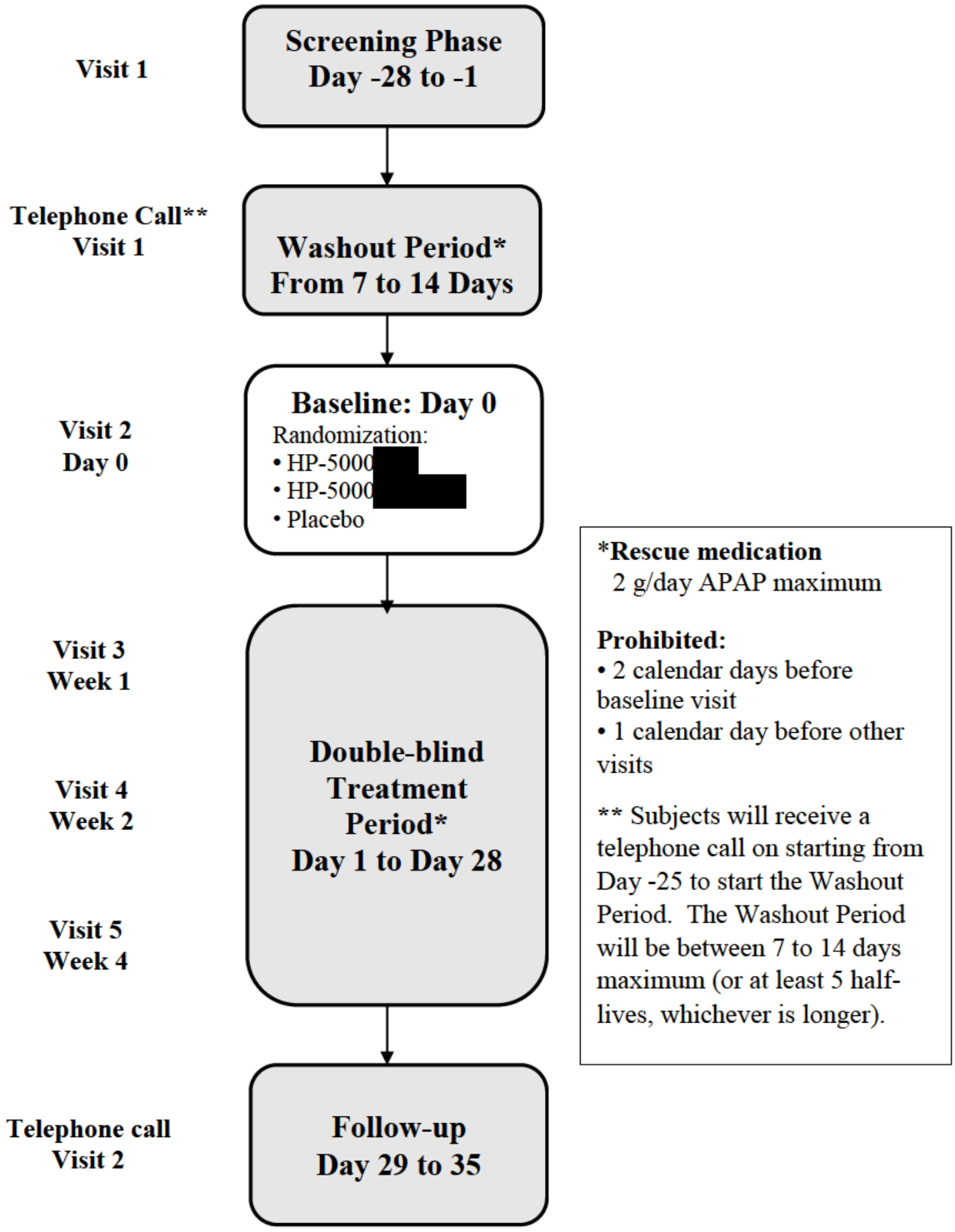
Safety evaluation will include collection of AEs, physical examination findings, vital sign measurements, electrocardiogram (ECGs), clinical laboratory test results, body weight, and dermal safety assessments. All AEs observed by the study personnel or reported by the subject during the study (from the time of study drug administration through the post treatment visit) will be documented.

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, and 5-point numerical scale of Adhesive Residue.[4] In addition, subjects will record at home the [redacted] patch application and removal times in eDiaries along with any incidence of patch detachment and any dermal safety experience.

Plasma pharmacokinetic sampling will be performed as scheduled. Plasma concentrations of diclofenac will be assessed by venous blood sampling on Day 14 and 28 (or at the Early Termination Visit). Study center personnel will also assess study drug and eDiary compliance.

Figure 1 presents a schematic view of the study design.

Figure 1 Study Design



7.2. Discussion of Study Design

The double-blind, placebo-controlled study uses 3 patches [redacted] HP-5000 and placebo) of identical appearance to ensure blinding. The total duration of study drug exposure will be 4 weeks. The follow-up safety evaluation will be performed one week after the last study dose.

The use of rescue medication is prohibited within 2 calendar days prior to the Baseline Visit (Day 0) and within 1 calendar day prior to each clinic visit during the Double-blind Treatment Phase, thus ensuring the integrity of the assessments.

7.3. Study Sites

The study will take place at approximately [redacted] sites in the US. Each site is anticipated to screen a sufficient number of subjects to be able to randomize an aggregate number of approximately 300 subjects.

8. SUBJECT POPULATION

8.1. Selection of Study Population

The study will enroll up to 300 subjects in a 1:1:2 ratio (HP-5000 HP-5000 Placebo) with osteoarthritis pain of the knee. The pain should have been stable over the previous six months prior to Screening (Visit 1).

A screening log of potential study candidates and/or an enrollment log of enrolled subjects must be maintained at each study site.

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. Provide 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. Knee 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 prescribed.
   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 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.
4. Has mild to moderate pain in the designated/target study knee:

[redacted]

5. Has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline Visit (V2).
6. If female:
   a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the Screening Visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile).
   b. Subject could not become pregnant because she is surgically sterile (hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months), or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the Screening Visit.
7. Able to swallow and tolerate rescue medication, APAP (moderately sized tablets).
8. Be reliable, willing, and able to cooperate with all study procedures including 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 symptoms (including treatment-emergent signs and symptoms).
   d. Use the patch as required by 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.
2. The non-target knee pain severity score is [redacted] at Screening and Baseline (Day 0).
3. Any subject who disobeyed the restriction of prohibited therapies (i.e., use rescue medication) during Screening prior to the start of the Washout Period and 2 days prior to the Baseline Visit (V2).
4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma).

5. Clinically significant elevation of serum creatinine (176.8 µmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN]) at the Screening Visit.
6. Known allergy or hypersensitivity to the use of diclofenac, [redacted] ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID. .
7. Severe uncontrolled cardiac, renal, hepatic or other systemic disease.
8. A documented gastroduodenal ulcer (upper GI series or endoscopy) or any GI bleeding (except hemorrhoidal) within 6 months prior to Screening Visit.
9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
11. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
12. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) within 1 year before study enrollment.
13. 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 (see **Section 9.10.2**).
14. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
15. Any subject who had used opioids 7 days prior to the Screening Visit.
16. Any subject who had previous exposure to HP-5000.
17. Any subject whose participation would conflict with contraindications, warnings or precautions as stated in the prescribing information for oral or topical diclofenac (e.g., any subject taking ACE inhibitors, cyclosporine, diuretics, lithium, or methotrexate – refer **Section 3.1.5** of the Investigator Brochure (IB) for prescribing information).
18. Use of another investigational drug within 30 days prior to study entry.
19. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause.
20. Any subject with fibromyalgia.
21. Any other painful or disabling conditions affecting the knee or leg.
22. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut

or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo.

23. Any subject expecting to have knee replacement surgery within 6 months.
24. Any subject with a psychiatric condition in the investigator's opinion may interfere with subject's participation in the study.
25. 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.

8.2.3 Premature Subject Withdrawal

In accordance with the Declaration of Helsinki (48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996), subjects have the right to withdraw participation from the study at any time for any reason. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must make at least 3 attempts to contact subjects who fail to attend scheduled visits by telephone or any other means.

The investigator also has the right to remove subjects from the study for the following reasons:

- Adverse events: If the reason for removal of a subject from the study is an AE, the principal specific event and any related test results will be recorded on the electronic case report form (eCRF). If a subject withdraws because of an AE plus another reason, 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 request of the subject, his/her representative, investigator or sponsor, whether for administrative or other reasons.
- Noncompliance with study drug or non-compliance with subject eDiary completion, protocol violation, or unreliable behavior.
- Pregnancy. If the subject becomes pregnant during the clinical study, the study drug should be stopped immediately and the subject will be withdrawn from the study and followed until delivery.

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

- The date of the last dose of study drug and all observations collected up to the time of termination will be recorded on the Early Withdrawal eCRF page along with the reason for termination. All Early Withdrawal procedures should be completed and recorded on the Early Withdrawal 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.

- In order to enable the most complete recording of any subject who withdraws early from the study, it is important to evaluate these subjects at the study center as soon as possible. Subjects who are withdrawing early should undergo an Early Withdrawal/Termination Visit and a Follow-up Safety Visit must be scheduled.

Subjects may be withdrawn if continuing in the study is not in the subject's best interest; their condition worsens during the study, or for safety reasons, as determined by the investigator. Subjects may also be withdrawn due to lack of compliance with the protocol or if the subject is unwilling to continue participation in the study.

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

One patch [redacted] will be applied [redacted] to alternate sides of the target knee (inner and outer knee). Detailed application instructions for subjects will be provided in a separate manual.

HP-5000 will be supplied as [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):

- Blinded packaged lot number
- Protocol number
- Subject number (record at the time of dispensing)
- Directions for use
- 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 [redacted] HP-5000 [redacted] 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 a maximum of 28 ± 2 days.

The treatment arms for this study are the following:

Treatment Arm	[redacted] **Treatment**
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
Placebo	One patch applied [redacted] to alternate side of the target knee (inner or outer).

Patch Application

A separate guidance for patch application will be provided to subjects for applying, securing, and removing the patch.

9.3. Dispensing and Storage

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

The investigator must confirm the receipt of study drug with his/her signature. A copy of this receipt must be kept by the investigator, and another copy will be stored at Noven Pharmaceuticals, Inc. (hereafter referred to as "Noven"), and/or [redacted] Until study drug is dispensed to the subjects, it must be stored at 25°C 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 1:1:2 ratios to receive HP-5000[redacted] HP-5000[redacted] or placebo patches, respectively. The randomization numbers will be assigned sequentially through a

central interactive voice response system (IVRS) 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 designated visits, subjects will be given a kit containing sufficient study drug to last until the next scheduled study visit.

The randomization schedule will be prepared by [redacted] before the start of the study. No one involved in the clinical conduct will have access to the randomization schedule before 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[redacted] and HP-5000-[redacted] patches.

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to study drug treatment assignment with the exception of a prespecified unblinded statistician/programmer from [redacted] 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, then 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 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. 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 whenever possible.

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.

The investigator or designee must record the date and reason for unblinding or study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

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 dose of diclofenac [redacted] in a patch size of [redacted] applied [redacted] and rotated between [redacted] on the knee (inner and outer knee) is based on the following considerations:

- [redacted]
- 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.
- The data from previous studies investigating irritation and PK support the proposed dose of [redacted] and a patch size of [redacted] applied [redacted] and rotated between [redacted] on the knee for the lead formulations (HP-5000[redacted] and HP-5000[redacted].

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 [and initials]) who received study drug and any reasons for departure from the

protocol-dispensing regimen. Receipt of study drug must also be confirmed within IVRS. The drug accountability records, along with used and unused packaging must be available for monitoring, auditing, or inspection. Each site must keep accurate records of drug received at site, dispensed to the subjects.

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 to 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 study drugs is not dispensed, 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 (used and unused) must 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 counts 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 3 through 5 or any Early Termination Visit, the study drug (patches) from the previous Double-blind Treatment Phase will be returned to the investigator. The study drug will be inventoried and noncompliance defined assuming less than 80% or more than 120% of study drug during any evaluation period (visit to visit). If the subject is noncompliant, the Medical Advisor should be contacted to discuss the subject's eligibility to continue in the study.

The subject must be counseled if compliance is not satisfactory (used 6 or less patches per week). If a subject has been noncompliant on two consecutive visits, the subject may be withdrawn early from the study for non-compliance.

For each 28-day study drug administration period, 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. These eDiaries will be reviewed by study personnel at each study visit and will be collected as source documents. Information from that subject eDiary will be transcribed on the appropriate eCRF pages for documentation of subject compliance with study drug. Compliance will include the following:

1. **Telephone Follow-up:** A telephone follow-up call will be performed between Screening (Visit 1) and Baseline (Visit 2), before the start of the Washout Period and another one during the Follow-up Period.

2. **Patient Education:** At all clinical study visits, the investigator will explain the importance of the following:

    a. applying study medication [redacted] to the target knee after showering/bathing;
    b. recording patient eDiary information every day;
    c. accurately reporting pain;
    d. accurately reporting rescue medication use;
    e. understanding when to return for next visit and the importance of returning on schedule; and
    f. adhering to the overall research plan.

During Screening (Visit 1), the investigator will provide the subject with an introduction to the various questionnaires including the [redacted] that will be used during the entire study and the patient eDiary.

3. **Patient eDiary :** The subject eDiary will be used by the subject to record required assessments including the time of patch application/removal, the NRS scores, the use of rescue medication, and questionnaires about adhesion, skin irritation, discomfort and adhesive residue.

4. **Rescue Medication:** If needed, subjects will be allowed to take up to a maximum of 2 grams (4 tablets) of oral acetaminophen per day as rescue medication for pain of the target and/or the non-target knee except within 2 calendar days prior to Baseline Visit (V2) and within 1 calendar day for all subsequent visits (V3, V4 and V5). Information

regarding the use of rescue medication, such as the number of tablets, will be recorded on the appropriate concomitant medication eCRF.

9.10. Permitted and Prohibited Therapies

Prior to the Double-blind Treatment Phase, subjects will discontinue all prescription and OTC analgesic medications for 7 days to 14 days (or at least 5 half-lives, whichever is longer); however, rescue medication (acetaminophen [APAP]) is permitted during the Washout Period, if required. A maximum of 2 g/day of APAP will be allowed as a rescue treatment of both target and non-target knee pain except within the 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited from Day -2 until clinic visit on Day 0) and within the 1 calendar day prior to each clinic visit (e.g., rescue medication is prohibited from Day 6 until clinic visit on Day 7 if the subject will visit the study site on Day 7). APAP will be provided by the Sponsor. 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.

All concomitant medications used prior or during treatment (including OTC medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF page.

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. 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

Any NSAIDs (selective or nonselective), any opioids, APAP (>2 g/day), ASA (>81 mg/day), corticosteroids (a stable dose by inhalation for seasonal allergies and/or topical use for dermatologic allergies are allowed), anticonvulsants (i.e., pregabalin and gabapentin etc...), muscle relaxants, other oral analgesics (prescription and/or 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] or capsaicin, any intra-articular treatments for the knee, any nonpharmaceutical therapy or device to relieve knee pain (including physiotherapy, massage therapy, hot wax therapy etc.) are not allowed to be taken during the study.

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

9.11. Treatment after End of Study

After completing the study, each subject will be referred to their primary care physician and treated 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 concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (see **Section 17.1**). 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/Washout Period

10.1.1.1 Screening Period (Visit 1)

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

1. Obtain written informed consent and assign a screening number.
2. Assess inclusion/exclusion criteria.
3. Collect demographic information and record medical history, including prior and current therapies (e.g., prescription and nonprescription medications).
4. 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. Weight (kg), height (cm), and vital signs will be measured.
5. Perform urine drug, alcohol and pregnancy tests.
6. Identify the target knee. The subject will be instructed to refer to this specific (target) knee throughout his/her participation in the study when responding to study efficacy assessment.
7. Instruct the subject on how to use NRS and WOMAC before performing first assessments.
8. Administer the WOMAC questionnaire.
9. Perform NRS evaluation for the target knee and the non-target knee pain.
10. Review of X-ray of the target knee and perform 12-lead ECG and laboratory tests to determine subject's eligibility. If subject does NOT have any 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.

11. Instruct the subject on how to use of an eDiary.
12. Dispense rescue medication.
13. Dispense an eDiary.

10.1.1.2 Washout Period

Subjects whose eligibility has been preliminarily confirmed at Screening will be asked to washout of current medications for at least 7 days to a maximum of 14 days (or at least 5 half-lives, whichever is longer). During this period, the following will take place:

Before the start of the Washout Period (i.e., 3 days after Visit 1), the following will take place:

1. Before the start of the Washout Period, eDiary NRS 11-point pain scores will be reviewed by the investigator or the study coordinator via telephone. A record of this review will be recorded in the source documents and eCRF pages.
2. An NRS assessment for the target knee pain will be performed. [redacted]

During the Washout Period, the following will take place:

1. 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., acetaminophen) may be used (a maximum of 2 g/day) as needed except within 2 calendar days prior to the Baseline Visit (V2).
2. Review subject's use of rescue medication.
3. Review subject's use of prior/concomitant medications.
4. Subject will be instructed to continue assessing and recording in the eDiary his/her pain of the target knee daily at home using the NRS 11-point pain scale during the Washout Period.

10.1.2 Baseline Visit (Visit 2, Day 0)

The following will take place during the Baseline Visit (Visit 2, Day 0):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Assign a subject ID number and randomly assign the subject to a treatment group using IVRS.

3. Obtain vital sign measurements, including weight.
4. Administer the WOMAC questionnaire.
5. Perform Patient's Global Assessment (PGA).
6. Perform an NRS 11-point pain assessment for the target knee and non-target knee pain.
7. Review subject's use of rescue medication.
8. Perform a 12-lead ECG.
9. Obtain blood and urine samples for laboratory testing.
10. Perform a urine drug, alcohol and pregnancy tests.
11. Review the subject's eDiary.
12. Perform Baseline dermal safety assessment (irritation only).
13. Review subject's use of prior/concomitant medications.
14. Dispense rescue medication and perform rescue medication accountability/reconciliation.
15. Dispense the Double-blind study drug and instruct subjects on proper patch application. Subjects should apply the patch at home the next day after showering/bathing.
16. Subjects will be instructed not to bathe or shower while wearing the study drug; a bath or a shower may be taken in the morning or in the evening before any patch is applied [redacted].
17. Subject will be instructed to report to the site and record on the eDiary patch detachment and incidences of irritation, discomfort, and adhesive residue and not to participate in strenuous activities or other activities that cause heavy perspiration during the double-blind treatment phase.

10.1.3 Double-blind Treatment Phase

During the 4-week Double-blind Treatment Phase, the following will take place:

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

1. Apply study medication on the target knee (inner or outer by [redacted] rotation) after showering/bathing.
2. Perform and complete the following assessments in an eDiary daily:
    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 application and removal.
    c. Record the time of complete patch detachment (if applicable).
    d. Record the number of tablets of rescue medication used.
    e. Record any issues with adhesion, skin irritation, discomfort and adhesive residue.

Note: Do **<u>NOT</u>** apply study medication on non-target knee at all times.

