STATISTICAL ANALYSIS PLAN

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 SAP:

21-Oct-2019

NCT Number:

NCT03277066

16.1.9 Documentation of Statistical Methods

Final Statistical Analysis Plan, Version 1.0, dated 21-Oct-2019

Statistical Analysis Plan

[redacted]

Sponsor	Noven Pharmaceuticals, Inc.
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 Number:	HP-5000-US-05
[redacted]	[redacted]
Document Version:	Version 1.0
Document Date:	21-Oct-2019

[redacted]

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
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Noven Pharmaceuticals, Inc. Clinical Representative	Print Name: [redacted] Sign Name: [redacted]	22/Oct/2019

Document History

Version	Date	Author	Description
0.1	31-Jul-2017	[redacted]	Initial Draft
0.2	24-Oct-2017	[redacted]	Updated Initial Draft from Noven Feedback
0.3	06-Apr-2018	[redacted]	Updated feedback on 0.2, and for Protocol Amendment 2
0.4	18-Mar-2019	[redacted]	Updated for finalization
0.5	13-May-2019	[redacted]	Updated based on feedback for 0.4, with clarification provided based on dry run comments.
0.6	08-Aug-2019	[redacted]	Updated based on feedback received on 0.5, 10JUL2019.
1.0	21-Oct-2019	[redacted]	Updated based on feedback received on 0.6, prepared for signoff

Table of Contents

List of Tables

List of Figures

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Noven Pharmaceuticals, Inc. protocol number HP-5000-US-05 (*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*), dated 12-Jan-2018, Amendment 2. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents[1, 2]. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[3], International Conference on Harmonization; Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials[4]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[5] and the Royal Statistical Society[6], for statistical practice.

The planned analyses identified in this SAP will be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Noven Pharmaceuticals, Inc.'s study HP-5000-US-05.

2. Study Objectives and Endpoints

This is a phase II study with the goal to evaluate efficacy, safety (including dermal), and PK of two active treatments: HP-5000-[redacted] (diclofenac sodium) [redacted] topical patch [redacted] and HP-5000[redacted] (diclofenac sodium) [redacted] topical patch [redacted]. [redacted] will be chosen to advance to phase III development.

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective:

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

2.1.2. Secondary Objectives

The secondary objectives 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 compared to placebo.
- To determine the plasma concentrations of diclofenac following administration of HP-5000.

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) LK3.1 OA pain score between Baseline and Week 4.

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- WOMAC LK3.1 OA Index (pain) – change in pain score between Baseline and Week 1 and 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 (PGA)* between Baseline and Week 4.
- *Patient Global Impression (PGI) of Change* between Week 1 and Week 4.
- *Pain intensity assessed on an 11-point numeric rating scale (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.

2.2.3. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse Events (AEs), AEs leading to discontinuation from the study drug, and serious AEs (SAEs).
- Change from baseline in clinical laboratory results (including fasting glucose and lipids

  [8 to 10 hours fasting is required for these laboratory testing]), electrocardiogram (ECG) results, body weight, and vital signs.
- Dermal performance: adhesion, irritation, discomfort, and adhesive residue.

2.2.4. Pharmacokinetic Endpoint

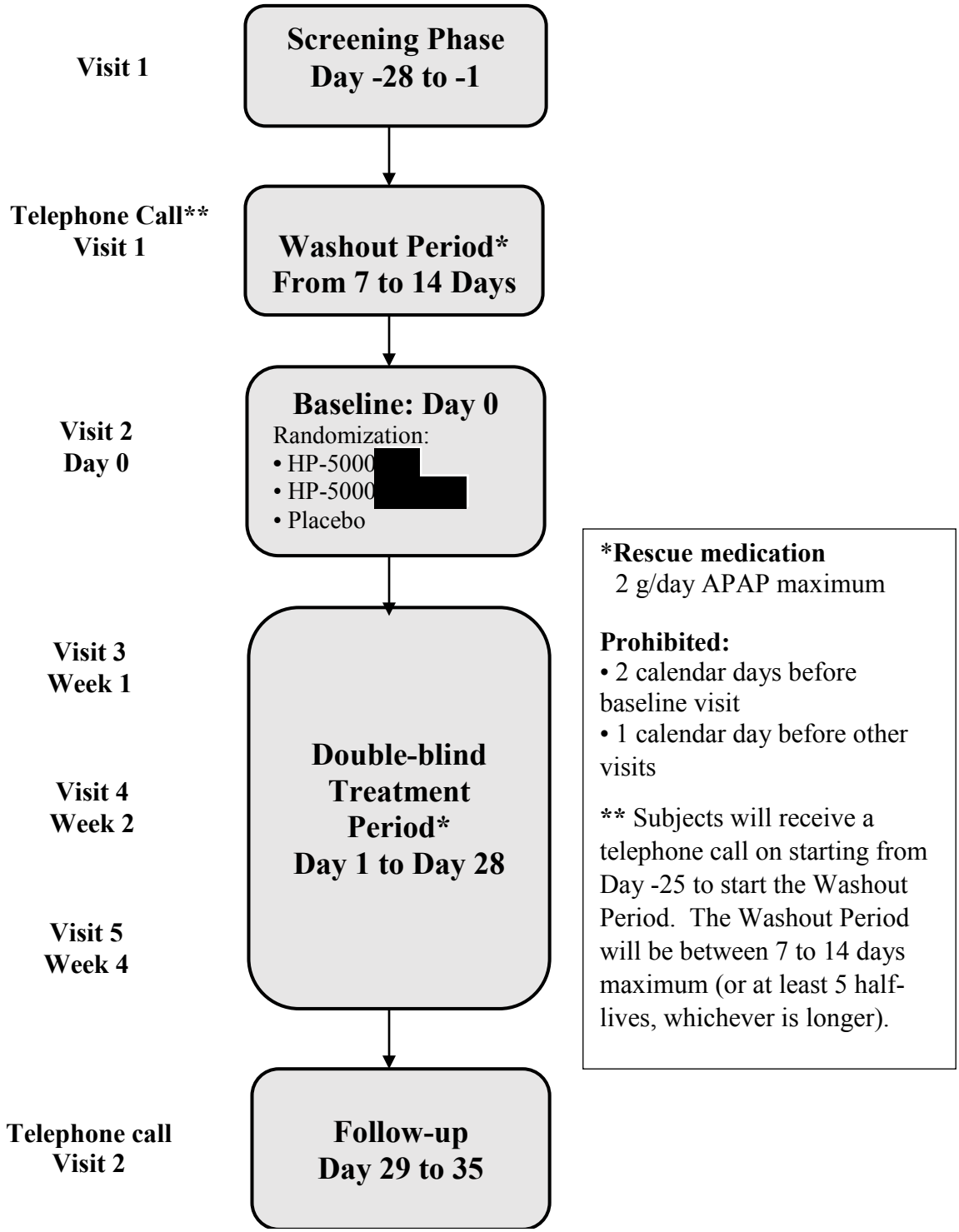
Plasma concentrations of diclofenac (for both HP-5000-[redacted] and HP-5000[redacted] on Days14 and 28 (or at the Early Termination Visit) will be assessed.

3. Overall Study Design and Plan

This is a 4-week, randomized, double-blind, multicenter, placebo-controlled phase 2 study to evaluate the efficacy and safety of HP-5000 in subjects with OA pain of the knee with that of placebo. Approximately 300 male and female subjects will be randomized to treatment with HP-5000[redacted], HP-5000[redacted], or Placebo in a 1:1:2 ratio (HP-5000[redacted]: HP-5000[redacted]: Placebo), respectively. Subjects must be between the ages of 40 to 85 with a clinical diagnosis of OA of the target knee according to the American College of Rheumatology (ACR) criteria. The study will take place in approximately [redacted] sites in the United States.

The overall maximum study duration for an individual subject is expected to be approximately 9 weeks with study drug treatment duration of 4 weeks. As per the schedule of events in Table 1, subjects will start treatment on Day 1. After the 4-week Treatment Phase, the study center will conduct a follow-up phone call for safety monitoring and based on the investigator's judgment, a subject may return to the study center for the safety Follow-up Visit. Dose modifications will not permitted in this study, and subjects who cannot tolerate their study drug dose will be withdrawn from the study. Figure 1 presents a schematic view of the study design.

Figure 1: Study Design



3.1. Overall Design

3.2. Sample Size and Power

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.

In case of lower subject enrollment, the power to detect clinically meaningful effect of active treatments may drop but not below the threshold of 40%.

3.3. Study Population and Treatments Administered

The study will enroll up to 300 subjects in a 1:1:2 ratio (HP-5000[redacted]: HP-5000[redacted]: Placebo) with osteoarthritis pain of the knee. Pain Symptoms should be present for at least 6 months prior to screening.

HP-5000 will be applied [redacted] for 4 weeks (28 days). The treatment arms for this study are the following:

- HP-5000[redacted] topical patch
- HP-5000-[redacted] topical patch
- Placebo

The dose of diclofenac [redacted] in a patch size of [redacted] applied [redacted] and rotated between 2 sites 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 2 sites on the knee (inner and outer) for the lead formulations (HP-5000[redacted] HP-5000-[redacted].

3.4. Method of Assigning Subjects to Treatment Groups

In this randomized parallel-group phase 2 study, subjects who meet study entry criteria will be randomly assigned to receive one of the following patches HP-5000[redacted], HP-5000-[redacted] or placebo as described above. The randomization numbers will be assigned sequentially through a central interactive voice response system (IVRS) as subjects who meet 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[8] was prepared by Premier Research before the start of the study. No one involved in the clinical conduct has or will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into the study more than once.

3.5. Blinding and Unblinding

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 the treatment assignment with the exception of a pre-specified independent statistician/programmer from [redacted] who will be involved in generation of the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data which will be performed after database lock.

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 but may be permitted in case of medical emergency only if that requires immediate knowledge of the subject's treatment assignment. The process of unbinding one subject should not jeopardize the validity and integrity of the whole study.

3.6. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 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 (Hematology, biochemistry &	X[f]		X						X		X

urinalysis)[f]											
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								
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 supine 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 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 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 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 on 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 will be initiated 3 days after Screening Visit.
l. During the treatment period at home, 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 after 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.

4. Statistical Analysis and Reporting

All final, planned analysis identified in this SAP will be performed after the study database has been locked and treatment codes have been unblinded.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® (release 9.4 or higher. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous variable summaries will include the number of subjects or patches (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, estimates will be presented with 95% confidence intervals (CIs) and standard error (SE).

Categorical variable summaries will include the frequency and percentage of subjects or patches that are in the particular category or each possible value. In general the denominator for the percentage calculation will be based upon the study population for the specified treatment group and overall, unless otherwise specified. The denominator for by-visit displays will be the number of subjects (or patches) in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD, SE) will be reported to 2 degrees of precision more than the observed data. Plasma concentration data will be treated as three significant figures for reporting purposes. Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and p-values will be reported in pvalue6.4 format. Corresponding 95% CIs will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

No interim analysis is currently planned. If an interim analysis is planned in the future, this will be amended in protocol and in the SAP text as applicable.

5. 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 treatment actually received.
- **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 patch of double-blind active study drug applied and who 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. Excluded cases will be documented together with the reason for exclusion. In the unlikely event that errors may have occurred in treatment arm assignments, then analyses using the PAS will be based on treatment actually received.

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

5.1. Statistical Definitions and Algorithms

5.1.1. Baseline

The last non-missing observation recorded on or prior to the first patch application of study drug will be used as the baseline observation for all calculations of change from baseline. Typically, baseline will be the value recorded on the Baseline visit (Randomization).

5.1.2. Adjustments for Covariates

Additional covariates for exploration include BMI, and Gender which may be added to analyses beyond baseline covariate factors, and will be noted in table outputs as appropriate. Further exploration of additional covariates will be considered as data becomes available and may

include subgroups described in section 5.1.8.

5.1.3. Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons for efficacy or safety endpoints.

5.1.4. Handling of Dropouts or Missing Data

Missing endpoint values in this study may result from patients discontinuing from the study prematurely or missing intermediate assessments while remaining on study. For primary analysis of the primary endpoint and other efficacy endpoints missing observations will not be imputed. The primary analysis method for continuous endpoints will be based on a mixed model with repeated measures (MMRM) which utilizes all available data (complete and partial) from subjects included in an analysis set. The MMRM-based approach assumes that data are missing at random (MAR). MAR refers to a missingness mechanism that is independent of missing responses, conditionally on observed response history and covariates. This assumption inherently implies that the treatment effect is similar for those who discontinue prematurely and for those who complete the study in their respective treatment arms.

Sensitivity analyses to investigate robustness to missing data will be performed for the primary endpoint as described in Section 7.1

Missing safety data including dermal evaluations will not be imputed.

5.1.5. Analysis Visit Windows

In general, analysis of all variables for this study will use the nominal visit or time point as collected in the CRF/database. Scheduled visits will be selected over unscheduled visits. Unscheduled visits will be presented in data listings. Only dermal evaluation data from unscheduled visits will be included into the summary tables.

