Statistical Analysis Plan

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Topically Applied TV-45070 (4% and 8% w/w Ointment) in Patients with Postherpetic Neuralgia

Study TV-45070-CNS-20013

NCT02365636

Date: 08 September 2015

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

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Study TV-45070-CNS-20013 **Phase** 2

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AR[1]	Autoregressive (1)
ARH[1]	Heterogeneous Autoregressive (1)
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CRF	Case Report Form
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
DSIS	Daily Sleep Interference Scale
ECG	Electrocardiogram
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
ML	Maximum Likelihood
MMRM	Mixed Model Repeated Measures
NePIQoL	Neuropathic Pain Impact on Quality of Life
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale
PGIC	Patient Global Impression of Change
PHN	Postherpetic Neuralgia
PP	Per Protocol
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class

TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products R&D, Inc. study TV-45070-CNS-20013 , (A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Topically Applied TV-45070 (4% and 8% w/w Ointment) in Patients with Postherpetic Neuralgia), and was written in accordance with SOP GBP_RD_702.

This phase 2 study is being completed to assess the safety and efficacy of topically applied TV-45070 (4% and 8% w/w Ointment) in patients with postherpetic neuralgia.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol TV-45070-CNS-20013, issued 20 November 2014.
- Case report forms (CRFs) for Study TV-45070-CNS-20013, issued 19 December 2014.
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the CSR.

1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of 4 weeks of topical administration of TV-45070 (4% and 8% ointment) compared with placebo for the relief of pain due to postherpetic neuralgia (PHN), as assessed by the change from baseline to week 4 in the weekly average of the daily average Numerical Rating Scale (NRS) scores. The daily average NRS score is the average of the 2 NRS scores (recorded in the morning and in the evening) of average pain, defined as the patient-reported average pain over the prior 12 hours.

1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of topical TV-45070 (4% and 8% ointment) compared with placebo by examining the following:
  - Change from baseline to week 4 in the weekly average of the average pain score recorded in the evening
  - Change from baseline to week 4 in the weekly average of the average pain score recorded in the morning
  - Change from baseline to week 4 in the weekly average of the worst pain score recorded in the evening (worst pain is defined as the patient-reported worst pain intensity over the prior 24 hours)
  - Percentage of patients with ≥ 30% improvement from baseline in the weekly average of the daily average NRS scores at week 4
  - Percentage of patients with ≥ 50% improvement from baseline in the weekly average of the daily average NRS scores at week 4
  - Change from baseline (randomization visit) to weeks 2 and 4 in the Neuropathic Pain Symptom Inventory (NPSI) score
  - Change from baseline (randomization visit) to week 4 in the Neuropathic Pain Impact on Quality of Life (NePIQoL)
  - Patient's global assessment of treatment as measured by the Patient Global Impression of Change (PGIC) scores at weeks 2 and 4
  - Change from baseline (randomization visit) in the Daily Sleep Interference Scale (DSIS) at weeks 2 and 4
  - Time to reach ≥ 30% improvement from baseline in the weekly average of the daily average NRS scores
  - Change from baseline (randomization visit) in maximal intensity of patients' brush-evoked allodynia, as measured on 11-point NRS at weeks 2 and 4

  - Change from baseline (randomization visit) in maximal intensity of patients' punctate-evoked hyperalgesia, as measured on 11-point NRS using a Medipin® (US Neurologicals, LLC / Medipin Ltd), at weeks 2 and 4

- To characterize the pharmacokinetics of TV-45070 in terms of the following. This will be conducted in another analysis plan.
  - Establishing the dose-exposure relationship of topical TV-45070 (4% and 8% w/w ointment under multiple-dose conditions in patients with PHN)
  - Estimating the apparent clearance (CL/F) and volume of distribution (V/F) of TV-45070 by incorporating the concentration data of this study into an enriched TV-45070 pharmacokinetics database and performing population pharmacokinetic modeling
  - Identifying the clinically relevant covariates (e.g. age, body weight, gender, and indication) affecting TV 45070 pharmacokinetics using the population pharmacokinetics model
- To evaluate the safety of topical TV-45070 (4% and 8% ointment) treatment compared with placebo, as assessed by the following at specific time points throughout the study based on the schedule of study procedures and assessments:
  - Occurrence of adverse events (AEs) throughout the study
  - Clinical safety laboratory (serum chemistry, hematology, and urinalysis) test results
  - Vital signs (heart rate, respiratory rate, body temperature, and blood pressure) measurements
  - Electrocardiogram (ECG) findings
  - Physical examination findings
  - Dermal irritation findings
  - Concomitant medication usage throughout the study

1.3. Exploratory Objectives

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

2. STUDY DESIGN

2.1. General Design and Study Schema

This is a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of 4% and 8% w/w TV-45070 ointment compared with placebo ointment applied topically and twice daily to the area of PHN pain for 4 weeks (days 1 through 28) in patients with PHN. For each patient, the duration of study participation will be approximately 12 weeks consisting of a 4-week screening period, a 4-week treatment period, and a 4-week follow-up period. There will be a total of 6 visits to the study center and 1 telephone contact as follows:

- Visit 1: screening visit (up to 28 days before randomization/first administration of study drug)
- Washout phone contact (approximately 1 week after the screening visit)
- Visit 2: baseline visit (day –10)
- Baseline pain assessment period (days -7 to -1; baseline pain score [average pain intensity score over this interval] obtained)
- Visit 3: randomization visit (day 1 [this is the day after day –1 and the first day of study drug application])
- Visit 4: week 2 visit (day 15 ±1)
- Visit 5: week 4 visit (day 29)
- Visit 6: follow-up visit (day 57 ±3) or early termination

The study schedule is provided in Table 1, and detailed descriptions of activities at each visit are included in the protocol (Section 3.11).

Visit-specific procedures and assessments are outlined in Table 1.

Table 1: Study Procedures and Assessments

Study period	**Screening**			**Randomization**	**Double-blind treatment**		**Follow-up / Early termination**	
Visit number	**Visit 1**	**--**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	
Visit day (window)[a]	**Day –28[b]**	**Day –21[c]**	**Day –10[c,d]**	**Day 1[d]**	**Day 15 (±1)**	**Day 29[e] (±0)**	**Day 57 (±3) / Not applicable**	
Procedures and assessments	**Screening visit**	**Washout phone contact[f]**	**Baseline visit[g]**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**Early Termination**
Informed consent	X							
Inclusion and exclusion criteria	X	X	X	X[h]				
Medical history and demography	X							
Adverse event inquiry		X	X	X[h]	X	X	X	X
Prior/concomitant medication	X[i]	X	X	X[h]	X	X	X	X
Start of washout of prior neuropathic pain therapy (if needed)		X						
Clinical laboratory tests (serum chemistry, hematology, and urinalysis)	X			X[h]	X	X	X	X
Urine drug screen	X			X[h]		X		
Vital sign measurements[j]	X		X	X[h]	X	X	X	X
Physical examination	X[k]			X[h]	X	X	X[k]	X[k]
12-lead ECG[l]	X			X[h]	X	X	X	X
Pregnancy test (urine)[m]	X			X[h]	X	X	X	X
Blood sample for pharmacogenomics assessments	X							
NPSI	X			X[h]	X	X		X
DSIS	X			X[h]	X	X		X
NePIQoL	X			X[h]		X		X
Measure maximal intensity of brush-evoked allodynia[n]	X			X[h]	X	X		X
Measure of maximal intensity of punctate-evoked hyperalgesia[n]	X			X[h]	X	X		X
Record average daily pain intensity (NRS) at study site	X							
Record worst daily pain intensity (NRS) at study site	X							

Study period	**Screening**			**Randomization**	**Double-blind treatment**		**Follow-up / Early termination**	
Visit number	**Visit 1**	**--**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	
Visit day (window)[a]	**Day –28[b]**	**Day –21[c]**	**Day –10[c,d]**	**Day 1[d]**	**Day 15 (±1)**	**Day 29[e] (±0)**	**Day 57 (±3) / Not applicable**	
Procedures and assessments	**Screening visit**	**Washout phone contact[f]**	**Baseline visit[g]**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**Early Termination**
Dispense/collect rescue medication (review accountability)	X		X[o]		X	X (collect only)		X (collect only)
Record rescue pain medication usage for PHN as a concomitant medication (ie, not using eDiary)		X						X
Provide/review/collect patient eDiary			X[p]	X[h,q]	X[q]	X[r]		X[r]
Record average daily pain intensity (over the previous 12 hours [NRS]) in the morning and evening using eDiary[s]			X[t]	X[h,u]	X[v]	X[v]		
[redacted]								
Randomization and instructions on application of drug				X[h]				
Study drug compliance check				X[h,x]	X	X		X
Rescue drug compliance check			X	X[h]	X	X		X
Dispense/collect study drug				X[h] (dispense study drug only)	X	X (collect study drug only)		X (collect if prior to V5)
Apply study drug twice daily to area of PHN pain[y]				X[z,aa]	X[bb]			
Dermal irritation evaluation			X	X[cc,dd]	X	X	X	X
Record date/time of study drug application using eDiary				X[aa,cc]	X[bb]			X (if prior to V5)
Record rescue pain medication usage for PHN via eDiary[ee]			X[t]	X[cc] (at home)	X[ff]	X[gg]		X (if prior to V5)
Record worst daily pain intensity (NRS) in the evening using eDiary			X[t]	X[cc] (at home)	X[hh]			X (if prior to V5)
Blood samples (including recording of sampling dates/times) for PK assessments[ii]					X[jj]			
PGIC					X	X		X