In clinic visits, investigators (or site personnel as appropriate) conduct the following:

Visit 3:

1. Obtain vital sign measurements.
2. Administer the WOMAC questionnaire.
3. Perform Patient Global Assessment.
4. Perform Patient Global Impression of Change (PGIC).
5. Perform daily NRS 11-point pain assessments for the target knee pain only.
6. Review subject's use of rescue medication/concomitant medication.
7. Perform a urine pregnancy test.
8. Re-instruct the subject concerning the patch application and removal method if the subject has a problem with patch application and/or patch adhesion.
9. Dispense study medication and rescue medication and perform drug accountability/ reconciliation of both.
10. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
11. Review AEs.
12. Review the subjects' eDiary entries.

Visit 4:

1. Obtain vital sign measurements.
2. Review the subjects' eDiary entries.
3. Administer the WOMAC questionnaire.
4. Perform Patient Global Assessment.
5. Perform Patient Global Impression of Change.
6. Perform daily NRS 11-point pain assessments for the target knee pain only.
7. Review subject's use of rescue medication/concomitant medication.
8. Perform a urine pregnancy test.
9. Re-instruct the subject concerning the patch application method if the subject has a problem with patch application and/or patch adhesion.
10. Dispense study medication and rescue medication and perform drug accountability/ reconciliation.
11. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
12. Review AEs.
13. Review the subjects' eDiary entries.
14. Obtain pharmacokinetic blood sample.

Visit 5

1. Obtain vital sign measurements.
2. Collect and review the subjects' eDiary entries.
3. Administer the WOMAC questionnaire.
4. Perform Patient Global Assessment.
5. Perform Patient Global Impression of Change.
6. Perform daily NRS 11-point pain assessments for the target knee pain only.
7. Review subject's use of rescue medication/concomitant medication.
8. Perform a urine pregnancy test.
9. Perform drug accountability/reconciliation.
10. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
11. Review AEs.
12. Obtain blood and urine samples for laboratory testing.
13. Obtain subject's weight.
14. Obtain pharmacokinetic blood sample.
15. Perform a 12-lead ECG.
16. Perform physical examination.

During the time interval between visits, the site coordinator may regularly contact (via telephone) the subjects to ensure that the subject's scheduled dose is administered and daily NRS pain scores are recorded correctly. The subjects will be informed by the site personnel that they may contact the site if problems/questions arise.

Note: After Visit 5, subjects may resume their standard of care treatment.

10.1.4 Follow-up Visit

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

1. Review subject's use of concomitant medications.
2. Review AEs.

10.1.5 Early Termination Visit (if applicable)

Subjects who are discontinued for any reason after Baseline (Visit 2) must complete the Early Withdrawal Visit. If the subject comes for an Unscheduled Visit and a decision to withdraw the subject is made, then the Early Withdrawal Visit procedures will be performed and the Early Withdrawal Visit eCRF will be completed (and not the Unscheduled Visit eCRF). During this visit the following assessments and procedures will be performed:

1. Collect and review the subject's eDiary entries.
2. Perform physical examination.
3. Obtain vital sign measurements including weight.
4. Administer the WOMAC questionnaire.
5. Perform Patient's Global Assessment.
6. Perform Patient's Global Impression of Change.
7. Perform a NRS 11-point pain assessment for the target knee pain only.
8. Review subject's use of rescue and concomitant medications.
9. Perform a 12-lead ECG.
10. Obtain blood and urine samples for laboratory testing.
11. Perform a urine pregnancy test.
12. Perform drug accountability/reconciliation.
13. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
14. Review AEs.
15. Obtain pharmacokinetic blood sample.

10.1.6 Overall Study Schedule

The planned sequence and approximate duration of the study periods will be as follows:

1. Screening/Washout Period: Up to 28 days (the Washout Period will occur the last 7 to 14 days of the Screening Phase).
2. Double-blind Treatment Phase: 4 weeks
3. Follow-up Period: 1 week

The maximum treatment duration for each subject is 4 weeks. The study duration for each subject is approximately 9 weeks.

10.2. Assessments

10.2.1 Efficacy

10.2.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

The Western Ontario and McMaster Universities Osteoarthritis Index Likert (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.[5,6,7]

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

1. Walking

2. Stair climbing
3. Noctural
4. Rest
5. Weight bearing

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

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

1. Morning stiffness, and
2. Stiffness occurring later in the day.

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

The **WOMAC Physical Function** assesses the following 17 categories using the 0 to 4 scale described previously:

1. Descending stairs
2. Ascending stairs
3. Rising from sitting
4. Standing
5. Bending to floor
6. Walking on a flat surface
7. Getting in/getting out of car
8. Going shopping
9. Putting on socks
10. Lying in bed
11. Taking off socks
12. Rising from bed
13. Getting in/out of bath
14. Sitting
15. Getting on/off toilet
16. Heavy domestic duties
17. Light domestic duties

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= __%

10.2.1.2 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". 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

10.2.1.3 Patient Global Impression of Change

The Patient Global Impression of Change 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." 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

10.2.1.4 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 two ways. One is the <u>average</u> pain condition over the last 24 hours, and the other is the <u>worst</u> painful condition over the last 24 hours.

The subject will rate his or her target knee pain intensity 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 pain that you have been feeling in your knee over the last 24 hours?"

<u>Note:</u>

1. The NRS pain score for assessment is an average of the NRS pain scores reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit except for Screening and Baseline Visits.
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]
3. The subject will continue assessing and recording the NRS pain score daily at home during the Washout Period. [redacted]

10.2.1.5 Use of Rescue Medication

For the 4-week Double-blind Treatment Phase, subjects will be asked to record their daily intake/use of rescue medication in the eDiary. Rescue medication will be limited as follows: 2 gram/day APAP may be used **Except** and within 1 calendar day prior to other clinic visits.

10.2.2 Safety

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

10.2.2.1 Laboratory Safety Assessments

10.2.2.1.1 Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the timepoints specified in the schedule of events (see **Section 17.1**).

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, 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, urinalysis samples. Urine drug screens and alcohol tests 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.

Note: Female subjects (of childbearing potential) will undergo a urine pregnancy test at Screening (Visit 1) and at every subsequent visit.

10.2.2.1.2 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-05 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.

10.2.2.2 Clinical Examinations

10.2.2.2.1 Vital Signs and Weight

Vital signs, including heart rate, respiratory rate, temperature and supine blood pressure will be measured at designated timepoints. 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 five minutes. Weight (kg) will also be measured.

10.2.2.2.2 Electrocardiogram

The 12-lead ECG will be a complete, standardized recording and will be performed at designated timepoints 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.

10.2.2.2.3 Physical Examination

The following physical examination will be performed at designated timepoints 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

10.2.2.3 Adverse Events

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

10.2.2.4 Evaluations of Patch and Dermal Assessment

Patch Adhesion

Patch adhesion will be assessed in two ways (in-clinic and at-home). At each clinic visit, patch adhesion will be assessed by the investigator or a designee 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 only report on any incidence of patch detachment in the eDiary.

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 (Berger and Bowman 1982) 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

- 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

- 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

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."

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."

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about skin irritation in the eDiary.

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. Any discomfort mentioned should be recorded 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.

Adhesive Residue

At each clinic visit, the amount of adhesive residue remaining at the application site where the previous patch was applied will be examined by the investigator or a designee and scored according to the scale below:

- 0 = None
- 1 = Light
- 2 = Medium
- 3 = Heavy
- 4 = Patch not present

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about adhesive residue in the eDiary.

10.2.3 Pharmacokinetic Assessments

Blood samples for the determination of plasma diclofenac concentrations will be collected at specified visits after the application of the study drug as per the Schedule of Events in **Section 17.1**. A volume of approximately 4 mL of blood will be collected at Visit 4 (Day 14) and Visit 5 (Day 28); or at the Early Termination Visit, if applicable. The LC/MS/MS validation method will be used to analyze the plasma sample to determine the diclofenac concentrations and blood sampling times will be recorded.

The total blood volume collected will be approximately 40 mL (inclusive of pharmacokinetic and clinical safety laboratory collections).

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as 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 quality, of the disease or condition during the Double-blind Treatment Phase (Worsening of a pre-existing condition is considered 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 and not the elevated ALT should be listed as the AE).
- 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 adverse event 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 adverse reaction 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
- 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.
- Is a congenital anomaly.

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 unless it is suspected that study drug interacted with a contraceptive method and led to the pregnancy.

- 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 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 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?"

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

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, if 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 AEs occur in a subject that is not tolerable, 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 medication) 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 [redacted] within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the sponsor by one of the following methods:

All SAEs, irrespective of relationship to study treatment, must be reported as soon as possible but no later than 1 business day by Fax to:

Email: [redacted]

The "Clinical Trial Serious Adverse Event Report Form (SAE form)" must be used for reporting.

It is very important that the SAE report form 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 serious adverse events should be forwarded within one business day 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.

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 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 year of birth
- Subject's gender
- Date of first dose of study drug
- Date of last dose of study drug, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria that were met
- 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? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

The investigator must fax/mail a written SAE Report Form that describes the SAE to the recipients of the initial information, who will forward the information to the sponsor.

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 Report Form, together with the following information (adverse event, date of occurrence, subject ID, 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 guidances) 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

Nonserious AEs will be recorded in the eCRF page and reported by [redacted] to Noven.

11.2.7 Adverse Events of Special Interest

The overall systemic safety profile of diclofenac is well known and established as reflected in the Investigator's Brochure (IB) including Developmental Core Safety Information, which are in part based on the current label of the [redacted] In patients taking [redacted]

The overall safety of HP-5000 patches at doses ranging from [redacted] The HP-5000 patches used in the clinical studies [redacted] Some of the commonly reported AEs across the [redacted] The remaining commonly reported AEs are either known adverse reactions to other commercially available dose forms that contain diclofenac (application site pruritus, back pain, and myalgia with diclofenac containing solutions or patches) or consistent with events of application site skin reactions commonly reported as AEs

with other topical medications that contain diclofenac [redacted]

11.2.8 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 [redacted] Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or 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 an Exposure in Utero form provided by the sponsor or its designee.

Pregnancies must be reported as soon as possible, but no later than 1 business day, by Fax to:

[redacted]

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy.

All Pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than one business day.

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

The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score from Baseline and Week 4.

13.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1, and Week 2
- WOMAC LK3.1 OA Index (stiffness) between Baseline and Week 1, Week 2, and Week 4
- WOMAC LK3.1 OA Index (physical function) between Baseline and Week 1, Week 2, and Week 4
- WOMAC LK3.1 OA Index (composite score) between Baseline and Week 1, Week 2, and Week 4
- Patient Global Assessment between Baseline and Week 4
- Patient Global Impression of Change between Week 1 and Week 4
- Pain intensity assessed on an 11-point NRS between Baseline and Week 1, Week 2, and Week 4
- Use of rescue medication between Baseline and Week 1, Week 2, and Week 4

13.1.3 Safety Endpoints

- Adverse events, AEs leading to discontinuation from the study drug, SAEs, and deaths.
- Change from Baseline in clinical laboratory results (including fasting glucose and total lipids [8 to 10 hours after fasting is required for these laboratory testing]), ECG results, body weight, and vital signs.
- Dermal safety: adhesion, irritation, discomfort, and adhesive residue.

13.1.4 Pharmacokinetics Endpoint

Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] on Day 14 and 28 (or at the Early Termination Visit).

13.2. Sample Size Determination

Assuming an effect size of [redacted] on the change in WOMAC pain score from Baseline to Week 4 between active HP-5000[redacted] and HP-

5000[redacted] treatments and placebo, the probability for detecting the clinically meaningful effect size [redacted] or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the study and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.

13.3. Analysis Populations

The following 4 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.
- Full Analysis Set (FAS): Includes all randomized subjects who have had at least 1 patch of double-blind study drug applied and who have a Baseline WOMAC pain score and at least 1 post-baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.
- 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.
- Pharmacokinetic Analysis Set (PAS): Includes all subjects who have received at least 1 dose of study drug during the Double-blind Treatment Phase and have at least 1 blood sample for PK assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion.

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 Clinical Study Report.

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, and weight. 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 FAS 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 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are:

- HP-5000[redacted] *versus* placebo
- HP-5000[redacted] *versus* placebo

The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-5000 dose group *vs*. placebo) in the change from Baseline to Week 4 in WOMAC pain score in all subjects as randomized, under the assumption that all randomized patients remain on their randomized treatment throughout the study. WOMAC scores obtained more than 24 hours after discontinuation of study drug will be excluded as a-priori defined outliers.

The primary efficacy variable, the change from Baseline to Week 4 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[redacted], HP-5000[redacted] 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.

The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed.

Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. These analyses may include multiple imputation and pattern-mixture models for handling of missing data. Details will be provided in the SAP. The analyses will be performed according to the National Academy of Sciences (2010) guidelines.[8]

13.4.3.2 Analyses for Secondary Endpoint

The secondary endpoints will use the change in mean for analysis (as applicable):

Additional categorical response analyses may be performed; additional details will be provided in the SAP.

13.4.4 Safety and Tolerability 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 safety 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 Medical Dictionary for Regulatory Activities (MedDRA), **Version 19**.

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 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 Anatomic Therapeutic Classification (ATC) codes using the current version (2017) of WHO Drug. Summaries will be prepared using the coded generic term. All prior and concomitant medications recorded in the eCRF will be listed.

13.4.4.3 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.

13.4.4.4 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, body-mass index, 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.

13.4.4.5 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, QTc interval (both correction methods), and HR for each treatment group at each time point.

13.4.4.6 Physical Examination Findings

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

13.4.4.7 Dermal Safety

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

13.4.5 Pharmacokinetic Analyses

Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] will be evaluated and summarized as descriptive statistics by treatment.

13.4.6 Interim Analysis

No interim analyses are planned.

13.5. Database

The final database will be compliant with 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 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 17.2**), 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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. 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 informed consent form (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. In certain cases, and case-by-case basis, a subject may be rescreened once and permitted into the study following consultation with the Sponsor and Medical Monitor who must make an assessment that the subject is eligible to participate in the study.

14.3. Study Documents

All documentation and material provided by Noven or [redacted] 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-05 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 17.2**), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

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.

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. 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. 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. While on site, 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 17.2**), 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.

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
- TMF 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 Closur*e**:

At the end of the study, all study sites will be closed. 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:

- Noncompliance 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.

14.5.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

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 informed consent form. After completion, informed consent forms will be kept and archived by the investigator in the investigator's study file.

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 informed consent form(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. REFERENCES

1 Barbour KE, Helmick CG, Theis KA, Murphy LB, Hootman JM, Brady TJ, Cheng YJ. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2010-2012. MMWR 2013;62 (44):869-873.

2 Centers for Disease Control and Prevention. https://www.cdc.gov/arthritis/data_statistics/index. htm. Accessed 24 June 2016.

3 Investigational Brochure, Diclofenac Sodium Transdermal Drug Delivery System, HP-5000 Transdermal Patch. Noven Pharmaceuticals, Inc. [redacted] Edition No. 03, September 9, 2014.

4 Berger, R.S., and .J.P. Bowman. "A Reappraisal of the 21 -day Cumulative Irritation Test in Man." Toxicol. - (It. 6' Ocz~lw Toxicol., 1982; l(2); 109- 115.

5 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.

6 Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14-17.

7 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.

8 National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The prevention and treatment of missing data in clinical trials. Washington (DC): National Academies Press (US); 2010.

17. ATTACHMENTS

17.1. Schedule of Events

Phase	Screening			Double-blind Treatment						Follow-up	End of Treatment
Period		**Washout**	**Baseline**								
Week	**-1**			**1**		**2**		**3**	**4**	**5**	
Clinic visit	**1**		**2**		**3**		**4**		**5**		
Phone visit		**1**								**2**	
Study Day	**-28 to -14[k]**	**-25 to -1[k]**	**0**	**1 to 6**	**7**	**8 to 13**	**14**	**15 to 27**	**28**	**35**	
Visit Window (Days)					**±2**		**±2**		**±2**	**±2**	
Assessments/Procedures											
Informed Consent	X										
Demographics	X										
Medical History	X										
I/E criteria	X		X								
Randomization (IVRS)[a]			X								
Physical Examination	X								X		X
Vital signs[b]	X		X		X		X		X		X
Height	X										
Weight	X		X						X		X
WOMAC Pain[c]	X		X		X		X		X		X
Patient Global Assessment			X		X		X		X		X
Patient Global Impression of Change					X		X		X		X
Pain Intensity 11-Point NRS	X	X	X	X	X	X	X	X	X		X
Dispense Rescue Medication	X		X		X		X				
Use of Rescue Medication[d]		X	X[d]	X	X	X	X	X	X		X
12-lead ECG[e]	X		X						X		X
Clinical Laboratory (Hematology, biochemistry & urinalysis)[f]	X[f]		X[f]						X		X
Fasting Glucose & Lipids[g]	X		X						X		X
Urine Pregnancy Test	X		X		X		X		X		X
Drug Screen	X		X								
Alcohol Test	X		X								

Phase	Screening			Double-blind Treatment						Follow-up	End of Treatment
Period		**Washout**	**Baseline**								
Week	**-1**			**1**		**2**		**3**	**4**	**5**	
Clinic visit	**1**		**2**		**3**		**4**		**5**		
Phone visit		**1**								**2**	
Study Day	**-28 to -14[k]**	**-25 to -1[k]**	**0**	**1 to 6**	**7**	**8 to 13**	**14**	**15 to 27**	**28**	**35**	
Visit Window (Days)					**±2**		**±2**		**±2**	**±2**	
Assessments/Procedures											
PK Blood Sample							X		X		X
Subject eDiary[h]	X	X	X	X	X	X	X	X	X		X
Study Medication Application[i]				X[h]	X	X	X	X			
Dermal Evaluations[j]			X	X[l]	X	X[l]	X	X[l]	X		X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[m]			X	X	X	X	X	X	X	X	X
X-Ray[n]	X										
Drug Accountability			X[o]		X		X		X		X

Abbreviations: AE = adverse event; ET = early termination; ECG = electrocardiogram; ID = identification; I/E = inclusion/exclusion; IVRS = interactive voice response system; NRS = numeric rating scale; PK = pharmacokinetic; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

a. Subjects will be randomized to HP-5000[redacted], HP-5000-[redacted], or placebo in a 1:1:2 ratio.
b. Vital signs, including heart rate, respiratory rate, and a supine blood pressure will be measured after the subject has been in a supine position for 5 minutes.
c. WOMAC Total Pain Score will include WOMAC pain intensity, WOMAC stiffness, and WOMAC physical function.
d. Rescue medication may be used during the Washout Period except within 2 calendar days prior to Visit 2 and within 1 day prior to each subsequent visit.
e. A standard 12-lead electrocardiogram (ECG) will be performed after the subject has been supine for at least 5 minutes.
f. Clinical laboratory testing includes hematology, biochemistry, and urinalysis. Results from laboratory testing done at Screening Visit will be used for confirmation of subject eligibility at Baseline Visit.
g. Fasting glucose and lipids should be performed after 8 to 10 hours of fasting. Subject must be instructed to fast for 8 to 10 hours (no food or drink, except for water) before coming for the Baseline assessments, if not done at Screening.
h Subjects will be instructed on how to use of the electronic diary (eDiary) at the Screening Visit. For each 28-day administration period, subjects will be asked to record their NRS score, their intake/use of study drug and rescue medication in the eDiary.
i. Study treatment will be applied on Day 1 of the Double-blind Treatment Phase. Instructions for application and removal of study drug patches will be provided to the subject at the Baseline Visit (V2).
j. Dermal evaluations will assess skin adhesion, irritation, discomfort, and adhesive residue.
k. Screening/Washout Period should be up to 28 days. Washout Period can be initiated 3 days after Screening Visit.

l. During the Double-blind Treatment Phase, subjects will report the incidence of patch detachment by answering Yes or No and will perform dermal assessments daily at home.
m. AEs will be collected starting from the first administered dose.
n. Historical X-rays done within one year prior to the Screening Visit are acceptable. If subject does NOT have any 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.
o. Only for rescue medication.