5.1.6. Derived Variables

- Study Day = Assessment Date – Date of First Dose + 1
- Change from Baseline = Value Post-Baseline – Value at Baseline
- % Change from Baseline = 100 * Change from Baseline / Value at Baseline
- WOMAC LK3.1 OA Sub-Index Pain = Range from 0 to 20 by summing each item relating to Pain (Walking, Stair climbing, Nocturnal, Rest, and Weight bearing) on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

- WOMAC LK3.1 OA Sub-Index Stiffness = Range from 0 to 8 by summing each item relating to Stiffness (Morning Stiffness, and Stiffness occurring later in the day) on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

- WOMAC LK3.1 OA Sub-Index Physical Function = Range from 0 to 68 by summing each item relating to Physical Function (Descending stairs, Ascending stairs, Rising from sitting, Standing, Bending to floor, Walking on a flat surface, Getting in/getting out of car, Going shopping, Putting on socks, Lying in bed, Taking off socks, Rising from bed, Getting in/out of bath, Sitting, Getting on/off toilet, Heavy domestic duties, Light domestic duties) on a scale of 0 to 4, with 0 being no difficulty and 4 being extreme difficulty.

- [redacted]) and then dividing by [redacted] Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

- NRS Pain Score Average = Average of NRS pain scores for target and non-target knee reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit except Screening Visit. The NRS pain scores in at least 2 of the last 3 days prior to washout start (Phone Visit 1) and Baseline is required. NRS is an 11-point scale from 0 to 10 where 0 = no pain and 10 = the worst pain imaginable.

- NRS Pain Score Worst = Worst NRS pain score for target and non-target knee reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit except Screening Visit.

It is expected additional derived variables will be needed, but the SAP will not be amended unless they are part of the primary or secondary endpoints in the study.

5.1.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

In general, for quantitative laboratory values reported as '<' or '≤', the lower limit of quantitation (LLOQ) or limit of detection (LOD), one-half of the reported value (i.e., LLOQ, LOD) will be used for analysis. For quantitative laboratory values reported as '>' or '≥', the upper limit of quantitation (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

Adverse events will be coded using the MedDRA version 19.0 thesaurus. Concomitant and Prior medications will be coded using WHO Drug Dictionary (WHO-DD) version 2017.

If partial dates occur for AEs or medications, the convention for replacing missing dates for analyses is as follows:

For partial start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then:
    - If the year matches the year of the randomization date, then impute the month and day of the randomization date.
    - Otherwise, assign 01 January
- If the day is unknown, then:
    - If the month and year match the month and year of the randomization date, then impute the day of the first study drug administration date.
    - Otherwise, assign 01.

For partial end dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then assign the last day of the year 31 December.
- If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant).
2. If the start date is missing but the stop date is not missing and is after the day of study drug administration, then the most conservative approach is taken and the AE (or medication) is considered to be treatment emergent (or concomitant).
3. If the start date is missing but the stop date is not missing and is on or before the day of study drug administration and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior).

If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant while the AE is defined by start date.

A treatment related AE is any AE with a relationship to the study drug of "Possibly Related" or "Definitely Related". Any AE with a missing relationship will be analyzed as treatment related. If an AE has a missing severity, it will be imputed as "Severe".

5.1.8. Examination of Subgroups

Subgroup analyses will be conducted for primary endpoint on the Full Analysis Set. It should be noted that the study is not designed to detect treatment differences within subgroups.

The following subgroups may be assessed and described within the exploratory analysis sections; however, categories for sub-grouping will be confirmed further based on the empirical data:

- Gender:
  - Female
  - Male
- Age (years):
  - 40 to 49
  - 50 to 59
  - ≥ 60
- Race in all categories:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
- Body Mass Index
  - Underweight: 15 to 18.4
  - Normal: 18.5 to 25
  - Overweight: 26 to 30
  - Moderately Obese: 31 to 35
  - Severely Obese: 36 to 40
- Severity at baseline
  - NRS Score
    - Moderate 5 to 6
    - Severe ≥ 7
  - WOMAC Pain
    - 0 to 9
    - 10 to 20
- Disease Symptoms
  - < 6 months

  - 6 months to 1 year
  - 2 to 5 years
  - > 5 years
- Pain in the target knee
  - 30 days to 59 days
  - 2 months to 1 year
  - 2 to 5 years
  - > 5 years
- Washout Period
  - Less than 7 days
  - 7 days
  - 7 to 14 days
- NSAIDs at Screening
  - Type of NSAIDs
    - Prescribed
    - Physician's recommended OTC
  - Number of NSAIDs
    - <=5
    - > 5
  - Prescription
    - At least 3 days per week for last 30 days
    - More than 3 days per week for the last 30 days
    - At least 3 days per week for more than 30 days
    - More than 3 days per week for more than 30 days
  - OTC
    - At least 3 days per week for last 30 days
    - More than 3 days per week for the last 30 days
    - At least 3 days per week for more than 30 days
    - More than 3 days per week for more than 30 days
- eDiary compliance at Screening
  - 70%
  - > 70%
- Rescue Medication during Screening
  - <= 4 tablets
  - > 4 tablets
  - None
- Used rescue medication within 2 calendar days prior to Baseline Visit
- Other concomitant Medications (Excluding Pain Medications)
  - Corticosteroids
  - ACE inhibitors
  - Diuretics

  - Methotrexate
  - Cyclosporine
  - Others
- Minor Surgeries
  - Type of surgery
  - Number of years prior to screening

6. Study Patients/Subjects and Demographics

6.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations by treatment group and overall of the number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

A by-subject listing of all disposition information will be presented.

6.2. Protocol Violations and Deviations

A by-subject listing of all protocol deviations and violations will be presented in Clinical Study Report from the source data.

6.3. Demographics and Other Baseline Characteristics

Descriptive summaries of demographic (age, gender, race, ethnicity, height, weight, and BMI) and other baseline characteristics (baseline NRS scores, baseline WOMAC scores, baseline PGA, and baseline severity as measured by categories of NRS: Moderate 5 to 6, Severe $\geq$ 7, WOMAC Pain: 0 to 9, 10 to 20) will be provided for all patients by treatment group and overall. These tabulations will be repeated for SAF populations. All demographic and other baseline characteristics will be presented in subject listings.

6.4. Medical History

Subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term will be listed.

6.5. Prior Medications

A prior medication is any non-protocol specified drug or substance administered prior to first date of study drug. Subjects taking prior medications will be listed by Anatomical Therapeutic Chemical (ATC) classification level 4 and preferred term and are coded using WHO-DD.

6.6. Concomitant Medications

Concomitant medications will be listed similarly to Prior medications. A concomitant medication is any non-protocol specified drug or substance administered during participation in the study on or after first date of study drug. A medication can be considered both concomitant and prior if the subject took medication prior to the study and continued taking it after first study drug administration.

6.7. Previous OA treatment modalities

The frequency and percentage of subjects with previous OA related treatment as captured on the concomitant medication eCRF page will be summarized by ATC classification level 4 and preferred term. Also, a summary of previous NSAID treatments will be summarized by ATC classification level 4 and preferred term.

6.8. Exposure and Compliance

The frequency and percentage of the number of patches applied and removed, the number of patches removed early along with reasons for early removal will be tabulated by treatment group and overall for the ITT population.

Within the same table, a summary of the mean duration of exposure will also be calculated. This descriptive summary will include quartiles in addition to the other descriptive statistics normally presented.

A separate summary table will present overall subject compliance with study drug. Compliance is defined as the number of patches given less the number of patches returned divided by the number of days for required applications (e.g. without counting of extra patches given just in case), expressed as a percentage. Number and percentage of subjects who are compliant (defined as using $\geq$ 80% and $\leq$ 120% of study medication) and noncompliant (defined as using less than 80% or more than 120% of study medication) at each treatment arm will be presented by weeks and overall. A by-subject listing of all drug exposure information collected will be presented.

7. Efficacy Analysis

All efficacy variables will be summarized and analyzed using the FAS population as the primary population of interest, unless otherwise specified.

7.1. Primary Efficacy Analysis

The estimand in the primary analysis for efficacy for each dose is the difference between treatments groups (each HP-5000 treatment 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 trial.

The comparisons of interest are:

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

WOMAC scores obtained 24 hours after removal/detachment of the study medication or WOMAC scores obtained within 24 the subject used rescue medication will be excluded as outliers. Outliers will be defined *a priori* as (i) WOMAC scores obtained more than 24 hours after removal/detachment of double-blind study medication; or (ii) WOMAC scores obtained within 24 hours the subject used rescue medication.

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. The mean difference of change will be compared for each active treatment arm, and overall active against placebo. An unstructured covariance matrix will be assumed. If the unstructured matrix fails to converge, a series of other covariance structures will be tested (AR(1), Toeplitz, and Compound Symmetry). The covariance structure which converges with the lowest Akaike information criterion (AIC) score will be chosen and noted in the resulting table. The Kenward-Roger approximation for denominator degrees of freedom will be implemented, and the restricted maximum likelihood (REML) approach for estimation will be specified in the model code.

Below is example SAS code for conducting the MMRM analysis specified. Note, the macro wrapper used in different covariance structures is not shown below (specified with type option):

```
ods output lsmeans = lsmn1
           lsmestimates = lsmest1
           ConvergenceStatus = MMRMconverge
           Tests3 = MMRMoverall;
proc mixed data=example method=reml;
  class trt avisitn usubjid;
  model chg = trt avisitn trt*avisitn base /alpha=0.05 solution ddfm=kr;
  repeated avisitn/subject=usubjid type=un;
  lsmeans trt*avisitn/cl alpha = 0.05;
  lsmestimate trt*avisitn 'Week 1 HP-5000[redacted] vs placebo' 1 0 0  0 0 0  -1 0 0 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 2 HP-5000[redacted] vs placebo' 0 1 0  0 0 0  0 -1 0 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 4 HP-[redacted] vs placebo' 0 0 1  0 0 0  0 0 -1 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 1 HP-[redacted]s placebo'   0 0 0  1 0 0  -1 0 0 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 2 HP-[redacted] vs placebo'   0 0 0  0 1 0  0 -1 0 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 4 HP-[redacted] vs placebo'   0 0 0  0 0 1  0 0 -1 divisor=1 /cl;
  lsmestimate trt*avisitn 'Week 1 Ove[redacted]ctive vs placebo' 1 0 0  1 0 0  -2 0 0 divisor=2 /cl;
  lsmestimate trt*avisitn 'Week 2 Overall Active vs placebo' 0 1 0  0 1 0  0 -2 0 divisor=2 /cl;
  lsmestimate trt*avisitn 'Week 4 Overall Active vs placebo' 0 0 1  0 0 1  0 0 -2 divisor=2 /cl;
run;
```

The estimate of the change from baseline to each time point from the model will be presented along with its 95% CI and p-value. The overall p-value of the model will also be presented to test the null hypothesis that there is no change at any timepoint will be presented.

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

Additionally, if the normality assumption is violated by the data, an analysis of covariance (ANCOVA) on rank-transformed data will be used as utility analysis and additional supportive analyses may be performed if necessary. First, the values of the change from baseline variable as well as baseline covariate will be transformed to standardized ranks using fractional ranks and mean method for ties. The ANCOVA will use the same model parameters as the MMRM with all visit effects dropped. Appendix A contains example code constructed to complete the ANCOVA analyses.

[redacted]

In addition, sensitivity analyses will be performed to test the robustness of the primary result. As described in detail in Section 7.1.1, multiple imputation and pattern-mixture models will be implemented on the WOMAC pain score data using the FAS. These analyses are useful in determining if missing-at-random (MAR) and not-missing-at-random (NMAR) missingness patterns are impactful to the model effects and results. These analyses will be performed according to the National Academy of Sciences (2010) guidelines[10].

7.1.1. Primary Efficacy Analysis Sensitivity Analyses

Analysis of sensitivity to missing data for the primary endpoint will be performed as follows. For the primary efficacy endpoint of WOMAC pain, the following two imputation methods will be implemented to assess the impact of missing data and robustness of the primary analysis.

Method 1: Multiple Imputation (MI), after subject uses rescue medication (intercurrent event)

MI assumes that the statistical behavior of drug- and placebo-treated patients after discontinuing study medication becomes that of the study cohort. Multiple-imputations are used to replace missing outcomes for patients who have prematurely withdrawn from the study using multiple draws from the posterior predictive distribution estimated from the treatment arms.

Data are processed sequentially be repeatedly calling SAS® PROC MI to impute missing outcomes at visit t = 1, …, T. The following procedure is followed:

- *Initialization (Step 1)*. Set t = 0 (baseline visit).
- *Iteration (Step 2)*. Set t = t + 1. Create a dataset combined records from drug- and placebo-treated patients with columns for covariates **X** and outcomes at visits 1, …, t with outcomes for all patients set to missing at visit t and set to observed or imputed values at visits 1, …, t-1.
- *Imputation (Step 3)*. Run Bayesian regression in SAS® PROC MI on this data to impute missing values for visit *t* using previous outcomes for visit 1 to t-1 and baseline covariates.
    - Replace imputed data for all patients at visit t with their observed values, whenever available. If t < T then go to Step 2, otherwise proceed to Step 4.
    - Repeat steps 1-3, *m* times with different seed values to create *m* imputed complete datasets. In this analysis, *m* will be assigned 1000.
- *Analysis (Step 4)*. For each completed dataset use the model as it would have been applied had the data been complete for the continuous outcome. The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

Method 2: Placebo-based Pattern-mixture model (PMM)

PMM is similar to MI but differs in that the strategy for missingness. Possible imputations do not come from the whole study cohort as mentioned above, but on the placebo group for the whole population. The idea is that discontinued subjects would be taking zero dose of the study drug after discontinuation and thus no longer exhibit any benefit from the treatment. In the above specified Step 3, instead of pulling from the entire study cohort, we will only draw from the placebo arm. The steps for this approach are detailed below:

1. Impute all non-monotone (intermittent) missing data using the MCMC method of PROC MI. Note that this imputation will sample data within each treatment group. SAS pseudo code is provided below.

```
PROC MI DATA=example seed = 6654 NIMPUTE = 20 OUT = outdata1;
       BY <treatment>;
       MCMC chain=multiple impute=monotone;
       VAR <treatment> <baseline> <V1> <V2> <V4>;
RUN;
```

2. Using the imputed datasets from Step #1 that are now monotone missing (no intermittent missing data), a single call to PROC MI (including the MNAR statement) will be utilized to impute the monotone missing data.