[a] There is no day 0 for this study. Day –1 is the day before study day 1. Day 1 is the day of both randomization and the first dose (application) of study drug.
[b] The screening visit should occur no more than 28 days before randomization; day –28 is the earliest possible day for the screening visit.
[c] Variable/flexible date, depending on the need for washout and the drug(s) to be washed out.
[d] The baseline visit (day –10) and the randomization visit (baseline +10; day 1) must be confirmed as weekdays.
[e] No time window (in days) is permitted for visit 5 (day 29, week 4).
[f] The washout phone contact (approximately 1 week after the screening visit or day –21 at the earliest) will be the start of the washout interval (day of the phone contact through the day before the baseline visit) during which, if needed, the patient will discontinue medications used to treat PHN pain, including opioids (rescue medications [protocol-specified and provided acetaminophen only] permitted during the washout interval). The duration of the washout interval will vary from patient to patient depending on which (if any) medications need to be discontinued. For patients who do not need to washout medications, the other activities in this phone contact (review of eligibility based on laboratory test results and scheduling the baseline visit) will be performed.
[g] The baseline visit (day –10) will be the start of the baseline period during which baseline information regarding pain will be collected while the patient refrains from all PHN rescue medications.
[h] Performed prior to first dose of study drug.
[i] Includes specific query regarding past use of topical therapy such as the 5% lidocaine patch or capsaicin.
[j] Includes heart rate, respiration rate, body temperature, and blood pressure.
[k] Includes body weight (screening and follow-up/ET visits only) and height (screening visit only).
[l] All ECGs will be taken in triplicate and read by a central reader for the study. The central reader will be blinded (will not know the randomization assignment of the patients).
[m] Only for women of child-bearing potential.
[n] For brush or punctate mechanical hyperalgesia. If either is not present at screening, it will not be rechecked on subsequent visits.
[o] Collect from patients not eligible to continue in the study.
[p] Provide eDiary to eligible patients and instructions on using it to record daily pain (11-point NRS), date/time of study drug applications, and rescue medication usage.
[q] Review eDiary and review eDiary data via website. Also, for patients not eligible to be randomly assigned to treatment, collect eDiary at the randomization visit (visit 3, day 1).
[r] Review eDiary, review eDiary data via website, and collect eDiary.
[s] The eDiary will be used to record responses to 11-point NRS each morning (0700 ±2 hours) and each evening (1900 ±2 hours) before applying the study drug.
[t] At home after baseline visit until randomization visit.
[u] At home before dosing and in the evening before dosing.
[v] At home through the morning of day 29.
[redacted]
[x] Note that tubes must be weighed at visit 3, to obtain a baseline weight for checking study drug compliance at visit 4 (day 15 ±1, week 2) and visit 5 (day 29, week 4) or ET visit.
[y] Patients will apply study drug twice daily in the morning (0700 ±2 hours) and again in the evening (1900 ±2 hours). The morning applications should take place after recording the morning (0700 ±2 hours) responses to the 11-point NRS, and the evening applications should take place after recording the evening (1900 ±2 hours) responses to the 11-point NRS. On day 1, the morning dose might not be applied at 0700 ±2 hours because this first dose of study drug will be applied at the randomization visit. Regardless of the clock time of the first dose application at the randomization visit, the evening dose for day 1 should be applied at 1900 ±2 hours.

[z] First dose will be applied by study site staff at randomization visit (visit 3, day 1) as per protocol section 3.4.
[aa] At visit and home on day 1; at home from day 2 onward.
[bb] At home through the evening of day 28.
[cc] Performed after first dose of study drug.
[dd] At the randomization visit, dermal irritation will be assessed 1 hour after application of the study drug.
[ee] Although rescue medication is not allowed during the baseline period and during the 7-day period before the week 4 visit (visit 5) of the treatment period, the eDiary will be used to record rescue medication usage, including usage when it is prohibited per protocol.
[ff] At home on day 2 through the morning of day 29.
[gg] At home on the morning of day 29.
[hh] At home on day 2 through the evening of day 28.
[ii] All patients will have blood samples drawn for pharmacokinetic assessments.
[jj] For visit 4 (day 15 ±1, week 2), patients will go to the study center after applying study drug at home so that 2 pharmacokinetics samples can be taken, with the first sample taken within approximately 1 to 4 hours of the morning dose of study drug and the second taken approximately 2 hours after collection of the first sample. The date and time of morning dose and the date and exact time for each of the 2 pharmacokinetics samples will be recorded.

DSIS=Daily Sleep Interference Scale; ECG=electrocardiogram; eDiary=electronic diary; ET=early termination; NePIQoL=Neuropathic Pain Impact on Quality of Life questionnaire; NPSI=Neuropathic Pain Symptom Inventory; NRS=Numeric Rating Scale; PGIC=Patient Global Impression of Change; PHN=postherpetic neuralgia; PK=pharmacokinetics; V5=visit 5.

2.2. Primary and Secondary Measures and Endpoints

2.2.1. Primary Efficacy Measure and Endpoint

The primary efficacy endpoint for this study is the change from baseline to week 4 in the weekly average of the daily average NRS scores. The daily average NRS score is the average of the 2 NRS scores (recorded in the morning and evening) of average pain, defined as the patient-reported average pain intensity over the prior 12 hours.

2.2.2. Secondary Efficacy Measures and Endpoints

The secondary efficacy endpoints for this study are as follows:

- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the average pain score recorded in the evening
- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the average pain score recorded in the morning
- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the worst pain score recorded in the evening (worst pain is defined as the patient-reported worst pain intensity over the prior 24 hours)
- Percentage of patients with ≥ 30% improvement from baseline in the weekly average of the daily average NRS scores at week 4
- Percentage of patients with ≥ 50% improvement from baseline in the weekly average of the daily average NRS scores at week 4
- Change from baseline (randomization visit) to weeks 2 and week 4 in the NPSI score
- Change from baseline (randomization visit) to week 4 in the NePIQoL score
- Patients' global assessment of treatment, as measured by PGIC scores, at weeks 2 and 4
- Change from baseline (randomization visit) in DSIS scores at weeks 2 and 4
- First time to reach ≥ 30% sustained improvement from baseline in the weekly average of the daily average NRS scores
- Change from baseline (randomization visit) to weeks 2 and 4 in maximal intensity of patients' brush-evoked allodynia, as measured on the 11-point NRS
- Change from baseline (randomization visit) to weeks 2 and 4 in maximal intensity of patients' punctate-evoked hyperalgesia, as measured on the 11-point NRS using a Medipin

2.2.3. Exploratory Efficacy Measures and Endpoints

[redacted]

2.2.4. Safety Measures and Endpoints

The safety of TV-45070 (4% and 8% ointment) will be assessed throughout the study by evaluating AEs, clinical safety laboratory test results, vital signs measurements, ECG findings, physical examination results, dermal irritation findings and concomitant medication usage. Skin rashes or skin irritation in the area of ointment application will be evaluated using a dermal irritation scale (modified Draize scale) at day 1 (at 1 hour after application of study drug), week 2, week 4, and week 8 for follow-up.

2.2.5. Tolerability Measures and Endpoints

The tolerability of TV-45070 (4% and 8% ointment) will be assessed during the study by using safety endpoints that also represent patients' experience of treatment, such as skin rashes and skin irritation.

2.2.6. Pharmacokinetic Measures and Endpoints

Two blood samples will be collected from each patient following 2 weeks of treatment with either 4% or 8% w/w TV-45070 ointment or matching placebo ointment, to quantitate the concentration of TV-45070 in plasma. Plasma samples will be analyzed for TV-45070. Population pharmacokinetic parameters, such as CL/F and V/F will be estimated when the sparse data from this study are combined with enriched pharmacokinetic data from other studies with topical TV-45070. A summary and listing of these results may be included in this study. These results will also be reported separately from the main study results.

2.2.7. Pharmacodynamic Measures and Endpoints

Pharmacodynamic endpoints assessed during the study are the following secondary efficacy endpoints: change from baseline in maximal intensity of patients' brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia.

2.2.8. Pharmacogenomic Analyses

[redacted] A pharmacogenomic blood sample may be used to assess the polymorphisms for CYP3A4 and CYP2C19 genes. Depending on the distribution of the allelic variations, these variations may be incorporated as covariates in the current or future population pharmacokinetic analyses. Exploratory analyses may be reported separately from the main study results.