Note: [redacted] should be administered at the Screening and Baseline Visits after the subject has been consented and passed all the eligibility criteria defined in the protocol first.

17.2. Investigator's Agreement

PROTOCOL NUMBER: HP-5000-US-05

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee

FINAL PROTOCOL: Amendment #2: 12 January 2018

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

This is an example of the WOMAC index. The actual index will be provided in the eCRF.

The Western Ontario and McMaster Universities Osteoarthritis Index
(WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

18.2. Patient Global Assessment Scale (PGA)

This is a sample questionnaire. The actual questionnaire will be provided in the study reference manual.

The subject will provide their overall impression of the status of their OA in the target knee on a 5-point scale where 0 = "Very Good" and 4 = "Very Poor."

Subjects will be asked to complete the following statement: "How would you rate your osteoarthritis condition over the last 24 hours?" The response options include the following:

1. Very Good
2. Good
3. Moderate
4. Poor
5. Very Poor

18.3. Patient Global Impression of Change Scale

This is an example of the Patient Global Impression of Change (PGIC) scale. The actual instrument will be included in the study reference manual.

The Patient Global Impression of Change 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." 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

18.4. 11-Point Numeric Rating Scale (NRS)

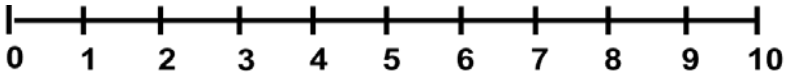
This is a sample of the Numerical Rating Scale. Please use the rating scale provided in the study reference manual.

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.

Ask the subject the following question: "On a scale of 0 – 10, with 0 being 'no pain' and 10 being the 'worst possible pain', how would you rate your pain over the last 24 hours?"

The intent of the question is to gain an understanding of the intensity of the subject's target knee pain at over the last 24 hours.



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 94 (2001) 149–158Regulations and Good Clinical Practice Guidelines.

18.4.1 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

18.4.2 Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

PROTOCOL

PRODUCT NAME/NUMBER: HP-5000 Topical Patch

PROTOCOL NUMBER: HP-5000-US-05

DEVELOPMENT PHASE: 2

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee

PROTOCOL DATE: Final Amendment #1: 22 May 2017

SPONSORED BY: Noven Pharmaceuticals, Inc.
350 Fifth Ave, 37th Floor
New York, New York, 10118 USA
1 (212) 682-4420

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-05

VERSION: Amendment #1

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) 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] Date

[redacted] Date

2. SYNOPSIS

PRODUCT NAME/NUMBER	HP-5000 Topical Patch
PROTOCOL NUMBER	HP-5000-US-05
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A 4-week, randomized, double-blind, multicenter, placebo-controlled phase 2 study to evaluate the efficacy and safety of HP-5000 in subjects with osteoarthritis (OA) of the knee.
INDICATION	Osteoarthritis pain of the knee
OBJECTIVES	**Primary:** • To evaluate the efficacy of HP-5000 compared to placebo • To evaluate the safety and tolerability of HP-5000 compared to placebo **Secondary:** • To evaluate the skin irritation, discomfort, adhesion, and adhesive residue following administration of HP-5000 • To determine the plasma concentrations of diclofenac following administration of HP-5000
STUDY DESIGN	This is a multicenter, randomized, double-blind, and placebo-controlled phase 2 study evaluating 2 formulations of HP-5000 in subjects with OA of the knee. The study will consist of up to 28-day Screening Phase that will include a Washout Period of current prescription and over the counter (OTC) analgesics, a 4-week double-blind Treatment Phase, and a 1-week safety Follow-up Period. Subjects will be seen in the clinic at the Screening Visit, Baseline Visit (Day 0), Day 7, Day 14, Day 28 (end of study), and Day 35 (safety Follow-up Visit). A ± 2 days window will be allowed for all clinic visits during the double-blind Treatment Phase. Site personnel will also contact the subjects by phone after the Screening Visit in order to instruct subjects on when to begin the Washout Period. **Screening Phase/Washout Period:** Subjects will be seen in the clinic, and the study will be described to them. Subjects will be asked to sign the informed consent form. 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. Subjects whose preliminary entry criteria have been met will be contacted by the site via telephone starting from Day -25 and will be instructed to begin the Washout Period for 7 up to 14 days prior to the Baseline Visit (Day 0). During the Washout Period, rescue medication (acetaminophen [APAP]) will be permitted (a maximum of 2 g/day) except within 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited for 2 days until clinic visit on Day 0). During the Washout Period, subjects will complete daily electronic diaries (eDiaries) to record pain severity of their target knee and rescue medication usage from the day of Screening Visit to the day of the Baseline Visit. **Double-blind Treatment Phase:** Following completion of the Screening/Washout Period, subjects will return to the clinic for their Baseline Visit (Day 0). Eligible subjects will be randomized to either HP-5000 [redacted] HP-5000 [redacted] or placebo in a 1:1:2 ratio. Subjects will apply a single patch to the outer target knee (i.e., outer knee) [redacted] starting from Day 1 of the Treatment Phase [redacted] The patch will be removed [redacted] and a new patch will be applied to a different site on the target knee (i.e. inner knee). Subjects will be instructed to rotate the patch application [redacted] to alternate sides of the target knee (between inner and outer). Subjects will also complete daily ediaries to record patch application and removal times, adhesion assessments, pain assessments, and amount of

	rescue medication taken daily, if applicable. A maximum of 2 g/day of acetaminophen, also known as APAP will be allowed as rescue medication for the treatment of target knee and non-target knee pain except within the 1 calendar day prior to each clinic visit (e.g., rescue medication is prohibited from Day 6 until clinic visit on Day 7 if subject will visit the study site on Day 7). **NOTE:** Subjects are NOT allowed to apply HP-5000 on the non-target knee at any time in the study period. Blood samples will be collected on Day 14 and 28 (or at the Early Termination Visit) where plasma will be analyzed for diclofenac concentrations. Actual blood sampling times will be recorded. **Follow-up Period:** Subjects will have a safety visit approximately 7 days after the End-of-Treatment Visit (Week 4). 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 clinical for their Follow-up Visit.
PLANNED NUMBER OF SUBJECTS	The total number of subjects randomized in the study and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY ENTRY CRITERIA	The following inclusion and exclusion criteria must be met by subjects to participate in this study: **Inclusion criteria**: 1. Provide 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. Knee pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.). c. The pain in the target knee required the use of prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prescribed over the counter (OTC). d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed by physician for 30 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. 4. Has at least moderate pain in the designated study knee: a. [redacted] 5. Has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline Visit. 6. If female: a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the Screening Visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile). b. Subject could not become pregnant because she is surgically sterile

(hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months), or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the Screening Visit.

7. Able to swallow and tolerate rescue medication with APAP (moderately sized tablets).
8. Be reliable, willing, and able to cooperate with all study procedures including the following:
   a. Accurately fill out the diary on a daily basis.
   b. Return for study visits on the required dates.
   c. Accurately and reliably report symptoms (including treatment-emergent signs and symptoms).
   d. Use the patch as required by protocol.

Exclusion criteria:

1. Body mass index (BMI) > 40
2. The non-target knee pain severity score is [redacted] at Screening or Baseline (Day 0) Visit.
3. Any subject who disobeyed the restriction of prohibited therapies (e.g., rescue medication) during Screening/Washout Period.
4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma).
5. Clinically significant elevation of serum creatinine (176.8 µmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN]).
6. Known allergy or hypersensitivity to the use of diclofenac, [redacted], ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID.
7. Severe, uncontrolled cardiac, renal, hepatic or other systemic disease.
8. A documented (upper gastrointestinal [GI] series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within 6 months prior to Screening Visit.
9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
11. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
12. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) for less than 1 year before study enrollment.
13. Current treatment with oral, topical, intra-articular, or intra-muscular corticosteroids on the target knee within 90 days of Screening Visit or into any other joint within 30 days of screening.
14. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
15. Any subject who had used opioids 7 days prior to the Screening Visit.
16. Any subject who had previous exposure to HP-5000.
17. Any subject whose participation would conflict with contraindications, warnings or precautions as stated in the prescribing information for oral or topical diclofenac (e.g., any subject taking ACE inhibitors, cyclosporine, diuretics, lithium, or methotrexate – refer to Investigator Brochure for prescribing information).
18. Use of another investigational drug within 30 days prior to study entry.
19. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause.
20. Any subject with fibromyalgia.
21. Any painful or disabling conditions affecting the knees or legs.

	22. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo. 23. Any subject expecting to have knee replacement surgery within 6 months. 24. Any subject with a psychiatric condition in the investigator's opinion may interfere with participation in the study. 25. 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.
INVESTIGATIONAL PRODUCTS	HP-5000 topical patch Each patch contains diclofenac sodium. HP-5000 topical patch Each patch contains diclofenac sodium.
REFERENCE PRODUCT	Placebo Patches identical in appearance to both HP-5000 patch and HP-5000 patch but without the active ingredient diclofenac.
TREATMENT REGIMENS	The treatments for each of the treatment arms will be as follows: **Treatment Arm** — **Treatment** HP-5000 — One patch applied to alternate side of the target knee (inner or outer). HP-5000 — One patch applied to alternate side of the target knee (inner or outer). Placebo — One patch applied to alternate side of the target knee (inner or outer).
PLANNED STUDY SITES	Approximately study sites in the United States.
CRITERIA FOR EVALUATION OF STUDY OBJECTIVES	**Primary efficacy endpoint**: The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score between Baseline and Week 4. **Secondary efficacy endpoints**: • WOMAC LK3.1 OA Index (pain) –change in pain score between Baseline and Week 1 and 2. • WOMAC LK3.1 OA Index (stiffness). • WOMAC LK3.1 OA Index (physical function). • WOMAC LK3.1 OA Index (composite score). • Patient Global Assessment. • Patient Global Impression of Change. • Pain intensity assessed on an 11-point NRS. • Use of rescue medication. **Safety endpoints:** • Adverse events, AEs leading to discontinuation from the study drug, and serious AEs (SAEs). • Change from baseline in clinical laboratory results (including fasting glucose and lipids), electrocardiogram (ECG) results, body weight, and vital signs. • Dermal performance: adhesion, irritation, discomfort, and adhesive residue. **Pharmacokinetic endpoint:** • Plasma concentrations of diclofenac on Day 14 and 28 (or at the Early Termination Visit).
STATISTICAL METHODS	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 statistics 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.

Analysis Populations

- Intent-to-Treat (ITT): Will include 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.

- Full Analysis Set (FAS): Will include all randomized subjects who have had at least 1 patch of double-blind study drug applied and who have a Baseline WOMAC pain score and at least 1 post-baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.

- Safety Analysis Set (SAF): Will include all subjects who have had at least 1 patch of double-blind study medication 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.

- Pharmacokinetic Analysis Set (PAS): Will include all subjects who have received at least 1 dose of study drug during the double-blind treatment phase and have at least 1 blood sample for pharmacokinetic (PK) assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion.

Primary Efficacy Analysis: The primary efficacy endpoint of this study is the change from Baseline to Week 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are:

- HP-5000 [redacted] versus placebo
- HP-5000 [redacted] versus placebo

The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-5000 dose group *vs*. placebo) in the change from Baseline to Week 4 in WOMAC pain score in all subjects as randomized, under the

	assumption that all randomized patients remain on their randomized treatment throughout the study. WOMAC scores obtained more than 24 hours after discontinuation of double-blind study drug will be excluded as a-priori defined outliers. The primary efficacy variable, the change from Baseline to Week 4 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 HP-5000 and placebo), 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. The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed. Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. These analyses may include multiple imputation and pattern-mixture models for handling of missing data. Details will be provided in the SAP. The analyses will be performed according to the National Academy of Sciences (2010) guidelines. **Analysis of Secondary Efficacy Endpoints**: Other secondary efficacy endpoints will be analyzed using the change in mean as appropriate. • WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1 and 2. • WOMAC LK3.1 OA Index (stiffness). • WOMAC LK3.1 OA Index (physical function). • WOMAC LK3.1 OA Index (composite score). • Patient Global Assessmen.t • Patient Global Impression of Change. • Pain intensity assessed on an 11-point NRS. • Use of rescue medication. Additional categorical response analyses may be performed; additional details will be provided in the SAP. Additional categorical response analyses may be performed; additional details will be provided in the SAP. **Analysis of Safety:** All safety summaries will be descriptive; statistical significance tests may be performed on safety data that will be described in the SAP. Safety variables include AEs, clinical laboratory values, vital signs, ECG readings, physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted. **Analysis of PK:** Plasma concentrations of diclofenac (for both HP-5000 and HP-5000 will be evaluated and summarized as descriptive statistics by treatment.
SAMPLE SIZE DETERMINATION	Assuming an effect size of 0.32 on the change in WOMAC pain score from Baseline to Week 4 between active HP-5000 and HP-5000 treatments and placebo, the probability for detecting the clinically meaningful effect size or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the study and included in the primary analysis set should be

	approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY TREATMENT DURATION	The maximum treatment duration for each subject is 4 weeks. The total duration of study participation for each subject is approximately 9 weeks.

3. TABLE OF CONTENTS

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APAP	acetaminophen
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	institutional review board
ITT	intent-to-treat
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	over the counter
PK	Pharmacokinetics
PAS	pharmacokinetic analysis set
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
TDDS	transdermal drug delivery system
ULN	upper limit of normal
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 doctor-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 doctor-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 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 their opioid pain reliever, thereby introducing additional health problems into the equation. There is an unmet need for a safe, reliable, and effective pain medication without the risk and lack of efficacy associated with those currently available.

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

Noven Pharmaceuticals, Inc. has started the development of a formulation of diclofenac sodium for topical administration via a transdermal patch system, the HP-5000 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:

- Transfer of drug into the treatment target area resulting in lower systemic and GI exposure when compared to 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 the diclofenac transdermal drug delivery system (TDDS), evaluating the PK and tolerability in 104 healthy volunteers. The lead formulations for this program, HP 5000 [redacted] and HP 5000 [redacted] both of which contain [redacted] diclofenac sodium [redacted] with a patch size of [redacted] were selected based on the diclofenac pharmacokinetic profile and patch performance characteristics, such as irritation and adhesion on the mobile knee joint application site.

It should be noted that the HP 5000 [redacted] formulation is also being developed [redacted] by Noven's parent company, [redacted] for different [redacted] indications (i.e., [redacted] and [redacted] and is referred to as the [redacted] (also known as [redacted]. Study [redacted] has been included in the development program to provide additional safety data. [redacted]

The phase 1 studies performed on healthy volunteers are as follows:

- [redacted]

[redacted]

Further details about HP-5000 are found in the Investigator's Brochure.

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with OA (1) may experience a reduction in pain and inflammation as a result of treatment with the HP-5000 patch and (2) will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for subjects with OA.

The potential risks of study participation include those associated with exposure to the HP-5000 patch and the risks of medical evaluation, including venipuncture.

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

6. OBJECTIVES

6.1. Primary Objectives

- To evaluate efficacy of HP-5000 in subjects with osteoarthritis of the knee compared to placebo.
- To evaluate the safety and tolerability of HP-5000 compared to placebo.

6.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate skin irritation, discomfort, adhesion, and adhesive residue following administration of HP-5000.
- To determine the plasma concentrations of diclofenac following administration of HP-5000.

7. STUDY DESIGN

7.1. Overall Study Design and Plan - Description

This is a 4-week, randomized, double-blind, multicenter, placebo-controlled phase 2 study to evaluate the efficacy, safety and tolerability of HP-5000 compared with that of placebo in the treatment of OA. The study will run for approximately 9 weeks comprised of up to a maximum of 28-day Screening Phase that will include a Washout Period of up to a maximum 14 days, a 4-week Treatment Phase, and a 1-week Follow-up Period. Subjects will be randomly assigned to receive [redacted] one of the following 3 treatments in a 1:1:2 ratio: HP-5000[redacted] [redacted] HP-5000-[redacted] [redacted] or placebo patch, respectively. The placebo patch will be identical in appearance to the 2 HP-5000 active patches. The total number of subjects randomized in the study and included in the primary analysis will be approximately 300.

The duration of double-blind treatment is expected to be 4 weeks and the total time in the study will be approximately 9 weeks.

- **Screening/Washout Period**: Visit 1 (up to 28 Days): Screening and start of baseline diary (BL): After signing the informed consent, the Screening Phase will begin. Subjects whose preliminary entry criteria have been met will be contacted by the site via telephone starting from Day -25 and will be instructed to begin the Washout Period for 7 to a maximum of 14 days prior to start the Baseline Visit. Subjects will receive instruction on how to use of the patient diary. Subjects should complete the patient diary every day during the Washout Period and record pain severity of their target knee and rescue medication usage from the day of Screening Visit to the day of the Baseline Visit. The mean score of the last 3 consecutive days immediately prior to the Baseline Visit will be calculated for subjects to be considered eligible for study participation. During the Washout Period, rescue medication (acetaminophen [APAP]) will be permitted (a maximum of 2 g/day) except within 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited from Day-2 until clinic visit on Day 0).

- **Baseline Visit:** Visit 2 (0 Day): Subjects will be reevaluated according to the inclusion and exclusion criteria and the average patient diary pain score will be calculated. Those subjects who continue to meet all of the inclusion criteria, none of the exclusion criteria, who have completed the patient diary for at least 3 consecutive days immediately prior to Baseline Visit, and whose average pain score is at least 5 will be randomized to receive one of 2 formulation of HP-5000 or placebo.

- **Double-blind Treatment Phase**: On Day 1 of the Treatment Phase, subjects will start applying their assigned patch for 4 Weeks (from Week 5 through 8): Subjects will be randomized to receive either HP-5000 [redacted] patch, HP-5000 [redacted] patch, or placebo patch. Dose modifications will NOT be permitted. Subjects who cannot tolerate their designated study drug dose will be withdrawn from the study.

- **Follow-up Period:** Visit 6 (Week 9): After the 4-week Treatment Phase, the study center will conduct a follow-up phone call for safety monitoring or based on the investigator's judgment, a subject may return to the study center for the safety Follow-up Visit.

All subjects will be contacted by phone between visits to assess AEs, general well-being, provide visit reminders, and reinforce diary record and treatment compliance. Dose modifications will NOT be permitted and study procedures will be reinforced.

At each study visit, subjects will undergo efficacy and safety evaluations. Efficacy evaluations will include the change from baseline values in the Western Ontario and McMaster Universities (WOMAC) LK3.1 OA index for pain, stiffness, physical function, and composite score, the Patient Global Assessment, the Patient Global Impression of Change, and pain intensity assessed on an 11-point NRS and the subjects' use of rescue medication.