   SAS pseudo code is provided below. SAS accomplishes this iterative process in one step. Note that the treatment level 3 is the placebo treatment group:

```
PROC MI DATA=example seed = 2617 NIMPUTE = 20 OUT = outdata1;
        BY <time>;
        CLASS <treatment>;
        MONOTONE REG (<score> = <baseline> / details);
        MNAR MODEL (<score> / modelobs=(<treatment>=3));
        VAR <treatment> <baseline> <score>;
RUN;
```

3. When all missing data are imputed, PROC MIANALYZE will be used to combine the parameters from the analyses for inference.

Method 1 and 2 are MAR-based MI and pMI respectively. After MI, MMRM (same as primary analysis model) will be applied to imputed dataset.

Thus, there are two intercurrent events (discontinuation and use of rescue medication) and two imputation strategies (MAR-based MI and pMI). The following table provides more details how they will be used.

		Summary of Analyses after intercurrent events		
Analysis	**Method**	**Discontinuation**	**Rescue Med.**	**Comment**
Primary	MMRM	NO	YES	
Sensitivity (1)	MMRM	pMI	YES	Method 2
Sensitivity (2)	MMRM	MAR-based MI	MAR-based MI	Method 1, Rescue Med. as a intercurrent event

Rules for handling missing or partial AE, concomitant medication data are described in Section 5.1.7.

7.2. Secondary Efficacy Analysis

The following secondary endpoints will be assessed using the FAS:

- WOMAC LK3.1 OA Index (pain) – change in pain score between Baseline and Week 1

and 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 (PGA)* between Baseline and Week 4.
- *Patient Global Impression (PGI) of Change* between Week 1 and Week 4.
- *Pain intensity assessed on an 11-point numeric rating scale (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.

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

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

Figures of the Least Squared Means (LSM) of change from baseline will be plotted by treatment group and overall for the FAS for all by-visit outcomes. Within these figures, treatments will be distinguished by color and line type and jittered to prevent over-plotting at each visit. Each LS mean will include whiskers within a 95% confidence interval around the plotted value.

7.2.1. Responder Based on ≥X% Improvement[11] from Baseline

At each time point, subjects having X% or greater improvement from baseline in WOMAC pain score will be defined as "responders". The percentage change will be defined as (Value at Week X – Baseline value) * 100 / (Baseline value). In other words, the responder indicator will be set to 1 if the percentage change is less than or equal to -X% and set to 0 if the percentage change is greater than -X% or missing. The different levels of required percent improvement from baseline are X=5% to 100% with 5% increments. These different thresholds for improvement will be summarized by visit for the FAS. Results will be reported by means of a graph with response threshold on the X-axis and proportion of responders in each treatment group on the Y-axis, this figure will only be completed for WOMAC pain. Corresponding data will be presented in a summary table. WOMAC stiffness, physical function, composite score, and NRS Pain improvement will be analysed similarly in separate tables.

7.2.2. Patient Global Impression of Change

The responders are defined as subjects achieving a score of
1: Very much improved or
2: Much improved or
Non-responders are defined as subjects achieving a score of
3: Minimally improved
4: No change or
5: Minimally worse or
6: Much worse or
7: Very much worse.
Subjects achieving a score of 0: Not assessed will be considered as missing data.

The proportion of PGI responders and non-responders will be summarized by visit. Treatment comparisons will be made using a logit model with treatment effect as the only term in the model analyzing the proportion of PGI responders. For each comparison, an estimate of the odds ratio, corresponding Wald 95% confidence interval and p-value will be presented. Appendix A contains example code constructed to complete the analyses. A plot showing the least square mean observed value by visit will also be presented.

7.2.3. Patient Global Assessment

The responders are defined as subjects achieving a score of
0: Very Good or
1: Good.
Non-responders are defined as subjects achieving a score of
2: Moderate or
3: Poor or
4: Very Poor.
Subjects not assessed will be considered as missing data.

The proportion of PGA responders and non-responders will be summarized by visit. Treatment comparisons will be made using a logit model as described in Section 7.2.2 adding PGA baseline as the covariate. This model will present an estimate of the odds ratio, Wald 95% confidence interval, and p-value.

7.2.4. Use of rescue medication

The proportion of subjects using rescue medication will be summarized by frequency and percentage by treatment and overall. As described in Section 7.2.2, a logit model will be employed similarly to compare treatments against placebo. This model will not contain any

baseline covariates but will present an estimate of the odds ratio, Wald 95% confidence interval, and p-value for use of rescue medication.

A by-subject listing of all efficacy assessments collected will be presented.

8. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, electrocardiogram (ECG), physical examination results, and dermal safety. No formal inferential analyses will be conducted for safety outcomes, unless otherwise noted. Unless otherwise specified, all safety analyses will be conducted on the Safety Analysis Set.

8.1. Adverse Events

All adverse events collected are treatment-emergent adverse events (TEAEs) since only AEs after treatment start are collected. All AEs, and SAEs will be coded using the MedDRA version 19.0 thesaurus.

The frequency and percentage of subjects reporting AEs, grouped by MedDRA system organ class and preferred term, will be tabulated by severity and treatment group for the SAF. Such summaries will be displayed for AEs, SAEs, AEs by relationship to study drug, and AEs by severity.

In the case of multiple occurrences of the same AE within the same subject, each subject will only be counted once for each preferred term. In the summaries showing severity and relationship to study medication the event with the maximum severity or strongest relationship will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = definitely related).

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 5.1.8.

In the AE data listings, all AEs will be displayed.

8.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of AEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

8.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

8.2. Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from baseline will be presented for each clinical laboratory analyte by treatment group and overall at each visit.

The number of subjects with clinical laboratory values below, within, or above the normal range by time point will be tabulated for each clinical laboratory analyte by treatment group and overall. These shift tables will tabulate the number and proportion of subjects from baseline to post-baseline categories of low, normal or high.

By-subject listings of laboratory analytes will be presented. Any out-of-range values that are identified by the investigator as being clinically significant will be shown on this listing.

8.3. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, BMI, body weight, and oral body temperature. This summary will be presented by treatment group and overall at each visit.

A by-subject listing of all vital sign measurements will be presented.

8.4. Electrocardiograms

Descriptive summaries will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (both correction methods), and HR. These summaries will be presented by treatment group and overall at each visit.

The frequency and percentage of subjects with normal and abnormal ECG results will be summarized by treatment group and overall at each visit. Shift tables presenting the tabulated number and proportion of subjects with abnormal and normal results post-baseline from baseline category will also be shown in a separate table.

A by-subject listing of all ECG measures and incidence of abnormalities will be presented.

8.5. Dermal Safety

The frequency and percentage of subjects and number of patches with findings related to dermal safety including adhesion, irritation, discomfort, and adhesive residue will be summarized as described below.

8.5.1. Adhesion

Patch adhesion will be evaluated using the following scale:

0 = ≥ 90% adhered (essentially no lift off of the skin)
1 = ≥ 75% to < 90% adhered (some lifting off of the skin e.g., edges only)
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)

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

8.5.2. Irritation

Irritation will be evaluated using the following scales:

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 (0) = slightly glazed appearance
B (1) = marked glazed appearance
C (2) = glazing with peeling and cracking
F (3) = glazing with fissures
G (3) = film of dried serous exudates covering all or part of the patch site
H (3) = small petechial erosions and/or scabs
N (0) = no other observations

The frequency and percentage of subjects with patches in each combined and concatenated category will be summarized from the above scales by treatment group and overall at each visit. The Concatenated Irritation score consists of numerical “Dermal Response” score + the “Other

Effects" lettered score; for example: 2N, 2A, 3G, etc. The Combined irritation score will be calculated as a numerical total; i.e., numerical "Dermal Response" score + numeric equivalent for the "Other Effects" lettered score (note that the "Other Notations" do not have numeric equivalents and do not contribute to the numeric Combined irritation score); for example 2N, 2A, and 3G will be reported as 2, 2, and 6 combined irritations scores respectively.

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

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

8.5.3. Discomfort

Discomfort will be evaluated using the following scale:

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

The frequency and percentage of subjects with patches in each category will be summarized from the above scale by treatment group and overall at each visit.

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

8.5.4. Adhesive Residue

Adhesive Reside will be evaluated using the following scale:

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

The frequency and percentage of patches in each category will be summarized from the above scale by treatment group and overall at each visit.

A by-subject listing of individual dermal safety findings will be presented for all dermal safety categories.

8.5.5. Dermal Evaluations at Home

During the Double-blind Treatment Phase at home, subjects will complete a questionnaire about adhesion, skin irritation, discomfort, and adhesive residue in the eDiary. A by-subject listing of this data will be presented in addition to summary tables for each dermal assessment.

8.6. Pharmacokinetic Analysis

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

A by-subject listing of all plasma concentration data will be presented.

9. Changes from Planned Analysis

None

10. Final Database Transfer

After finalization of the analysis, the following will be transferred to the study sponsor:

- Randomization List
- Statistical Analysis Plan
- Data Management Plan
- Annotated CRF
- All SAS code used in the project for statistical analysis, report tables generation, and analysis dataset creation (including all source code for any macros that may be used)
- Tables, listings, and figures as included in the clinical study report
- Final SAS datasets, with full audit trail from initial data entry through final accepted version
- ADaM datasets that are necessary for analysis will be programmed in addition to SDTM (to be modeled in accordance with the Analysis Data Model version 2.1: Implementation Guide version 1.0, and the CDISC Study Data Tabulation Model version 1.4: Implementation Guide version 3.2)
- Define.xml for ADaM and SDTM data sets (to be modeled in accordance with the CDISC Define-XML Specification Version 2.0)
- Study data and analysis data reviewer guides (to be modeled in accordance with the Analysis Data Reviewer's Guide Completion Guidelines Version 1.1, and the Study Data
- Reviewer's Guide Completion Guidelines Version 1.2) for any unavoidable CDISC checker errors or warnings (found using Pinnacle21)
- Pinnicle21 reports with explanation for errors/warnings if any
- Relevant Correspondence

Database archiving at Premier is performed in accordance with Premier SOPs, which ensure security, integrity, disaster recovery, and adequate backup.

11. References

1. Noven Pharmaceuticals, Inc. protocol number HP-5000-US-05, *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, dated 12-JAN-2018, Amendment 2
2. [redacted]
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. US Federal Register. (2017) International Conference on Harmonization; Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. FDA-2017-D-6113-0002]. October 31, 2017.
5. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
6. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
7. [redacted]
8. [redacted] HP-5000-US-05 Randomization Signoff, dated 18-Nov-2016
9. EMA Guideline on the clinical development of medicinal products intended for the treatment of pain (2011)
10. 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.
11. FDA Analgesic Indications: Developing Drug and Biological Products; CDER February 2014

12. Appendix A - Example Analysis Code

Ranking:

```
proc rank data=example out=ranked ties=mean fraction
  by paramcd avisitn;
  var chg base;
  ranks chgRank baseRank;
run;
```

ANCOVA:

```
ods output lsmeans = lsmn1;
ods output diffs = diffp(where=(_trt=9));
ods output lsmestimates = lsmest1;
proc mixed data=ranked method=reml;
  by paramcd avisitn;
  class trt;
  model chg = trt base/ddfm=kr;
  lsmeans trt/cl diff alph    0.05;
  lsmestimate trt 'HP      vs placebo' 1 0 -1  divisor=1 / cl;
  lsmestimate trt 'HP      s placebo'   0 1 -1  divisor=1 / cl;
run;
```

Logit Model:

```
ods output OddsRatios = model_odds
ods output ContrastEstimate = model_pvals
proc logistic data=example;
  by paramcd avisitn;
  class trt (ref='placebo') /param=ref;
  model resp(event='1')     rt;
  contrast trt 'HP-5000    vs placebo' 1 0 / estimate=exp
  contrast trt 'HP-5000    vs placebo' 0 1 / estimate=exp
run;
```

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor's company name and protocol, the footer indicates the version of SAS®, the file name, path, and the source of the data (listing number).

General Reporting Conventions:

- All tables and data listings will be developed in landscape orientation.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all outputs.
- All footnotes will be left justified and at the bottom of a page.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A value of zero may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as ddmmmyyyy (e.g., 29AUG2011) format. A 4-digit year is preferred for all dates.
- If applicable, all observed time values will be presented by using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- All tables and data listings will have the name of the program, the location, and a run date and time stamp on the bottom of each output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the sample size (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed, however counts and percentages of missing

values may be needed.