2.3. Sample Size and Power Considerations

In prior studies of gabapentin or pregabalin treatment of PHN, the difference in mean pain scores between active- and placebo-treated groups ranged from 1.0 to 1.3. For this study, a conservative estimate of 1.0 will be used. Assuming a standard deviation of 2.35, a sample size of 88 per arm (a total of 264 patients) would be needed to provide 80% power with a 2-sided test at 5% significance level to detect a 1.0-point difference. Assuming an approximately 20% dropout rate, 110 patients per arm (a total of 330 patients) will be randomly assigned to each treatment group.

2.4. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. All tubes of study drug will be identical, and the ointments will be indistinguishable. Patients, investigators, and all clinical study center staff will remain blinded to treatment assignment during the study. Eligible patients will be randomly assigned via interactive-response technology (IRT) in a 1:1:1 ratio to 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo ointment. Randomization will be stratified by the R1150W underlying genotype in the SCN9A gene: homozygous minor allele (positive, AA), heterozygous (positive, AG), and homozygous common allele (negative, GG).

In addition, the Sponsor's clinical personnel involved in the study will be blinded to the study drug identity until the database is locked for analysis and the treatment assignment revealed. A statistician not assigned to the study will be responsible for the randomization code, and the final randomization code will be maintained by the service provider.

Patients will be randomly assigned to treatment through a qualified randomization service provider (eg, IRT). This system will be used to ensure a balance across treatment groups; no effort will be made to maintain a balance among treatment groups within a study center.

The clinical study center will receive study drug kits, and kits will be assigned to individual patients by the IRT system based on the patients' randomization assignments. The IRT system will record the kit numbers for all patients. Designated study center staff, who will remain blinded to the treatment assignments, will dispense the kits to patients based on the kit numbers

assigned to patients by the IRT system. In case of emergency, the investigator and designated study center staff can call the IRT system to unblind the treatment for a specific patient.

2.5. Sequence of Planned Analyses

2.5.1. Interim Analyses

No interim analysis is planned for this study.

2.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed only after the last patient has completed the study. The randomization codes will not be unblinded until this SAP has been approved, the database is locked, and the analysis populations are determined.

Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

3. POPULATIONS /ANALYSIS SETS

3.1. Intent to Treat (ITT) Population

The ITT population will include all randomized patients. In this population, treatment will be assigned based upon the treatment to which patients were randomized, regardless of which treatment they actually received.

3.2. Safety Population

The safety population will include all randomized patients who receive at least 1 dose of study medication. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

3.3. Full Analysis Set (FAS)

The FAS, defined as all patients in the ITT population (all patients randomly assigned to a treatment) who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment, will be used for all efficacy analyses. Summaries will be presented by treatment group. The FAS will serve as the primary analysis set for efficacy analyses.

3.4. Per Protocol Population

The per protocol analysis set (PP) will include all patients in the FAS who 1) met all inclusion and none of the exclusion criteria, and 2) did not use > 4 days of rescue medication in baseline (days –7 to –1 prior to randomization) and last 7-day window (days 22 to 28) and did not have > 6 pills of rescue medication (1950 mg/day) for any day during that time, and 3) had at least 4 daily average NRS scores for last 7 days of treatment (days 22 to 28) and 4) had at least 70% of study medication compliance between visits 4 and 5.

3.5. Pharmacokinetic Analysis Set (PK)

The population pharmacokinetic analysis set will include all patients in the pharmacokinetic subset who had at least 1 pharmacokinetic plasma sample analyzed for TV-45070.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error of the mean (SE), median, minimum, and maximum. If inferential statistics are computed, it will also include least square mean and standard error of the least square mean, 95% confidence interval, and p-value, unless otherwise specified. Descriptive statistics for categorical variables include patient counts and percentages.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits).

The last visit for efficacy and safety analyses and summaries is the last observed postbaseline data up to Week 4 visit.

4.2. Specification of Baseline Values

For efficacy variables based on the weekly average of the daily average NRS scores, baseline is defined as the weekly average over the 7 days before randomization (day -7 to day -1). For other efficacy variables the baseline value is the last non-missing assessment on or before the first dose date if no assessment time is available. Otherwise, the baseline value is defined as the last non-missing assessment before the first dose of study medication.

The baseline value for safety variables (i.e., clinical laboratory, vital signs, ECG, and physical examination) is defined as the last non-missing assessment on or before the first dose date if no assessment time is available. Otherwise, the baseline value is defined as the last non-missing assessment before the first dose of study medication.

4.3. Multiple Comparisons and Multiplicity

This is a Phase 2 study, and there is no plan to adjust for multiplicity.

4.4. Handling Withdrawals and Missing Data

Missing onset/stop dates of AEs and prior/concomitant mediations will not be imputed, and a conservative approach will be taken when assigning treatment-emergent AEs or concomitant medications.

The daily average NRS score is the average of the 2 NRS scores (recorded in the morning and evening). At least 1 of the 2 NRS scores must be non-missing or the daily average will be considered missing. The weekly average NRS score is the average of the daily average over 7 days.

For NePIQoL and NPSI questionnaires that include multiple items/tests, the measurement value at each timepoint is the sum of responses of all items/tests. If the entire questionnaire is not done at a scheduled time point, it will be considered missing and won't be imputed unless otherwise specified. Missing responses for individual items/tests will be imputed if up to 10% of the total items/tests for that scale are missing (up to 4 missing responses for NePIQoL, and 1 missing

response for NPSI). The imputed total is equal to the number of items in the scale times the sum of the non-missing responses divided by the number of non-missing items. If more than 10% of the responses are missing, then the total will be considered missing.

4.5. Study Days and Visit Windows

For both safety and efficacy by-visit summaries, the assessments at the scheduled visits will be summarized in the tables while all of the assessments including unscheduled visits will be listed. For patients who withdraw from the study, data at the early termination visit will be included in the last visit summaries. The last visit is defined as last observed postbaseline data up to Week 4 visit.

If there are multiple assessments at a scheduled postbaseline visit then the last non-missing value at that visit will be used for the by visit summary.

Study days will be numbered relative to the first day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient applies the first dose of study drug, as recorded on the study drug diary. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

4.6. Center

The trial will be conducted in approximately 55 study centers in the United States. In order to include center into the model, centers will need to be combined to create approximately 15 big centers. Centers may be pooled according to the number of patients enrolled at each site by keeping the largest sites intact and pooling the remainder of the larger sites with smaller sites to form pooled sites. A final plan for pooling will be made and documented in Statistical Data Review meeting minutes prior to unblinding. The pooled centers will be used in the efficacy analyses as appropriate.

5. STUDY POPULATION

5.1. General

All randomized patients will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients (overall) unless otherwise noted.

5.2. Patient Disposition

Data from patients screened, patients screened but not randomized and reason not randomized will be summarized only for the overall group using patient counts. Patients randomized, patients randomized but not treated (and reason), patients in the ITT, safety, FAS, and PP populations, patients who complete double-blind treatment, patients who withdraw from double-blind treatment, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the double-blind treatment and from the study will also be summarized by reason for withdrawal using descriptive statistics. This summary will include all patients screened into the study. The denominator for calculating percentages will be the number of randomized patients.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and ECG findings will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics by treatment group and total. For continuous variables, descriptive statistics (number [n], mean, standard deviation (SD), standard error (SE), median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

5.4. Medical History

Patients with a medical history assessment will be summarized using descriptive statistics.

5.5. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug Version March 2014 enhanced B2 format) . The incidence of prior medications will be summarized using descriptive statistics by therapeutic class (ATC level 2) and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug.

5.6. Electrocardiography

Electrocardiogram findings (normal, abnormal, and missing) at baseline will be summarized using descriptive statistics.

5.7. Protocol Violations

Patients with at least 1 protocol violation for each category will be summarized using descriptive statistics. Patients with at least 1 major protocol violation for each category will also be summarized using descriptive statistics. Descriptions will be reviewed and rescue medication overuse will be summarized as a separate category.

5.8. Childbearing Potential

For female patients, information related to childbearing potential, contraception, and menopause will be collected at screening visit. The number of patients in each category will be reported by treatment group for randomized patients.

6. EFFICACY ANALYSIS

6.1. General

The FAS will be used as the primary analysis for all efficacy analyses. The PP population will be supportive for efficacy analyses. All statistical testing will be carried out using 2-tailed tests at the 5% level of significance. Summaries will be presented by treatment group as randomized/assigned unless specified otherwise.