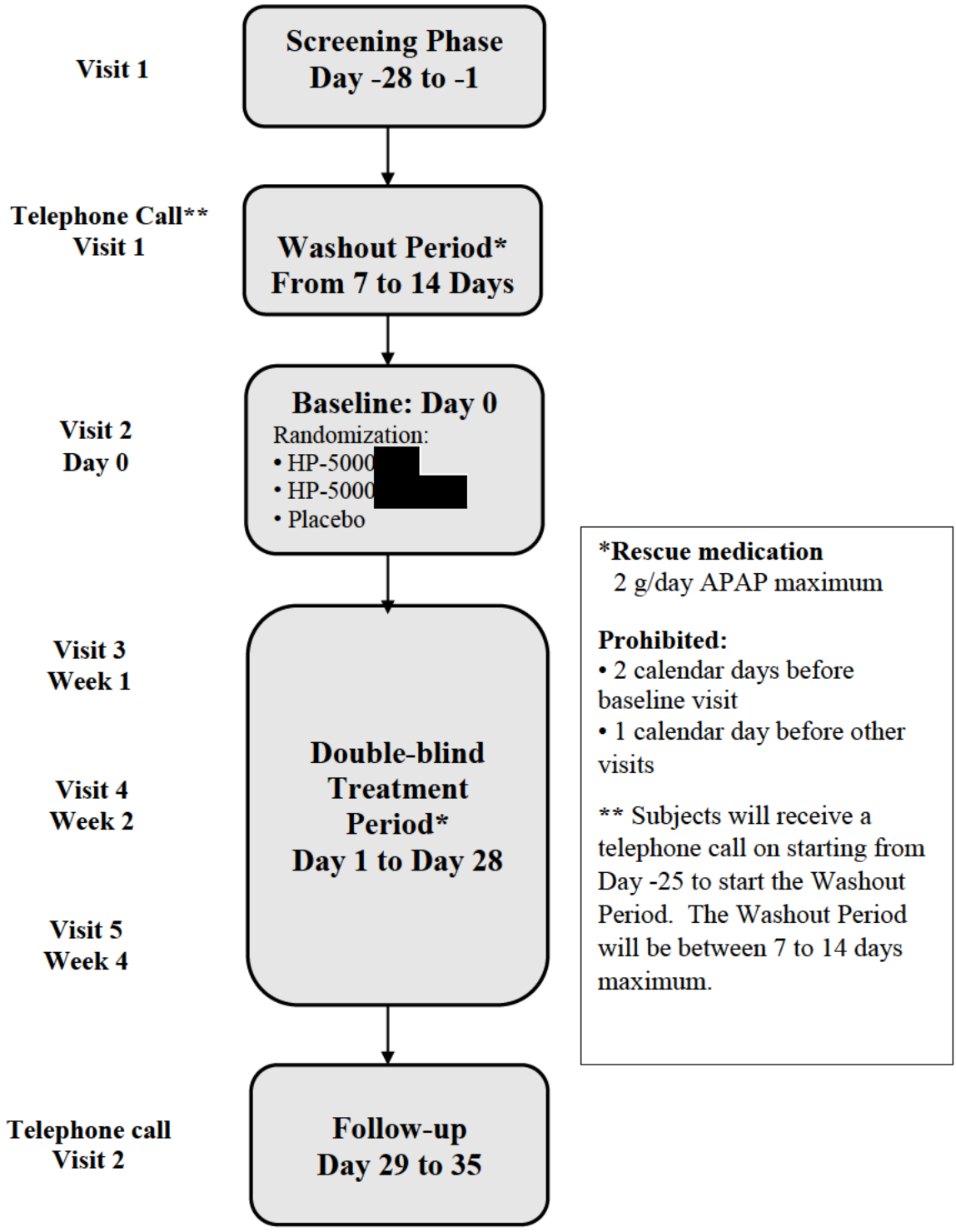
Safety evaluation will include collection of AEs, physical examination findings, vital sign measurements, electrocardiogram (ECGs), clinical laboratory test results, and body weight. All AEs observed by the study personnel or reported by the subject during the study (from the time of study drug administration through the post treatment visit) will be documented.

Dermal characteristics will be assessed by 5-point numerical scale of adhesion, Berger and Bowman scale of Irritation, 5-point numerical scale of Discomfort, and 5-point numerical scale of Adhesive Residue.[4] In addition, subjects will record the [redacted] patch application and removal times in electronic diaries along with any incidence of patch detachment.

Plasma pharmacokinetic sampling will be performed as scheduled. Plasma concentrations of diclofenac will be assessed by venous blood sampling on Day 14 and 28 (or at the Early Termination Visit). Study center personnel will also assess study drug and diary compliance.

Figure 1 presents a schematic view of the study design.

Figure 1 Study Design



7.2. Discussion of Study Design

The double-blind, placebo-controlled study uses 3 patches [redacted] HP-5000 and placebo) of identical appearance to ensure blinding. The total duration of study drug exposure will be approximately 4 weeks. The safety evaluation will be performed one week after the last dose.

The use of rescue medication is prohibited within 2 calendar days prior to the Baseline Visit and within 1 calendar day prior to clinic visits during the Treatment Phase, thus ensuring the integrity of the assessments.

7.3. Study Sites

The study will take place at approximately [redacted] sites in the US. Each site is anticipated to screen a sufficient number of subjects to be able to randomize an aggregate number of approximately 300 subjects.

8. SUBJECT POPULATION

8.1. Selection of Study Population

The study will enroll up to 300 subjects in a 1:1:2 ratio (HP-5000 HP-5000 Placebo) with osteoarthritis of the knee. The pain should have been stable over the previous six months prior to Screening (Visit 1).

A screening log of potential study candidates and/or an enrollment log of enrolled subjects must be maintained at each study site.

8.2. Study Entry Criteria

All subjects being considered for participation in this 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. Provide 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. Knee pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.).
   c. The pain in the target knee required the use of prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and/or prescribed over the counter (OTC) medication.
   d. On stable pain therapy (i.e., at least 3 days per week for the previous month) with an oral or topical NSAID prescribed by a clinician for 30 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.
4. Has at least moderate pain in the designated study knee:

[redacted]

5. Has a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline Visit.
6. If female:
   a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the Screening Visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile).
   b. Subject could not become pregnant because she is surgically sterile (hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months), or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the Screening Visit.
7. Able to swallow and tolerate rescue medication with APAP (moderately sized tablets).
8. Be reliable, willing, and able to cooperate with all study procedures including the following:
   a. Accurately fill out the diary on a daily basis.
   b. Return for study visits on the required dates.
   c. Accurately and reliably report symptoms (including treatment-emergent signs and symptoms).
   d. Use the patch as required by 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.
2. The non-target knee pain severity score is [redacted] at Screening and Baseline (Day 0).
3. Any subject who disobeyed the restriction of prohibited therapies (e.g., rescue medication) during Screening/Washout Period.
4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma).
5. Clinically significant elevation of serum creatinine (176.8 µmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN]) at the Screening Visit.
6. Known allergy or hypersensitivity to the use of diclofenac, [redacted], [redacted] [redacted] [redacted] ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID.

7. Severe, uncontrolled cardiac, renal, hepatic or other systemic disease.
8. A documented (upper GI series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within 6 months prior to Screening Visit.
9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at Screening or Baseline.
10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups.
11. MAJOR SURGERY: Previous damage or surgery to the target knee at any time (i.e., damage/reconstruction of the anterior or posterior cruciate ligaments).
12. MINOR SURGERY on the target knee defined as anything other than major surgery (as defined above) for less than 1 year before study enrollment.
13. Current treatment with oral, topical, intra-articular, or intra-muscular corticosteroids on the target knee within 90 days of Screening Visit or into any other joint within 30 days of screening.
14. Any subject who had received intra-articular viscosupplementation (e.g., Synvisc®) in the target knee 90 days prior to Screening Visit.
15. Any subject who had used opioids 7 days prior to the Screening Visit.
16. Any subject who had previous exposure to HP-5000.
17. Any subject whose participation would conflict with contraindications, warnings or precautions as stated in the prescribing information for oral or topical diclofenac (e.g., any subject taking ACE inhibitors, cyclosporine, diuretics, lithium, or methotrexate – refer to Investigator Brochure for prescribing information).
18. Use of another investigational drug within 30 days prior to study entry.
19. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause.
20. Any subject with fibromyalgia.
21. Any painful or disabling conditions affecting the knee or leg.
22. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (i.e., infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo.
23. Any subject expecting to have knee replacement surgery within 6 months.
24. Any subject with a psychiatric condition in the investigator's opinion may interfere with participation in the study.
25. 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.

8.2.3 Premature Subject Withdrawal

In accordance with the Declaration of Helsinki (48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996), subjects have the right to withdraw participation from the study at any time for any reason. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must make at least 3 attempts to contact subjects who fail to attend scheduled visits by telephone or other means.

The investigator also has the right to remove subjects from the study. Subjects may be removed from the study for the following reasons:

- Adverse events: If the reason for removal of a subject from the study is an AE, the principal specific event and any related test results will be recorded on the electronic case report form (eCRF). If a subject withdraws because of an AE plus another reason, 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 request of the subject, his/her representative, investigator or sponsor, whether for administrative or other reasons.
- Noncompliance with study drug or non-compliance with subject diary completion, protocol violation, or unreliable behavior.
- Pregnancy. If the subject becomes pregnant during the clinical study, the study drug should be stopped immediately and the subject withdrawn from the study.

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

- The date of the last dose of study drug and all observations collected up to the time of termination will be recorded on the Early Withdrawal eCRF page along with the reason for termination. All Early Withdrawal procedures should be completed and recorded on the Early Withdrawal eCRF page. If withdrawal occurs at a regularly 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.
- In order to enable the most complete recording of any subject who withdraws early from the study, it is important to evaluate these subjects at the study center as soon as possible. Subjects who are withdrawing early should undergo an Early Withdrawal Visit and a Follow-Up Visit must be scheduled.

Subjects may be withdrawn if continuing in the study is not in the subject's best interest; their condition worsens during the study, or for safety reasons, as determined by the investigator. Subjects may also be withdrawn due to lack of compliance with the protocol or if the subject is unwilling to continue participation in the study.

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

One patch [redacted] will be applied [redacted] to alternate sides of the target knee (inner and outer knee). Detailed application instructions for subjects will be provided in a separate manual.

HP-5000 will be supplied as [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):

- Blinded packaged lot number
- Protocol number
- Subject number (record at the time of dispensing)
- Directions for use
- 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 [redacted] HP-5000 [redacted] and placebo patches will be packaged so as to be blinded to the investigator, the study clinic personnel, and 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 a maximum of 28 ± 2 days.

The treatment arms for this study are the following:

Treatment Arm	[redacted] **Treatment**
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
Placebo	One patch applied [redacted] to alternate side of the target knee (inner or outer).

Patch Application

A separate guidance for patch application will be provided to subjects for applying, securing, and removing the patch.

9.3. Dispensing and Storage

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

The investigator must confirm the receipt of study drug with his/her signature. A copy of this receipt must be kept by the investigator, and another copy will be stored at Noven Pharmaceuticals, Inc. (hereafter referred to as "Noven"), and/or [redacted] Until study drug is dispensed to the subjects, it must be stored at 25°C 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 meet study entry criteria will be randomly assigned in a 1:1:2 ratios to receive HP-5000[redacted] HP-5000[redacted] or placebo patches. The randomization numbers will be assigned sequentially through a central interactive voice response

system (IVRS) 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 designated visits, subjects will be given a kit containing sufficient study drug to last until the next scheduled study visit.

The randomization schedule will be prepared by [redacted] before the start of the study. No one involved in the clinical conduct will have access to the randomization schedule before 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[redacted] and HP-5000[redacted] patches.

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a prespecified unblinded statistician/programmer from [redacted] 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, then 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 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 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. 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 whenever possible.

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.

The investigator or designee must record the date and reason for unblinding or study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

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 dose of diclofenac [redacted] in a patch size of [redacted] applied [redacted] and rotated between [redacted] on the knee (inner and outer knee) is based on the following considerations:

- [redacted]
- 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.

The data from previous studies investigating irritation and PK support the proposed dose of [redacted] and a patch size of [redacted] applied [redacted] and rotated between [redacted] on the knee for the lead formulations (HP-5000[redacted] and HP-5000[redacted]

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 [and initials]) who received study drug and any reasons for departure from the protocol-dispensing regimen. Receipt of study drug must also be confirmed within IVRS. The drug accountability records, along with used and unused packaging must be available for monitoring, auditing, or inspection. Each site must keep accurate records of drug received at site, dispensed to the subjects.

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 study drugs is either not dispensed, 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 (used and unused) must performed and 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 counts 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 3 through 5 or any Early Termination Visit, the study drug (patches) from the previous Treatment Phase will be returned to the investigator. The study drug will be inventoried and noncompliance defined asusing less than 80% or more than 120% of study drug during any evaluation period (visit to visit). If the subject is noncompliant, the Medical Advisor should be contacted to discuss the subject's eligibility to continue in the study.

The subject must be counseled if compliance is not satisfactory (used 6 or less patches per week). If a subject has been noncompliant on two consecutive visits, the subject may be withdrawn early from the study for non-compliance.

For each 28-day study drug administration period, subjects will be asked to record their daily intake/use of rescue medication/study drug in the diary. Deviations from the planned doses (overdose, missed dose or timing) will be recorded on the subjects' eCRF. These diaries will be reviewed by study personnel at each visit and will be collected as source documents. Information from that subject diary will be transcribed on the appropriate eCRF pages for documentation of subject compliance with study drug. Compliance will include the following:

1. **Telephone follow-up:** A telephone follow-up call will be performed between Screening (Visit 1) and Baseline (Visit 2), before the start of the Washout Period and another one during the Follow-up Period.

2. **Patient Education:** At all study visits, the investigator will explain the importance of the following:

    a. applying study medication [redacted] to the target knee after showering/bathing;
    b. recording patient diary information every day;
    c. accurately reporting pain;
    d. accurately reporting rescue medication use;
    e. understanding when to return for next visit and the importance of returning on schedule; and
    f. adhering to the overall research plan.

During Screening (Visit 1), the investigator will provide the subject with an introduction to the various questionnaires that will be used during the study and the patient diary.

3. **Patient Dairy (e-Diary):** The patient diary will be used by the subject to record required assessments including the time of patch application/removal, the NRS scores, the use of rescue medication, and questionnaires about adhesion, skin irritation, discomfort and adhesive residue.

4. **Rescue Medication:** If needed, patients will be allowed to take up to 2 grams of acetaminophen per day as rescue medication for pain of the target and/or the non-target knee. Information regarding the use of rescue medication will be recorded on the appropriate concomitant medication eCRF.

9.10. Permitted and Prohibited Therapies

Prior to the double-blind treatment period, subjects will stop taking all prescription and prescribed OTC analgesic medications for at least 7 days; however, rescue medication (acetaminophen [APAP]) is permitted during the Washout Period if required. A maximum of 2 g/day of APAP will be allowed for rescue treatment of both target and non-target knee pain except within the 2 calendar days prior to the Baseline Visit (i.e., rescue medication is prohibited from Day -2 until clinic visit on Day 0) and within the 1 calendar day prior to each clinic visit (e.g., rescue medication is prohibited from Day 6 until clinic visit on Day 7 if the subject will visit the study site on Day 7). APAP will be provided by the Sponsor. Subjects are NOT allowed to apply study treatment drug (HP-5000/Placebo) on the non-target knee at any time during the study period.

All concomitant medications used (including OTC medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF page.

9.10.1 Permitted Therapies

Glucosamine, chondroitin, and antidepressants (for indication of depression) will be allowed if used as stable therapy for at least 90 days prior to Screening Visit. 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

Any NSAIDs (selective or nonselective), any opioids, APAP (>2 g/day), ASA (>81 mg/day), corticosteroids (a stable does by inhalation for seasonal allergies and/or topical use for dermatologic allergies are allowed), anticonvulsants (i.e., pregabalin and gabapentin etc.), muscle relaxants, other oral analgesics (prescription and/or 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] or capsaicin, any intra-articular treatments for the knee, any nonpharmaceutical therapy or device to relieve knee pain (including physiotherapy, massage therapy, hot wax therapy etc.) may not be taken during the study.

Note: Glucosamine, chondroitin, and antidepressants (for the indication of depression) will be allowed if used as stable therapy for 90 days prior to Screening Visit. However, if in use for fewer than 90 days, these drugs will be considered as 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).

9.11. Treatment after End of Study

After completing the study, each subject will be referred to their primary care physician and treated 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 concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (see **Section 17.1**). 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 study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Periods and Visits

10.1.1 Screening/Washout Period

10.1.1.1 Screening Period

Screening/Washout Period should be up to 28 days prior to the Baseline Visit. The subject must be screened before entering the Washout Period of the study. The following procedures will be performed at Screening Visit:

1. Obtain written informed consent and assign a screening number.
2. Assess inclusion/exclusion criteria.
3. Collect demographic information and record medical history, including prior and current therapies (e.g., prescription and nonprescription medications).
4. 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. Weight (kg), height (cm), and vital signs will be measured.
5. Perform urine drug, alcohol and pregnancy tests.
6. Identify the target knee. The subject will be instructed to refer to this specific (target) knee throughout his/her participation in the study when responding to study efficacy assessment.
7. Instruct the subject how to use NRS and WOMAC before performing first assessments.
8. Administer the WOMAC questionnaire and calculate the composite score.
9. Perform NRS evaluation for the target knee and the non-target knee pain.
10. Review of x-ray of the target knee and perform 12-lead ECG and laboratory tests to determine subject's eligibility. If subject does NOT have any 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.

11. Instruct the subject on how to use of an electronic diary (eDiary).
12. Dispense rescue medication.
13. Dispense an eDairy.

10.1.1.2 Washout Period

Subjects whose eligibility has been preliminarily confirmed at screening will be asked to washout of current medications for at least 7 days (up to a maximum of 14 days). During this period, the following will take place:

1. Electronic diary NRS pain scores before the start of the Washout Period will be reviewed by the investigator or the study coordinator. A record of this review will be recorded in the source documents and eCRF pages.
2. Subjects will stop taking all prescription and OTC analgesic medications, but will be informed that rescue medication (i.e., acetaminophen) may be used (a maximum of 2 g/day) except within 2 calendar days prior to the Baseline Visit.
3. Perform an NRS assessment for the target knee pain and calculate the mean score for the least 3 days before the Baseline Visit.
4. Review subject's use of rescue medication.
5. Review subject's use of prior/concomitants medications.
6. Dispense and review electronic diary (eDairy).

10.1.2 Baseline Visit (Day 0)

The following will take place during the Baseline Visit (Day 0):

1. Confirm subject's continued eligibility relative to inclusion/exclusion criteria.
2. Assign a subject ID number and randomly assign the subject to a treatment group using IVRS.
3. Obtain vital sign measurements, including weight.
4. Administer the WOMAC questionnaire and calculate the composite score.
5. Perform Patient's Global Assessment.
6. Perform an NRS 11-point pain assessment for the target knee and non-target knee pain.
7. Review subject's use of rescue medication.
8. Perform a 12-lead ECG.
9. Obtain blood and urine samples for laboratory testing.
10. Perform a urine drug, alcohol and pregnancy tests.
11. Review and dispense the subject's diary.
12. Perform baseline dermal safety assessment (irritation only).
13. Review subject's use of prior/concomitants medications.