- All population summaries for continuous variables will include: N, mean, median, SD, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, quartiles, 95% CIs) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x %). A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number HP-5000-US-05. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Please note, the following six tables will be generated as top-line deliverables:

1. Tables 14.1.1 “Study Population and Subject Disposition”, All Enrolled Subjects;
2. Table 14.2.1.2.2 “MMRM Analysis of WOMAC Pain Score by Study Visit”, FAS;
3. Table 14.2.2.2 “MMRM Analysis of WOMAC Stiffness Score by Study Visit”, FAS;
4. Table 14.2.3.2 “MMRM Analysis of WOMAC Physical Function Score by Study Visit”, FAS;
5. Table 14.2.7.2 “MMRM Analysis of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit”, FAS;
6. Table 14.3.4.1.1 “Dermal Safety for Adhesion Assessment by Study Visit”, SAF

Table Number	Population	Table Title
14.1 Demographics and Baseline Tables		
14.1.1	All Enrolled Subjects	Study Populations and Subject Disposition
14.1.2	SAF	Demographics and Baseline Characteristics
14.1.3	ITT	Previous Osteoarthritis (OA) Treatment Modalities
14.1.4	ITT	Exposure to Study Drug
14.1.5	ITT	Previous NSAID Treatments
14.2 Efficacy Tables		
14.2.1.1	FAS	Summary of WOMAC Pain Score by Study Visit
14.2.1.2.1	FAS	MMRM Analysis of WOMAC Pain Score at Week 4
14.2.1.2.2	FAS	MMRM Analysis of WOMAC Pain Score by Study Visit
14.2.1.2.3	ITT	MMRM Analysis of WOMAC Pain Score by Study Visit
14.2.1.4	FAS	ANCOVA Analysis on Rank-Transformed WOMAC Pain Score by Study Visit
14.2.1.5.1	FAS	MMRM Analysis of WOMAC Pain Score, Multiple Imputation by Study Visit, Discontinuation as Intercurrent Event
14.2.1.5.2	FAS	MMRM Analysis Of WOMAC Pain Score, Multiple Imputation By Study Visit, Rescue Medication As Intercurrent Event
14.2.1.6.1	FAS	MMRM Analysis of WOMAC Pain Score, Pattern-Mixture Model by Study Visit, Discontinuation as Intercurrent Event
14.2.1.6.2	FAS	MMRM Analysis of WOMAC Pain Score, Pattern-Mixture Model by Study

		Visit, Rescue Medication as Intercurrent Event
14.2.1.7	FAS	Responder Analysis of WOMAC Pain Score by Study Visit
14.2.2.1	FAS	Summary of WOMAC Stiffness Score by Study Visit
14.2.2.2	FAS	MMRM Analysis of WOMAC Stiffness Score by Study Visit
14.2.2.3	FAS	Responder Analysis of WOMAC Stiffness Score by Study Visit
14.2.3.1	FAS	Summary of WOMAC Physical Function Score by Study Visit
14.2.3.2	FAS	MMRM Analysis of WOMAC Physical Function Score by Study Visit
14.2.3.3	FAS	Responder Analysis of WOMAC Physical Function Score by Study Visit
14.2.4.1	FAS	Summary of WOMAC Composite Score by Study Visit
14.2.4.2	FAS	MMRM Analysis of WOMAC Composite Score by Study Visit
14.2.4.3	FAS	Responder Analysis of WOMAC Composite Score by Study Visit
14.2.5.1	FAS	Summary of Patient Global Assessment by Study Visit
14.2.5.2	FAS	MMRM Analysis of Patient Global Assessment by Study Visit
14.2.5.3	FAS	Responder Analysis of Patient Global Assessment by Study Visit
14.2.6.1	FAS	Summary of Patient Global Impression of Change by Study Visit
14.2.6.2	FAS	MMRM Analysis of Patient Global Impression of Change by Study Visit
14.2.6.3	FAS	Responder Analysis of Patient Global Impression of Change by Study Visit
14.2.7.1	FAS	Summary of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
14.2.7.2	FAS	MMRM Analysis of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
14.2.7.3	FAS	Responder Analysis of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
14.2.8.1	FAS	Incidence of Rescue Medication Use
14.2.9	PAS	Plasma Concentrations of Diclofenac for HP-5000-[redacted] and HP-5000[redacted] by Study Visit
14.3 Safety And Tolerability Tables		
14.3.1 Displays Of Adverse Events		
14.3.1.1	SAF	Summary of all Adverse Events
14.3.1.2	SAF	Summary of Adverse Events by System Organ Class and Preferred Term
14.3.1.3	SAF	Summary of Adverse Events by Severity and Relationship to Study Medication, System Organ Class and Preferred Term
14.3.1.4	SAF	Adverse Events Leading to Premature Withdrawal from the Study by System Organ Class and Preferred Term
14.3.1.5	SAF	Summary of Serious Adverse Events by System Organ Class and Preferred Term
14.3.1.6	SAF	Adverse Events Leading to Death by System Organ Class and Preferred Term
14.3.2 Laboratory Safety Data		
14.3.2.1.1	SAF	Summary of Change from Baseline for Clinical Chemistry parameters at Week 4
14.3.2.1.2	SAF	Summary of Change from Baseline for Clinical Hematology parameters at Week 4
14.3.2.1.3	SAF	Summary of Change from Baseline for Clinical Urinalysis parameters at Week 4
14.3.2.2.1	SAF	Shift from Baseline to Week 4 for Clinical Chemistry parameters
14.3.2.2.2	SAF	Shift from Baseline to Week 4 for Clinical Hematology parameters
14.3.2.2.3	SAF	Shift from Baseline to Week 4 for Clinical Urinalysis parameters
14.3.3 Vital Signs And ECG Data		
14.3.3.1	SAF	Summary of Vital Signs by Study Visit
14.3.3.2	SAF	Summary of ECG Parameters by Study Visit
14.3.3.3	SAF	Incidence of Abnormal ECG Findings by Study Visit
14.3.3.4	SAF	Shift from Baseline to Week 4 for ECG Findings
14.3.4 Other Safety Data		
14.3.4.1.1	SAF	Dermal Safety for Adhesion Assessment by Study Visit
14.3.4.1.2.1	SAF	Dermal Safety for Irritation Dermal Response by Study Visit
14.3.4.1.2.2	SAF	Dermal Safety for Concatenated Irritation Score by Study Visit
14.3.4.1.2.3	SAF	Dermal Safety for Combined Irritation Score by Study Visit
14.3.4.1.3	SAF	Dermal Safety for Discomfort Assessment by Study Visit

14.3.4.1.4	SAF	Dermal Safety for Adhesive Residue by Study Visit
14.3.4.1.5	SAF	Dermal Evaluations at Home – Adhesion
14.3.4.1.6	SAF	Dermal Evaluations at Home – Skin Irritation
14.3.4.1.7	SAF	Dermal Evaluations at Home – Discomfort
14.3.4.1.8	SAF	Dermal Evaluations at Home – Adhesive Residue
14.3.4.2	SAF	Overall Treatment Compliance

13.2. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number HP-5000-US-05.

All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings. In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (e.g., repetition of subject number), then only the first occurrence will be displayed. In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Listing Number	Population	Listing Title
16.2.1 Subject Disposition		
16.2.1.1	All Enrolled Subjects	Assignment to Analysis Populations and Treatment Cohort
16.2.1.2	All Enrolled Subjects	Study Completion Status and Reasons for Discontinuation
16.2.4 Demographics And Other Baseline Characteristics		
16.2.4.1	SAF	Demographics
16.2.4.2	SAF	Medical History
16.2.4.3	SAF	Concomitant and Prior Medications
16.2.5 Drug Exposure And Concentration Data		
16.2.5.1	SAF	Drug Accountability and Compliance
16.2.5.2	PAS	Plasma Concentrations
16.2.6 Efficacy Listings		
16.2.6.1.1	FAS	WOMAC Items
16.2.6.1.2	FAS	WOMAC Scores
16.2.6.2	FAS	Patient Global Assessment (PGA)
16.2.6.3	FAS	Patient Global Impression of Change (PGI)
16.2.6.4	FAS	Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS)
16.2.6.5	FAS	Rescue Medication Use
16.2.7 Adverse Event Listings		
16.2.7.1	SAF	Adverse Events
16.2.7.2	SAF	Serious Adverse Events
16.2.7.3	SAF	Adverse Events Leading to Withdrawal
16.2.7.4	SAF	Listing of Deaths
16.2.8 Laboratory Data Listings		
16.2.8.1	SAF	Clinical Chemistry
16.2.8.2	SAF	Hematology
16.2.8.3	SAF	Urinalysis
16.2.8.4	SAF	Pregnancy Test
16.2.8.5	SAF	Drug Screen
16.2.9 Other Clinical Observations And Measurements		
16.2.9.1	SAF	Vital Signs
16.2.9.2	SAF	12-Lead Electrocardiograms (ECG)
16.2.9.3	SAF	12-Lead Electrocardiogram (ECG) Abnormalities
16.2.9.4	SAF	Physical Examination (PE)
16.2.9.5.1	SAF	Dermal Safety for Adhesion
16.2.9.5.2	SAF	Dermal Safety for Irritation
16.2.9.5.3	SAF	Dermal Safety for Discomfort
16.2.9.5.4	SAF	Dermal Safety for Adhesive Residue
16.2.9.6	SAF	X-Ray

13.3. Planned Figure Descriptions

The following are planned summary figures for protocol number HP-5000-US-05. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Figure Number	Population	Figure Title
14.2 Efficacy Figures		
14.2.1.1	FAS	LSMean Change from Baseline over time of WOMAC Pain Score
14.2.1.2	FAS	AUC Analysis of WOMAC Pain Score
14.2.1.3	FAS	Responder Analysis of WOMAC Pain Score
14.2.2	FAS	LSMean Change from Baseline over time of WOMAC Stiffness Score
14.2.3	FAS	LSMean Change from Baseline over time of WOMAC Physical Function Score
14.2.4	FAS	LSMean Change from Baseline over time of WOMAC Composite Score
14.2.5	FAS	LSMean Change from Baseline over time of Patient Global Assessment
14.2.6	FAS	LS Mean Observed Value over time of Patient Global Impression of Change
14.2.7	FAS	LSMean Change from Baseline over time of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS)
14.2.8	PAS	Mean Plasma Concentration (Logarithmic Scale)

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell as noted by {}.

Figure 2: Standardized Layout

Noven Pharmaceuticals, Inc. Page xx of xx

Protocol: HP-5000-US-05 <version>

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

Note: *<Note: If directly Applicable>*

Footnote 1 *<if applicable>*

Footnote 2 *<if applicable>*

Footnote n *<if applicable>*

SOURCE: Listings xx.x.x, xx.x.x

T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

14.2. Planned Table Shells

Table 14.1.1
Study Populations and Subject Disposition
All Enrolled Subjects

Status or Variable/Statistic	HP-5000-[redacted]	HP-5000[redacted]	Placebo	Overall
Randomized N	xx	xx	xx	xx
ITT Population [1]	xx	xx	xx	Xx
FAS Population [2] n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAF Population [3] n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
PAS Population [4] n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Completed Study Treatment n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Early Termination n(%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of subjects in the ITT Population. Treatment arms: HP-5000[redacted] topical patch, HP-[redacted] topical patch, and Placebo.
[1] The Intent-to-Treat (ITT) Population includes all consented and randomized subjects. Assigned/planned treatment groups are presented.
[2] The Full Analysis Set (FAS) Population 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). Analysis is based on the actual treatment received.
[3] The Safety Analysis Set (SAF) Population includes all subjects who have 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. Analysis is based on the actual treatment received.
[4] The Pharmacokinetic Analysis (PAS) Population includes all subjects who have received at least 1 patch of double-blind study drug applied and who have at least 1 blood sample for PK assessment.
[5] The Reason for Early Termination percentages are the number of early terminations per applicable treatment column.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.1
Study Populations and Subject Disposition
All Enrolled Subjects

Status or Variable/Statistic	HP-5000[redacted]	HP-5000-[redacted]	Placebo	Overall
Primary Reason for Early Termination [5] n(%)				
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-compliance	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol Violation	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Request of primary care physician or investigator	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Sponsor request subject to be withdrawn	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Subject withdrawal of consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are based on the number of subjects in the ITT Population. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] The Intent-to-Treat (ITT) Population includes all consented and randomized subjects. Assigned/planned treatment groups are presented
[2] The Full Analysis Set (FAS) Population 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). Analysis is based on the actual treatment received.
[3] The Safety Analysis Set (SAF) Population includes all subjects who have 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. Analysis is based on the actual treatment received.
[4] The Pharmacokinetic Analysis (PAS) Population includes all subjects who have received at least 1 patch of double-blind study drug applied and who have at least 1 blood sample for PK assessment. Analysis is based on the actual treatment received.
[5] The Reason for Early Termination percentages are the number of early terminations per applicable treatment column.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.2
Demographics and Baseline Characteristics
Safety Analysis Set

Variable Statistics or Category	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Age (years)				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx, xx	xx, xx	xx, xx	xx, xx
Age Group (years) (n (%))				
40 to 59	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
50 to 59	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
>= 60	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gender (n (%))				
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Race (n (%))				
American Indian or Alaska Native	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
<< Other Categories >>	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100. Treatment arms: HP-5000[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.2
Demographics and Baseline Characteristics
Safety Analysis Set

Variable Statistics or Category	HP-5000-[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Ethnicity (n (%))				
Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Not Hispanic or Latino	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Height (cm)				
N	xx	xx	xx	Xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x
Standard Deviation	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x	xxx.x
Minimum, Maximum	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Weight (kg)				
N	xx	xx	xx	Xx
Mean	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Standard Deviation	xxx.xxx	xxx.xxx	xxx.xxx	xxx.xxx
Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx
BMI (kg/m^2)				
n	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Standard Deviation	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Minimum, Maximum	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx

Note: Percentages are (n/N)*100. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.2
Demographics and Baseline Characteristics
Safety Analysis Set

Variable Statistics or Category	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
BMI group (kg/m^2)				
Underweight: 15 to 18.4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal: 18.5 to 25	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overweight: 26 to 30	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Moderately Obese: 31 to 35	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Severely Obese: 36 to 40	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

{Programming notes: Please also include the following summaries: Baseline NRS Score, Baseline WOMAC Scores (including sub-scores), Baseline PGA, Baseline severity with NRS Score: Moderate 5 to 6, Severe ≥ 7, WOMAC Pain: 0 to 9, 10 to 20, }

Note: Percentages are (n/N)*100. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.3
Previous Osteoarthritis (OA) Treatment Modalities
Intent-to-Treat Set

ATC Preferred Term [1]	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of Subjects with previous OA treatment	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 1 (n (%))	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 2 (n (%))	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100. Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or Preferred Term. Treatment arms: HP-5000-[redacted]: [redacted]mg[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Medications were coded using WHO-DD (Enhanced version 2017) ATC Level 4
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.4
Exposure to Study Drug
Intent-to-Treat Set

Variable Statistics or Category	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Duration of Exposure (days) Overall				
N	xx	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x	xxx.x
Standard Deviation	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Q1	xxx.x	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x	xxx.x
Q3	xxx.x	xxx.x	xxx.x	xxx.x
Minimum, Maximum	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Week X				
<< Repeat >>				
Number of Patches Applied Overall, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week X				
<< Repeat >>				
Number of Patches Removed Overall, n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week X				
<< Repeat >>				

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. Duration of Exposure (days) = Treatment End Date – Treatment Start Date + 1. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.4
Exposure to Study Drug
Intent-to-Treat Set

Variable Statistics or Category	HP-5000-[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of Patches Removed Early Overall , n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week X				
<< Repeat >>				
Reasons for Patch Removal				
Overall, n (%)				
Xxxxxxxxxxxxxxxxxxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxx xxxxxxxx xxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxxxx xxxxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
xxxxxxxxxxxxxxxx xxxxxx xxxxxxxxxx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week X				
<< Repeat categories >>				

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. Duration of Exposure (days) = Treatment End Date – Treatment Start Date + 1. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.1.5
Previous NSAID Treatments
Intent-to-Treat Set

ATC Preferred Term [1]	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Placebo (N=xx)	Overall (N=xx)
Number of Subjects with previous NSAID treatment	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 1 (n (%))	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
ATC 2 (n (%))	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Medication 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100.. Subjects were counted only once for each Anatomical Therapeutic Chemical (ATC) or Preferred Term. Treatment arms: HP-5000-[redacted]: [redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Medications were coded using WHO-DD (Enhanced version 2017) ATC Level 4
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.2.1.1
Summary of WOMAC Pain Score by Study Visit
Full Analysis Set

Visit Statistics	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Placebo (N=xx)
Baseline			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 1			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 1 Change from Baseline			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: CI = confidence interval, WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Continue for all applicable visits collected per protocol}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

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Table 14.2.1.2.1
MMRM Analysis of WOMAC Pain Score at Week 4
Full Analysis Set

Visit/Category Statistics [1]	HP-5000[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 4 Change from Baseline				
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (LS Mean = 0)	x.xxx	x.xxx	x.xxx	x.xxx
LS Mean Difference from Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	
(95% CI for Mean Difference from Placebo)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value (LS Mean = Placebo LS Mean)	x.xxx	x.xxx	x.xxx	

Note: CI = confidence interval, LS = least-squares, MMRM = repeated measures mixed model, SE = standard error, WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Estimates are from a repeated measures mixed model with change from baseline as the dependent variable and subject as the random repeated factor. Terms for treatment, visit, treatment-by-visit, and baseline WOMAC Pain Score as covariates are included. The Kenward Roger approximation for denominator degrees of freedom is implemented and the restricted maximum likelihood (REML) approach for estimation is used. An unstructured covariance matrix converged.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.2.1.2.2 MMRM Analysis of WOMAC Pain Score by Study Visit
Full Analysis Set
{Programming Note: If type=un fails to converge, follow SAP guidance and update footnote indicating which covariance structure is used}

Table 14.2.1.2.3
MMRM Analysis of WOMAC Pain Score by Study Visit
Intent-to-Treat Set

Visit/Category Statistics [1]	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 1 Change from Baseline				
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (LS Mean = 0)	x.xxx	x.xxx	x.xxx	x.xxx
LS Mean Difference from Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	
(95% CI for Mean Difference from Placebo)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value (LS Mean = Placebo LS Mean)	x.xxx	x.xxx	x.xxx	

Note: Assigned/planned treatment groups are presented. CI = confidence interval, LS = least-squares, MMRM = repeated measures mixed model, SE = standard error, WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000[redacted] topical patch, and Placebo.
[1] Estimates are from a repeated measures mixed model with change from baseline as the dependent variable and subject as the random repeated factor. Terms for treatment, visit, treatment-by-visit, and baseline WOMAC Pain Score as covariates are included. The Kenward Roger approximation for denominator degrees of freedom is implemented and the restricted maximum likelihood (REML) approach for estimation is used. An unstructured covariance matrix converged.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If type=un fails to converge, follow SAP guidance and update footnote indicating which covariance structure is used.
Repeat above layout for Week 2, and Week 4}

Table 14.2.1.4
ANCOVA Analysis on Rank-Transformed WOMAC Pain Score by Study Visit
Full Analysis Set

Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 1 Change from Baseline				
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (LS Mean = 0)	x.xxx	x.xxx	x.xxx	x.xxx
LS Mean Difference from Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	
(95% CI for Mean Difference from Placebo)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value (LS Mean = Placebo LS Mean)	x.xxx	x.xxx	x.xxx	

Note: ANCOVA = analysis of covariance, CI = confidence interval, LS = least-squares, SE = standard error, WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Estimates are from an analysis of covariance model with change from baseline as the dependent variable. Terms for treatment, and baseline WOMAC Pain Score as covariates are included. The restricted maximum likelihood (REML) approach for estimation is used.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat above layout for Week 2, and Week 4}

Table 14.2.1.5.1
MMRM Analysis of WOMAC Pain Score, Multiple Imputation by Study Visit, Discontinuation as Intercurrent Event
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3 using MI imputed records for analyses. Add footnote referencing Section 7.1.1 implementation for MI}

Table 14.2.1.5.2
MMRM Analysis of WOMAC Pain Score, Multiple Imputation by Study Visit, Rescue Medication as Intercurrent Event
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3 using MI imputed records for analyses. Add footnote referencing Section 7.1.1 implementation for MI}

Table 14.2.1.6.1
MMRM Analysis of WOMAC Pain Score, Pattern-Mixture Model by Study Visit, Discontinuation as Intercurrent Event
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3 using PMM imputed records for analyses. Add footnote referencing Section 7.1.1 implementation for PMM}

Table 14.2.1.6.2
MMRM Analysis of WOMAC Pain Score, Pattern-Mixture Model by Study Visit, Rescue Medication as Intercurrent Event
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3 using PMM imputed records for analyses. Add footnote referencing Section 7.1.1 implementation for PMM}

Table 14.2.1.7
Responder Analysis of WOMAC Pain Score by Study Visit
Full Analysis Set

Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx) n (%)	HP-5000-[redacted] (N=xx) n (%)	Overall HP-5000 (N=xx) n (%)	Placebo (N=xx) n (%)
Week 1				
n	xx	xx	xx	xx
5% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
15% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. WOMAC = West Ontario and McMasters Universities Osteoarthritis Index.
Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] At each time point, subjects having a x% or greater improvement from baseline in WOMAC pain score will be defined as a "Responder", where x% ranges from 5% to 100%.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat above layout %'s from 5% to 100% for Responders and for Week 2, and Week 4}

Table 14.2.2.1
Summary of WOMAC Stiffness Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.1}

Table 14.2.2.2
MMRM Analysis of WOMAC Stiffness Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3}

Table 14.2.2.3
Responder Analysis of WOMAC Stiffness Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.7}

Table 14.2.3.1
Summary of WOMAC Physical Function Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.1}

Table 14.2.3.2
MMRM Analysis of WOMAC Physical Function Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3}

Table 14.2.3.3
Responder Analysis of WOMAC Physical Function Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.7}

Table 14.2.4.1
Summary of WOMAC Composite Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.1}

Table 14.2.4.2
MMRM Analysis of WOMAC Composite Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3}

Table 14.2.4.3
Responder Analysis of WOMAC Composite Score by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.7}

Table 14.2.5.1
Summary of Patient Global Assessment by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.1}

Table 14.2.5.2
MMRM Analysis of Patient Global Assessment by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.2.3}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.2.5.3
Responder Analysis of Patient Global Assessment by Study Visit
Full Analysis Set

Visit/Category Statistics [1]	HP-5000[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 1 (n (%))				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Response (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	
Week 2 (n (%))				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Response (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. CI = confidence interval. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Odds ratio, CI, and p-value are from a logit model estimating the probability of response with treatment and PGA baseline as a covariate in the model. Responder is defined as a result of "Very Good" or "Good" and Non-Responder is defined as a result of "Moderate", "Poor", or "Very Poor".
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat above layout for Week 4}

Table 14.2.6.1

Summary of Patient Global Impression of Change by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.1}

Table 14.2.6.2
MMRM Analysis of Patient Global Impression of Change by Study Visit
Full Analysis Set

{Programming Note: Repeat table 14.2.1.3. Remove Baseline covariate (no baseline) and model aval instead of chg}

Table 14.2.6.3
Responder Analysis of Patient Global Impression of Change by Study Visit
Full Analysis Set

Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 1 (n (%))				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Response (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	
Week 2 (n (%))				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Response (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. CI = confidence interval. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] mg/24h) topical patch, and Placebo.
[1] Odds ratio, CI, and p-value are from a logit model estimating the probability of response with treatment in the model. Responder is defined as a result of "Very much improved", "Much Improved", and Non-Responder is defined as a result of "No change", "Minimally improved", "Minimally worse", "Much worse" or "Very much worse".
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat above layout for Week 4}

Table 14.2.7.1
Summary of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
Full Analysis Set

Parameter Visit Statistics	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Placebo (N=xx)
Target Knee			
Baseline			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 1			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 1 Change from Baseline			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: CI = confidence interval, NRS = Numeric Rating Scale. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Continue for all applicable visits collected per protocol, and also repeat for Non-Target Knee}

Table 14.2.7.2
MMRM Analysis of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
Full Analysis Set

Parameter Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Target Knee				
Week 1 Change from Baseline				
LS Mean (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)
(95% CI for LS Mean)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
p-value (LS Mean = 0)	x.xxx	x.xxx	x.xxx	x.xxx
LS Mean Difference from Placebo (SE)	x.xx (x.xxx)	x.xx (x.xxx)	x.xx (x.xxx)	
(95% CI for Mean Difference from Placebo)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value (LS Mean = Placebo LS Mean)	x.xxx	x.xxx	x.xxx	
<< Repeat for all study visits and CFB>>				

Note: Analysis is based on the actual treatment received. CI = confidence interval, LS = least-squares, MMRM = repeated measures mixed model, SE = standard error, WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Estimates are from a repeated measures mixed model with change from baseline as the dependent variable and subject as the random repeated factor. Terms for treatment, visit, treatment-by-visit, and baseline WOMAC Pain Score as covariates are included. The Kenward Roger approximation for denominator degrees of freedom is implemented and the restricted maximum likelihood (REML) approach for estimation is used. An unstructured covariance matrix converged.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If type=un fails to converge, follow SAP guidance and update footnote indicating which covariance structure is used.
Repeat above layout for Week 2, and Week 4, and also repeat for Non-Target Knee }

Table 14.2.7.3
Responder Analysis of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS) by Study Visit
Full Analysis Set

Parameter Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx) n (%)	HP-5000-[redacted] (N=xx) n (%)	Overall HP-5000 (N=xx) n (%)	Placebo (N=xx) n (%)
Target Knee				
Week 1				
n	xx	xx	xx	xx
5% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
10% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
15% Improvement				
Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Non-Responder	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. WOMAC = West Ontario and McMasters Universities Osteoarthritis Index.
Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] At each time point, subjects having a x% or greater improvement from baseline in WOMAC pain score will be defined as a "Responder", where x% ranges from 5% to 100%.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat above layout %'s from 5% to 100% for Responders and for Week 2, and Week 4}

Table 14.2.8.1
Incidence of Rescue Medication Use
Full Analysis Set

Visit/Category Statistics [1]	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Week 1 (n (%))				
Rescue Medication Used	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Rescue Medication Not Used	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Rescue Medication (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	
Week 2 (n (%))				
Rescue Medication Used	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Rescue Medication Not Used	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Odds Ratio for Rescue Medication (Active / Placebo)	x.xx	x.xx	x.xx	
(95% CI for proportion)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	x.xxx	

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. CI = confidence interval. Treatment arms: HP-5000[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Odds ratio, CI, and p-value are from a logit model estimating the probability of Rescue Medication Use with treatment in the model.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Repeat for all post-baseline visits (Week 4, etc.)}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

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Table 14.2.9
Plasma Concentrations of Diclofenac for HP-5000-[redacted] and HP-5000-[redacted] by Study Visit
Pharmacokinetic Analysis Set

Analyte Visit Statistics	HP-5000[redacted] (N=xx)	HP-5000[redacted] (N=xx)	Overall Active (N=xx)
Plasma concentration (ng/mL)			
Day 14			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Day 28			
n	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.1.1
Summary of all Adverse Events
Safety Analysis Set

Category	HP-5000-[redacted] (N=xx) n (%)	HP-5000-[redacted] (N=xx) n (%)	Overall HP-5000 (N=xx) n (%)	Placebo (N=xx) n (%)
Subjects with at Least One				
Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Potentially Related to Study Drug [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event Potentially Related to Study Drug [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Study Drug Withdrawal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event Leading to Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100. Treatment groups are based on treatment received. All adverse events collected are treatment-emergent adverse events (TEAEs) since only AEs after treatment start are collected. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Any AE determined as “Possibly Related” or “Definitely Related” are considered as potentially related to study drug.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.1.2
Summary of Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class Preferred Term	HP-5000-[redacted] (N=xx)		HP-5000-[redacted] (N=xx)		Overall HP-5000 (N=xx)		Placebo (N=xx)	
	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)
Number of Subjects with at Least One AE	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
SOC 1	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
PT 1	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
PT 2	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
PT 3	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
SOC 2	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
PT 1	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
PT 2	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)

Note: Percentages are (n/N)*100. Treatment groups are based on treatment received. Subjects were counted only once for each System Organ Class and Preferred Term for Subjects (%) column. For the Events column, multiple events for a subject that are in the same AE category are counted multiple times in that AE category. All adverse events collected are treatment-emergent adverse events (TEAEs) since only AEs after treatment start are collected. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Adverse events were coded using MedDRA version 19.0.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Sort alphabetically for SOC and decreasing frequency for PT of overall}

Table 14.3.1.3
Summary of Adverse Events by Severity and Relationship to Study Medication, System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class [1] Preferred Term Severity Relationship to Study Medication	HP-5000[redacted] (N=xx)		HP-5000[redacted] (N=xx)		Overall HP-5000 (N=xx)		Placebo (N=xx)	
	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)	Events n	Subjects n(%)
Number of Subjects with at Least One AE	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
SOC 1								
PT 1	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Mild	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Not Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Unlikely Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Possibly Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Definitely Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Moderate	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Not Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
Unlikely Related	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)
{... continue as appropriate}								

Note: Percentages are (n/N)*100. Treatment groups are based on treatment received. Subjects were counted only once for each System Organ Class and Preferred Term. A subject with multiple events per System Organ Class or per Preferred Term is counted only once at maximum reported severity. For the Events column, multiple events for a subject that are in the same AE category are counted multiple times in that AE category. All adverse events collected are treatment-emergent adverse events (TEAEs) since only AEs after treatment start are collected. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Adverse events were coded using MedDRA version 19.0.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Sort alphabetically for SOC and decreasing frequency for PT of overall, continue for all combinations of severity and relationship. Do not show 0 count rows}

Table 14.3.1.4
Adverse Events Leading to Premature Withdrawal from the Study by System Organ Class and Preferred Term
Safety Analysis Set

{Programming Note: Repeat table 14.3.1.2}

Table 14.3.1.5
Summary of Serious Adverse Events by System Organ Class and Preferred Term
Safety Analysis Set

{Programming Note: Repeat table 14.3.1.2}

Table 14.3.1.6
Adverse Events Leading to Death by System Organ Class and Preferred Term
Safety Analysis Set

{Programming Note: Repeat table 14.3.1.2}

Table 14.3.2.1.1
Summary of Change from Baseline for Clinical Chemistry parameters at Week 4
Safety Analysis Set

Analyte Visit Statistics	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Analyte (unit)				
Baseline				
n	xx	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 4				
n	xx	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Week 4 Change from Baseline				
n	xx	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: Treatment groups are based on treatment received. CI = confidence interval. Treatment arms: HP-5000-[redacted] topical patch, HP-5000[redacted] ([redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: Continue for all applicable parameters collected per protocol}

Table 14.3.2.1.2
Summary of Change from Baseline for Clinical Hematology parameters at Week 4
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.1.1}

Table 14.3.2.1.3
Summary of Change from Baseline for Clinical Urinalysis parameters at Week 4
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.1.1}

Table 14.3.2.2.1
Shift from Baseline to Week 4 for Clinical Chemistry parameters
Safety Analysis Set

	BASELINE											
Analyte	HP-5000-[redacted] (N=xx) n (%)			HP-5000[redacted] (N=xx) n (%)			Overall HP-5000 (N=xx) n (%)			Placebo (N=xx) n (%)		
Visit	Low	Normal	High	Low	Normal	High	Low	Normal	High	Low	Normal	High
Analyte (unit)												
Week 4												
Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Analyte 2 (unit)												
Week 4												
Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Analyte 2 (unit)												
Week 4												
Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. Treatment groups are based on treatment received. Baseline result is presented horizontally across the top, and Post Baseline is presented vertically in the first column. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Continue for all applicable parameters collected per protocol}

Table 14.3.2.2.2
Shift from Baseline to Week 4 for Clinical Hematology parameters
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.2.1}

Table 14.3.2.2.3
Shift from Baseline to Week 4 for Clinical Urinalysis parameters
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.2.1}

Table 14.3.3.1
Summary of Vital Signs by Study Visit
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.1.1, present all applicable study visits}

Table 14.3.3.2
Summary of ECG Parameters by Study Visit
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.1.1, present all applicable study visits}

Table 14.3.3.3
Incidence of Abnormal ECG Findings by Study Visit
Safety Analysis Set

Visit Category	HP-5000-[redacted] (N=xx) n (%)	HP-5000-[redacted] (N=xx) n (%)	Overall HP-5000 (N=xx) n (%)	Placebo (N=xx) n (%)
Baseline				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 4				
Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal NCS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Abnormal CS	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing subjects at a given study visit. Treatment groups are based on treatment received. CS = clinically significant; NCS = not clinically significant. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.3.3.4
Shift from Baseline to Week 4 for ECG Findings
Safety Analysis Set

{Programming Note: Repeat table 14.3.2.2.1, categories displayed will be Normal, Abnormal NCS, Abnormal CS}

Noven Pharmaceuticals, Inc. Page 1 of x
Protocol HP-5000-US-05 FINAL

Table 14.3.4.1.1
Dermal Safety for Adhesion by Study Visit
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	---- Amount Adhered ---- 0: >= 90% n (%)	1: >= 75% to < 90% n (%)	2: >= 50% to < 75% n (%)	3: < 50% n (%)	4: Detached Completely n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of subjects with the worst scores			xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. Full Descriptions:
0: >= 90% adhered (essentially no lift off of the skin),
1: >= 75% to < 90% adhered (some lifting off of the skin e.g., edges only),
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).
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: continue for all applicable treatments}

Noven Pharmaceuticals, Inc. Page 1 of x
Protocol HP-5000-US-05 FINAL

Table 14.3.4.1.2.1
Dermal Safety for Irritation Dermal Response by Study Visit
Safety Analysis Set

			---------- Irritation Dermal Response ----------							
Treatment	Study Day	N (Applied Patches)	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)
HP-5000-[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted]topical patch, and Placebo. Full Descriptions:
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
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: continue for all applicable treatments and repeat for SUBJECT counts instead of PATCH counts}

Noven Pharmaceuticals, Inc. Page 1 of x
Protocol HP-5000-US-05 FINAL

Table 14.3.4.1.2.2
Dermal Safety for Concatenated Irritation Score by Study Visit
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	---------- Concatenated Irritation Score ---------- 0A n (%)	0B n (%)	0C n (%)	0F n (%)	0G n (%)	0H n (%)	0N n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. Full Descriptions:
A (0) = slightly glazed appearance
B (1) = marked glazed appearance
C (2) = glazing with peeling and cracking
F (3) = glazing with fissures
G (3) = film of dried serous exudates covering all or part of the patch site
H (3) = small petechial erosions and/or scabs
N (0) = no other observations
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: continue for all applicable treatments and all combinations of concatenated score, 1 through 7, effects A, B, C, F, G, H, N and repeat for SUBJECT counts instead of PATCH counts }

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Table 14.3.4.1.2.3
Dermal Safety for Combined Irritation Score by Study Visit
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Combined Irritation Score 0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)	10 n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of subjects with a score of >=3						xx (xx.x%)							

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. The combined irritation score will be calculated as a numerical total; i.e., numerical "Dermal Response" score + numeric equivalent for the "Other Effects" lettered score (note that the "Other Notations" do not have numeric equivalents and do not contribute to the numeric Combined irritation score). Treatment arms: HP-5000-[redacted]topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: continue for all applicable treatments and repeat for SUBJECT counts instead of PATCH counts }

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.4.1.3
Dermal Safety for Discomfort by Study Visit
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Discomfort 0 n (%)	Discomfort 1 n (%)	Discomfort 2 n (%)	Discomfort 3 n (%)	Discomfort 4 n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. Full Descriptions:
0: No discomfort
1: Mild discomfort
2: Moderate but tolerable discomfort
3: Severe, intolerable discomfort
4: Patch not present
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: continue for all applicable treatments and repeat for SUBJECT counts instead of PATCH counts}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.4.1.4
Dermal Safety for Adhesive Residue by Study Visit
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Adhesive Residue 0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study visit. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. Full Descriptions:
0: None
1: Light
2: Medium
3: Heavy
4: Patch not present
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: continue for all applicable treatments and repeat for SUBJECT counts instead of PATCH counts}

Table 14.3.4.1.5
Dermal Evaluations at Home – Adhesion
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Adhesion: Is the patch 100% attached to the skin? Yes n (%)	Adhesion: Is the patch 100% attached to the skin? No n (%)	Adhesion: Is more than half of the patch still attached? Yes n (%)	Adhesion: Is more than half of the patch still attached? No n (%)
HP-5000[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Number of subjects with full detachment			xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study day with that response. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc. Page 1 of x
Protocol HP-5000-US-05 FINAL

Table 14.3.4.1.6
Dermal Evaluations at Home – Skin Irritation
Safety Analysis Set

			Skin Irritation					
			Any Irritation where the patch was applied?		Describe your irritation			
Treatment	Study Day	N (Applied Patches)	Yes n (%)	No n (%)	Redness n (%)	Swelling n (%)	Itching n (%)	Other n (%)
HP-5000-[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study day with that response. Treatment groups are based on treatment received.
Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.4.1.7
Dermal Evaluations at Home - Discomfort
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Discomfort: Any Discomfort? Yes n (%)	Discomfort: Any Discomfort? No n (%)	Discomfort: Describe Discomfort Burning n (%)	Discomfort: Describe Discomfort Itching n (%)	Discomfort: Describe Discomfort Pain n (%)
HP-5000-[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study day with that response. Treatment groups are based on treatment received.
Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Table 14.3.4.1.8
Dermal Evaluations at Home – Adhesive Residue
Safety Analysis Set

Treatment	Study Day	N (Applied Patches)	Adhesive Residue: Is there any residue on your skin after removing the patch? Yes n (%)	Adhesive Residue: Is there any residue on your skin after removing the patch? No n (%)
HP-5000-[redacted]	xx	xx	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)
	xx	xx	xx (xx.x%)	xx (xx.x%)

Note: Percentages are (n/N)*100, where N is the number of non-missing patches at a given study day with that response. Treatment groups are based on treatment received. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Table 14.3.4.2
Overall Treatment Compliance
Safety Analysis Set

Visit Statistics	HP-5000-[redacted] (N=xx)	HP-5000-[redacted] (N=xx)	Overall HP-5000 (N=xx)	Placebo (N=xx)
Overall Compliance				
n	xx	xx	xx	xx
Mean (95% CI)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)	xx.xx (x.xx, x.xx)
Standard Deviation	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx
Minimum, Maximum	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note: Treatment groups are based on treatment received. CI = confidence interval. Compliance is defined as the number of patches given less the number of patches returned divided by the number of days for required applications (e.g. without counting of extra patches given just in case), expressed as a percentage. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
SOURCE: Listings xx.x.x, xx.x.x
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

14.3. Planned Listing Shells

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.1.1
Assignment to Analysis Populations and Treatment Cohort
All Subjects Enrolled

Subject ID	Randomization Date	Randomization ID	Randomized Treatment	ITT	FAS	SAF	PAS
XXXXX	DDMMMYYYY	XXXX	Placebo	Yes	Yes	Yes	Yes
XXXXX	DDMMMYYYY	XXXX	HP-5000-[redacted]	Yes	No; xxx xxxxxx xxxxxx xxxxx xxxxxxxx	No; xxx xxxxxx xxxxxx xxxxx xxxxxxxx	No; xxx xxxxxx xxxxxx xxxxx xxxxxxxx
XXXXX	DDMMMYYYY	XXXX	Placebo	Yes	No; xxx xxxxxxxx xxxxx xxxxxxxx	No; xxx xxxxxx xxxxxx	No; xxx xxxxxxxxx
XXXXX	DDMMMYYYY	XXXX	HP-5000[redacted]	Yes	Yes	Yes	Yes

Note: ITT = Intent-to-Treat, FAS = Full Analysis Set, PAS = Pharmacokinetic Analysis Set, SAF = Safety Analysis Set. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.

T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If any population is listed as 'No', list the reason for exclusion from the population after a semicolon}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.1.2
Study Completion Status and Reasons for Discontinuation
All Subjects Enrolled

Actual Treatment: XXXXXXX

Subject ID	Screen Date	Completed Treatment?	Date Completed	Date of Discontinuation	Date of Last Contact	Date of Last Patch	Reason for Discontinuation	Date of Death Adverse Event
XXXXX	DDMMMYYYY	Yes	DDMMMYYYY		DDMMMYYYY	DDMMMYYYY		
XXXXX	DDMMMYYYY	Yes	DDMMMYYYY		DDMMMYYYY	DDMMMYYYY		
XXXXX	DDMMMYYYY	No		DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxx	
XXXXX	DDMMMYYYY	Yes	DDMMMYYYY		DDMMMYYYY	DDMMMYYYY		

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If reason discontinuation is pregnancy, or withdrawal by subject, include date after reason separated by a semicolon.

***If the reason of discontinuation is adverse event, please provide this adverse event*}**

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.4.1
Demographics
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Informed Consent Date	Date of Birth	Age (yrs)	Gender	Childbearing potential?	Ethnicity	Race	Baseline Weight (kg)	Baseline Height (cm)	Baseline BMI (kg/m2)
XXXXX	DDMMMYYYY	DDMMMYYYY	xx	Female	Yes	xxxxxxxx	xxxxxxxxxxx	xx.x	xx	xx.xx
XXXXX	DDMMMYYYY	DDMMMYYYY	xx	Male		xxxxxxx	xxxxx	xx.x	xx	xx.xx
XXXXX	DDMMMYYYY	DDMMMYYYY	xx	Male		xxxxxx	xxxx	xx.x	xx	xx.xx
XXXXX	DDMMMYYYY	DDMMMYYYY	xx	Female	Yes	xxxxxxxxxx	xxxxxxxxxxx	xx.x	xx	xx.xx

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.4.2
Medical History
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Any History?	Ongoing at Study Start?	System Organ Class/ Preferred Term/ Verbatim Term	Start Date	End Date
XXXXX	Yes	No	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY
		Yes	XXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	ONGOING
XXXXX	No				
XXXXX	Yes	No	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY

Note: Medical history coded using MedDRA version 19.0. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.4.3
Concomitant and Prior Medications
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Prior	Concomitant	Anatomic Therapeutic Class/ Preferred Term/ Verbatim Term	Start Date/ End Date	Indication: Pre-Existing	Onset Indication: AE from Therapeutic Use	Dose (unit)/ Dose Form/ Route/ Frequency
XXXXX	Yes	No	XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY/ DDMMMYYYY	xxxxxxxxx	xxxxxxx	XXXXXXXXXXXXXXXXXX <units> / XXXXXXXXXX XXXXXXX/ XXXXXXXXXXXXXXXXXXXXX
			XXXXXXXXXXXXXXXXXX/ XXXXXXX/ XXXXXXXXXXXXXXXXXXXXXXXXXX	DDMMMYYYY/ ONGOING	xxxxxxx	xxxxxxx	XXXXXXXXXXXXXXXXXX <units> / XXXXXXXXXX XXXXXXX/ XXXXXXXXXXXXXXXXXXXXX
XXXXX	No	Yes					

Note: Medication coded using WHO-DD (Enhanced version 2017), ATC level 4. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If indication is pre-existing or adverse event, please add MH/AE number to indication separated by a semi-colon. Please add all abbreviations that are not units that present on this table}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.5.1
Drug Accountability and Compliance
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Dispense Date (Study Day)	Treatment Duration (days)	Kit Number	Dispensed Amount	Date Returned	Returned Amount	Overall Compliance (%) [1]
XXXXX	Week 1	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	xx.x%
	Week 2	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	
	Week 4	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	
XXXXX	Week 1	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	xx.x%
	Week 2	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	
	Week 4	DDMMMYYYY (xx)	xx	XXXXXX	XX	DDMMMYYYY	XX	

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. [1] Compliance is defined as the number of patches given less the number of patches returned divided by the number of days for required applications (e.g. without counting of extra patches given just in case), expressed as a percentage.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.5.2
Plasma Concentration
Pharmacokinetic Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Dosing Date and Time	Was PK Sample collected?	Reason Not Collected	Sample Collection Date	Time Blood Drawn	Plasma Concentration (ng/mL)
XXXXX	Week 2	DDMMMYYYY/HH:MM	Yes		DDMMMYYYY	HH:MM	xx.xx
	Week 4	DDMMMYYYY/HH:MM	Yes		DDMMMYYYY	HH:MM	xx.xx
XXXXX	Week 2	DDMMMYYYY/HH:MM	No	xxxxxxxxx			
	Week 4	DDMMMYYYY/HH:MM	Yes		DDMMMYYYY	HH:MM	xx.xx
XXXXX	Week 2	DDMMMYYYY/HH:MM	Yes		DDMMMYYYY	HH:MM	xx.xx
	Week 4	DDMMMYYYY/HH:MM	Yes		DDMMMYYYY	HH:MM	xx.xx
XXXXX	Week 2	DDMMMYYYY/HH:MM	No	xxxxxxxxxxxxxxxxxx			
	Week 4	DDMMMYYYY/HH:MM	No	xxxxxxxxxxx			

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.

T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Listing 16.2.6.1.1
WOMAC Items
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit/ Assessment Date	Pain [1]					Stiffness [2]		Physical Function [3]																
		1	2	3	4	5	1	2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
XXXXX	Baseline/ DDMMMYYYY	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Week 1/ DDMMMYYYY	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Week 2/ DDMMMYYYY	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Week 4/ DDMMMYYYY	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: Individual WOMAC scores are evaluated based on a likert scale and range from 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Extremely. WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo..
[1] 1. Walking, 2. Stair Climbing, 3. Nocturnal, 4. Rest, 5. Weight bearing.
[2] 1. Morning stiffness, 2. Stiffness occurring later in the day.
[3] 1. Descending stairs, 2. Ascending Stairs, 3. Rising from sitting, 4. Standing, 5. Bending to floor, 6. Walking on flat surface, 7. Getting in/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.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.6.1.2
WOMAC Scores
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Assessment Date	Pain Score [1]	Stiffness Score [2]	Physical Function Score [3]	Composite Score [4]
XXXXX	Baseline	DDMMMYYYY	xx	xx	xx	xx
	Week 1	DDMMMYYYY	xx	xx	xx	xx
	Week 2	DDMMMYYYY	xx	xx	xx	xx
	Week 4	DDMMMYYYY	xx	xx	xx	xx
XXXXX	Baseline	DDMMMYYYY	xx	xx	xx	xx
	Week 1	DDMMMYYYY	xx	xx	xx	xx
	Week 2	DDMMMYYYY	xx	xx	xx	xx
	Week 4	DDMMMYYYY	xx	xx	xx	xx

Note: WOMAC = West Ontario and McMasters Universities Osteoarthritis Index. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Range from 0 to 20 by summing each item relating to Pain.
[2] Range from 0 to 8 by summing each item relating to Stiffness.
[3] Range from 0 to 68 by summing each item relating to Physical Function.
[4] Calculated by summing the items for all 3 subscales (Pain, Stiffness, and Physical Function) and then dividing by 96. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.6.2
Patient Global Assessment (PGA)
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Assessment Date	How would you rate your osteoarthritis condition over the last 24 hours?
XXXXX	Baseline	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxx
	Week 1	DDMMMYYYY	xxxxxxxxx
	Week 2	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxx
	Week 4	DDMMMYYYY	xxxxxxxxxxxx
XXXXX	Baseline	DDMMMYYYY	xxxxxxxxxxxx
	Week 1	DDMMMYYYY	xxxxxxxxxx
	Week 2	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxxxx
	Week 4	DDMMMYYYY	xxxxxxxxxxxxxxxxx

Note: PGA is a 1 to 7 scale where 1 = “Very Much Improved”, 2 = “Much Improved”, 3 = “Minimally Improved”, 4 = “No Change”, 5 = “Minimally Worse”, 6 = “Much Worse”, and 7 = “Very Much Worse”. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.6.3
Patient Global Impression (PGI) of Change
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Assessment Date	How would you rate your overall improvement with treatment during the clinical trial?
XXXXX	Week 1	DDMMMYYYY	xxxxxxxxx
	Week 2	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxx
	Week 4	DDMMMYYYY	xxxxxxxxxxxx
XXXXX	Week 1	DDMMMYYYY	xxxxxxxxxx
	Week 2	DDMMMYYYY	xxxxxxxxxxxxxxxxxxxxxxx
	Week 4	DDMMMYYYY	xxxxxxxxxxxxxxxxx

Note: PGI is a 0 to 4 scale where 0 = “Very Good”, 1 =”Good”, 2 = “Moderate”, 3 = “Poor”, and 4 = “Very Poor”. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.6.4
Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS)
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Assessment Date	Worst NRS Pain (Target Knee)	Worst NRS Pain (Non-Target Knee)	Worst NRS Pain Score [2]	Overall NRS Pain (Target Knee)	Overall NRS Pain (Non-Target Knee)	Average NRS Pain Score [1]
XXXXX	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Baseline	DDMMMYYYY	xx	xx	xx	xx	xx	xx
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Diary	DDMMMYYYY	xx	xx		xx	xx	
	Week 1	DDMMMYYYY	xx	xx	xx	xx	xx	xx

Note: NRS is an 11-point scale from 0 to 10 where 0 = no pain and 10 = the worst pain imaginable , a value in the middle, around 5 would be moderate pain; a value of 2 or 3 would be mild pain and value of 7 or higher is considered severe pain. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
[1] Average of NRS pain scores reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit.
[2] Worst NRS pain score reported for pain over the last 24 hours for the last 3 days prior to each clinic or phone visit
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Listing 16.2.6.5
Rescue Medication Use
Full Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit (Study Day)	Rescue medication dispensed?	Medication Name/ Bottle No./ Date Dispensed	Dispensed Amount (units)	Date Dispensed/ Date Returned	Returned Amount (units)	Lose Dose YN?	Reason
XXXXX	Baseline (xx)	No						
	Week 1 (xx)	No						
	Week 2 (xx)	Yes	xxxxxxxxxxxxxxxxxxxxxx xxxxxxx/ xxxxx	xxxx (xxx)	DDMMMYYYY/ DDMMMYYYY	xxxx (xxx)	No	
	Week 4 (xx)	Yes	xxxxxxxxxxxx/ xxxx	xxxx (xxx)	DDMMMYYYY/ DDMMMYYYY	xxxx (xxx)	No	
XXXXX	Baseline (xx)	Yes	xxxxxxxxxxxxxxxxxxxxxx xxxxxxx/ xxxx	xxxx (xxx)	DDMMMYYYY/ DDMMMYYYY	xxxx (xxx)	No	
	Week 1 (xx)	Yes	xxxxxxxxxxxx/ xxxx	xxxx (xxx)	DDMMMYYYY/ DDMMMYYYY	xxxx (xxx)	Yes	xxxxxxxxxxx
	Week 2 (xx)	No						
	Week 4 (xx)	No						

Note: Study Day = Dispense Date – Date of First Dose + 1. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.7.1
Adverse Events
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	AE Number	System Organ Class/ Preferred Term/ Verbatim Term	Start Date/ Start Time (Study Day)	End Date/ End Time	Event Duration (days)	Severity/ Relationship to Study Drug	Outcome/ Action Taken with Study Medication	Serious? /Disc.	CA/DIS/HO/ DE/LT/OTH/ OA/DISC
XXXXX	xxx	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	DDMMMYYYY/ HH:MM (xx)	DDMMMYYYY/ HH:MM	xxx	xxxxxxx/ xxxxxxxxxxxxxx	xxxxxxxxxxxx/ xxxxxxxxxx xxxxxx	No/No	No/No/No/ No/No/No/ No/No
	xxx	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	DDMMMYYYY/ HH:MM (xx)	ONGOING	xxx	xxxxxxx/ xxxxxxxxxxxxxx	xxxxxxxxxxxx/ xxxxxxxxxx xxxxxx	Yes/Yes	No/No/Yes/ No/No/Yes No/Yes
XXXXX	xxx	xxxxxxxxxx xxxxx xxxxx/ xxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	DDMMMYYYY/ HH:MM (xx)	DDMMMYYYY/ HH:MM	xxx	xxxxxxx/ xxxxxxxxxxxxxx	xxxxxxxxxxxx/ xxxxxxxxxx xxxxxx	No/No	No/No/No/ No/No/No No/No

Note: Study Day = AE Start Date – Date of First Dose + 1. Adverse Events coded using MedDRA version 19.0. CA = congenital abnormality, DE = death, DIS = disability, Disc. = discontinued from study, DISC = Did AE cause discontinuation from the study?, HO = hospitalization, LT = life threatening, OA = other action, OTH = other medically important event. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: if other action is populated, concatenate with action taken with study medication separated by semi-colon}

Listing 16.2.7.2
Serious Adverse Events
Safety Analysis Set

{Programming Note: Repeat listing 16.2.7.1, constrain to only serious adverse events}

Listing 16.2.7.3
Adverse Events Leading to Withdrawal
Safety Analysis Set

{Programming Note: Repeat listing 16.2.7.1, constrain to only adverse events leading to ET}

Listing 16.2.7.4
Listing of Deaths
Safety Analysis Set

{Programming Note: Repeat listing 16.2.7.1, constrain to only adverse events with fatal outcome}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.8.1
Clinical Chemistry
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Laboratory Test	Visit	Collection Date	Sample Collected?	Test Result	Units	Standard Reference Range		Change from Baseline	Testing Conditions Met?
							Low	High		
XXXXX	xxxxxxxxxxx	Baseline	DDMMMYYYY	Yes	xxxxx	xxxxx	xx	xx		Yes
		Week 4	DDMMMYYYY	Yes	xxxxx*	xxxx	xx	xx	xxx	Yes
	xxxxxxxxxxx	Baseline	DDMMMYYYY	Yes	xxxxx^	xxxxx	xx	xx		Yes
		Week 4	DDMMMYYYY	Yes	xxxxx	xxxx	xx	xx	xxx	Yes
	xxxxxxxxxxx	Baseline	DDMMMYYYY	Yes	xxxxx	xxxxx	xx	xx		Yes
		Week 4	DDMMMYYYY	Yes	xxxxx	xxxx	xx	xx	xxx	Yes

Note: ^ = above normal range, * = below normal range. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Listing 16.2.8.2
Hematology
Safety Analysis Set

{Programming Note: Repeat listing 16.2.8.1}

Listing 16.2.8.3
Urinalysis
Safety Analysis Set

{Programming Note: Repeat listing 16.2.8.1}

Listing 16.2.8.4
Pregnancy Test
Safety Analysis Set

{Programming Note: Repeat listing 16.2.8.1, drop low/high/flag/change from baseline columns}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.8.5
Drug Screen
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Sample Type	Sample collected?	Reason not performed	Visit	Collection Date	Test Result
XXXXX	xxxxxxxxxxxx	Yes		Baseline	DDMMMYYYY	xxxxx
XXXXXX	xxxxxxxxxxxx	No	xxxxxxxxxxxxxxx	Baseline	DDMMMYYYY	xxxxx
XXXXX	xxxxxxxxxxxx	Yes		Baseline	DDMMMYYYY	xxxxx
XXXXX	xxxxxxxxxxxx	Yes		Baseline	DDMMMYYYY	xxxxx

Note: Treatment arms: HP-5000[redacted] topical patch, HP-5000-[redacted]) topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: Include alcohol test as well in this listing}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.9.1
Vital Signs
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Date of Measurement	Vital Signs Collected?	Reason not collected	Height (cm)	Weight (kg)	BMI (kg/m2)	Temp (C)	HR (beats/ min)	RR (breaths/ min)	SysBP/ DiaBP (mmHg)
XXXXX	Baseline	DDMMMYYYY	Yes		xx.x	xx.x	xx.xx	xx	xx	xx	xxx/xxx
	Week 1	DDMMMYYYY	Yes		xx.x	xx.x		xx	xx	xx	xxx/xxx
	Week 2		No	xxxxxxxxxxxxx							
	Week 4	DDMMMYYYY	Yes			xx.x		xx	xx	xx	xxx/xxx
XXXXX	Baseline	DDMMMYYYY	Yes		xx.x	xx.x	xx.xx	xx	xx	xx	xxx/xxx
	Week 1	DDMMMYYYY	Yes			xx.x		xx	xx	xx	xxx/xxx
	Week 2	DDMMMYYYY	Yes			xx.x		xx	xx	xx	xxx/xxx
	Week 4	DDMMMYYYY	Yes			xx.x		xx	xx	xx	xxx/xxx

Note: BMI = body mass index, C = Celsius, cm = centimeter, DiaBP = diastolic blood pressure, HR = heart rate, kg = kilogram, mmHg = millimeters of mercury, RR = respiratory rate, SysBP = systolic blood pressure, Temp = temperature. Treatment arms: HP-5000[redacted]) topical patch, HP-5000[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Listing 16.2.9.2
12-Lead Electrocardiogram (ECG)
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Date of Measurement/ Time of Measurement	ECG Collected?	Reason not collected	PR (msec)	QRS (msec)	QT (msec)	QTcB (msec)	QTcF (msec)	HR (bpm)	Interpretation
XXXXX	Baseline	DDMMMYYYY/ HH:MM	Yes		xxx	xxx	xxx	xxx	xxx	xxx	xxxxx
	Week 4	DDMMMYYYY/ HH:MM	No	xxxxxxxxxxxx xx							
XXXXX	Baseline	DDMMMYYYY/ HH:MM	Yes		xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxxxxxx
	Week 4	DDMMMYYYY/ HH:MM	Yes		xxx	xxx	xxx	xxx	xxx	xxx	xxxxxxxxxxxxxx xxxxxx

Note: bpm = beats per minute, msec = millisecond. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.9.3
Electrocardiogram (ECG) Abnormalities
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Date of Measurement/ Time of Measurement	ECG Collected?	Reason not collected	Assessment	Specify
XXXXX	Baseline	DDMMMYYYY/HH:MM	Yes		Normal	
	Week 4	DDMMMYYYY/HH:MM	No	xxxxxxxxxx xxxx		
XXXXX	Baseline	DDMMMYYYY/HH:MM	Yes		Abnormal NCS	xxxxxxxxxxx
	Week 4	DDMMMYYYY/HH:MM	Yes		Abnormal CS	xxxxxxxxxxxxxxxxxxx

Note: CS = clinically significant, NCS = not clinically significant. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.9.4
Physical Examination (PE)
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Date of Assessment	PE Collected?	Reason not collected	Body System	Assessment	Specify
XXXXX	Screening	DDMMMYYYY	Yes		xxxxxxxxx	xxxxxxxx	
					xxxx	xxxxxxxxxx	xxxxxxxxxxxxx
					xxxxxxxxx	xxxxxxxx	
					xxxxxxxxxx	xxxxxxxxx	
					xxxxxxxxx	xxxxxxxx	
					xxxxxxxxxx	xxxxxxxxx	
					xxxxxxxxx	xxxxxxxx	
					xxxxxxxxxx	xxxxxxxxx	
					xxxxxxxxx	xxxxxxxx	
					xxxxxxxxxx	xxxxxxxxx	

Note: Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.9.5.1
Dermal Safety for Adhesion
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit (Study Day)	Date of Assessment	Patch Adhesion Performed?	Reason not collected	Result	Reason for partial or complete detachment (Adhesion Score >1)	Fully detach?	Date patch detached/ Time patch detached/ Activity at detachment
XXXXX	Baseline (xx)	DDMMMYYYY	Yes		0		No	
	Diary (xx)	DDMMMYYYY	Yes		No			
	Diary (xx)	DDMMMYYYY	Yes		No			
	Diary (xx)	DDMMMYYYY	Yes		No			
	Diary (xx)	DDMMMYYYY	Yes		Yes; xxxxxxxxxx			
	Week 1 (xx)		No	xxxxxxxxx				
	Diary (xx)	DDMMMYYYY	Yes		Yes; xxxxxxxxxx			
	Diary (xx)	DDMMMYYYY	Yes		Yes; xxxxxxxxxx			
	Diary (xx)	DDMMMYYYY	Yes		No			
	Diary (xx)	DDMMMYYYY	Yes		No			
	Week 2 (xx)	DDMMMYYYY	Yes		4	xxxxxxxxxxxxx	Yes	DDMMMYYYY/ HH:MM/ xxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxx

Note: Study Day = Assessment Date – Date of First Dose + 1. Result: 0: >= 90% adhered (essentially no lift off of the skin), 1: >= 75% to < 90% adhered (some lifting off of the skin e.g., edges only), 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). Treatment arms: HP-5000-[redacted] topical patch, HP-5000[redacted] ([redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: If Diary data is 'Yes' for any prompt, add the descriptive text, i.e., "More than half of the patch still attached"}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.9.5.2
Dermal Safety for Irritation
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit (Study Day)	Date of Assessment	Was Irritation Assessment Performed?	Result	Other Effects
XXXXX	Baseline (xx)	DDMMMYYYY	Yes	1	A
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Week 1 (xx)		No		
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Week 2 (xx)	DDMMMYYYY	No		
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Week 4 (xx)	DDMMMYYYY	Yes	4	C

Note: Study Day = Assessment Date – Date of First Dose + 1. Result: 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. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo.
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
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4
{Programming Note: If Diary data is 'Yes' for any prompt, add the descriptive text, i.e., "Redness"}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.9.5.3
Dermal Safety for Discomfort
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit (Study Day)	Date of Assessment	Are you experiencing any discomfort related to the patch?	Result	Describe the discomfort
XXXXX	Baseline (xx)	DDMMMYYYY	Yes	1	xxxxxxxxx
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Week 1 (xx)		No		
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Diary (xx)	DDMMMYYYY	Yes	No	
	Diary (xx)	DDMMMYYYY	Yes	Yes; xxxxxxxxxx	
	Week 2 (xx)	DDMMMYYYY	Yes	3	xxxxxxxxxxxxxxxxxxxxxxxxxxx

Note: Study Day = Assessment Date – Date of First Dose + 1. Result: 0=No discomfort, 1= Mild discomfort, 2= Moderate, but tolerable discomfort, 3= Severe, intolerable discomfort, 4= Patch not present. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

{Programming Note: If Diary data is 'Yes' for any prompt, add the descriptive text, i.e., "Burning"}

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Page 1 of x
FINAL

Listing 16.2.9.5.4
Dermal Safety for Adhesive Residue
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit (Study Day)	Date of Assessment	Any adhesive residue remaining?	Result
XXXXX	Baseline (xx)	DDMMMYYYY	Yes	1
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Week 1 (xx)		No	
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Diary (xx)	DDMMMYYYY	Yes	Yes
	Week 2 (xx)	DDMMMYYYY	Yes	3

Note: Study Day = Assessment Date – Date of First Dose + 1. Result: 0= None, 1= Light, 2= Medium, 3= Heavy, 4= Patch not present. Treatment arms: HP-5000-[redacted] topical patch, HP-5000-[redacted] topical patch, and Placebo. T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

Noven Pharmaceuticals, Inc.
Protocol HP-5000-US-05

Listing 16.2.9.6
X-Ray
Safety Analysis Set

Actual Treatment: XXXXXXX

Subject ID	Visit	Date of Assessment	X-Ray Performed?	Target Knee	Kellgren-Lawrence radiographic grading system for osteoarthritis
XXXXX	Screening	DDMMMYYYY	Yes	Left	Grade 2
XXXXX	Screening	DDMMMYYYY	Yes	Right	Grade 3

Note: Grade 0= Normal; No features of osteoarthritis, Grade 1= Doubtful; Minute osteophyte, doubtful significant, Grade 3= Moderate; Moderate diminution of joint space, Grade 4= Severe; Joint space greatly impaired with sclerosis of subchondral bone. Treatment arms: HP-5000-[redacted] topical patch, HP-5000[redacted] topical patch, and Placebo.
T:\Noven\HP-5000-US-05\...\xxxxxx.sas run on DDMMMYYYY at HH:MM for data extracted on DDMMMYYYY, on SAS v9.4

14.4. Planned Figure Shell Descriptions

Figure 14.2.1.1
LSMean Change from Baseline over time of WOMAC Pain Score
Full Analysis Set

**{Programmer Notes: X axis; Study Visit Y axis; LSMean CFB WOMAC Pain Score,
individual plotted points connected by a line, split by treatment arm.
Placebo = Black, HP-5000-[redacted] = Blue, HP-[redacted] = Red. Plot only scheduled visits}**

Figure 14.2.1.2
AUC Analysis of WOMAC Pain Score
Full Analysis Set

**{Programmer Notes: X axis; Study Visit, Y axis; LSMean CFB WOMAC Pain Score,
individual plotted points connected by a line, split by treatment arm. Shade in area under plotted points, add annotation for each section on AUC value
Placebo = Black, HP-5000-[redacted] = Blue, HP-[redacted] = Red. Plot only scheduled visits}**

Figure 14.2.1.3
Responder Analysis of WOMAC Pain Score
Full Analysis Set
{Programmer Notes: X axis; response threshold and proportion of responders in each treatment group on the Y-axis}

Figure 14.2.2
LSMean Change from Baseline over time of WOMAC Stiffness Score
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean CFB WOMAC Stiffness Score as Y axis}

Figure 14.2.3
LSMean Change from Baseline over time of WOMAC Physical Function Score
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean CFB WOMAC Physical Function Score as Y axis}

Figure 14.2.4
LSMean Change from Baseline over time of WOMAC Composite Score
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean CFB WOMAC Composite Score as Y axis}

Figure 14.2.5
LSMean Change from Baseline over time of Patient Global Assessment
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean CFB Patient Global Assessment as Y axis}

Figure 14.2.6
LS Mean Observed Value over time of Patient Global Impression of Change
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean Observed Patient Global Impression of Change as Y axis}

Figure 14.2.7
LSMean Change from Baseline over time of Pain Intensity Assessed on an 11-Point Numeric Rating Scale (NRS)
Full Analysis Set

{Programmer Notes: Follow layout of 14.2.1.1 using LSMean CFB Pain intensity assessed on an 11-point numeric rating scale (NRS) as Y axis}

Figure 14.2.8
Mean Plasma Concentration (Logarithmic Scale)
Pharmacokinetic Analysis Set

{Programmer Notes: X axis; Study Visit Y axis Observed mean plasma concentration individual plotted points connected by a line, split by treatment.}

Appendix 1: Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AD	associated documents
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the curve
BLQ	beneath limit of quantification
BMI	body mass index
BRD	business requirements document
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
DB	database
DBL	database lock

Abbreviation	Definition
DBP	diastolic blood pressure
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eTMF	electronic trial master file
FA	full analysis
FDA	food and drug administration
GCP	good clinical practice
GMP	good manufacturing practices
HR	heart rate
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
IDM	independent drug monitoring
IEC	independent ethics committee
IND	investigational new drug
IP	investigational product
IRB	institutional review board

Abbreviation	Definition
ITT	intent-to-treat
IVRS	interactive voice response system
LMS	learning management system
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MMRM	mixed effect model repeat measurement
NA	not applicable
NCS	non-clinically significant
NRS	numeric rating scale
PAS	pharmacokinetic analysis set
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PK	pharmacokinetic
PMM	pattern-mixture model
PP	per-protocol
QA	quality assurance
QC	quality control
SAE	serious adverse event

Abbreviation	Definition
SAF	safety analysis set
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TMF	trial master file
ULOQ	upper limit of quantification
WG	working guideline
WHO	world health organization
WHO-DD	world health organization drug dictionary
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index