6.2. Primary Efficacy Variable and Analysis

6.2.1. Variable Definition

The NRS is a widely-used, standard one-dimensional scale from 0 to 10 for patient self-reporting of pain. The daily average NRS scores are the average of the 2 NRS scores (recorded in the morning and in the evening) of average pain, defined as the patient-reported average pain intensity over the prior 12 hours. At least 1 of the 2 daily scores must be recorded (non-missing) or the daily average will be considered missing. The daily average NRS scores are the average of evening NRS score on day x and morning NRS score on day x+1. For example, the daily average NRS score on day 1 (day of first study medication) is the average of evening NRS score on day 1 and morning NRS score on day 2. Similarly the daily average NRS score on day 28 is the average of evening NRS score on day 28 and morning NRS score on day 29. The weekly average of the daily average is computed over the 7 days. Baseline is computed using days -7 to -1, week 1 using days 1 to 7, week 2 using days 8 to 14, week 3 using days 15 to 21 and week 4 using days 22 to 28.

6.2.2. Primary Analysis

The primary efficacy variable for this study is the change from baseline to week 4 in the weekly average of the daily average NRS pain scores. This variable will be analyzed using a Mixed Model Repeated Measures (MMRM) model with change from baseline in the weekly average of the daily average NRS scores at weeks 1, 2, 3 and 4 as the dependent variable; week, pooled study center, treatment, and treatment by visit interaction as fixed factors, baseline weekly average of the daily average NRS scores as covariate; and patient as a random effect. The unstructured covariance matrix for repeated observations within patients will be used. If the model does not converge, the maximum-likelihood (ML) estimation method will be used instead of the default restricted ML (REML) method. If the model still does not converge, then simpler covariance structures with less parameters will be used in the following order until the model does converge: heterogeneous autoregressive (1) (ARH[1]); heterogeneous compound symmetry (CSH); autoregressive (1) (AR[1]); and compound symmetry (CS). The primary treatment comparison will be conducted at week 4 in this model.

The least square (LS) means and standard error of each treatment group, LS means differences including standard error, 95% confident interval (CI) and p-values, between each active group and the placebo group for the change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the daily average NRS pain scores will be presented in the tables.

SAS code for primary endpoint:

```
Proc mixed data=datain;
Class treatment week patient;
Model change=base treatment center week treatment*week/ddfm=kr;
Repeated week/sub=patient type=un;
Lsmean treatment*week/pdiff cl ;
*** treatment order in the data will be placebo, 4%, 8%*********;

Estimate '4% vs. Placebo at week 4' treatment -1 1 0 treatment*week  0 0 0 -1
0 0 0 1 0 0 0 0/ cl;
Estimate '8% vs. Placebo at week 4' treatment  -1 0 1 treatment*week 0 0 0 -1
0 0 0 0 0 0 0 1/cl;

Run;
```

A descriptive summary of the weekly average of the daily average NRS pain scores at baseline, weeks 1, 2, 3 and 4, as well as the change from baseline will be provided by treatment group.

6.2.3. Sensitivity Analysis

Two sensitivity analyses will be performed in order to assess the robustness of the results of the primary analysis to changes in the assumptions and data characteristics. The first sensitivity analysis is a multiple imputation method to handle missing weekly average of the daily average NRS pain scores for week 4. Consistent with the recommendations of the National Academy of Sciences report (National Research Council 2010), under the assumption of missing at random (MAR) and taking into account of potential bias towards the active arm for patients who withdrew from the study due to adverse events, the following steps will be carried out in SAS using the MI, Mixed, and MIANALYZE procedures:

- Step 1: prepare data set for MI procedure (PROC MI)

  The following auxiliary variables are to be included in the model for PROC MI:

  - Treatment (1=placebo, 2=TV45070 4%, 3=TV45070 8%)
  - R1150W genotype (1=AA, 2=GA, 3=GG)
  - All observed pain scores, screening, baseline, and weekly averages at each post randomization week (week 1, week 2, week 3, week 4)

  The treatment will be coded to 1 (placebo) for those in the active arms withdrawn from study due to an adverse event or lack of efficacy. Thus, the missing week 4 pain scores will be imputed based on the observed placebo patient's data. In order to adjust for the use of rescue medication at week 4, the average weekly pain intensity at week 4 will be set to missing for patients who used an excessive amount of rescue medication during the week before the multiple imputation. Excessive use of rescue medication is defined as the use of rescue medication on at least 4 out of 7 days of the week 4 treatment.

- Step 2: run PROC MI. The following SAS code may be used to generate the imputed data sets:

```
Proc mi data=datain nimpute=5 seed=598719001 out=mi_out
   Maximum=10 minimum=0 round=0.01;
   Class treat genotype;
   Var treat genotype screening baseline week1 week2 week3 week4;
   Monotone reg;
```

```
Run;
```

Note: if the missing data pattern is not monotonic, a Markov Chain Monte Carlo (MCMC) method will be used instead of a regression method for imputing missing data. R1150W genotype will be used, with all 3 possible categories.

- Step 3: run mixed procedure (PROC MIXED) using the data from PROC MI

  The output data set MI_OUT, from the above MI procedure, will contain 5 complete data sets with the missing data points filled using the specified imputation methods, and 1 additional variable, _IMPUTATION_, to indicate the order of the imputed data sets. Then within each data set, the primary variable, change from baseline at week 4, will be derived by subtracting baseline from week 4. Each data set will be analyzed using the ANCOVA model with the primary variable and the dependent variables, the screening and baseline scores as covariates, pooled study center, treatment and genotype as factors in the model. The following SAS code may be used to analyze the imputed data sets.

```
ODS output diffs=mixed_out;
Proc mixed data=mi_out method=reml;
   By _imputation_;
   Class center armcd genotype;
   Model change4 = center armcd genotype baseline screening;
   Lsmeans armcd/diff;
Run;
```

  ARMCD represents the treatment the patient was randomized to receive.

- Step 4: calculate overall p-value and construct 95% confidence interval for the treatment difference.

  The output data from the above SAS code will contain the estimate of the mean difference and the standard error of the estimate from each of the 5 data sets. The SAS procedure mianalyze (PROC MIANALYZE) will be used to generate an overall p-value and 95% confidence interval for the treatment difference. The following SAS code may be used.

```
ODS output parameterestimates=parmest;
Proc mianalyze data=mixed_out alpha=0.05 theta0=0;
   Modeleffects estimate;
   Stderr stderr;
Run;
```

The second sensitivity analysis will be similar to the first one except that the baseline observation carried forward (BOCF) method will be used to impute the missing week 4 weekly average of the daily average NRS pain scores for those who discontinued the study early due to adverse event or lack of efficacy. Details for the week 4 imputation methods for missing weekly average of the daily average NRS pain scores for the two sensitivity analyses are given in Table 2 below.

Table 2: Imputation Methods for Weekly Average of the Daily Average NRS Pain Scores

Double-blind Treatment	Reason	Efficacy Analysis	
		Sensitivity 1	Sensitivity 2
Placebo	Discontinued due to AE or Lack of Efficacy	Multiple imputation	Baseline (BOCF)
	Discontinued due to all other reasons	Multiple imputation	Multiple imputation
	Completed study but took excessive rescue medication before week 4 visit	Multiple imputation	Multiple imputation
TV-45070	Discontinued due to any AE or Lack of Efficacy	Multiple imputation with treatment code set to placebo	Baseline (BOCF)
	Discontinued due to other reasons	Multiple imputation	Multiple imputation
	Completed study but took excessive rescue medication before week 4 visit	Multiple imputation	Multiple imputation

6.3. Secondary Efficacy Variables and Analysis

6.3.1. Variable Definition

- Weekly average of the average pain score recorded in the evening.
- Weekly average of the average pain score recorded in the morning.
- Weekly average of the worst pain score recorded in the evening (worst pain is defined as the patient-reported worst pain intensity over the prior 24 hours).
- ≥ 30% improvement from baseline in the weekly average of the daily average NRS scores, where improvement from baseline is defined as 100*(weekly average of the daily average NRS scores at week 4– baseline weekly average of daily average NRS scores) / baseline weekly average of daily average NRS scores.
- ≥ 50% improvement from baseline in the weekly average of the daily average NRS scores, where improvement from baseline is defined as 100*(weekly average of the daily average NRS scores at week 4 – baseline weekly average of daily average NRS scores) / baseline weekly average of daily average NRS scores.
- NPSI is a patient-reported questionnaire to evaluate the severity of different symptoms of neuropathic pain. The questionnaire contains 10 descriptors and 2 temporal items. Descriptors are scored from 0 to 10, where 0 represents no pain and 10 represents worst pain imaginable. The total score is the sum of the scores of the 10 descriptors (Bouhassira, Attal, Fermanian, Alchaar, et al, 2004). The total score ranges from 0 to 100, where higher scores represent worse pain. If the score for one question is missing the total score will be computed as 10 times sum of scores of 9 descriptors divided by 9. If more than one question is missing then the total score will

be missing. The 2 temporal items will be summarized as continuous variable using descriptive statistics.