14. Dispense rescue medication and perform rescue medication accountability/reconciliation.
15. Dispense the double-blind study medication and instruct subjects on proper patch application. Subjects should apply the patch at home after showering/bathing [redacted]
16. Subjects will be instructed not to bathe or shower while wearing the study medication; a bath or a shower may be taken in the morning/in the evening before any patch is applied.
17. Subject will be instructed to report patch detachment and incidences of irritation, discomfort, and adhesive residue and not to participate in strenuous activities or other activities that cause heavy perspiration during the double-blind treatment phase.

10.1.3 Double-blind Treatment Phase

During the 4-week double-blind treatment phase, the following will take place:

At home, subjects are required to conduct the following:

1. Apply study medication on the target knee (inner or outer by [redacted] rotation) after showering/bathing.
2. Complete daily assessments in an e-Diary, which include the time of patch application and removal, the NRS pain score, the use of rescue medication, adhesion, skin irritation, discomfort and adhesive residue.

In clinic visits, investigators (or site personnel as appropriate) conduct the following:

Visit 3:

1. Obtain vital sign measurements.
2. Administer the WOMAC questionnaire and calculate the composite score.
3. Perform Patient Global Assessment.
4. Perform Patient Global Impression of Change.
5. Perform daily NRS 11-point pain assessments for the target knee pain.
6. Review subject's use of rescue medication/concomitant medication.
7. Perform a urine pregnancy test.
8. Re-instruct the subject concerning the patch application method if the subject has a problem with patch application and/or patch adhesion.
9. Dispense study medication/rescue medication and perform drug accountability/ reconciliation.
10. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
11. Review AEs.
12. Review the subjects' diary entries.

Visit 4:

1. Obtain vital sign measurements.
2. Administer the WOMAC questionnaire and calculate the composite score.
3. Perform Patient Global Assessment.
4. Perform Patient Global Impression of Change.
5. Perform daily NRS 11-point pain assessments for the target knee pain.
6. Review subject's use of rescue medication/concomitant medication.
7. Perform a urine pregnancy test.
8. Re-instruct the subject concerning the patch application method if the subject has a problem with patch application and/or patch adhesion.
9. Dispense study medication/rescue medication and perform drug accountability/ reconciliation.
10. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
11. Review AEs.
12. Review the subjects' diary entries.
13. Obtain pharmacokinetic blood sample.

Visit 5

1. Obtain vital sign measurements.
2. Administer the WOMAC questionnaire and calculate the composite score.
3. Perform Patient Global Assessment.
4. Perform Patient Global Impression of Change.
5. Perform daily NRS 11-point pain assessments for the target knee pain.
6. Review subject's use of rescue medication/concomitant medication.
7. Perform a urine pregnancy test.
8. Perform drug accountability/ reconciliation.
9. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
10. Review AEs.
11. Review the subjects' diary entries.
12. Obtain blood and urine samples for laboratory testing.
13. Obtain subject's weight.
14. Obtain pharmacokinetic blood sample.
15. Perform a 12-lead ECG.
16. Perform physical examination.

During the time interval between visits, the site coordinator may regularly contact (by telephone) the subjects to ensure that the subject's scheduled dose is administered and daily NRS pain scores are recorded correctly. The subjects will be informed that they may contact the site if problems/questions arise.

10.1.4 Follow-up Visit

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

1. Review subject's use of concomitant medications.
2. Review AEs.

10.1.5 Early Termination Visit (if applicable)

Subjects who are discontinued for any reason after Baseline (Visit 2) must complete the Early Withdrawal Visit. If the subject comes for an Unscheduled Visit and a decision to withdraw the subject is made, then the Early Withdrawal Visit procedures will be performed and the Early Withdrawal 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 sign measurements including weight.
3. Administer the WOMAC questionnaire and calculate the composite score.
4. Perform Patient's Global Assessment.
5. Perform Patient's Global Impression of Change.
6. Perform a NRS 11-point pain assessment for the target knee pain.
7. Review subject's use of rescue and concomitant medications.
8. Perform a 12-lead ECG.
9. Obtain blood and urine samples for laboratory testing.
10. Perform a urine pregnancy test.
11. Collect and review the subject's diary entries.
12. Perform drug accountability.
13. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
14. Review AEs.
15. Obtain pharmacokinetic blood sample.

10.1.6 Overall Study Schedule

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening/Washout Period: Up to 28 days (the Washout Period will occur the last 7 to 14 days of the Screening Phase).

2. Double-blind Treatment Phase: 4 weeks
3. Follow-up Period: 1 week

The maximum treatment duration for each subject is approximately 4 weeks. The maximum study duration for each subject is approximately 9 weeks.

10.2. Assessments

10.2.1 Efficacy

10.2.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

The Western Ontario and McMaster Universities Osteoarthritis Index Likert (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.[5,6,7]

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.

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.

The **WOMAC Physical Function** assesses the following categories using the 0 to 4 scale 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= __%

10.2.1.2 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". 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

10.2.1.3 Patient Global Impression of Change

The Patient Global Impression of Change 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." 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

10.2.1.4 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 will be assessed in two 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 pain intensity 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 pain that you have been feeling in your knee over the last 24 hours?"

Note:

1. The NRS pain score for assessment is an average of the NRS pain scores reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit except Screening Visit.
2. The NRS pain scores in at least 2 of the last 3 days prior to washout start (Phone Visit 1) and Baseline (Visit 2) is required.

10.2.1.5 Use of Rescue Medication

For the 4-week double-blind treatment phase, subjects will be asked to record their daily intake/use of rescue medication in the diary. Rescue medication will be limited as follows: 2 gram/day APAP may be used except and within 1 calendar day prior to other visits.

10.2.2 Safety

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

10.2.2.1 Laboratory Safety Assessments

10.2.2.1.1 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 17.1**).

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, blood urea nitrogen, creatinine, fasting glucose, 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, urinalysis samples. Urine drug screens and alcohol tests 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.

Note: Female patients (of childbearing potential) will undergo a urine pregnancy test at Screening (Visit 1) and a urine pregnancy test at every subsequent visit.

10.2.2.1.2 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-05 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.

10.2.2.2 Clinical Examinations

10.2.2.2.1 Vital Signs and Weight

Vital signs, including heart rate, respiratory rate, temperature and supine blood pressure will be measured at designated timepoints. 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 five minutes. Weight (kg) will also be measured.

10.2.2.2.2 Electrocardiogram

The 12-lead ECG will be a complete, standardized recording and will be performed at designated timepoints after the subject has been 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.

10.2.2.2.3 Physical Examination

The following physical examination will be performed at designated timepoints 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

10.2.2.3 Adverse Events

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

10.2.2.4 Evaluations of Patch and Dermal Assessment

Patch Adhesion

Patch adhesion will be assessed in two ways (in-clinic and at-home). At each clinic visit, patch adhesion will be assessed by the investigator or a designee 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 Treatment Phase at home, subjects will report on any incidence of patch detachment in the diary.

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 (Berger and Bowman 1982) 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

- 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

- 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

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."

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."

During the treatment phase at home, subjects will complete a questionnaire about skin irritation in the diary.

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. Any discomfort mentioned should be recorded 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 Treatment Phase at home, subjects will complete a questionnaire about discomfort in the diary.

Adhesive Residue

At each clinic visit, the amount of adhesive residue remaining at the application site where the previous patch was applied will be examined by the investigator or a designee and scored according to the scale below:

- 0 = None
- 1 = Light
- 2 = Medium
- 3 = Heavy
- 4 = Patch not present

During the treatment phase at home, subjects will complete a questionnaire about adhesive residue in the diary.

10.2.3 Pharmacokinetic Assessments

Blood samples for the determination of plasma diclofenac concentrations will be collected at specified visits after the application of the study drug as per the Schedule of Events in attachment 17.1. A volume of approximately 4 mL of blood will be collected at Visit 4 (Day 14) and Visit 5 (Day 28); or at the Early Termination Visit, if applicable. The LC/MS/MS validation method will be used to analyze the plasma sample to determine the diclofenac concentrations and blood sampling times will be recorded.

The total blood volume collected will be approximately 40 mL (inclusive of pharmacokinetic and clinical safety laboratory collections).

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as 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 quality, of the disease or condition during the Treatment Phase (Worsening of a pre-existing condition is considered an AE.).

Events occurring in subjects treated with placebo are also 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 and not the elevated ALT should be listed as the AE).
- 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 adverse event 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 adverse reaction 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
- 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.
- Is a congenital anomaly.

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 unless it is suspected that study drug interacted with a contraceptive method and led to the pregnancy.

- 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 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 Treatment Phase or terminate early will continue to be monitored for AEs for 30 days from last day for study treatment, unless 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.
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.

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, if 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 AEs occur in a subject that is not tolerable, 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 medication) 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 [redacted] within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the sponsor by one of the following methods:

All SAEs, irrespective of relationship to study treatment, must be reported as soon as possible but no later than 1 business day by Fax to:

Email: [redacted]

The "Clinical Trial Serious Adverse Event Report Form (SAE form)" must be used for reporting.

It is very important that the SAE report form 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 serious adverse events should be forwarded within one business day 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.

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 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 year of birth
- Subject's gender
- Date of first dose of study drug
- Date of last dose of study drug, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria that were met
- 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? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

The investigator must fax/mail a written SAE Report Form that describes the SAE to the recipients of the initial information, who will forward the information to the sponsor.

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 Report Form, together with the following information (adverse event, date of occurrence, subject ID, 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 guidances) 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

Nonserious AEs will be recorded in the eCRF page and reported by [redacted] to Noven. Special Considerations.

11.2.7 Adverse Events of Special Interest

The overall systemic safety profile of diclofenac is well known and established as reflected in the Investigator's Brochure (IB) including Developmental Core Safety Information, which are in part based on the current label of the [redacted] In patients taking [redacted]

The overall safety of HP-5000 patches at doses ranging from [redacted]. The HP-5000 patches used in the clinical studies [redacted] Some of the commonly reported AEs across the [redacted] remaining commonly reported AEs are

either known adverse reactions to other commercially available dose forms that contain diclofenac (application site pruritus, back pain, and myalgia with diclofenac containing solutions or patches) or consistent with events of application site skin reactions commonly reported as AEs with other topical medications that contain diclofenac [redacted]

11.2.8 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 [redacted] Pharmacovigilance using the Pregnancy Data Collection Form via the same fax number and/or 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 an Exposure in Utero form provided by the sponsor or its designee.

Pregnancies must be reported as soon as possible, but no later than 1 business day, by Fax to:

Email: [redacted]

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy.

All Pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than one business day.

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

The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score from Baseline and Week 4.

13.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1, and Week 2
- WOMAC LK3.1 OA Index (stiffness)
- WOMAC LK3.1 OA Index (physical function)
- WOMAC LK3.1 OA Index (composite score)
- Patient Global Assessment
- Patient Global Impression of Change
- Pain intensity assessed on an 11-point NRS
- Use of rescue medication

13.1.3 Safety Endpoints

- Adverse events, AEs leading to discontinuation from the study drug, SAEs, and deaths.
- Change from baseline in clinical laboratory results (including fasting glucose and lipids), ECG results, body weight, and vital signs.
- Dermal safety: adhesion, irritation, discomfort, and adhesive residue.

13.1.4 Pharmacokinetics Endpoint

Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] on Day 14 and 28 (or at the Early Termination Visit).

13.2. Sample Size Determination

Assuming an effect size of [redacted] on the change in WOMAC pain score from baseline to Week 4 between active HP-5000[redacted] and HP-5000-[redacted] treatments and placebo, the probability for detecting the clinically meaningful effect size [redacted] or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the study and included in the primary analysis set should be

approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.

13.3. Analysis Populations

The following 4 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.
- Full Analysis Set (FAS): Includes all randomized subjects who have had at least 1 patch of double-blind study drug applied and who have a Baseline WOMAC pain score and at least 1 post-Baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.
- 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. I n 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.
- Pharmacokinetic Analysis Set (PAS): Includes all subjects who have received at least 1 dose of study drug during the double-blind treatment phase and have at least 1 blood sample for PK assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (e.g., early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion.

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 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 statistics 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 Clinical Study Report.

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, and weight. 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 FAS 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 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are:

- HP-5000[redacted] versus placebo
- HP-5000[redacted] versus placebo

The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (HP-5000 dose group *vs*. placebo) in the change from Baseline to Week 4 in WOMAC pain score in all subjects as randomized, under the assumption that all randomized patients remain on their randomized treatment throughout the study. WOMAC scores obtained more than 24 hours after discontinuation of study drug will be excluded as a-priori defined outliers.

The primary efficacy variable, the change from Baseline to Week 4 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[redacted] HP-5000-[redacted] 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.

The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed.

Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. These analyses may include multiple imputation and pattern-mixture models for handling of missing data. Details will be provided in the SAP. The analyses will be performed according to the National Academy of Sciences (2010) guidelines.[8]

13.4.3.2 Analyses for Secondary Endpoint

The following secondary endpoints will use the change in mean for analysis (as applicable):

- WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1, and Week 2
- WOMAC LK3.1 OA Index (stiffness)
- WOMAC LK3.1 OA Index (physical function)
- WOMAC LK3.1 OA Index (composite score)
- Patient Global Assessment
- Patient Global Impression of Change
- Pain intensity assessed on an 11-point NRS
- Use of rescue medication

Additional categorical response analyses may be performed; additional details will be provided in the SAP.

13.4.4 Safety and Tolerability 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 safety 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 Medical Dictionary for Regulatory Activities (MedDRA), **Version 19**.

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 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 Anatomic Therapeutic Classification (ATC) codes using the current version (2017) of WHO Drug. Summaries will be prepared using the coded generic term. All prior and concomitant medications recorded in the eCRF will be listed.

13.4.4.3 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.

13.4.4.4 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, body-mass index, 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.

13.4.4.5 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, QTc interval (both correction methods), and HR for each treatment group at each time point.

13.4.4.6 Physical Examination Findings

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

13.4.4.7 Dermal Safety

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

13.4.5 Pharmacokinetic Analyses

Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] will be evaluated and summarized as descriptive statistics by treatment.

13.4.6 Interim Analysis

No interim analyses are planned.

13.5. Database

The final database will be compliant with 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 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 17.2**), 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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. 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 informed consent form (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. In certain cases, and case-by-case basis, a subject may be rescreened once and permitted into the study following consultation with the Sponsor and Medical Monitor who must make an assessment that the subject is eligible to participate in the study.

14.3. Study Documents

All documentation and material provided by Noven or [redacted] 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-05 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 17.2**), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

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.

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. 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. 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. While on site, 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 17.2**), 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.

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
- TMF 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 Closur*e**:

At the end of the study, all study sites will be closed. 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:

- Noncompliance 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.

14.5.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

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 informed consent form. After completion, informed consent forms will be kept and archived by the investigator in the investigator's study file.

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 informed consent form(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. REFERENCES

1 Barbour KE, Helmick CG, Theis KA, Murphy LB, Hootman JM, Brady TJ, Cheng YJ. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2010-2012. MMWR 2013;62 (44):869-873.

2 Centers for Disease Control and Prevention. https://www.cdc.gov/arthritis/data_statistics/index. htm. Accessed 24 June 2016.

3 Investigational Brochure, Diclofenac Sodium Transdermal Drug Delivery System, HP-5000 Transdermal Patch. Noven Pharmaceuticals, Inc. [redacted]. Edition No. 03, September 9, 2014.

4 Berger, R.S., and .J.P. Bowman. "A Reappraisal of the 21 -day Cumulative Irritation Test in Man." Toxicol. - (It. 6' Ocz~lw Toxicol., 1982; l(2); 109- 115.

5 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.

6 Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14-17.

7 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.

8 National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The prevention and treatment of missing data in clinical trials. Washington (DC): National Academies Press (US); 2010.

17. ATTACHMENTS

17.1. Schedule of Events

Phase	Screening			Double-blind Treatment						Follow-up	End of Treatment
Period		**Washout**	**Baseline**								
Week	**-1**				**1**		**2**		**4**	**5**	
Clinic visit	**1**		**2**		**3**		**4**		**5**		
Phone visit		**1**								**2**	
Study Day	**-28 to -14**[j]	**-25 to -1**[j]	**0**	**1 to 6**	**7**	**8 to 13**	**14**	**15 to 27**	**28**	**35**	
Visit Window (Days)					**±2**		**±2**		**±2**		
Assessments/Procedures											
Informed Consent	X										
Demographics	X										
Medical History	X										
I/E criteria	X		X								
Randomization (IVRS)[a]			X								
Physical Examination	X								X		X
Vital signs[b]	X		X		X		X		X		X
Height	X										
Weight	X		X						X		X
WOMAC Pain[c]	X		X		X		X		X		X
Patient Global Assessment			X		X		X		X		X
Patient Global Impression of Change					X		X		X		X
Pain Intensity 11-Point NRS	X	X	X	X	X	X	X	X	X		X
Dispense Rescue Medication	X		X		X		X				
Use of Rescue Medication[d]		X	X[d]	X	X	X	X	X	X		X
12-lead ECG[e]	X		X						X		X
Clinical Laboratory[f]	X[f]		X						X		X
Urine Pregnancy Test	X		X		X		X		X		X
Drug Screen	X		X								
Alcohol Test	X		X								
PK Blood Sample							X		X		X

Subject Diary[g]	X	X	X	X	X	X	X	X	X		X
Study Medication Application[h]				X[h]	X	X	X	X			
Dermal Evaluations[i]			X	X[k]	X	X[k]	X	X[k]	X		X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[l]			X	X	X	X	X	X	X	X	X
X-Ray[m]	X										
Drug Accountability			X[n]		X		X		X		X

Abbreviations: AE = adverse event; ET = early termination; ECG = electrocardiogram; ID = identification; I/E = inclusion/exclusion; IVRS = interactive voice response system; NRS = numeric rating scale; PK = pharmacokinetic; WOMAC = Western Ontario and McMaster Universities Arthritis Index.

a. Subjects will be randomized to HP-5000[redacted] HP-5000[redacted] or placebo in a 1:1:2 ratio.
b. Vital signs, including heart rate, respiratory rate, and sitting blood pressure will be measured after the subject has been in a sitting position for 5 minutes.
c. WOMAC Pain will include WOMAC pain intensity, WOMAC stiffness, and WOMAC physical function.
d. Rescue medication may be used during the Washout Period except within 2 calendar days prior to Visit 2.
e. A standard 12-lead electrocardiogram (ECG) will be performed after the subject has been supine for at least 5 minutes.
f. Clinical laboratory testing includes hematology, biochemistry, and urinalysis. Results from laboratory testing done at Screening Visit will used for confirmation of subject eligibility at Baseline Visit.
g. Subjects will be instructed in the use in the use of the electronic diary at the Screening Visit. For each 28-day administration period, subjects will be asked to record their daily intake/use of study drug in the electronic diary.
h. Study treatment will applied on Day 1 of the Treatment Phase. Instructions for application and removal of study drug patches will be provided to the subject on Baseline Visit.
i. Dermal evaluations will assess skin adhesion, irritation, discomfort, and adhesive residue.
j. Screening/Washout Period should be up to 28 days. Washout Period will be initiated 3 days after Screening Visit.
k. During the treatment period at home, subjects will report the incidence of patch detachment by answering Yes or No.
l. AEs will be collected after the first dosing.
m. Historical X-rays done within one year prior to the Screening Visit are acceptable. If subject does NOT have any 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.
n. Only for rescue medication.

17.2. Investigator's Agreement

PROTOCOL NUMBER: HP-5000-US-05

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2 Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee

FINAL PROTOCOL: Amendment #1: 22 May 2017

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

This is an example of the WOMAC index. The actual index will be provided in the eCRF.

The Western Ontario and McMaster Universities Osteoarthritis Index
(WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

18.2. Patient Global Assessment Scale (PGA)

This is a sample questionnaire. The actual questionnaire will be provided in the study reference manual.

The subject will provide their overall impression of the status of their OA in the target knee on a 5-point scale where 0 = "Very Good" and 4 = "Very Poor."

Subjects will be asked to complete the following statement: "How would you rate your osteoarthritis condition over the last 24 hours?" The response options include the following:

1. Very Good
2. Good
3. Moderate
4. Poor
5. Very Poor

18.3. Patient Global Impression of Change Scale

This is an example of the Patient Global Impression of Change (PGIC) scale. The actual instrument will be included in the study reference manual.

The Patient Global Impression of Change 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." 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

18.4. 11-Point Numeric Rating Scale (NRS)

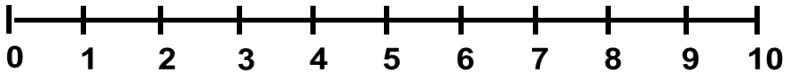
This is a sample of the Numerical Rating Scale. Please use the rating scale provided in the study reference manual.

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.

Ask the subject the following question: "On a scale of 0 – 10, with 0 being 'no pain' and 10 being the 'worst possible pain', how would you rate your pain over the last 24 hours?"

The intent of the question is to gain an understanding of the intensity of the patient's target knee pain at over the last 24 hours.



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 94 (2001) 149–158Regulations and Good Clinical Practice Guidelines.

18.4.1 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

18.4.2 Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

[redacted]

PROTOCOL

PRODUCT NAME/NUMBER:	HP-5000 topical patch
PROTOCOL NUMBER:	HP-5000-US-05
DEVELOPMENT PHASE:	2
PROTOCOL TITLE:	A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee
PROTOCOL DATE:	Final v1.0; 31 Oct 2016
SPONSORED BY:	Noven Pharmaceuticals, Inc. 350 Fifth Ave, 37th Floor New York, New York, 10118 USA 1 (212) 682-4420
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-05

PROTOCOL TITLE: A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) 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]

Date

[redacted]

Date

2. SYNOPSIS

PRODUCT NAME/NUMBER	HP-5000
PROTOCOL NUMBER	HP-5000-US-05
DEVELOPMENT PHASE	2
PROTOCOL TITLE	A 4-week, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of HP-5000 in subjects with osteoarthritis (OA) of the knee
INDICATION	Osteoarthritis pain of the knee
OBJECTIVES	Primary: • To evaluate the efficacy of HP-5000 compared to placebo • To evaluate the safety of HP-5000 compared to placebo Secondary: • To assess the skin irritation, discomfort, adhesion, and adhesive residue of HP-5000 • To assess the plasma concentrations of diclofenac following administration of HP-5000
STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled study evaluating 2 formulations of HP-5000 in subjects with OA of the knee. The study will consist of a 10- to 17-day screening period that includes washout of current prescription and over the counter (OTC) analgesics, a 4-week double-blind treatment period, and a 1-week safety follow-up period. Subjects will be seen in the clinic at the screening visit, baseline visit (Day 0), Day 7, Day 14, Day 28 (end of study), and Day 35 (safety follow-up visit). A ±2-day window will be allowed for all clinic visits during the double-blind treatment period. Site personnel will also contact the subjects by phone 3 days after the screening visit in order to instruct them to begin the washout period. **Screening/Washout Period:** Subjects will be seen in the clinic, and the study will be described to them. Subjects will be asked to sign the informed consent form. 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. Upon completion of screening, subjects whose eligibility has been preliminarily confirmed will be contacted by telephone (3 days after the screening visit) and asked to wash out of current medications for at least 7 days (up to 14 days) prior to the baseline visit. During the washout period, rescue medication (acetaminophen [APAP]) will be permitted (a maximum of 2 g/day) except within 2 calendar days prior to the baseline visit (ie, rescue medication is prohibited from Day -2 until clinic visit on Day 0). Subjects will complete daily electronic diaries (eDiaries) to record pain severity of their target knee and rescue medication usage from the day of screening visit to the day of the baseline visit. **Double-blind Treatment Period:** Following completion of the Screening/Wash-out Period, subjects will return to the clinic for their Baseline visit (Day 0). Eligible subjects will be randomized to either HP-5000[redacted] HP-5000-[redacted] or placebo in a 1:1:2 ratio. Subjects will apply a single patch to the target knee [redacted] The patch will be removed [redacted] and a new patch will be applied to a different site on the target knee. Subjects will be instructed to rotate the patch application [redacted] to alternate sides of the target knee. Subjects will also complete daily diaries to record patch application and removal times, adhesion assessments, pain assessments, and amount of rescue medication

	taken daily, if applicable. A maximum of 2 g/day of acetaminophen, also known as APAP will be allowed as rescue medication for the treatment of target knee and non-target knee pain except within the 1 calendar day prior to each clinic visit (eg, rescue medication is prohibited from Day 6 until clinic visit on Day 7 if subject will visit the study site on Day 7). Subjects are not allowed to apply HP-5000 on the non-target knee at any time in the study period. Blood samples will be collected on Day 14 and 28 (or at the early termination-visit) where plasma will be analyzed for diclofenac concentrations. Actual blood sampling times will be recorded. **Follow-up Period:** Subjects will have a safety visit approximately 7 days after the end-of-treatment visit (Week 4). Subjects will return to the clinic or will receive a telephone call, at the discretion of the investigator.
PLANNED NUMBER OF SUBJECTS	The total number of subjects randomized in the trial and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY ENTRY CRITERIA	The following inclusion and exclusion criteria must be met by subjects to participate in this study: **Inclusion criteria**: 1. Healthy 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, AND b. Knee pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.) AND c. The pain in the target knee required the use of nonsteroidal antiinflammatory drugs (NSAIDs) 2. On stable pain therapy (ie, at least 3 days per week for the previous month) with an oral or topical NSAID prescribed by physician for 30 days prior to the screening visit 3. Have 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 4. Have at least moderate pain in the designated study knee; [redacted] 5. Have a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline visit 6. If female: a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the screening visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile). b. Subject could not become pregnant because she is surgically sterile (hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months), or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the screening visit

	7. Signed informed consent form 8. Able to swallow and tolerate rescue medication with APAP (moderately sized tablets) **Exclusion criteria:** 1. Body mass index (BMI) > 40 2. At Screening and Baseline (Day 0), the non-target knee pain severity score is [redacted] 3. Any subject who disobeyed the restriction of prohibited therapies (eg, rescue medication) during Screening/Washout period. 4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma) 5. Clinically significant elevation of serum creatinine (176.8 μmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN]) 6. Known allergy or hypersensitivity to the use of diclofenac, [redacted], ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID 7. Severe, uncontrolled cardiac, renal, hepatic or other systemic disease 8. A documented (upper GI series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within 6 months prior to screening visit 9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at screening or baseline 10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups 11. MAJOR SURGERY: Previous damage or surgery to the knee at any time (ie, damage/reconstruction of the anterior or posterior cruciate ligaments) 12. MINOR SURGERY on the target knee defined as anything other than major surgery as defined above less than 1 year before enrolment 13. Current treatment with oral, topical, intra-articular, or intra-muscular corticosteroids on the target knee within 90 days of screening visit or into any other joint within 30 days of screening 14. Any subject who had received intra-articular viscosupplementation (eg, Synvisc®) in the target knee 90 days prior to screening visit 15. Any subject who had used opioids 7 days prior to the screening visit. 16. Any subject who had previous exposure to HP-5000 17. Use of another investigational drug within 30 days prior to study entry 18. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause 19. Any subject with fibromyalgia 20. Any painful or disabling conditions affecting the knee or leg 21. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (ie, infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo 22. Any subject expecting to have knee replacement surgery within 6 months 23. Any subject with a psychiatric condition which in opinion of the investigator, may interfere with participation in the study

	24. 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.
INVESTIGATIONAL PRODUCT	HP-5000 [redacted] topical patch Each patch contains [redacted] diclofenac sodium. HP-5000 [redacted] topical patch Each patch contains [redacted] diclofenac sodium.
REFERENCE PRODUCTS	Placebo [redacted]: Patches identical in appearance to both HP-5000 [redacted] patch and HP-5000 [redacted] patch but without the active ingredient diclofenac.
TREATMENT REGIMENS	The treatments for each of the treatment arms will be as follows: Treatment Arm — [redacted] Treatment HP-5000 [redacted] — One patch applied [redacted] to alternate side of the target knee (inner or outer). HP-5000 [redacted] — One patch applied [redacted] to alternate side of the target knee (inner or outer). Placebo — One patch applied [redacted] to alternate side of the target knee (inner or outer).
PLANNED STUDY SITES	Approximately [redacted] study sites in the United States.
CRITERIA FOR EVALUATION	Primary efficacy endpoint: The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score between Baseline and Week 4. Secondary efficacy endpoints: • WOMAC LK3.1 OA Index (pain) –change in pain score between Baseline and Week 1 and 2 • WOMAC LK3.1 OA Index (stiffness) • WOMAC LK3.1 OA Index (physical function) • WOMAC LK3.1 OA Index (composite score) • Patient Global Assessment • Patient Global Impression of Change • Pain intensity assessed on an 11-point NRS • Use of rescue medication Safety endpoints: • Adverse events (AEs), AEs leading to discontinuation from the study drug, serious AEs (SAEs), and deaths • Change from baseline in clinical laboratory results (including fasting glucose and lipids), electrocardiogram (ECG) results, body weight, and vital signs • Dermal performance: adhesion, irritation, discomfort, and adhesive residue. Pharmacokinetic endpoint: • Plasma concentrations of diclofenac on Day 14 and 28 (or at the early termination visit).
STATISTICAL METHODS	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 statistics 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. Analysis Populations • 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. • Full Analysis Set (FAS): includes all randomized subjects who have had at least 1 patch of double-blind study medication applied and who have a Baseline WOMAC pain score and at least 1 post-baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment. • Safety Analysis Set (SAF): includes all subjects who have had at least 1 patch of double-blind study medication applied and who have at least 1 post-dose safety measurement during the double-blind treatment period. 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. • Pharmacokinetic Analysis Set (PAS): includes all subjects who have received at least 1 dose of study medication during the double blind treatment period and have at least 1 blood sample for pharmacokinetic (PK) assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (eg, early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion. Primary Efficacy Analysis: The primary efficacy endpoint of this trial is the change from Baseline to Week 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are: • HP-5000[redacted] versus placebo • HP-5000[redacted] versus placebo The primary efficacy variable, the change from baseline to Week 4 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[redacted] HP-5000[redacted] 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. The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed. Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. This analyses may include multiple imputation and pattern-mixture models for handling of missing

	data. Details will be provided in the SAP. The analyses will be performed according to the National Academy of Sciences (2010) guidelines. Analysis of Secondary Efficacy Endpoints: Other secondary efficacy endpoints will be analyzed using the change in mean as appropriate. • WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1 and 2 • WOMAC LK3.1 OA Index (stiffness) • WOMAC LK3.1 OA Index (physical function) • WOMAC LK3.1 OA Index (composite score) • Patient Global Assessment • Patient Global Impression of Change • Pain intensity assessed on an 11-point NRS • Use of rescue medication Additional categorical response analyses may be performed; additional details will be provided in the SAP. Additional categorical response analyses may be performed; additional details will be provided in the SAP. Analysis of Safety: All safety summaries will be descriptive; statistical significance tests may be performed on safety data that will be described in the SAP. Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted. Analysis of PK: Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] will be evaluated and summarized as descriptive statistics by treatment.
SAMPLE SIZE DETERMINATION	Assuming an effect size of [redacted] on the change in WOMAC pain score from baseline to Week 4 between active HP-5000[redacted] and HP-5000[redacted] treatments and placebo, the probability for detecting the clinically meaningful effect size [redacted] or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the trial and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.
STUDY TREATMENT DURATION	The maximum treatment duration for each subject is 4 weeks. The total duration of study participation for each subject is approximately 7 weeks.

3. TABLE OF CONTENTS

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APAP	acetaminophen
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
GCP	Good Clinical Practice
GI	Gastrointestinal
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
IVRS	interactive voice response system
LD	low dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	over the counter
PK	Pharmacokinetics
PAS	pharmacokinetic analysis set
SAE	serious adverse event

SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operation procedure
TEAE	treatment-emergent adverse event
TDDS	transdermal drug delivery system
ULN	upper limit of normal
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 have doctor-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 doctor-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 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 their opioid pain reliever, thereby introducing additional health problems into the equation. There is an unmet need for a safe, reliable, and effective pain medication without the risk and lack of efficacy associated with those currently available.

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

Noven Pharmaceuticals, Inc. has started the development of a formulation of diclofenac sodium for topical administration via a transdermal patch system, the HP-5000 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:

- Transfer of drug into the treatment target area resulting in lower systemic and GI exposure when compared to 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 [redacted] diclofenac transdermal drug delivery system (TDDS), evaluating the pharmacokinetics (PK) and tolerability in 104 healthy volunteers. The lead formulations for this program, HP 5000 [redacted] and HP 5000 [redacted] both of which contain [redacted] diclofenac sodium [redacted] with a patch size of [redacted] were selected based on the diclofenac pharmacokinetic (PK) profile and patch performance characteristics, such as irritation and adhesion on the mobile knee joint application site.

It should be noted that the HP 5000 formulation is also being developed by Noven's parent company, for different indications (ie, and and is referred to as the (also known as . Study has been included in the development program to provide additional safety data.
.

Further details about HP-5000 are found in the Investigator's Brochure.

5.3. Summary of Potential Risks and Benefits

The potential benefits of study participation are that subjects with OA (1) may experience a reduction in pain and inflammation as a result of treatment with the HP-5000 patch and (2) will understand that they are contributing to the scientific knowledge that may lead to expansion of the treatment options for subjects with OA.

The potential risks of study participation include those associated with exposure to the HP-5000 patch and the risks of medical evaluation, including venipuncture.

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

6. OBJECTIVES

6.1. Primary Objective

- To evaluate efficacy of HP-5000 compared to placebo
- To evaluate the safety of HP-5000 compared to placebo

6.2. Secondary Objectives

- Secondary objectives include the following:To assess the skin irritation, discomfort, adhesion, and adhesive residue of HP-5000
- To assess the plasma concentrations of diclofenac following administration of HP-5000

7. STUDY DESIGN

7.1. Overall Study Design and Plan

This 4-week, randomized, double-blind, multicenter, placebo-controlled study is designed to compare the safety and efficacy of HP-5000 with that of placebo in the treatment of OA. Subjects will be randomly assigned to receive 1 of the following 3 treatments in a 1:1:2 ratio: HP-5000 [redacted] patch, HP-5000 [redacted] patch, or placebo patch [redacted] The placebo patch will be identical in appearance to the 2 HP-5000 active patches. The total number of subjects randomized in the trial and included in the primary analysis will be approximately 300. The duration of double-blind treatment is expected to be 4 weeks and the total time in the study will be approximately 7 weeks.

Efficacy will be assessed by the change from baseline values in the Western Ontario and McMaster Universities (WOMAC) LK3.1 OA index for pain. Efficacy assessments will also include the use of the WOMAC LK3.1 OA index for stiffness, physical function, and composite score, the Patient Global Assessment, the Patient Global Impression of Change, pain intensity assessed on an 11-point NRS and the subjects' use of rescue medication.

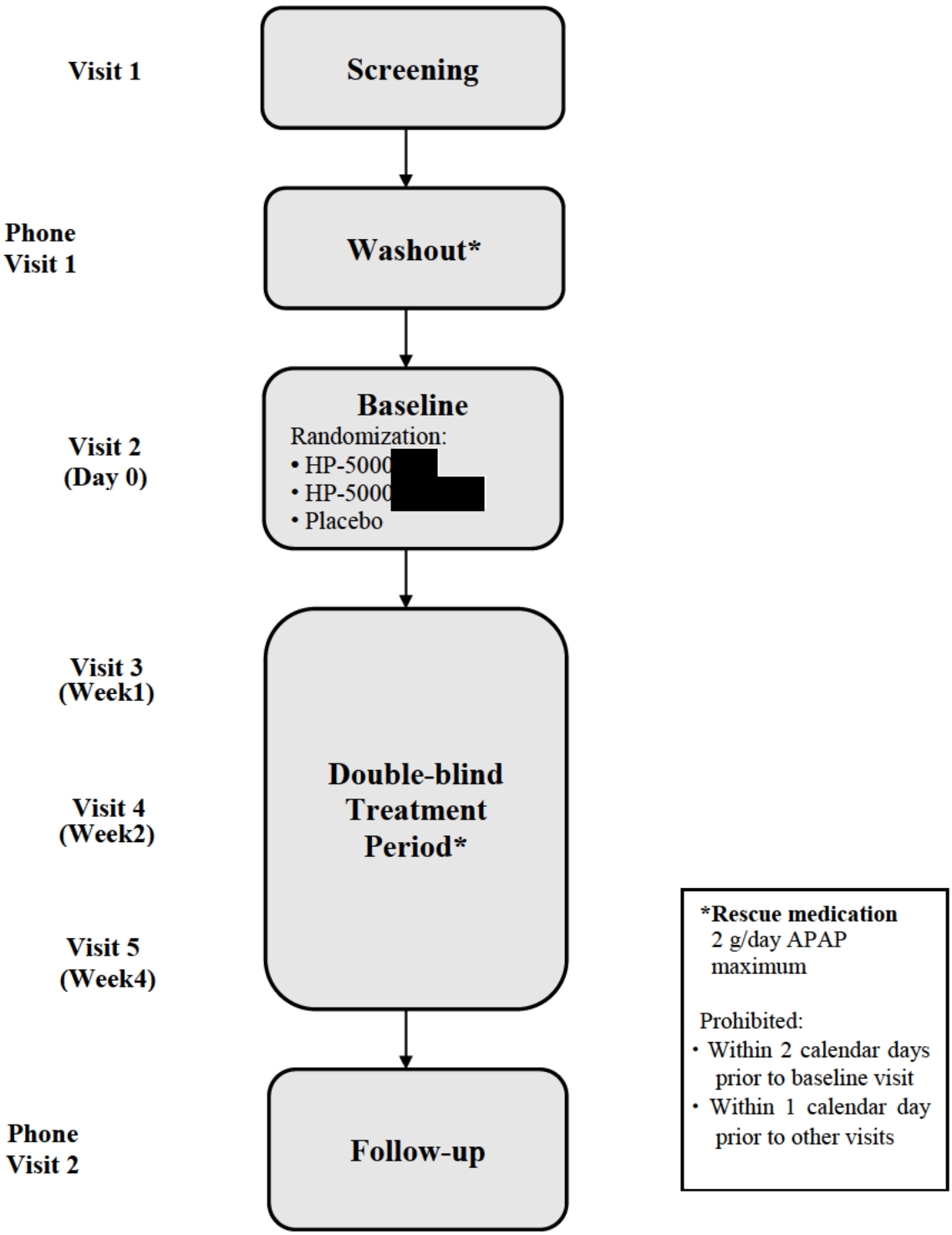
Safety will be assessed by evaluating adverse events (AEs), physical examination findings, vital sign measurements, electrocardiogram (ECGs), clinical laboratory test results, and body weight. All AEs observed by the study personnel or reported by the subject during the study (from the time of study drug administration through the posttreatment visit) will be documented.