- NePIQoL is a questionnaire that contains 41 items to evaluate quality of life in patients with neuropathic pain. Each question has responses ranging from strongly agree or always to strongly disagree or never. Questions are scored on a 5-point scale from 1 to 5, where higher scores represent greater pain-related interference in the quality of life (four items will have scores inverted so that higher scores reflect greater pain. "I involve myself with people I am close to as much as I used to despite the pain", "I can distract myself from the pain", "I can cope with the pain", and "I still enjoy my hobbies/leisure activities despite the pain."). The total score is calculated as the sum of the scores for the individual questions (Poole and Nurmikko 2009). If scores for up to 4 questions are missing then the total score will be computed as 41 times sum of non-missing scores divided by the number of non-missing questions. If responses for more than 4 questions are missing then the total score will be considered missing.
- PGIC is a standardized self-report tool that measures the change in a patient's overall status rating since the start of treatment (Hurst and Bolton 2004) on 7-point scale. The 7-point scale is defined as: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.
- DSIS is an 11-point scale that asks the patient to "select the number that best describes how much your pain has interfered with your sleep during the past 24 hours." Response options range from 0 (Did not interfere with sleep) to 10 (Completely interfered with sleep/unable to sleep due to pain).
- First time to reach ≥ 30% sustained improvement from baseline in the weekly average of the daily average NRS scores will be computed in days from the date of first dose, where the date of first dose is day 1. Those who do not achieve ≥ 30% sustained improvement from baseline will be censored at date of last dose of study medication. Sustained improvement is defined as an improvement of ≥ 30% that is maintained until the end of the treatment period.
- Maximal intensity of patients' brush-evoked allodynia, as measured on the 11-point NRS.
- Maximal intensity of patients' punctate-evoked hyperalgesia, as measured on the 11-point NRS using a Medipin.

6.3.2. Secondary Efficacy Analysis

The above secondary efficacy variables will be analyzed in the similar way as the primary analysis for the primary efficacy variable.

- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the average pain score recorded in the evening
- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the average pain score recorded in the morning

- Change from baseline to weeks 1, 2, 3 and 4 in the weekly average of the worst pain score recorded in the evening (worst pain is defined as the patient-reported worst pain intensity over the prior 24 hours)
- Change from baseline (randomization visit) to weeks 2 and 4 in the NPSI score
- Change from baseline (randomization visit) in DSIS scores at weeks 2 and 4
- Change from baseline (randomization visit) to weeks 2 and 4 in maximal intensity of patients' brush-evoked allodynia, as measured on the 11-point NRS
- Change from baseline (randomization visit) to weeks 2 and 4 in maximal intensity of patients' punctate-evoked hyperalgesia using a Medipin, as measured on the 11-point NRS

In addition, the following analyses will be done:

- Percentage of patients with ≥ 30% improvement and ≥ 50% improvement from baseline in the weekly average of the daily average NRS scores at week 4 will be analyzed using logistic regression model with pooled study center, treatment as fixed factors and baseline NRS scores as covariate.
- Time to reach ≥ 30% sustained improvement from baseline in the weekly average of the daily average NRS scores will be summarized using Kaplan-Meier method.
- Patients' global assessment of treatment, as measured by PGIC scores, at weeks 2 and 4 will be analyzed using a MMRM model similar to the primary efficacy variable with pooled study center, week, treatment, and treatment by week interaction as fixed factors and patient as a random factor. The unstructured covariance matrix for repeated observations within patients will be used.
- Change from baseline (randomization visit) to week 4 in the NePIQoL score will be analyzed using an analysis of covariance (ANCOVA) model with pooled study center, treatment as fixed factors and baseline value as covariate. The missing week 4 values will be imputed using last observation carried forward (LOCF) method.

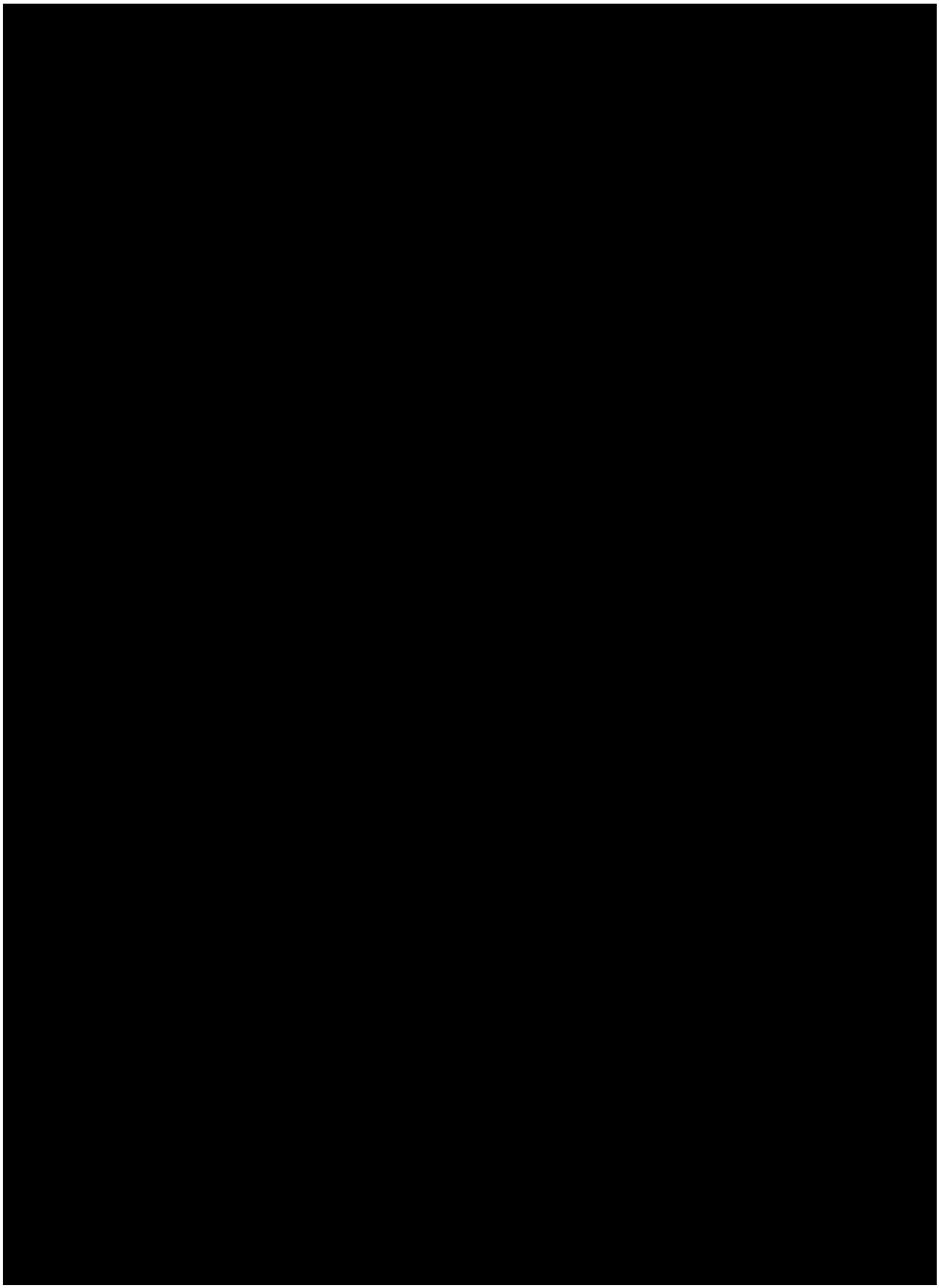
SAS code for ANCOVA model

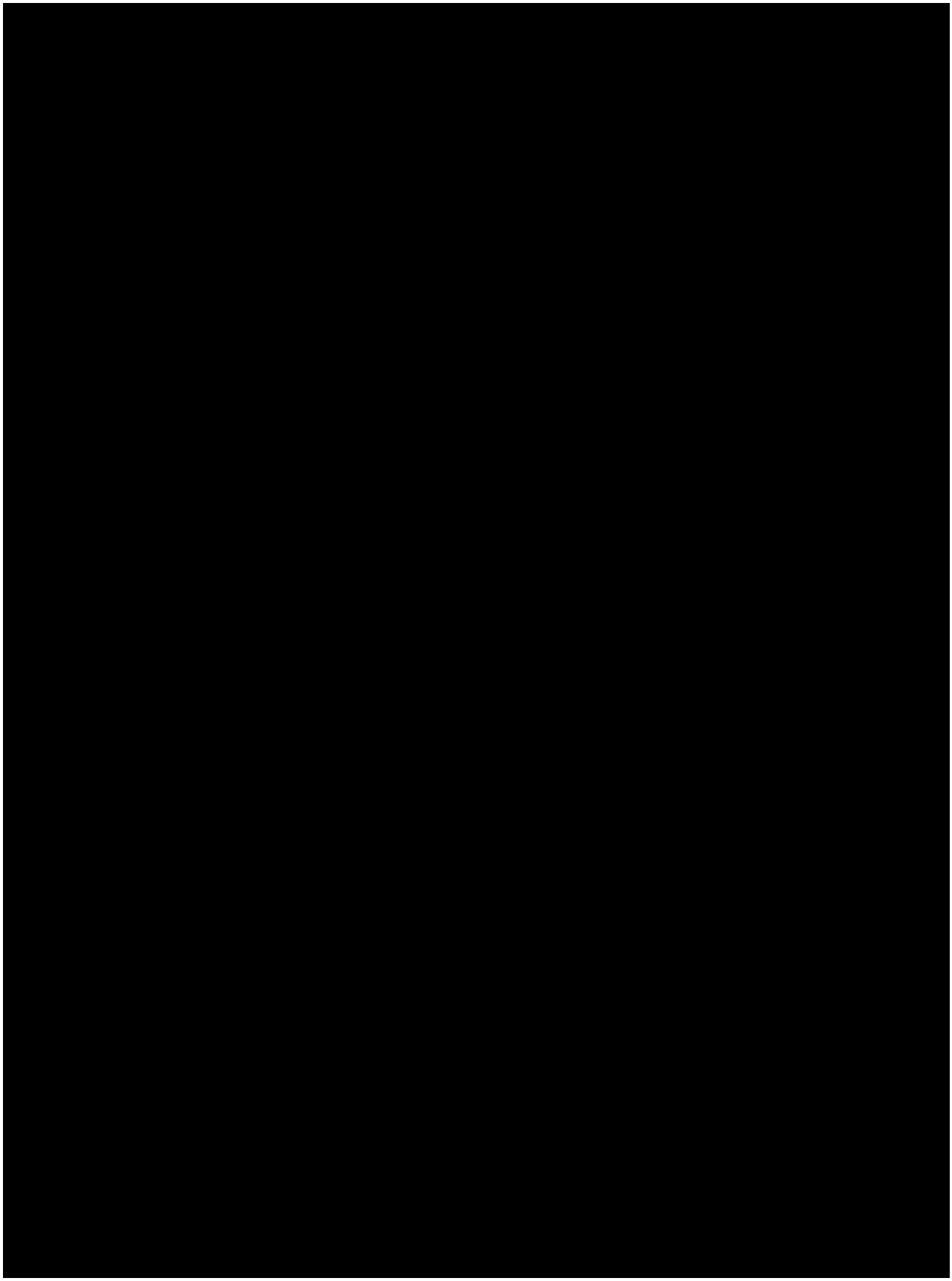
```
Proc mixed data=datain order=data;
Class center treatment;
Model change = base center treatment;
Lsmean treatment /pdiff cl ;
Run;
```

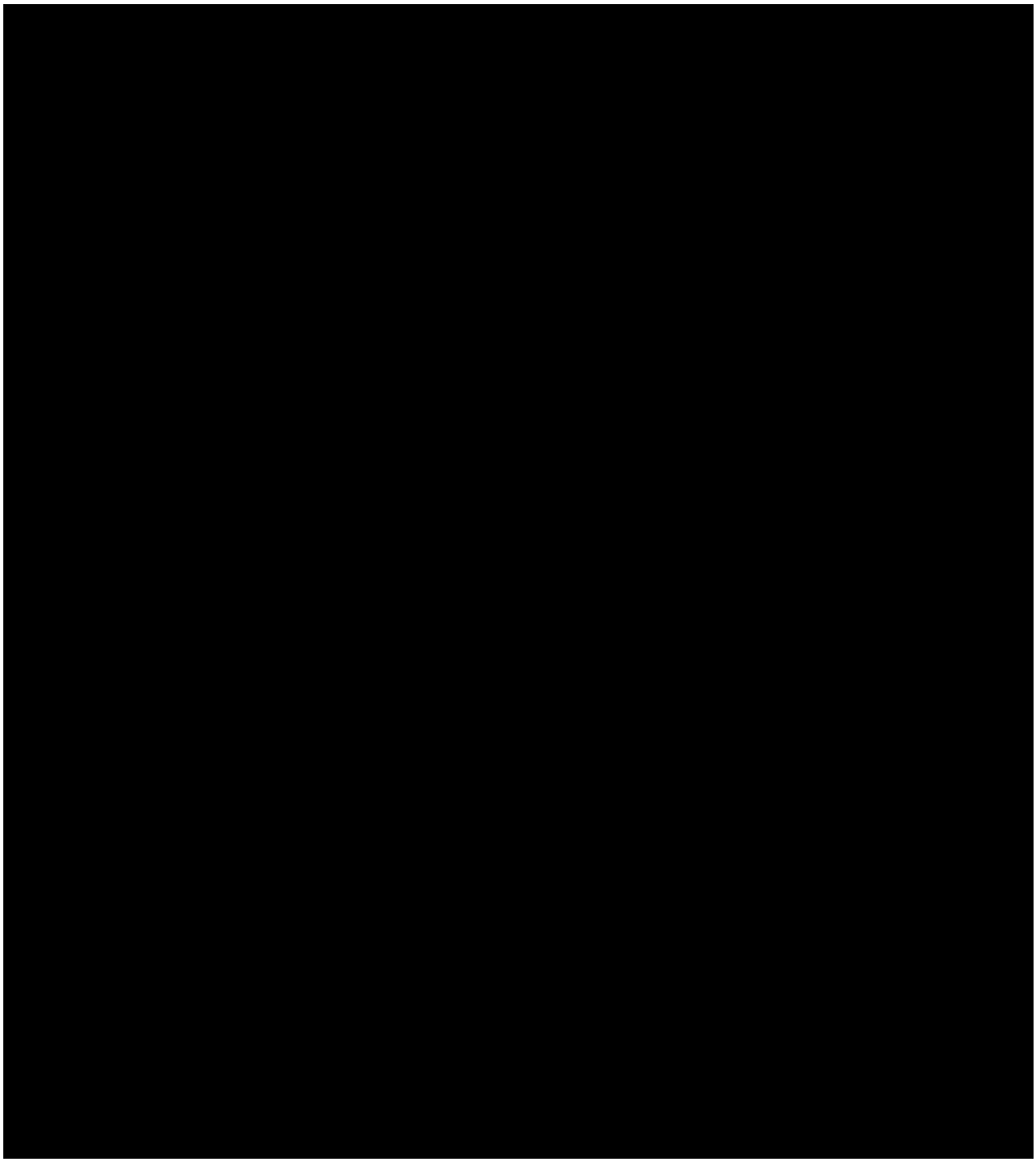
A descriptive summary of the secondary efficacy variables will be provided by treatment group for scheduled visits. Change from baseline will be provided for continuous variables.

6.4. Exploratory Efficacy Analysis

[redacted]







7. SAFETY ANALYSIS

7.1. General

The safety population will be used for all safety analyses. Summaries will be presented by treatment group as actually received unless specified otherwise.

7.2. Study Drug Administration

Duration of treatment (days treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1). The first day of study drug and the last day of study drug will be derived from eDiary data. Total amount of study medication used at each visit (visits 4 and 5) and overall will be calculated as amount (weight in grams) of study medication dispensed minus amount of study medication returned. The expected amount of study medication usage will be calculated as (duration of treatment in days x 2 – 1) x 2 x number of dosing cards per application x 0.6 gram for visits 4 and 5; and duration of treatment in days x 2 x 2 x number of dosing cards per application x 0.6 gram for overall. Study drug compliance, derived as the percentage of total amount of study medication used divided by the expected amount of study medication usage will be descriptively summarized by treatment group for the following categories: > 120%, 100% (inclusive) - 120%, 70% (inclusive) - 100%, and < 70%. Duration of treatment (days) will also be summarized using descriptive statistics by treatment group.

7.3. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

For AE recorded in this study, the study period is defined for each patient as the time period from signature of the ICF through the end of the follow-up period (the day 57 [±3] follow-up visit or when a patient is confirmed as lost to follow-up). Any AE occurring on or after the first application of study drug is considered a treatment-emergent adverse event (TEAE). Unless there is a clear evidence that the onset date of an AE is prior to the first dose date, AEs with missing or partial onset dates will be classified as TEAEs as the conservative approach. All AE summaries will be conducted for TEAEs with the exception of serious adverse event (SAE) related summaries.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 17.1). The incidence of AEs will be summarized using descriptive statistics by system organ class (SOC) and preferred term.

Summaries will be presented for all AEs (overall, by severity and by causality), AEs determined by the investigator to be related to study treatment (ie, reasonable possibility; defined as related or with missing relationship), AEs determined by the investigator to be related to study treatment by severity, serious adverse event (SAEs), and AEs causing withdrawal from study. Summaries will be presented by treatment group and for all patients.

Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. For the summaries by severity, patients are counted at the greatest severity. AEs with missing severity will be considered severe.

In addition, time to the first objective application site irritation, which is defined as the number of days between first dose date and the start of first objective application site irritation, will be analyzed using Kaplan-Meier methods by treatment group. The objective application site irritation is defined by AEs with preferred terms of 'Application site erythema', 'Application site exfoliation', 'Application site oedema', 'Application site papules' and 'Application site rash'. Those who did not experience objective application site irritation will be censored at last dose date.

Patient listings of SAEs and AEs leading to withdrawal from treatment will be presented.

7.4. Deaths

If any patient dies during the study all relevant information will be discussed in the patient's narratives included in CSR.

7.5. Clinical Laboratory Tests

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented at baseline, week 2, week 4, last visit, and follow-up. Laboratory tests results and changes from baseline to each visit and last visit will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit and last visit will be summarized using patient counts. The incidence of potentially clinically significant abnormal results will be summarized for laboratory data using descriptive statistics with the criteria specified in Table 3.

Table 3: Criteria for Potentially Clinically Significant Abnormal Laboratory Values

Test		Criterion value
Serum chemistry		
Alanine aminotransferase (ALT)		≥3x ULN
Aspartate aminotransferase (AST)		≥3x ULN
Alkaline phosphatase		≥3x ULN
Gamma-glutamyl transpeptidase (GGT)		≥3x ULN
Lactate dehydrogenase (LDH)		≥3x ULN
Blood urea nitrogen (BUN)		≥10.71 mmol/L
Creatinine		≥177 µmol/L
Uric acid	Men	≥625 µmol/L
	Women	≥506 µmol/L
Bilirubin (total)		≥34.2 µmol/L
Hematology		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L

Test	Criterion value
Women	≤95 g/L
White blood cell (WBC) counts	≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils	≥10%
Absolute neutrophil counts (ANC)	≤1 x 10^9/L
Platelet counts	≤75 x 10^9/L ≥700 x 10^9/L
Urinalysis	
Blood (HGB)	≥2 unit increase from baseline
Glucose	≥2 unit increase from baseline
Ketones	≥2 unit increase from baseline
Total protein	≥2 unit increase from baseline

ULN=upper limit of normal range.

Listings for potentially clinically significant abnormal laboratory data will be presented.

7.6. Vital Signs

Summary statistics for vital signs will be presented at baseline, weeks 2, 4, last visit, and follow-up. Vital signs values and changes from baseline to each visit and last visit will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Table 4 specifies the criteria for identifying vital signs as potentially clinically significant abnormal. Note that in order to be identified as potentially clinically significant abnormal, a value would need to meet both conditions below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15
	≤50 bpm	Decrease of ≥15
Systolic blood pressure	≥180 mm Hg	Increase of ≥20
	≤90 mm Hg	Decrease of ≥20
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15
	≤50 mm Hg	Decrease of ≥15
Body temperature	≥38.3°C	Change of ≥1.1°C

A listing for potentially clinically significant abnormal vital signs will be presented.

7.7. Electrocardiography

Shifts (normal and abnormal) from baseline to overall, weeks 2, 4, last visit, and follow-up will be summarized using patient counts. For overall, the worst postbaseline finding (the abnormal finding if there are both normal and abnormal findings) for the patient will be summarized. Summary statistics for electrocardiogram variables will be presented at baseline, each visit, and last visit. Electrocardiogram variables results and changes from baseline to each visit and last visit will be summarized using descriptive statistics.

7.8. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight will be performed at screening, baseline, week 2, week 4, follow-up, and early termination. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an adverse event and reported as such.

7.9. Dermal Irritation Findings

Dermal irritation will be evaluated at baseline, week 2, week 4, follow-up, and early termination using the scale below:

- 0 = no evidence of irritation
- 1 = minimal erythema (barely perceptible)
- 2 = definite erythema, readily visible; minimal edema or minimal popular response
- 3 = erythema and papules
- 4 = definite edema
- 5 = erythema, edema, and papules
- 6 = vesicular eruption
- 7 = strong reaction spreading beyond test site

The frequency and percentage of patients falling into each scale at each visit and last visit will be descriptively summarized in the table.

7.10. Concomitant Medications

Concomitant medications will include all medications taken while the patient on study drug and are defined as any medications other than the study drug with stop dates on or after the first dose date. Medications with partial or missing stop dates will be assigned as concomitant medications unless the stop dates are apparently prior to the first dose date.

All concomitant medications will be coded using the WHO Drug Dictionary version March 2014 enhanced B2 format. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken while the patient takes study drug.

8. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The population pharmacokinetic analysis will be detailed in a separate analysis plan, and results will be reported separately from the main study results.

The pharmacodyamic variables of maximal intensity of patients' brush-evoked allodynia and maximal intensity of patients' punctate-evoked hyperalgesia are detailed in section 6.3, Secondary Efficacy Variables and Analyses. Exploratory analyses may be reported separately from the main study results.

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.3 or higher.

10. CHANGES TO PROTOCOL SPECIFIED ANALYSES

Protocol Section 9.5.2, Demographics and Baseline Characteristics, states that treatment groups will be compared for all categorical variables using a Pearson chi-square (or Fisher's exact test if cell sizes are too small). No comparisons will be done for demographic variables.

Protocol Section 9.6.1.1, Primary Efficacy Analysis, states that the MMRM model will analyze change from baseline in the weekly average of the daily average NRS scores at weeks 2 and 4 as the dependent variable. The change from baseline in the weekly average of the daily average NRS scores at weeks 1, 2, 3, and 4 will be used. Weeks 1 and 3 will also be included in the model.

Protocol Section 9.6.1.3, Secondary Efficacy Analysis, states that the time to reach ≥ 30% improvement in weekly average NRS scores from baseline will be summarized using descriptive statistics. This analysis will be reporting using Kaplan-Meier.

11. REFERENCES

Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004; 108:248-257.

Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative Physiological Therapeutics (JMPT) 2004;27:26-35.

Poole H, Nurmikko T. Development and Preliminary Validation of the NePIQoL: A Quality-of-Life Measure for Neuropathic Pain. Journal of Pain and Symptom Management 2009;37:233-245.

National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials*. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press, 2010.

12. LIST OF SUMMARIES AND LISTINGS

12.1. Summary Tables

Summary number	Title	Population
15.1.1	Patient Disposition by Treatment Group	All Patients
15.1.2	Demographics by Treatment Group	Intent-to-Treat Population
15.1.3	Childbearing Potential by Treatment Group	Intent-to-Treat Population
15.1.4	General Medical History by Treatment Group	Intent-to-Treat Population
15.1.5	Prior Medications by Therapeutic Class, Preferred Term, and Treatment Group	Intent-to-Treat Population
15.1.6	Electrocardiogram Findings at Baseline by Treatment Group	Intent-to-Treat Population
15.1.7	Protocol Violations by Treatment Group	Intent-to-Treat Population
15.2.1.1	Summary of Change from Baseline in Weekly Average of the Daily Average NRS Pain Scores	Full Analysis Set
15.2.1.2	Summary of Change from Baseline in Weekly Average of the Daily Average NRS Pain Scores	Per Protocol Population
15.2.1.3	Sensitivity Analysis of Change from Baseline to Week 4 in Weekly Average of the Daily Average NRS Pain Scores	Full Analysis Set
15.2.2.1	Summary of Change from Baseline in Weekly Average of Average NRS Pain Score Recorded in the Evening	Full Analysis Set
15.2.2.2	Summary of Change from Baseline in Weekly Average of Average NRS Pain Score Recorded in the Evening	Per Protocol Population
15.2.3.1	Summary of Change from Baseline in Weekly Average of Average NRS Pain Score Recorded in the Morning	Full Analysis Set
15.2.4.1	Summary of Change from Baseline in Weekly Average of Worst NRS Pain Score Recorded in the Evening	Full Analysis Set
15.2.5.1	Responder Rate in Weekly Average of the Daily Average NRS Pain Scores at Week 4	Full Analysis Set
15.2.5.2	Responder Rate in Weekly Average of the Daily Average NRS Pain Scores at Week 4	Per Protocol Population
15.2.6.1	Summary of Change from Baseline in Neuropathic Pain Symptom Inventory (NPSI)	Full Analysis Set
15.2.7.1	Summary of Change from Baseline to Week 4 in Neuropathic Pain Impact on Quality of Life (NePIQoL)	Full Analysis Set
15.2.8.1	Summary of PGIC Scores after 2 Weeks and 4 Weeks of Study Drug Treatment	Full Analysis Set
15.2.8.2	Summary of PGIC Scores after 2 Weeks and 4 Weeks of Study Drug Treatment	Per Protocol Population