Dermal characteristics will be assessed by 5-point numerical scale of adhesion, Berger and Bowman scale of Irritation, 5-point numerical scale of Discomfort, and 5-point numerical scale of Adhesive Residue.[4] In addition, subjects will record the [redacted] patch application and removal times in electronic diaries along with any incidence of patch detachment.

Plasma concentrations of diclofenac will be assessed by venous blood sampling on Day 14 and 28 (or at the early termination visit).

Figure 1 presents a schematic view of the study design.

Figure 1 Study Design



7.2. Discussion of Study Design

The double-blind, placebo-controlled study uses 3 patches (2 formulations of HP-5000 and placebo) of identical appearance to ensure blinding.

The use of rescue medication is prohibited within 2 calendar days prior to the baseline visit and within 1 calender day prior to clinic visits during the treatment period, thus ensuring the integrity of the assessments.

7.3. Study Sites

The study will take place at approximately [redacted] sites in the US. Each site is anticipated to screen a sufficient number of subjects to be able to randomize an aggregate number of approximately 300 subjects.

8. SUBJECT POPULATION

8.1. Selection of Study Population

A screening log of potential study candidates and/or an enrollment log of enrolled subjects must be maintained at each study site.

8.2. Study Entry Criteria

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

8.2.1 Inclusion Criteria

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

1. Healthy 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, AND
    b. Knee pain in the target knee for 30 days of the preceding month (periarticular knee pain due to OA and not due to other conditions such as bursitis, tendonitis, etc.) AND
    c. The pain in the target knee required the use of nonsteroidal antiinflammatory drugs (NSAIDs)
2. On stable pain therapy (ie, at least 3 days per week for the previous month) with an oral or topical NSAID prescribed by physician for 30 days prior to the screening visit
3. Have 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
4. Have at least moderate pain in the designated study knee;

5. Have a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score of [redacted] at the Baseline visit
6. If female:
    a. Subject is not breastfeeding or pregnant as confirmed by a negative pregnancy test at or within 48 hours of the screening visit. Women of child-bearing potential must use an acceptable method of contraception (including oral contraceptives, hormone implant, intrauterine device, and spermicide with barrier method, or male sexual partner[s] surgically sterile).
    b. Subject could not become pregnant because she is surgically sterile (hysterectomy or tubal ligation), confirmed to be postmenopausal (having amenorrhea for ≥12 months),

or has had a hysterectomy with or without bilateral oophorectomy at least 6 months prior to the screening visit

7. Signed informed consent form
8. Able to swallow and tolerate rescue medication with APAP (moderately sized tablets)

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
2. At Screening and Baseline (Day 0), the non-target knee pain severity score is [redacted]
3. Any subject who disobeyed the restriction of prohibited therapies (eg, rescue medication) during Screening/Washout period.
4. Secondary OA of the knee (rheumatoid arthritis, gout, psoriasis, syphilitic neuropathy, ochronosis, metabolic or other primary bone disease or acute trauma)
5. Clinically significant elevation of serum creatinine (176.8 µmol/L), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (3 x upper limit of normal [ULN])
6. Known allergy or hypersensitivity to the use of diclofenac, [redacted] ethanol, acetylsalicylic acid (aspirin [ASA]), or any other NSAID
7. Severe, uncontrolled cardiac, renal, hepatic or other systemic disease
8. A documented (upper GI series or endoscopy) gastroduodenal ulcer or any GI bleeding (except hemorrhoidal) within 6 months prior to screening visit
9. Documented history of alcohol or drug abuse within 1 year prior to study entry or positive alcohol/drug screen findings at screening or baseline
10. Presence of chondrocalcinosis on X-ray if associated with a history of pseudogout or inflammatory flare-ups
11. MAJOR SURGERY: Previous damage or surgery to the knee at any time (ie, damage/reconstruction of the anterior or posterior cruciate ligaments)
12. MINOR SURGERY on the target knee defined as anything other than major surgery as defined above less than 1 year before enrolment
13. Current treatment with oral, topical, intra-articular, or intra-muscular corticosteroids on the target knee within 90 days of screening visit or into any other joint within 30 days of screening
14. Any subject who had received intra-articular viscosupplementation (eg, Synvisc®) in the target knee 90 days prior to screening visit
15. Any subject who had used opioids 7 days prior to the screening visit.
16. Any subject who had previous exposure to HP-5000
17. Use of another investigational drug within 30 days prior to study entry
18. Any subject with resolved, ongoing, or pending litigation or disability related to any health-related cause
19. Any subject with fibromyalgia
20. Any painful or disabling conditions affecting the knee or leg

21. Any skin abnormality present at the potential patch application site that is likely to be aggravated by the study drug (ie, infection, rash, excessive fragility or dryness, any cut or abrasion), presence of tattoo, excessive hair or open sores, or scar tissue. Presence of significant skin disorder such as atrophy, psoriasis, or vitiligo
22. Any subject expecting to have knee replacement surgery within 6 months
23. Any subject with a psychiatric condition which in opinion of the investigator, may interfere with participation in the study
24. 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..

8.3. Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means.

Subjects may be withdrawn if continuing in the study is not in the subject's best interest, their condition worsens during the study, or for safety reasons, as determined by the investigator. Subjects may also be withdrawn due to lack of compliance with the protocol or if the subject is unwilling to continue participation in the trial.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that are to be conducted at the completion of the study should be performed at the time of premature discontinuation.

8.4. 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 the IP:

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

One patch [redacted] will be applied [redacted] to alternate sides of the target knee. Detailed application instructions for subjects will be provided in a separate manual.

HP-5000 will be supplied as [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):

- Blinded packaged lot number
- Protocol number
- Subject number (record at the time of dispensing)
- Directions for use
- 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

Sites and subjects will be instructed to save all empty packaging or packaging containing unused patches for final disposition by the sponsor or contract pharmacy.

9.1.2 Packaging

In the double-blind treatment phase HP-5000 [redacted] HP-5000 [redacted] and placebo patches will be packaged so as to be blinded to the investigator, the study clinic personnel, and subjects.

9.2. Treatments Administered

HP-5000 will be administered [redacted] for a maximum of 28 days.

The treatment arms for this study are the following:

Treatment Arm	[redacted] Treatment
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
HP-5000[redacted]	One patch applied [redacted] to alternate side of the target knee (inner or outer).
Placebo	One patch applied [redacted] to alternate side of the target knee (inner or outer).

Patch Application

An example of the guidance information to be provided to subjects for applying, securing, and removing the patch will be provided separately.

9.3. Dispensing and Storage

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

The investigator must confirm the receipt of the IP with his/her signature. A copy of this receipt must be kept by the investigator, and another copy will be stored at Noven Pharmaceuticals, Inc. (hereafter referred to as "Noven"), and/or [redacted] Until the IP is dispensed to the subjects, it must be stored at 25°C and in a dry place in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The storage area will be accessible only to those persons authorized by the investigator to dispense the IP.

9.4. Method of Assigning Subjects to Treatment Groups

In this parallel-group randomized study, subjects who meet study entry criteria will be randomly assigned in a 1:1:2 ratio to HP-5000[redacted] HP-5000[redacted] or placebo patches. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. The randomization numbers will be assigned sequentially through a central interactive voice response system (IVRS) as subjects are entered into the study. The study center will not be a blocking factor in the randomization schedule.

The randomization schedule will be prepared by Premier Research before the start of the study. No one involved in the clinical conduct will have access to the randomization schedule before 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 supplied that will be identical in appearance to the HP-5000 and HP-5000 patches.

All subjects, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a prespecified unblinded statistician and programmer from who will have access to the randomization code, and the unblinded pharmacist at each study site. 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, then 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 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 permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment.

Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study personnel will use the IVRS. If the investigator is not able to discuss treatment unblinding in advance, then he/she must notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment.

The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

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 dose of diclofenac in a patch size of applied and rotated between 2 sites on the knee is based on the following considerations:

-
- 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.

The data from previous studies investigating irritation and PK support the proposed dose of and a patch size of and rotated between on the knee for the lead formulations (HP-5000 and HP-5000

9.7. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.8. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IP including the date, quantity, batch or code number, and identification of subjects (subject number [and initials]) who received the IP. The investigator will not supply the IP to any person except those named as subinvestigators (on the Form FDA 1572), designated study personnel, and subjects in this study. The investigator will not dispense the IP from any study sites other than those listed (on the Form FDA 1572). The IPs may not be relabeled or reassigned for use by other subjects. If any of the IP 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.

Upon completion of the study, the IP must be left in the original packaging and returned to the sponsor or designee for destruction or return.

9.9. Treatment Compliance

Treatment compliance with IP regimens will be assessed by study personnel via the counts of returned unused patches and by questioning the subject, if necessary, at every post-randomization visit. A subject who is not compliant (used 6 or less patches per week) will be counseled at each visit on the importance of taking the IP as instructed. A subject who is deemed noncompliant on 2 consecutive visits may be withdrawn from the study.

For each 28-day administration period, subjects will be asked to record their daily intake/use of rescue medication/IP in the diary. Deviations from the planned doses (missed dose or timing) will be recorded on the subjects' eCRF. These diaries will be reviewed by study personnel at each visit and will be collected as source documents. Information from that subject diary will be transcribed on the appropriate eCRF pages for documentation of subject compliance with IP.

9.10. Permitted and Prohibited Therapies

Some designated therapies are prohibited during the study. Prior to the double-blind treatment period, subjects will stop taking all prescription and over-the-counter (OTC) analgesic medications for at least 7 days; however, rescue medication (acetaminophen [APAP]) is permitted during the wash-out if required. A maximum of 2 g/day of APAP will be allowed for rescue treatment of both target and non-target knee pain except within the 2 calendar days prior to the baseline visit (ie, rescue medication is prohibited from Day -2 until clinic visit on Day 0) and within the 1 calendar day prior to each clinic visit (eg, rescue medication is prohibited from Day 6 until clinic visit on Day 7 if the subject will visit the study site on Day 7). APAP will be prepared by the Sponsor. Subjects are not allowed to apply HP-5000 on the non-target knee at any time in the study period.

All concomitant medications used (including OTC medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.10.1 Permitted Therapies

Glucosamine, chondroitin, and antidepressants (for indication of depression) will be allowed if used as stable therapy for 90 days prior to screening visit. 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

Any NSAIDs (selective or nonselective), any opioids, APAP (>2 g/day), ASA (>81 mg/day), corticosteroids (a stable does by inhalation for seasonal allergies and/or topical use for dermatologic allergies are allowed), anticonvulsants (ie, pregabalin and gabapentine), muscle relaxants, other oral analgesics (prescribed or 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] or capsaicin, any intra-articular treatments for the knee, any nonpharmaceutical therapy or device to relieve knee pain (including physiotherapy, massage therapy, hot wax therapy etc.) may not be taken during the study.

Glucosamine, chondroitin, and antidepressants (for the indication of depression) will be allowed if used as stable therapy for 90 days prior to screening visit. However, if in use for fewer than 90 days, these drugs will be considered as prohibited concomitant medications and will require washout.

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

9.11. Treatment after End of Study

After completing the study, each subject will be referred to their primary care physician and treated 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 concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Section 17.1). 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 study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Periods and Visits

10.1.1 Screening and Washout

10.1.1.1 Screening

Screening/Washout period should be at least 10 days up to 17 days prior to the baseline visit. The subject must be screened before entering the washout period of the study. The following procedures will be performed at screening:

1. Obtain written informed consent and assign a screening number.
2. Assess inclusion/exclusion criteria.
3. Collect demographic information and record medical history, including current therapies (eg, prescription and nonprescription medications).
4. Perform a physical examination including weight, height, and vital signs.
5. Perform urine drug, alcohol and pregnancy tests.
6. Identify the target knee. The subject will be instructed to refer to this specific (target) knee throughout his/her participation in the study when responding to study efficacy assessment.
7. Instruct the subject how to use NRS and WOMAC before performing first assessments
8. Perform WOMAC pain intensity, stiffness and physical function assessments
9. Calculate WOMAC composite score
10. Perform NRS evaluation for the target knee and the non-target knee pain, review of x-ray of the target knee, 12-lead ECG, and laboratory tests to determine eligibility.
11. Instruct the subject in the use of an electronic diary
12. Dispense rescue medication.
13. Dispense electronic diary.

10.1.1.2 Washout Period

Three days after the screening visit, subjects whose eligibility has been preliminarily confirmed at screening will be asked to wash out of current medications for at least 7 days (up to 14 days). During this period, the following will take place:

1. Electronic diary NRS pain scores before the Washout Period will be reviewed by the investigator or the study coordinator. A record of this review will be recorded in the source documents and eCRFs.

2. Subjects will stop taking all prescription and OTC analgesic medications, but will be informed that rescue medication may be used (a maximum of 2 g/day) except within 2 calendar days prior to the baseline visit.
3. Perform an NRS assessment for the target knee pain.
4. Review subject's use of rescue medication.

10.1.2 Baseline Visit (Day 0)

The following will take place during the baseline visit (Day 0):

1. Review subject's continued eligibility relative to inclusion/exclusion criteria.
2. Randomly assign the subject to a treatment group using IVRS and assign a subject ID number.
3. Obtain vital sign measurements, including weight.
4. Perform WOMAC pain intensity, stiffness and physical function assessments.
5. Calculate WOMAC composite score
6. Perform Patient's Global Assessment.
7. Perform an NRS 11-point pain assessment for the target knee and non-target knee pain.
8. Review subject's use of rescue medication.
9. Perform a 12-lead ECG.
10. Obtain blood and urine samples for laboratory testing.
11. Perform a urine pregnancy test.
12. Review the subject's diary entries.
13. Perform baseline dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
14. Review subject's use of prior medications.
15. Dispense rescue medication and perform rescue medication accountability/ reconciliation
16. Dispense double-blind study medication and instruct subjects on proper patch application. Subjects should apply the first day of study medication to the target knee in the presence of site staff, unless the subject intends to shower/bathe later in the day. For this scenario, the first patch should be applied at home after showering/bathing.
17. Subjects will be instructed not to bathe or shower while wearing the study medication; a bath or a shower may be taken in the morning/in the evening before the first patch is applied.
18. Subjects will also be instructed not to participate in strenuous activities or other activities that cause heavy perspiration during the double-blind treatment period.

10.1.3 Double-blind Treatment Period

During the 4-week double-blind treatment period, the following will take place:

1. Obtain vital sign measurements (during clinic Visits 3, 4, and 5, only).
2. Perform WOMAC pain intensity, stiffness and physical function assessments (during clinic Visits 3, 4, and 5, only).
3. Calculate WOMAC composite score (during clinic Visits 3, 4, and 5, only).
4. Perform Patient Global Assessment (during clinic Visits 3, 4, and 5)
5. Perform Patient Global Impression of Change (during clinic Visits 3, 4, and 5).

6. Perform daily NRS 11-point pain assessments for the target knee pain.
7. Review subject's use of rescue medication
8. Perform a urine pregnancy test (during clinic Visits 3, 4, and 5)
9. Re-instruct the subject concerning the patch application method if the subject has a problem with patch application and/or patch adhesion
10. Dispense study medication/rescue medication and perform drug accountability/ reconciliation
11. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
12. Review subject's use of concomitant medications
13. Review AEs
14. Review the subjects' diary entries
15. Obtain blood samples for laboratory testing (clinic Visit 5).
16. Obtain subject's weight (clinic Visit 5).
17. Obtain pharmacokinetic blood sample (clinic Visit 4 and 5).
18. Perform a 12-lead ECG (clinic Visit 5).
19. Perform physical examination (clinic Visit 5).
20. During the time interval between visits, the site coordinator may regularly contact (by telephone) the subjects to ensure that the subject's scheduled dose is administered and daily NRS pain scores are recorded correctly. The subjects will be informed that they may contact the site if problems/questions arise.

10.1.4 Follow-up Visit

This visit will take place approximately 7 days after the end-of-treatment visit (or early termination visit), and will include the following assessment and procedures:

1. Collect and review the subjects' electronic diaries.
2. Review subject's use of concomitant medications.
3. Review AEs.

10.1.5 Early Termination Visit (if applicable)

If this visit is required, the following assessment and procedures will be performed:

1. Perform physical examination.
2. Obtain vital sign measurements.
3. Obtain subject's weight.
4. Perform WOMAC pain intensity, stiffness and physical function assessment.
5. Calculate WOMAC composite score
6. Perform Patient's Global Assessment.
7. Perform Patient's Global Impression of Changes
8. Perform a NRS 11-point pain assessment for the target knee pain.
9. Review subject's use of rescue medication.
10. Perform a 12-lead ECG.
11. Obtain blood samples for laboratory testing.

12. Collect and review the subject's diary entries.
13. Perform drug accountability.
14. Perform dermal safety assessment (irritation, discomfort, adhesion, adhesive residue).
15. Review subject's use of concomitant medications.
16. Review AEs.
17. Obtain pharmacokinetic blood sample.

10.1.6 Overall Study Schedule

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening and Washout Periods: 10 to 17 days
2. Double-blind Treatment Period: 4 weeks
3. Follow up Period: 1 week

The maximum treatment duration for each subject is approximately 4 weeks. The maximum study duration for each subject is approximately 7 weeks.

10.2. Assessments

10.2.1 Efficacy

10.2.1.1 Western Ontario and McMaster Universities Osteoarthritis Index

The Western Ontario and McMaster Universities Osteoarthritis Index Likert (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 a widely used, self-administered assessment used to measure pain, stiffness, and physical function in subjects with OA. It is considered to be a reliable and valid instrument.[5,6,7]

The WOMAC Pain scale evaluates the following 5 items:

1. Walking
2. Stair climbing
3. Noctural
4. Rest
5. Weight bearing

Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

The WOMAC Stiffness scale assesses 2 items: morning stiffness and stiffness occurring later in the day. Each item is rated on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

The WOMAC Physical Function assesses the following the following categories using the 0 to 4 scale described previously:

1. Descending stairs
2. Ascending stairs
3. Rising from sitting
4. Standing

5. Bending to floor
6. Walking on a flat surface
7. Getting in/getting out of car
8. Going shopping
9. Putting on socks
10. Lying in bed
11. Taking off socks
12. Rising from bed
13. Getting in/out of bath
14. Sitting
15. Getting on/off toilet
16. Heavy domestic duties
17. Light domenstic duties

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= __%

10.2.1.2 Patient Global Assessment

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

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

10.2.1.3 Patient Global Impression of Change

The Patient Global Impression of Change 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." 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

10.2.1.4 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 will be assessed in two 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.