Summary number	Title	Population
15.2.9.1	Summary of Change from Baseline in Daily Sleep Interference Scale (DSIS)	Full Analysis Set
15.2.9.2	Summary of Change from Baseline in Daily Sleep Interference Scale (DSIS)	Per Protocol Population
15.2.10.1	First Time to Reach 30% or More Sustained Improvement in Weekly Average of the Daily Average NRS Pain Scores	Full Analysis Set
15.2.11.1	Summary of Change from Baseline in Maximal Intensity of Brush-Evoked Allodynia as Measured on 11-point NRS	Full Analysis Set
15.2.12.1	Summary of Change from Baseline in Maximal Intensity of Punctate-Evoked Hyperalgesia as Measured on 11-point NRS	Full Analysis Set
15.2.13.1	[redacted]	Full Analysis Set
15.2.13.2		Per Protocol Population
15.2.13.3		Full Analysis Set
15.2.13.4		Full Analysis Set
15.2.13.5		Full Analysis Set
15.2.13.6		Full Analysis Set
15.2.13.7		Per Protocol Population
15.2.13.8		Full Analysis Set
15.2.13.9		Full Analysis Set
15.2.13.10		Full Analysis Set
15.2.13.11		Full Analysis Set
15.2.13.12		Full Analysis Set
15.2.13.13		Full Analysis Set
15.2.13.14		Full Analysis Set

Summary number	Title	Population
15.2.14	[redacted]	Full Analysis Set
15.2.15.1	[redacted]	Full Analysis Set
15.2.15.2	[redacted]	Full Analysis Set
15.2.15.3	[redacted]	Full Analysis Set
15.2.15.4	[redacted]	Full Analysis Set
15.2.16	Association of CYP3A4 and CYP2C19 with Response Variables	Full Analysis Set
15.3.1.1	Study Drug Exposure by Treatment Group	Safety Analysis Set
15.3.1.2	Study Drug Compliance by Treatment Group	Safety Analysis Set
15.3.1.3	Pharmacokinetic Plasma Concentrations	Safety Analysis Set
15.3.2	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Analysis Set
15.3.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Analysis Set
15.3.4	Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Analysis Set
15.3.5	Treatment-Related Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Analysis Set
15.3.6	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, Causality, and Treatment Group	Safety Analysis Set
15.3.7	Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Analysis Set
15.3.8	Treatment Emergent Adverse Events Causing Discontinuation From the Study by System Organ Class, Preferred Term, and Treatment Group	Safety Analysis Set
15.3.9	Treatment Emergent Non-Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Analysis Set
15.3.10	Serum Chemistry Laboratory Tests Results and Changes From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.11	Hematology Laboratory Tests Results and Changes From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.12	Urinalysis Laboratory Tests Results and Changes From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.13	Serum Chemistry Laboratory Tests Results Shifts From Baseline to Each Visit by Treatment Group	Safety Analysis Set

Summary number	Title	Population
15.3.14	Hematology Laboratory Tests Results Shifts From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.15	Urinalysis Laboratory Tests Results Shifts From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.16	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Analysis Set
15.3.17	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Analysis Set
15.3.18	Urinalysis Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Analysis Set
15.3.19	Vital Signs Values and Changes From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.20	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	Safety Analysis Set
15.3.21	Electrocardiogram Findings Shifts From Baseline to Overall and Each Visit by Treatment Group	Safety Analysis Set
15.3.22	Electrocardiogram Variables Results and Changes From Baseline to Each Visit by Treatment Group	Safety Analysis Set
15.3.23	Dermal Irritation Finding at Each Visit by Treatment Group	Safety Analysis Set
15.3.24	Summary of Time (days) to First Application Site Skin Irritation by Treatment Group	Safety Analysis Set
15.3.25	Concomitant Medications by Therapeutic Class and Treatment Group	Safety Analysis Set

12.2. Individual Patient Data Listings

Listing Number	Title	Population
16.2.1.1	Patient Disposition by Treatment Group	Intent-to-Treat Population
16.2.1.2	Patients Who Did Not Meet Screening Criteria	
16.2.2	Protocol Violations by Treatment Group	Intent-to-Treat Population
16.2.4.1	Demographics by Treatment Group	Intent-to-Treat Population
16.2.4.2	Childbearing Potential by Treatment Group (Females Only)	Intent-to-Treat Population
16.2.4.3	Telephone Contact and Patient Continuation at Washout Period by Treatment Group	Intent-to-Treat Population
16.2.4.4	Medical History by Treatment Group	Intent-to-Treat Population
16.2.5.1	Study Drug Record by Treatment Group	Intent-to-Treat Population
16.2.5.2	Study Drug Accountability by Treatment Group	Intent-to-Treat Population
16.2.5.3	Rescue Drug Accountability by Treatment Group	Intent-to-Treat Population
16.2.5.4	Rescue Drug Record by Treatment Group	Intent-to-Treat Population
16.2.6.1	Numerical Rating Scale (NRS) Pain Scores by Treatment Group	Intent-to-Treat Population

Listing Number	Title	Population
16.2.6.2	Neuropathic Pain Symptom Inventory (NPSI) by Treatment Group	Intent-to-Treat Population
16.2.6.3	Neuropathic Pain Impact on Quality of Life (NePIQoL) by Treatment Group	Intent-to-Treat Population
16.2.6.4	Patient Global Impression of Change (PGIC) by Treatment Group	Intent-to-Treat Population
16.2.6.5	Daily Sleep Interference Scale (DSIS) by Treatment Group	Intent-to-Treat Population
16.2.6.6	Brush-Evoked Allodynia and Punctate-Evoked Hyperalgesia by Treatment Group	Intent-to-Treat Population
16.2.6.7	[redacted]	Intent-to-Treat Population
16.2.6.8	Genetic Variables by Treatment Group	Intent-to-Treat Population
16.2.7.1	Adverse Events by Treatment Group	Intent-to-Treat Population
16.2.7.2	Deaths by Treatment Group	Intent-to-Treat Population
16.2.7.3	Serious Adverse Events by Treatment Group	Intent-to-Treat Population
16.2.7.4	Adverse Events Causing Discontinuation From the Study by Treatment Group	Intent-to-Treat Population
16.2.8.1	Laboratory Reference Ranges	
16.2.8.2	Serum Chemistry Laboratory Tests Results by Treatment Group	Intent-to-Treat Population
16.2.8.3	Hematology and Coagulation Laboratory Tests Results by Treatment Group	Intent-to-Treat Population
16.2.8.4	Urinalysis Laboratory Tests Results by Treatment Group	Intent-to-Treat Population
16.2.8.5	Urine Drug Screen Results by Treatment Group	Intent-to-Treat Population
16.2.8.6	Pregnancy Test Results by Treatment Group (Females Only)	Intent-to-Treat Population
16.2.8.7	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Intent-to-Treat Population
16.2.8.8	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Intent-to-Treat Population
16.2.8.9	Urinalysis Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Intent-to-Treat Population
16.2.8.10	Treatment Schedule	Intent-to-Treat Population
16.2.8.11	Vital Signs Values by Treatment Group	Intent-to-Treat Population
16.2.8.12	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	Intent-to-Treat Population
16.2.8.13	Electrocardiogram Findings by Treatment Group	Intent-to-Treat Population
16.2.8.14	Electrocardiogram Variable Results by Treatment Group	Intent-to-Treat Population
16.2.8.15	Dermal Irritation Evaluation by Treatment Group	Intent-to-Treat Population
16.2.8.16	Prior and Concomitant Medications by Treatment Group	Intent-to-Treat Population
16.2.8.17	Pharmacokinetic Plasma Concentrations	Intent-to-Treat Population

Listing Number	Title	Population
16.2.8.18	Adverse Events for Patients Who Did Not Meet Screening Criteria	

12.3. Graphs

Graph Number	Title	Population
17.1.1	Mean Weekly Average of the Daily Average NRS Pain Scores versus Week by Treatment Group	Full Analysis Set
17.1.2	Mean Weekly Average of the Daily Average NRS Pain Scores versus Week by Treatment Group	Per Protocol Population
17.1.3	[redacted]	Full Analysis Set
17.1.4	[redacted]	Full Analysis Set
17.2	Mean Weekly Average of Average NRS Pain Score Recorded in the Evening versus Week by Treatment Group	Full Analysis Set
17.3	Mean Weekly Average of Average NRS Pain Score Recorded in the Morning versus Week by Treatment Group	Full Analysis Set
17.4	Mean Weekly Average of the Worst NRS Pain Score Recorded in the Evening versus Week by Treatment Group	Full Analysis Set
17.5.1	Responder Rate versus Percent of Improvement from Baseline in Weekly Average of the Daily Average NRS Pain Score at Week 4	Full Analysis Set
17.5.2	Responder Rate versus Percent of Improvement from Baseline in Weekly Average of the Daily Average NRS Pain Score at Week 4	Per Protocol Population
17.5.3	[redacted]	Full Analysis Set
17.5.4	[redacted]	Per Protocol Population
17.6	Kaplan-Meier Plot of First Time to Reach 30% or More Sustained Improvement from Baseline in Weekly Average of the Daily Average NRS Pain Score	Full Analysis Set
17.7	Box Plot of PGIC Scores after 2 Weeks and 4 Weeks of Study Drug Treatment	Full Analysis Set