Pain intensity in the target knee will be assessed using an 11-point NRS.The subject will rate his or her target knee pain intensity 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 pain that you have been feeling in your knee over the last 24 hours?”

Note:

1. The NRS pain score for assessment is an average of the NRS pain scores reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit except Screening Visit.
2. The NRS pain scores in at least 2 of the last 3 days prior to wash-out start (Phone Visit 1) and Baseline (Visit 2) are required.

10.2.1.5 Use of Rescue Medication

For the 4-week double-blind treatment period, subjects will be asked to record their daily intake/use of rescue medication in the diary. Rescue medication will be limited as follows: 2 gram/day APAP may be used except within 2 calendar days prior to the baseline visit and within 1 calendar day prior to other visits.

10.2.2 Safety

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

10.2.2.1 Laboratory Safety Assessments

10.2.2.1.1 Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Section 17.1).

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, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid
Coagulation panel:	prothrombin time, partial thromboplastin time, fibrinogen
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones
Pregnancy test (urine):	for women of childbearing potential only
Urine drug screen:	amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol.

Blood and urine samples for hematology, serum chemistry, and urinalysis will be sent to a central laboratory for analysis. Urine drug screens and pregnancy tests will be conducted at the study sites.

10.2.2.1.2 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-05 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.

10.2.2.2 Clinical Examinations

10.2.2.2.1 Vital Signs

Vital signs, including heart rate, respiratory rate, and sitting blood pressure will be measured at designated timepoints after the subject has been in a sitting position for 5 minutes. Temperature will also be measured.

10.2.2.2.2 Electrocardiogram

A standard 12-lead ECG will be performed at designated timepoints after the subject has been supine for at least 5 minutes. 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.

10.2.2.2.3 Physical Examination

The following physical examination will be performed at designated timepoints before potential exposure to the IP 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

10.2.2.3 Adverse Events

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

10.2.2.4 Evaluations of Patch and Dermal Assessment

Patch Adhesion

Patch adhesion will be assessed in two ways. In the clinic, patch adhesion will be assessed by the investigator or a designee using a predefined patch adhesion scale with scores on a 5-point numerical scale, by reference to the Abbreviated New Drug Application draft guidance of June 2016, at each clinic visit. The following information will be included in the full protocol that will be submitted with the IND:

- 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 treatment period at home, subjects will report the incidence of patch detachment by answering Yes or No.

Irritation

application site where the previous patch was applied will be examined for signs of skin irritation at each clinic visit. All subjects will be evaluated by a trained investigator or designee using the Berger and Bowman scale (Berger and Bowman 1982) 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. Findings will be graded using the following 2 scales, which will be included in the full protocol that will be submitted with the IND:

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

- 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

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.”

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.”

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. Any discomfort mentioned should be recorded and rated as follows:

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

Adhesive Residue

The amount of adhesive residue remaining at the application site where the previous patch was applied will be examined by the investigator or a designee at each clinic visit and scored according to the scale below:

- 0 = None
- 1 = Light
- 2 = Medium
- 3 = Heavy
- 4 = Patch not present

10.2.3 Pharmacokinetic Assessments

Blood samples for plasma concentrations of diclofenac will be obtained on Day 14 and 28 or at the early termination visit.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as 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 quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events occurring in subjects treated with placebo are also considered AEs. However, AEs reported during treatment-free periods before IP has been administered are not considered AEs; these events are captured on the eCRF as updates to the subject's medical history.

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 an IP, the known information is contained in the IB which includes the HP-5000 Develepmental Core Safety Information.

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

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction 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
- 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
- is a congenital anomaly
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP interacted with a contraceptive method and led to the pregnancy.*

- 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 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*

11.1.4 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

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 terminate early will continue to be monitored for 30 days from last treatment for AEs, unless 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 nonleading 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

Dose increased	An indication that a medication schedule was modified by addition; either by changing the frequency, strength or amount.
Dose not changed	An indication that a medication schedule was maintained.
Dose reduced	An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
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

*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 the IP. 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 IP administration (eg, 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 IP 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 IP, 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 IP 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.

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 the IP

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if 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 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 AEs occur in a subject that are not tolerable, the investigator must decide whether to stop the subject's involvement in the study and/or treat the subject. Special procedures may be recommended for the specific IP, such as the collection of a serum sample for determining blood concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For doubleblinded studies like HP-5000-US-05, 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

Any AE will be followed (up to a maximum of 30 days after the last dose of study medication) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known

causes (ie, concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. 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 Notification

11.2.6.1 Serious Adverse Events

The investigator or designee must report all SAEs promptly to [redacted] within 24 hours of first becoming aware of the event by completing, signing and dating the Serious Adverse Event Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the sponsor by one of the following methods:

Email: [redacted]

Fax number: [redacted]

The written report should be submitted on the SAE form 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 year of birth
- Subject's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP. ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the subject's treatment assignment

The investigator must fax/mail a written SAE Report Form that describes the SAE to the recipients of the initial information, who will forward the information to the sponsor.

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 Report Form, together with the following information (adverse event, date of occurrence, subject ID, study ID, IP, and site number); 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 guidances) 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

Nonserious AEs will be recorded in the eCRF and reported by [redacted] to Noven. Special Considerations

11.2.7 Adverse Events of Special Interest

The overall systemic safety profile of diclofenac is well known and established as reflected in the Investigators Brochure including Develomental Core Safety Infocmation which are in part based on the current label of the [redacted].

The overall safety of HP-5000 patches at doses ranging from [redacted] The HP-5000 patches used in the clinical studies [redacted] Some of the commonly reported AEs across the [redacted] The remaining commonly reported AEs are either known adverse reactions to other commercially available dose forms that contain diclofenac (application site pruritus, back pain, and myalgia with diclofenac containing solutions or patches) or consistent with events of application site skin reactions commonly reported as AEs with other topical medications that contain diclofenac [redacted]

11.2.8 Pregnancy

All women 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. Women 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 IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a screening failure.

A woman who becomes pregnant during IP treatment or within 30 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy within 48 hours of learning of the pregnancy, to [redacted] Pharmacovigilance

using the Pregnancy Data Collection Form via the same fax number and/or 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 an Exposure in Utero form provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form and forwarded to the designated individuals. The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

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

The primary efficacy endpoint is the change in WOMAC LK3.1 OA pain score between baseline and Week 4.

13.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1 and 2
- WOMAC LK3.1 OA Index (stiffness)
- WOMAC LK3.1 OA Index (physical function)
- WOMAC LK3.1 OA Index (composite score)
- Patient Global Assessment
- Patient Global Impression of Change
- Pain intensity assessed on an 11-point NRS
- Use of rescue medication

13.1.3 Safety Endpoints

- Adverse events, AEs leading to discontinuation from the study drug, SAEs, and deaths
- Change from baseline in clinical laboratory results (including fasting glucose and lipids), ECG results, body weight, and vital signs
- Dermal safety: adhesion, irritation, discomfort, and adhesive residue

13.1.4 Pharmacokinetics Endpoint

- Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] on Day 14 and 28 (or at the early termination visit).

13.2. Sample Size Determination

Assuming an effect size of [redacted] on the change in WOMAC pain score from baseline to Week 4 between active HP-5000[redacted] and HP-5000[redacted] treatments and placebo, the probability for detecting the clinically meaningful effect size[redacted] or higher will be approximately 67% having 75 evaluable subjects per each active arm and 150 evaluable subjects in the placebo arm. Having 3 treatment arms, the total number of subjects randomized in the trial and included in the primary analysis set should be approximately 300. A sufficient number of subjects will be screened to randomize the proposed sample size.

13.3. Analysis Populations

The following 4 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.
- Full Analysis Set (FAS): includes all randomized subjects who have had at least 1 patch of double-blind study medication applied and who have a Baseline WOMAC pain score and at least 1 post-Baseline assessment of the primary efficacy measure (WOMAC pain score). Evaluable subjects will be defined as those who meet the FAS definition. The FAS will be used as the primary set for analysis of efficacy endpoints based on randomized treatment assignment.
- Safety Analysis Set (SAF): includes all subjects who have had at least 1 patch of double-blind study medication applied and who have at least 1 post-dose safety measurement during the double-blind treatment period. 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.
- Pharmacokinetic Analysis Set (PAS): includes all subjects who have received at least 1 dose of study medication during the double blind treatment period and have at least 1 blood sample for PK assessment. Subjects may be excluded from the PAS set if they significantly violate inclusion or exclusion criteria, significantly violate the protocol in a way that may influence the PK analysis, if any unexpected error occurs during the study that may influence the PK analysis (eg, early detachment of transdermal systems, apparent sample switching, etc.) or if their data are unavailable or incomplete. The PAS will be used for the analysis with model-based approach. Excluded cases will be documented together with the reason for exclusion.

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

If a subject is randomized incorrectly or is administered the incorrect IP, 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 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 statistics 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.

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, and weight. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IP, 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 each subject's mean, mode, and final dose, and in terms of duration of exposure. 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 FAS population as primary, unless otherwise specified.

13.4.3.1 Primary Analysis

The primary efficacy endpoint of this trial is the change from Baseline to Week 4 in the WOMAC pain score; the primary analysis set is the FAS. The comparisons of interest are:

- HP-5000 [redacted] versus placebo
- HP-5000 [redacted] versus placebo

The primary efficacy variable, the change from baseline to Week 4 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 [redacted] HP-5000 [redacted] 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. The MMRM model may be repeated on additional analysis sets as a sensitivity analysis. If the normality assumption is violated, analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed.

Other sensitivity analyses may be performed on the primary endpoint to assess the robustness of the results based on the model used for primary analysis. This analyses may include multiple imputation and pattern-mixture models for handling of missing data. Details will be provided in the Statistical Analysis Plan (SAP). The analyses will be performed according to the National Academy of Sciences (2010) guidelines.[8]

13.4.3.2 Analyses for Secondary Endpoint

The following secondary endpoints will use the change in mean for analysis (as applicable):

- WOMAC LK3.1 OA Index (pain) – change between Baseline and Week 1 and 2
- WOMAC LK3.1 OA Index (stiffness)
- WOMAC LK3.1 OA Index (physical function)
- WOMAC LK3.1 OA Index (composite score)
- Patient Global Assessment
- Patient Global Impression of Change
- Pain intensity assessed on an 11-point NRS
- Use of rescue medication

Additional categorical response analyses may be performed; additional details will be provided in the SAP.

13.4.4 Safety and Tolerability 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 safety population (as defined in Section 13.3). Safety variables include treatment-emergent AEs, clinical laboratory values, vital signs, ECG readings, physical examination results, and dermal safety results. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.4.5 Pharmacokinetic Analyses

Plasma concentrations of diclofenac (for both HP-5000[redacted] and HP-5000[redacted] will be evaluated and summarized as descriptive statistics by treatment.

13.4.5.1 Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 19.

Treatment-emergent AEs are defined as:

- AEs with onset at the time of or following the start of treatment with IP 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 IP will also be provided. Serious adverse events and AEs resulting in discontinuation of IP will be summarized separately in a similar manner. Subject listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.4.5.2 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.

13.4.5.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for 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.

13.4.5.4 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, QTc interval (both correction methods), and HR for each treatment group at each time point.

13.4.5.5 Physical Examination Findings

The number and percentage of subjects with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

13.4.5.6 Dermal Safety

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

13.4.6 Interim Analysis

No interim analyses are planned.

14. STUDY CONDUCT

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 (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.6), and/or to discontinue the study (Section 14.6 for US studies).

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 (Section 17.2), 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Industry E6 Good Clinical Practise (GCP), and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators 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 (eg, subinvestigators 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, IPs, 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.

14.2. Site Initiation

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. 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 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.

14.3. Screen Failures

Subjects who fail inclusion and/or exclusion criteria may not be rescreened for the study.

14.4. Study Documents

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

14.4.1 Investigator's Regulatory Documents

The regulatory documents are listed in the HP-5000-US-05 Study Manual.

The 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 IP 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 IP 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.

14.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents 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. 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 subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.3 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.

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.

14.5. Data Quality Control

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

14.5.1 Monitoring Procedures

Noven and/or its designee will conduct site visits to monitor the study and ensure compliance 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. The investigator agrees to allow the CRAs and other authorized Noven personnel access. 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. While on site, the CRAs will review

- regulatory documents, directly comparing entries in the EDC system with the source documents
- consenting procedures
- AE procedures
- storage and accountability of IP 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 (Section 17.2), 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.

14.5.2 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.

14.5.3 Quality Assurance/Audit

This study will be subject to audit by Noven or its designee. Audits may be undertaken to check compliance with GCP guidelines, and can include:

- site audits
- TMF audits
- database audits
- document audits (eg, protocol and/or CSR)

Noven or its designee may conduct additional audits on a selection of study sites, requiring 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 according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

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

14.6. Study Termination

The study may be terminated at Noven's discretion at any time and for any reason.

Study Site Closure:

At the end of the study, all study sites will be closed. 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:

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

14.6.1 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 IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP

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.

14.6.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

14.7. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Noven. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency having jurisdiction over the conduct of the study.

14.8. Use of Information and Publication

All information concerning IP, 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 IP 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 IP 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.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 2013 version of the Declaration of Helsinki, and the applicable regulations of the country in which the study is conducted.

15.2. Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed consent document, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine 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.

A valid IRB must review and approve this protocol before study initiation. 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.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure not part of routine care for the subject's condition.

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.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

1 Barbour KE, Helmick CG, Theis KA, Murphy LB, Hootman JM, Brady TJ, Cheng YJ. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation-United States, 2010-2012. MMWR 2013;62 (44):869-873.

2 Centers for Disease Control and Prevention. https://www.cdc.gov/arthritis/data_statistics/index. htm. Accessed 24 June 2016.

3 Investigational Brochure, Diclofenac Sodium Transdermal Drug Delivery System, HP-5000 Transdermal Patch. Noven Pharmaceuticals, Inc. [redacted] Edition No. 03, September 9, 2014.

4 Berger, R.S., and .J.P. Bowman, 1982, "A Reappraisal of the 21 -day Cumulative Irritation Test in Man," ./. Toxicol. - (It. 6' Ocz~lw Toxicol., l(2); 109- 1 15.

5 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.

6 Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14-17.

7 Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006;113(12):1578-1587.

8 National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The prevention and treatment of missing data in clinical trials. Washington (DC): National Academies Press (US); 2010.

17. ATTACHMENTS

17.1. Schedule of Events

		Screening Visit	Wash-out Period	Baseline Visit	Double-blind Treatment Period						Follow up	ET
	Week	-1				1		2		4	5	
	Clinic visit	**1**		**2**		**3**		**4**		**5**		
	Phone visit		**1**								**2**	
	Study Day	-17 to -10[i]	-14~-7 to -1[i]	0	1 to 6	7	8 to 13	14	15 to 27	28	35	
Assessment	**Visit Window (Days)**					±2		±2		±2		
Informed consent		X										
Subject ID card		X										
Demographics		X										
Medical history		X										
I/E criteria		X		X								
Randomization (IVRS)[a]				X								
Physical examination		X								X		X
Vital signs[b]		X		X		X		X		X		X
Height		X										
Weight		X		X						X		X
WOMAC pain intensity		X		X		X		X		X		X
WOMAC stiffness		X		X		X		X		X		X
WOMAC physical function		X		X		X		X		X		X
Patient Global Assessment				X		X		X		X		X
Patient Global Impression of Change						X		X		X		X
Pain intensity 11-point NRS		X	X	X	X	X	X	X	X	X		X
Dispense rescue medication		X		X		X		X				
Use of rescue medication[c]			X	X[c]	X	X	X	X	X	X		X
12-lead ECG[d]		X		X						X		X
Clinical laboratory[e]		X		X						X		X
Urine pregnancy test		X		X		X		X		X		X
PK blood sample								X		X		X
Subject diary[f]		X	X	X	X	X	X	X	X	X	X	X
Apply study medication[g]					X	X	X	X	X			
Drug accountability				X[l]		X		X		X		X
Dermal evaluations[h]				X	X[j]	X	X[j]	X	X[j]	X		X
Prior/Concomitant medications		X	X	X	X	X	X	X	X	X	X	X
AEs[k]				X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; ET = early termination; ECG = electrocardiogram; ID = identification; I/E = inclusion/exclusion; IVRS = interactive voice response system; NRS = numeric rating scale; PK = pharmacokinetic; WOMAC = Western Ontario and McMaster Universities Arthritis Index

a. Subjects will be randomized either HP-5000[redacted] HP-5000[redacted] or placebo in a 1:1:2 ratio.
b. Vital signs, including heart rate, respiratory rate, and sitting blood pressure will be measured after the subject has been in a sitting position for 5 minutes
c. Rescue medication may be used during the Washout Period except within 2 calendar days prior to Visit 2.
d. A standard 12-lead electrocardiogram (ECG) will be performed after the subject has been supine for at least 5 minutes
e. Clinical laboratory testing includes hematology, biochemistry, and urinalysis.
f. Subjects will be instructed in the use in the use of the electronic diary at the screening visit.For each 28-day administration period, subjects will be asked to record their daily intake/use of IP in the electronic diary.
g. Instructions for application and removal of study drug patches will be provided to the subject
h. Dermal evaluations will assess skin adhesion, irritation, discomfort, and adhesive residue.
i. Screening/Washout period should be 10 to 17 days. Washout period will be initiated 3 days after Screening Visit.
j. During the treatment period at home, subjects will report the incidence of patch detachement by answering Yes or No.
k. AEs will be collected after the first dosing.
l. Rescue medication only.

17.2. Investigator's Agreement

PROTOCOL NUMBER:	HP-5000-US-05
PROTOCOL TITLE:	A 4-week, Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy and Safety of HP-5000 in Subjects with Osteoarthritis (OA) of the Knee
FINAL PROTOCOL:	31 Oct 2016

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators 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

This is an example of the WOMAC index. The actual index will be provided in the eCRF.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____ Date:_____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

18.2. Patient Global Assessment Scale (PGA)

This is a sample questionnaire. The actual questionnaire will be provided in the study reference manual.

The subject will provide their overall impression of the status of their OA in the target knee on a 5-point scale where 0 = “Very Good” and 4 = “Very Poor.”

Subjects will be asked to complete the following statement: “How would you rate your osteoarthritis condition over the last 24 hours?” The response options include the following:

1. Very Good
2. Good
3. Moderate
4. Poor
5. Very Poor

18.3. Patient Global Impression of Change Scale

This is an example of the Patient Global Impression of Change (PGIC) scale. The actual instrument will be included in the study reference manual.

The Patient Global Impression of Change 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." 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

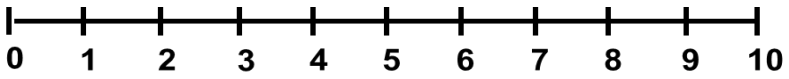
18.4. 11-Point Numeric Rating Scale (NRS)

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.

Ask the subject the following question: "On a scale of 0 – 10, with 0 being 'no pain' and 10 being the 'worst possible pain', how would you rate your pain over the last 24 hours?"

The intent of the question is to gain an understanding of the intensity of the patient's target knee pain at over the last 24 hours.



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 94 (2001) 149–158

18.5. Regulations and Good Clinical Practice Guidelines

18.5.1 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

18.5.2 Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf