Clinical Study Protocol with Amendment 03

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 TV45070-CNS-20013

NCT02365636

Protocol With Amendment 03 Approval Date: 21 April 2016

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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

Phase 2

IND 108802

Protocol Approval Date: 21 April 2016

Sponsor
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Teva Branded Pharmaceutical Products R&D, Inc.

Sponsor's Medical Expert

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Sponsor's Safety Officer

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Teva Pharmaceuticals
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Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the Sponsor's Standard Operating Procedures (SOPs).

This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc., and its affiliate, Cephalon, Inc. (collectively the "Sponsor"). The recipient agrees that no information contained herein may be published or disclosed without written approval from the Sponsor.

AMENDMENT HISTORY

The protocol for Study TV45070-CNS-20013 (original protocol dated 20 November 2014) has been amended and reissued as follows:

Amendment 03	21 April 2016 107 patients enrolled to date
Administrative Letter	28 September 2015 41 patients enrolled
Amendment 02	09 September 2015 41 patients enrolled to date
Amendment 01	18 February 2015 0 patients enrolled to date
Administrative Letter	17 December 2014 0 patients enrolled

Details about the changes and rationale for each change are provided in Section 17.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 03

Original Protocol Dated 20 November 2014

IND 108802

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

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 03 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information, study drug shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Principal Investigator	Signature	Date

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	4/21/2016

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

This study employs the services of multiple third-party vendors (central clinical laboratory, bioanalytical laboratory, pharmacogenomics laboratory, electronic data capture, electronic diary [eDiary] services, electrocardiogram [ECG] services, radiography services, interactive response technology [IRT] services, etc). The names and addresses of the vendors are provided in the Study Laboratory Manual and/or manuals from the various vendors. These manuals will be in the trial master file (TMF).

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

[redacted]
INC Research, LLC
Role in the Study: Medical Monitor
[redacted]

For operational issues, contact the operational lead listed below:

[redacted]
INC Research, LLC
Role in the Study: Project Manager
[redacted]

For serious adverse events:

The serious adverse event form should be sent to the Sponsor's local safety officer (LSO). The LSO will forward the report to the Sponsor's Global Patient Safety & Pharmacovigilance Department. For this study, the e-mail address for the USA LSO is:
[redacted]

In the event of difficulty transmitting the form, contact the Sponsor's study personnel identified above for further instruction.

These instructions also apply to pregnancy reporting (see Section 7.2).

CLINICAL STUDY PROTOCOL SYNOPSIS

With Amendment 03

Study Number: TV45070-CNS-20013

Title of Study: 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

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

IND Number: 108802

Name of Active Ingredient: TV-45070

Name of Investigational Product: Topical TV-45070 ointment

Phase of Clinical Development: 2

Number of Study Sites Planned: Up to approximately 70 study sites

Country Planned: United States

Planned Study Period: March 2015 (first patient randomly assigned to treatment) to late 2016 up to mid 2017 (last patient last visit)

Number of Patients Planned: 330 patients randomly assigned to treatment (110 per arm) to have up to approximately 88 patients who complete the study per arm, assuming a 20% dropout rate

Study Population: Men and women 18 years of age or older, with chronic postherpetic neuralgia (PHN)

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% weight per weight [w/w] ointment) compared with placebo for the relief of pain due to PHN, as assessed by the change from baseline to week 4 in the weekly average of the daily average Numeric 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 intensity over the prior 12 hours.

Secondary Objectives: The secondary objectives of the study are as follows:

- to evaluate the efficacy of topical TV-45070 (4% and 8% w/w 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) score
  - patients' 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 (randomization visit) 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 the 11-point NRS, at weeks 2 and 4
  - change from baseline (randomization visit) in maximal intensity of patients' punctate-evoked hyperalgesia, as measured on the 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:
  - 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 clinically relevant covariates (eg, age, body weight, gender, and indication) affecting the pharmacokinetics of TV-45070 using the population pharmacokinetics model
- to evaluate the safety of topical TV-45070 (4% and 8% w/w 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 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

[redacted]

- [redacted]

Study Endpoints:

Primary Efficacy 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 in the evening) of average pain, defined as the patient-reported average pain intensity over the prior 12 hours.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are as follows:

- 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 NPSI score
- change from baseline (randomization visit) to week 4 in the NePIQoL score
- patients' global assessment of treatment at weeks 2 and 4, as measured by PGIC scores
- change from baseline (randomization visit) in DSIS scores 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) 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

[redacted]

Safety Variables and Endpoints: The safety of TV-45070 (4% and 8% w/w ointment) will be assessed throughout the study by evaluating adverse events, clinical safety laboratory test results, vital signs measurements, ECG and physical examination results, dermal irritation, and concomitant medication usage. Skin rashes or skin irritation in the area of ointment application will be evaluated using a dermal irritation evaluation (modified Draize scale) at day 1 (at 1 hour [±30 minutes] after application of study drug), week 2, week 4, and week 8 for follow-up.

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

Pharmacokinetic Measures and Endpoints: Two blood samples will be taken 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. Patients will go to the study center after applying study drug at home so that the 2 pharmacokinetic samples can be taken. The first sample will be taken within approximately 1 to 4 hours after the dose of study drug in the morning and the second sample taken approximately 2 hours after collection of the first sample. The date and time of the morning dose and the date and exact time for each of the 2 pharmacokinetic samples will be recorded. Plasma samples will be analyzed for TV-45070. Population pharmacokinetic parameters, such as CL/F and V/F, following topical TV-45070 administration to patients with PHN, will be estimated when the sparse data from this study are combined with enriched pharmacokinetic data from other studies with topical TV-45070. Clinically relevant covariates affecting the pharmacokinetics of TV-45070 will be identified as data permit. These results will be reported separately from the main study results.

Pharmacodynamic Measures and Endpoints: Pharmacodynamic endpoints assessed during the study are the secondary efficacy endpoints change from baseline in maximal intensity of patients' brush-evoked allodynia and change from baseline in maximal intensity of punctate-evoked hyperalgesia. Exploratory analyses, if performed, may be reported separately from the main study results.

Pharmacogenomic Analyses: Two blood samples (approximately 10 mL total) for pharmacogenomic analyses will be taken from all patients at the screening visit. Patients who refuse to give these blood samples will be excluded

from the study. One sample will be analyzed to identify the nucleotide (G or A) underlying the R1150W polymorphism in the *SCN9A* gene and may identify whether there are any other sequence variants in the *SCN9A* gene region. All samples will be retained for a maximum of 15 years after completion of the study [redacted] A pharmacogenomic blood sample may be used to assess the polymorphisms of the *CYP3A4* and *CYP2C19* genes. Depending on the distribution of allelic variations for CYP3A4 and CYP2C19, these results may be incorporated as covariates in the current or future population pharmacokinetic analyses. [redacted]

General Design and Methodology: 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, there will be a total of 6 visits to the study site and 1 telephone contact as follows:

- screening period
  - visit 1: screening (up to 28 days before randomization/first administration of study drug)
  - washout phone contact (approximately 1 week after visit 1 for screening)
  - washout interval (if needed) of variable/flexible length during which the patient will discontinue oral analgesic therapy, topical pain therapy, and/or non-pharmacologic therapies before initiation of the baseline period (Appendix A, Table 2)
  - 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)
- treatment period
  - visit 3: randomization (day 1 [this is the day after day –1 and the first day of study drug application])
  - visit 4: day 15 ±1, week 2
  - visit 5: day 29, week 4
- follow-up period
  - visit 6: follow-up (day 57 ±3) or early termination (ET)

The screening period consists of a screening visit (informed consent and preliminary eligibility assessment are obtained); a washout phone contact during which eligibility based on laboratory test results will be reviewed and, as needed, patients will be given instructions to washout (discontinue) oral analgesic or topical pain therapy; a washout interval (if needed) of variable/flexible length during which appropriate patients will discontinue oral analgesic therapy, topical pain therapy, and/or non-pharmacologic therapies; and a baseline pain assessment interval, when each eligible patient will be given an eDiary to record pain intensity from days –10 to –1. (To allow for training in the use of eDiaries, patients will use eDiaries from day –10, but baseline pain assessment will be defined as the last 7 days prior to randomization, ie, calculated from the values recorded from days –7 through –1). During the baseline

pain assessment interval, rescue medications for PHN pain will not be allowed. Rescue medication will also not be allowed during the last 7 days of treatment. Starting with the baseline pain assessment interval, patients will use eDiaries to record pain, using an 11-point NRS each morning (0700 ±2 hours) and evening (1900 ±2 hours), and any rescue pain medication usage. [redacted]

At visit 3 (day 1, randomization), visit 4 (day 15 ±1, week 2), and visit 5 (day 29, week 4), the NPSI and the DSIS will be administered, and the results will be recorded. On the same visit days, the results of maximal intensity evoked allodynia and maximal intensity evoked hyperalgesia will be recorded. The NePIQoL will be evaluated at visit 3 and visit 5. The PGIC will be evaluated at visits 4 and 5. Efficacy measures are not collected at visit 6 (day 57 ±3), except for ET visits.

At visit 1 (screening), the patient will identify the location of his/her most severe allodynia, and this location will be used for assessments at all subsequent visits. If allodynia or hyperalgesia is not present at screening, it will not be tested at subsequent visits. The investigator will establish normal sensation by using a standardized 1-inch foam brush (light pressure just sufficient to bend the tip of the brush) to stroke an area of skin that is unaffected by pain. The region of allodynia will then be mapped by applying brush strokes moving from normal skin toward the painful region. A felt-tip pen will be used to mark the point where sensation changes from normal to painful. This process will be repeated until 8 to 10 points are marked in a radial fashion to define the area of allodynia. The marks will then be connected with a continuous line. To assess the intensity of allodynia, the investigator will use the brush to perform 3 brush strokes within the mapped area of allodynia. The patient will then assess pain intensity using an 11-point NRS to answer the question “Please rate the intensity of pain caused by brushing the area of skin where 0=not painful at all and 10=worst pain possible.” The pain will be rated for intensity (using the highest pain rating reported) both at prebrush testing and during application of the brush and recorded; additionally, the difference between the 2 scores will be calculated and recorded.

In addition, at visit 1 (screening), the patient will identify the location of his/her most severe hyperalgesia, and this location will be used for assessments at all subsequent visits. To assess the intensity of punctate hyperalgesia, a Medipin will be applied in 3 successive applications to the area of skin identified at screening. The patient will then assess the pain intensity using an 11-point NRS to answer the question “Please rate the intensity of pain caused by application of the Medipin where 0=not painful at all and 10=worst pain possible.” The highest pain rating will be recorded.

Patients will be provided with acetaminophen (TYLENOL®, McNeil Consumer Healthcare Division of McNEIL-PPC, Inc) as 325-mg tablets in bottles of 100 tablets and allowed to take 1 to 2 tablets per dose every 6 hours, as needed, and up to 6 tablets or 1950 mg per day (over a 24-hour period) for rescue relief of PHN pain. Rescue medication will be provided at the screening visit. Rescue medication compliance will be checked at all visits until used rescue medication is collected after the baseline pain assessment interval or at randomization for patients not continuing in the study, at visit 5 (day 29, week 4) for patients who complete the treatment period or at the ET visit for patients who prematurely discontinue study drug.

No other rescue medications will be provided or allowed from the washout phone contact through visit 5 (day 29, week 4) or the ET visit. Patients will not be permitted to use rescue medication during the baseline pain assessment interval (days –10 through –1) and during the final week of treatment (the 7-day period before visit 5). During the washout interval, rescue medication use (dates of use and dose taken) will be recorded as concomitant medication. During the baseline period and the treatment period, rescue medication use will be recorded using the eDiary.

At the randomization visit (visit 3, day 1), eligible patients will be randomly assigned via IRT in a 1:1:1 fashion to 1 of 3 treatment groups: 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo ointment.

Randomization will be stratified by test results of the pharmacogenomic sample collected at the screening visit (homozygous minor allele [positive, AA], heterozygous [positive, AG], and homozygous common allele [negative, GG]) for R1150W polymorphism in the *SCN9A* gene. The patient will be instructed on how to apply the study drug. Under study site staff supervision, the area affected by PHN pain will be carefully defined by mapping the area of pain, and dosing will be prescribed to fully cover the affected area.

Efficacy assessments of pain NRS, NPSI, NePIQoL, and DSIS scores will be conducted at visit 3 (day 1, randomization) to establish baseline measurements. The site staff will apply the first dose of blinded study drug and the patient will record the date/time in the eDiary. Subsequent study drug applications will be performed by the patient at home. (If the affected area is not within reach of application by the patient [such as the posterior thoracic region], the patient's designated caregiver will apply the ointment, but the patient will record the time of application in the eDiary.)

During the 4-week treatment period, patients will apply double-blind study drug to the area of PHN pain twice daily in the morning (0700 ±2 hours) and again in the evening (1900 ±2 hours). The first dose of study drug will be applied at the clinic on day 1 (visit 3). Regardless of the clock time of the first dose application at visit 3, the evening dose for day 1 should be applied at 1900 ±2 hours. The last dose of study drug will be applied at home on the evening of day 28, which is the day before visit 5. In the event that the patient cannot keep the scheduled appointment on day 29, it is nevertheless important for the patient to stop dosing on the evening of day 28. The morning and evening drug applications will be done after recording the response for the NRS pain score. At the start of the baseline pain assessment interval when the eDiary is provided, the eDiary will be used to record the NRS responses, PHN rescue medication use, and then, after randomization, the dates/times of study drug administration.

Patients will return to the study site for visit 4 (day 15 ±1, week 2) and again for visit 5 (day 29, week 4). Routine efficacy evaluations (including pain NRS, NPSI, DSIS, and PGIC scores) and safety assessments will be done at visit 4 (day 15 ±1, week 2) and visit 5 (day 29, week 4). At visit 4 (day 15 ±1, week 2), 2 blood samples will be taken from each patient for pharmacokinetic analysis: the first sample within approximately 1 to 4 hours after the dose of study drug in the morning and the second sample approximately 2 hours after collection of the first sample. The dates and times of the pharmacokinetic sample collections and time of the morning dose will be recorded.

At visit 5 (day 29, week 4), the efficacy evaluation NePIQoL will also be performed, and the eDiary will be collected along with the tubes of study drug and bottles of rescue medication. Patients will be instructed to return to their primary care physician to resume therapy deemed appropriate for their PHN.

Four weeks after visit 5, the patients who completed the double-blind treatment period will return to the study site for a follow-up (visit 6, day 57 ±3). Activities will include safety assessments for all patients.

Patients who prematurely discontinue study drug will have an ET visit within 2 weeks after the last study drug administration. During the ET visit, the same activities will be conducted as those administered for follow-up at visit 6, the eDiary and any unused study drug/rescue medication will be collected, and compliance checks will be performed. Any treatment-emergent adverse event or serious adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; until the patient is referred to the care of a health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made during the study period. For adverse event recording, the study period is defined for each patient as that time period from signature of the ICF through the end of the follow-up period, day 57 (±3). For patients who prematurely discontinue study drug and do not have a treatment-emergent adverse event or serious adverse event, the ET visit will be the last study visit.

Method of Blinding and Randomization: All tubes of the study drug will be identical, and the ointments will be indistinguishable. Patients, investigators, and all clinical study site 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).

Study Drug Dose, Mode of Administration, and Administration Rate: The study drug is double-blind TV-45070 ointment (4% or 8% w/w) or placebo ointment for topical administration. Study drug will be applied twice daily to the painful area in the morning (0700 ±2 hours) and again in the evening (1900 ±2 hours) from days 1 through 28. Study drug will be applied at approximately 3 $\mu L/cm^2$ per application. The actual amount (mg of ointment) of study drug per application will be measured (as length of ointment) using one or more dosing cards based upon the area of pain determined at randomization (visit 3, day 1).

Investigational Product: TV-45070 ointment (4% or 8% w/w)

Reference Therapy:

Placebo: Matching placebo ointment

Duration of Patient Participation: Approximately 12 weeks (up to 4 weeks screening, 4 weeks double-blind treatment, 4 weeks follow-up)

Diagnosis and Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

a. **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than 10 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.

b. Patient has average daily pain of at least 4 on the 11-point NRS at screening and during the baseline pain assessment interval (days –7 to –1) immediately before randomization.

c. Patient must properly assess and record pain intensity in an electronic diary (eDiary) for at least 5 of the 7 daily morning measurements and at least 5 of the 7 daily evening measurements during the 7 days immediately before randomization.

d. **[Revision 1**] Patient is ≥18 years of age, with a body mass index (BMI) between 18 and 34 kg/m^2, inclusive, at the screening visit.

e. If the patient is a woman:

   – The patient cannot become pregnant because she is surgically sterile (hysterectomy or tubal ligation) or postmenopausal for at least 6 months.

     OR

   – If fertile, the patient is not pregnant and has negative pregnancy tests at both the screening and randomization visits, and agrees to use an acceptable method of contraception (ie, oral contraceptives, hormone implant, intrauterine device, spermicide with barrier method, surgically sterile male sexual partner[s], or no sexual partners) for the duration of the study, including follow-up.

f. If the patient is a man:

   – The patient is surgically sterile.

     OR

- If capable of producing offspring, the patient must agree to use a barrier method of contraception in combination with a spermicide with any female partner, unless the partner cannot become pregnant because she is surgically sterile (hysterectomy or tubal ligation), she has been postmenopausal for at least 6 months, or she is fertile but using an acceptable method of contraception (ie, oral contraceptives, hormone implant, or intrauterine device) for the duration of the study, including follow-up.

g. Patient must sign the written Informed Consent Form (ICF) for the study and be willing to comply with all study procedures and restrictions.

h. Patient must be judged by the investigator to be medically healthy (except for PHN) and able to participate in the study.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet 1 or more of the following criteria:

a. Patient has any other severe pain that might confound assessment or self-evaluation of pain due to PHN.

b. Patient has PHN affecting the face (trigeminal nerve distribution).

c. **[Revision 1]** Patient has a history, in the judgment of the investigator, of inadequate response to more than 3 adequate courses of treatment with other medications used to treat neuropathic pain (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.

d. Patient is taking oral analgesics (either opioid or non-opioid) or is receiving topical therapy such as the 5% topical lidocaine patch for the treatment of pain and is unwilling or unable to complete a washout period during which the patient will discontinue analgesic therapy or topical pain therapy.

e. Patient has been treated with topical capsaicin at any time in the past 6 months for neuropathic pain.

f. Patient has an NRS score of 10 on 1 or more occasions during the baseline pain assessment interval (days –7 to –1) immediately before randomization or NRS scores of 9 on 3 or more occasions during the same time frame.

g. Patient used rescue medication during the 7-day baseline period.

h. Patient has a history of fibromyalgia.

i. Patient has uncontrolled cardiac, renal, hepatic, or other systemic disorders that, in the opinion of the investigator, may jeopardize the patient.

j. Patient uses Class Ic anti-arrhythmic drugs such as flecainide or propafenone.

k. Patient has a resting heart rate <45 or >100 beats per minute (bpm), QRS ≥120 milliseconds (including complete left and/or right bundle branch block), QT interval corrected for heart rate by Fridericia's formula (QTcF) ≤320 milliseconds or ≥470 milliseconds, and, for patients in sinus rhythm, PR <120 milliseconds or ≥220 milliseconds. (These numerical exclusion criteria will be applied using the mean values of 3 ECGs.)

l. Patient has second- or third-degree atrioventricular block unless treated with a permanent pacemaker.

m. Patient has uncontrolled atrial fibrillation or flutter (ventricular rate >100 bpm).

n. Patient has a congenital arrhythmia syndrome (eg, Brugada syndrome or long or short QT syndrome).

o. Patient has had myocardial infarction within the past 12 months or current unstable angina, coronary ischemia, or heart failure.

p. Patient has significant edema or loss of skin integrity (including sores or ulcers) other than healed herpes zoster skin rash affecting the region of pain and surrounding area.

q. Patient is intolerant to study drug, its excipients, and/or acetaminophen.

r. Patient uses any over-the-counter (OTC) analgesic medication/topical therapy for the duration of the study except for permitted rescue (for PHN pain) medications. Stable therapy of more than 30 days for aspirin (up to 81 mg/day) is allowed as cardiovascular prophylaxis.

s. Patient uses any non-pharmacologic pain management techniques (eg, physical techniques, physiotherapy, massage therapy, acupuncture, biofeedback, and/or psychological support) and is unable or unwilling to discontinue prior to baseline pain assessment.

t. [**Criterion removed]**.

u. Patient uses any topical/cosmetic products (eg, lotions and tanning products) on the skin in the painful region of PHN.

v. Patient has a history of alcohol or drug abuse within 1 year before the screening visit, or a positive urine drug test at the screening visit for cocaine, marijuana, opioids, amphetamines, methamphetamines, benzodiazepines, barbiturates, methadone, and/or tricyclic antidepressants unless explained by the use of prescription medication. (The use of medical marijuana is not permitted and excludes the patient from the study.)

w. Patient is pregnant or breast-feeding at the time of the screening visit.

x. Patient has findings in laboratory data, vital signs measurements, or physical examination at the screening, baseline pain assessment interval, or randomization visit that, in the opinion of the investigator, may pose undue risk to the patient or may interfere with study data interpretation.

y. Patient was previously randomly assigned to treatment in this study and received/subsequently discontinued study drug.

z. Patient used another investigational drug within 30 days or 5 half-lives (whichever is longer) before the planned first day of study drug application (day 1) in this study.

aa. Patient refuses to provide 2 blood samples at the screening visit for pharmacogenomic analyses.

bb. Patient is a study site or Sponsor employee who is directly involved in the study or the relative of such an employee.

cc. There is any other reason that would make the patient, in the opinion of either the investigator or the Sponsor, unsuitable for the study.

Allowed and Disallowed Medications Before and During the Study: Prior to the study, patients taking opioid or non-opioid oral analgesics or topical therapy must discontinue therapy as part of a washout period. Patients cannot have been treated with topical capsaicin for neuropathic pain at any time in the past 6 months, and cannot use Class Ic anti-arrhythmic drugs such as flecainide or propafenone. During the study, the following medications are not permitted: oral analgesics; topical analgesics including lidocaine (gels, creams and patches) and capsaicin patches; Class Ic anti-arrhythmic drugs such as flecainide or propafenone; rescue pain medication except for permitted

acetaminophen rescue. Permitted acetaminophen rescue consisted of 325 mg tablets, in doses of up to 1 to 2 tablets per 6 hours as needed, up to 6 tablets per 24 hours.

Statistical Considerations: 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. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided.

The full analysis set (FAS), defined as all patients in the intent-to-treat (ITT) population (all patients randomly assigned to 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 primary efficacy variable, change from baseline to week 4 in the weekly average of the daily average NRS scores, will be analyzed using a Mixed Model Repeated Measures (MMRM) with change from baseline in the weekly average of the daily average NRS scores at weeks 2 and 4 as the dependent variable; visit in weeks, treatment, and treatment by visit interaction as fixed factors; baseline weekly average of the daily average NRS scores as covariate; and patient as random effect. The unstructured covariance matrix for repeated observations within patients will be used. The primary treatment comparison will be conducted at week 4 in this model. All tests will be 2-sided at a significance level of 0.05. More details will be provided in the Statistical Analysis Plan.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, based on reasonable possibility; adverse events defined as related or with missing relationship will be summarized overall and by severity), serious adverse events, and adverse events causing withdrawal from study drug treatment and/or the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

The population pharmacokinetic analyses will be detailed in a population pharmacokinetic analysis plan for this study. Results will be reported separately from the main study results.

Sample Size Rationale: 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 (Rice et al 2001) to 1.3 (Dworkin et al 2003). For this decision-making, proof-of-concept study, it is reasonable to use a conservative estimate of 1.0. If we assume a standard deviation of 2.35, a sample size of up to approximately 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. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.

Amendment 03: The primary reason for amendment 03 is to facilitate timely enrollment of patients by broadening the inclusion criterion for the maximum duration of PHN and the exclusion criterion for the number of adequate courses of treatment with other medications for which response was inadequate; by allowing rescreening of patients excluded under these criteria before implementation of amendment 03; and by increasing the number of study sites.

Amendment 02: The primary reason for amendment 02 is to remove the stipulation in exclusion criterion "t" that excludes patients from participating in the study if they used any of the CYP3A4 or CYP2C19 inhibitors or substrates that were listed in Table 2 under Appendix A to this protocol. Related editorial changes have been made as a result of this removal, including: 1) replacement of the previous Table 2 (CYP3A4 and CYP2C19 Substrates and Inhibitors with Documented Clinically Significant Interactions) in Appendix A with a new Table 2 entitled Washout Periods for Specific Drugs; and 2) revision of any statement(s) and cross-reference(s) within the protocol referring to information previously provided in Table 2 of Appendix A.

An additional reason for amendment 02 is to revise inclusion criterion "d" to broaden the recruitment criterion for BMI by increasing the upper limit of the range for BMI from 32 to 34 kg/m^2.

Amendment 02 also serves to correct the list of drugs, as described in Section 7.3.4.2 that are detected by the urine drug screen performed to detect the presence of drugs prohibited by protocol. Alcohol was incorrectly listed in Section 7.3.4.2 as a substance detected by the drug screen, and has been deleted from Section 7.3.4.2 as part of this amendment.

Time windows have been added for the timing of the dermal irritation test and for the triplicate ECGs to allow for natural variability in timing and to avoid unnecessary protocol deviations.

Minor editorial changes for improved text flow and clarity have been incorporated into the protocol text as part of this amendment.

Finally, the protocol is now presented in an updated protocol template maintained by the Sponsor. The change to an updated template is an administrative change per Sponsor policy, and is not intended to alter the clinical conduct of the study.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of Abbreviations

Abbreviation	Term
(A)	adenine
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
AUC	area under the drug concentration by time curve
AUC_{0-24h}	area under the concentration-time curve from 0 to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to infinity
average pain	the patient-reported average pain intensity over the prior 12 hours
BMI	body mass index
bpm	beats per minute
BSA	body surface area
CCI	chronic constriction injury
CDMS	clinical data management system
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	clinical leader
CL/F	apparent clearance
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
CPP	clinical project physician
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
CYP450	cytochrome P450
CYP2C19	cytochrome P450 2C19
CYP3A4	cytochrome P450 3A4
daily average NRS score	the average of the two Numeric Rating Scale scores recorded per day (the score in the morning and the score in the evening)
DDI	drug-drug interaction(s)

Abbreviation	Term
DNA	deoxyribonucleic acid
DRF	dose range-finding
DSIS	Daily Sleep Interference Scale
EDTA	ethylenediaminetetraacetic acid
ECG	electrocardiography, electrocardiogram(s)
eDiary	electronic diary
EM	erythromelalgia
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration (US)
(G)	guanine
GCP	Good Clinical Practice
GD	gestation day
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
hERG	human ether-a-go-go-related gene
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	International Ethics Committee
IEM	inherited or primary erythromelalgia
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LDH	lactic dehydrogenase
LOCF	last observation carried forward
LSO	local safety officer
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MMRM	Mixed Model Repeated Measures
MTD	maximum tolerated dose
Na_V	voltage-dependent sodium channel
NePIQoL	Neuropathic Pain Impact on Quality of Life (questionnaire, score)
NNT	number-needed-to-treat
NOAEL	no-observed-adverse-effect level
non-GLP	not conducted according to Good Laboratory Practice
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numeric Rating Scale
OA	osteoarthritis
OTC	over-the-counter
PGIC	Patient Global Impression of Change (scale, score)
PHN	postherpetic neuralgia
PP	per protocol
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate by Fridericia's formula
RBC	red blood cell
SAD	single-ascending dose
SDV	source document verification
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of the normal range
US(A)	United States (of America)
V/F	volume of distribution
w/w	weight per weight
WBC	white blood cell
WHO Drug	World Health Organization (WHO) drug dictionary
worst pain	the patient-reported worst pain intensity over the prior 24 hours

1. BACKGROUND INFORMATION

1.1. Introduction

Postherpetic neuralgia (PHN) is a complication of herpes zoster in which pain persists for more than 3 months after resolution of the rash. (Three months is the most commonly identified duration, although definitions of duration for PHN vary from >1 months to >6 months.) Postherpetic neuralgia affects between 10% to 15% of people who have herpes zoster and increases with age, affecting up to 70% of those infected who are more than 70 years old (Davies and Galer 2004, Dubinsky et al 2004, Kost and Straus 1996). Elderly patients tend to have more severe and longer lasting PHN.

Postherpetic neuralgia is a classical neuropathic pain condition in which damage to peripheral sensory nerves (and the dorsal horn regions of the spinal cord) is believed to generate spontaneous peripheral neural discharges that lead secondarily to hyperexcitability of dorsal horn sensory neurons and result in exaggerated central nervous system (CNS) responses to all input, a condition known as central sensitization (Kost and Straus 1996). Typically, patients with PHN have both a zone of loss of sensation and zones of altered sensation to light touch and temperature. Pain is described as deep aching or burning in quality and may be triggered by non-painful stimulus (mechanical allodynia) or temperature change (warm or cold allodynia). It may last for years, although there is a tendency for it to wane over time. In those patients whose pain is persistent and severe, PHN becomes debilitating, markedly restricting the patient's activity and quality of life.

Despite the numerous compounds available for treating PHN, 40% to 50% of PHN patients do not respond to any treatment (Rowbotham and Petersen 2001). Antiviral therapy for acute herpes zoster has been shown to speed clearing of the rash, but a recent meta-analysis showed that it does not reduce the likelihood of the development of PHN (Li et al 2009). Antivirals also have no demonstrable benefit after the rash has cleared and are of no use once PHN is established. Tricyclic antidepressants were the first analgesic agents that showed efficacy in randomized controlled trials of PHN, and, subsequently, anticonvulsant agents, strong opioids, and topical analgesics have also demonstrated efficacy.

A topical patch containing 5% lidocaine, a nonselective sodium channel blocker (LIDODERM®, Endo Pharmaceuticals Inc), was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of PHN. In 2004, a subcommittee of the American Academy of Neurology determined that there was solid Class I evidence of efficacy for the lidocaine patch in PHN (Dubinsky et al 2004). The lidocaine patch, if perhaps less effective than other approved treatments such as gabapentin and pregabalin (Dworkin et al 2003), is considered highly efficacious in PHN, although there have been no head-to-head comparisons with other agents and the number-needed-to-treat (NNT) varies from study to study (Davies and Galer 2004). The safety and tolerability of the lidocaine patch has probably contributed most to its widespread use in PHN. Safety and the reduced risk of drug-drug interactions (DDIs) with a topical formulation are particularly relevant, given the elderly age of most patients affected by PHN and their need for concomitant medications.

TV-45070 is a novel, potent, voltage-dependent sodium channel (Na_V) blocker being developed for the treatment of patients with various neuropathic pain indications. Unlike lidocaine, TV-45070 has been designed to selectively block activity in the $Na_V1.7$ channel, which is believed to be the most important sodium channel contributing to spontaneous and hyperactive discharges emanating from peripheral nociceptive neurons. Nonclinical studies have demonstrated that TV-45070 has efficacy in several classical neuropathic pain models, with comparable efficacy to gabapentin in the chronic constriction injury (CCI) model and superior efficacy to 5% lidocaine in a topical streptozotocin-induced diabetic neuropathic pain model.

TV-45070 has been studied in a 2-period crossover trial (each period lasting 3 weeks) in 62 PHN patients who received 1 or more TV-45070 doses. Although it did not meet the primary endpoint (change in mean daily pain score during the last week compared to baseline as measured by the Numeric Rating Scale [NRS]), a significantly larger percentage of patients with 50% reductions in pain were seen during the TV-45070 treatment period in the efficacy evaluable and per protocol (PP) analysis groups. The current study is designed to further evaluate the efficacy of TV-45070 in a larger, parallel-group study design.

1.2. Name and Description of Investigational Product

TV-45070 (formerly known as XEN402 [active pharmaceutical ingredient]) is a white to yellowish crystalline powder. Its chemical name is (S)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo [2,3 f][1,3]benzodioxole-7,3'-indol]-2'(1H)-one. Its chemical formula is $C_{22}H_{14}F_3NO_5$.

Topical TV-45070 is an unscented, off-white to yellowish, opaque ointment with a smooth texture. The clinical formulation contains 4% or 8% (weight per weight [w/w]) TV-45070 with the excipients described in Section 4 of the Investigator's Brochure. The matching placebo ointment contains only the excipients.

A more detailed description of the product is given in Section 3.6.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

Nonclinical studies have been completed to characterize the tolerability, toxicity, pharmacokinetics, and efficacy of TV-45070 following dermal application and oral administration. Prior to development of TV-45070, a package of nonclinical studies was conducted using the racemic compound XEN401 (where TV-45070 comprises 50% of the racemate by weight).

1.3.1.1. Pharmacology Studies

In vitro electrophysiologic studies indicated that TV-45070 is a potent Na_V blocker active against several Na_V subtypes, including those associated with pain signaling. [redacted]

In vivo studies in neuropathic and inflammatory pain models in the rat demonstrated that topical administration of TV-45070 provides analgesic relief superior to current marketed topical therapeutics such as lidocaine and diclofenac. [redacted] Based on these data, the analgesic effect of topical TV-45070 in these animal models is considered to be due to a local rather than a systemic drug effect.

1.3.1.2. Pharmacokinetic Studies

[redacted]

[redacted]

1.3.1.3. Toxicology Studies and Toxicokinetics

[redacted]

[redacted]

1.3.1.4. Safety Pharmacology Studies

[redacted] As suggested by previously published data (Redfern et al 2003), a 30-fold margin between the unbound maximal plasma concentration and the hERG IC_{50} is considered adequate to ensure an acceptable degree of safety from arrhythmogenesis. [redacted]

[redacted]

Further details may be found in the current Investigator's Brochure.

1.3.2. Clinical Studies

To date, topically administered TV-45070 (formerly known as XEN402) has been evaluated in 3 clinical studies: a Phase 1 study in healthy subjects, a Phase 2a study in patients with PHN, and a Phase 2a study in patients with inherited erythromelalgia (IEM). Eighty-nine subjects (20 healthy subjects, 62 PHN patients, and 7 IEM patients) received multiple applications of TV-45070 ointment.

Additionally, topical TV-45070 has been evaluated in a Phase 2 study in patients with osteoarthritis (OA) of the knee, a Phase 1 dose-escalation study in healthy volunteers, and a Phase 1 DDI study with midazolam and omeprazole. Final data are not yet available from these studies.

Oral TV-45070 has been evaluated in 3 clinical studies: a Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study, a Phase 2a study in patients with pain following third molar extractions, and a Phase 2a study in patients with IEM.

The clinical conduct of the OA study, the dose-escalation study, and the DDI study have been completed, but analysis is ongoing. A brief summary of the results of all completed topical and selected oral TV-45070 studies is presented below with more details available in the Investigator's Brochure. The results of the other oral TV-45070 studies are available in the Investigator's Brochure.

1.3.2.1. Clinical Pharmacology Studies

Topical TV-45070 results in minimal to negligible systemic exposure to TV-45070. The TV-45070 plasma concentrations in this paragraph are maximum individual (not group mean) values. Topical TV-45070 was administered to 20 healthy subjects for 21 days in a Phase 1 study (Study XPF-002-101) in which topical TV-45070 was shown to be safe and well tolerated with low plasma exposure (highest observed plasma TV-45070 concentrations <1 ng/mL). In a Phase 2a study (Study XPF-002-201) conducted in 68 patients with PHN, 62 patients were treated with topical TV-45070 for 21 days, and in a Phase 2a study (Study XPF-002-202) conducted in 8 patients with IEM, 7 patients were treated with topical TV-45070 for 14 or 21 days. The amount of drug applied was calculated based on the patient's BSA and a pre-determined fixed-dose volume. The highest plasma TV-45070 concentration observed in any patient was approximately 14 ng/mL.

In the oral TV-45070 SAD/MAD study (Study XPF-001-101), oral TV-45070 was shown to be safe at single doses up to 500 mg (ie, maximum tolerated dose [MTD]) and at doses up to 400 mg twice daily for 5.5 days. The SAD pharmacokinetic profiles had a mean C_{max} of 1410 ng/mL and a mean area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) of 7305 ng•h/mL in cohort 5 (500 mg). Dose-limiting toxicity due to dizziness and somnolence was seen in healthy subjects following single oral doses of 800 mg TV-45070.

No QTc interval changes were observed in any of the oral TV-45070 clinical studies. Furthermore, except for single reports of non-sustained ventricular tachycardia and ventricular

extrasystoles, no other observations of clinically significant QRS prolongation were observed in studies of orally or topically administered TV-45070. More details are available in Section 7.11.3 of the Investigator's Brochure.

The highest (maximum individual) C_{max} values observed in the topical TV-45070 studies were 100-fold lower than the mean C_{max} at the oral MTD for a single dose.

1.3.2.2. Clinical Safety and Efficacy Studies

The safety, tolerability, pharmacokinetics, and efficacy of topical TV-45070 were evaluated in 68 patients with PHN in a Phase 2a, randomized, double-blind, placebo-controlled, crossover study using 8% w/w TV-45070 ointment applied twice daily for 3 weeks (Study XPF-002-201). Topical TV-45070 was found to be safe and well tolerated with low plasma exposure (mean C_{max} 2 ng/mL). The primary endpoint of mean change from baseline in pain scores in the last week was similar between topical TV-45070 and placebo treatments. However, a responder analysis demonstrated that a greater proportion of patients achieved at least 50% reduction in pain from baseline while using topical TV-45070 treatment (26.8%) compared with placebo (10.7%) (p=0.0039). There were no fatal events reported during the study. Two serious adverse events were reported in 2 patients: a tooth abscess that occurred during placebo treatment and worsening coronary artery disease that occurred during topical TV-45070 treatment. Treatment was discontinued in the patient with coronary artery disease. Neither serious adverse event was considered related to study drug treatment. Seven other patients discontinued treatment due to local skin reactions (5 patients during placebo treatment and 2 during topical TV-45070 treatment). The most frequently reported treatment-emergent adverse events were application site reactions, which were more common with placebo treatment than with topical TV-45070 treatment. The majority of application site reactions were mild or moderate; no patient had a severe application site reaction while on TV-45070 treatment.

Additionally, topical TV-45070 was tested in 8 patients with IEM in an exploratory Phase 2a, randomized, double-blind, placebo-controlled study using 8% w/w TV-45070 ointment applied twice daily for 14 or 21 days (Study XPF-002-202). Topical TV-45070 was found to be safe and well tolerated with low plasma exposure (mean C_{max} 4.64 ng/mL). For 3 of the 7 patients treated with topical TV-45070, pain was consistently inhibited by TV-45070 (as measured by the standard heat inductions, self-provoked inductions, and daily pain scores) with corresponding trends in sleep interference scores and minimal use of rescue measures in treatment period 2 compared with baseline. These 3 patients were considered to be responders. There were no fatal events. No serious adverse events were reported during the study. However, several months following study completion and 131 days after the last dose of study drug, a patient (Patient [redacted], topical TV-45070 treatment) was hospitalized for worsening EM pain. The serious adverse event was considered by both the investigator and Sponsor to be unrelated to study drug treatment. One patient (Patient [redacted], topical TV-45070 treatment) was withdrawn from the study due to 2 adverse events (nodules on hands and cyanosis on hands) considered unrelated to study drug treatment. The most frequently reported treatment-emergent adverse events were headache and nasopharyngitis. The vast majority of treatment-emergent adverse events were considered unrelated to study drug treatment. The most frequently occurring, study drug-related treatment-emergent adverse events appeared to be local reactions to the ointment. These events were experienced by patients treated with TV-45070 and the patient treated with placebo.

1.3.2.3. Pharmacogenomic Studies

Although not an endpoint itself, R1150W polymorphism status will be used to stratify patients for randomization [redacted]. Those who carry the R1150W polymorphism have a nucleotide containing adenine (A) instead of guanine (G) in the rs6746030 single nucleotide polymorphism in the *SCN9A* gene. This change causes an arginine to tryptophan amino acid residue change at position 1150 in the alpha subunit of the voltage-gated sodium channel $Na_V1.7$. Those who carry the R1150W polymorphism may be heterozygous (GA) or homozygous (AA) for the minor allele. This R1150W polymorphism in the *SCN9A* gene may affect pain perception (Reimann et al 2010).

[redacted] In the Phase 2a PHN study (Study XPF-002-201), the prevalence of R1150W in exon 19 of the *SCN9A* gene among study patients was investigated. Of the 52 patients tested, 9 patients had the R1150W polymorphism. Of the subgroup of patients test who were efficacy evaluable (n=45), 8 patients had the R1150W polymorphism. The rate of response to treatment was summarized by genotype. Patients who were heterozygous for the R1150W polymorphism showed higher response rates to TV-45070 than those without the polymorphism, although this result did not reach statistical significance. In addition, patients with the R1150W polymorphism were less likely to respond to placebo, although this subgroup was too small to demonstrate statistical significance.

Further details may be found in the current Investigator's Brochure.

1.4. Known and Potential Risks and Benefits to Human Subjects

1.4.1. Risks of TV-45070

Following topical administration, no observed CNS adverse events were considered related to TV-45070 treatment by the investigator. Similarly, with the exception of 1 case of worsening coronary artery disease assessed as unrelated to study drug treatment, no significant ECG findings or cardiac arrhythmias were observed in studies of topical TV-45070.

In nonclinical dermal toxicology studies performed in minipigs, skin irritation was seen frequently in animals dosed either with TV-45070 or vehicle ointment, most often within the first week of dosing. The skin reactions are predominantly erythema and appear to be due to the ointment vehicle itself. In prior clinical studies, however, local reactions at the site of topical application of TV-45070 or matching placebo were seen infrequently. These reactions usually consisted of erythema or skin dryness with scaling of skin, were generally mild to moderate, and were approximately the same in frequency and severity for patients treated with either TV-45070 or placebo. Although the skin reactions may appear within a couple of days of exposure, they more often occur after a delay of 2 to 3 weeks and resolve soon after cessation of dosing. Worsening skin reactions should be monitored closely.

Due to low systemic exposure following topical administration of TV-45070 in humans, the DDI risk due to effects on CYP450 enzymes is thought to be low following topical administration. In vitro data using human liver microsomes have shown that TV-45070 is an inhibitor of several CYP450 enzymes. However, the compound is also highly bound to constituents in human plasma, so distribution into hepatocytes may be hindered, reducing the inhibition potential. In

vitro data using human cryopreserved hepatocytes have also shown that TV-45070 metabolite (M3) is an inhibitor of CYP3A4 and CYP2C19, which indicates a potential DDI risk between TV-45070 and medications that are primarily metabolized by CYP3A4 or CYP2C19. However, the preliminary results of a clinical study designed to assess the risk of these DDIs revealed no significant risk of an interaction.

1.4.2. Benefits of TV-45070

The difficulty of treating PHN adequately, with many patients refractory to available therapies, means that there is an ongoing medical need for new treatment options providing effective topical pain relief with a good safety profile. As a topical sodium channel blocker, TV-45070 may have potent local effects in terms of reducing pain in PHN.

1.4.3. Overall Risk and Benefit Assessment for This Study

In summary, topically administered TV-45070 showed a generally favorable safety profile in nonclinical and clinical studies. Overall, the data for both oral and topically administered TV-45070 support the continued evaluation of topical TV-45070 in clinical studies conducted in patients with chronic pain.

A listing of adverse events observed during studies of topical TV-45070, which were judged to represent adverse drug reactions, is provided in the Investigator's Brochure.

Additional information regarding risks and benefits of TV-45070 to humans may be found in the Investigator's Brochure.

1.5. Selection of Drugs and Dosages

The dosage regimens selected for this study are 4% and 8% w/w TV-45070 ointment, each administered twice daily.

1.5.1. Justification for Dosage of Active Drug

The selected dosage regimens are based on results from animal pharmacology studies, safety information from previous toxicology and clinical studies, and clinical efficacy previously observed with the topical TV-45070 formulation.

TV-45070 has been administered topically to 20 healthy subjects for 21 days, 62 patients with PHN for 21 days, and 7 patients with EM for 14 or 21 days. In all of these studies, the treatment was safe and well tolerated. In the healthy subject study, the ointment was found to be a nonirritant. In the PHN and EM studies, local application site reactions were the most common treatment-emergent adverse events. In addition, TV-45070 has been administered orally to 93 healthy subjects and 4 patients with EM. Exposure data from all of these studies are presented in Section 6.2 of the Investigator's Brochure.

Given that the planned dosage regimens in this study are similar or lower than those employed previously in the PHN and IEM studies, and the amount applied per surface area is less than that used in previous studies (3 $\mu L/cm^2$ in this study compared with 7.5 and 4 $\mu L/cm^2$ in the previous PHN and EM studies, respectively), the safety profile is anticipated to be similar to that observed previously in the topical PHN and EM studies. In addition, signals of efficacy were observed in both the PHN and EM studies in which 8% w/w TV-45070 ointment was applied twice daily.

Therefore, it is reasonable to include the 8% w/w TV-45070 dose as a high dose in this proof-of-concept study in PHN.

A more detailed description of study drug administration is presented in Section 5.1.

1.5.2. Justification for Use of Placebo

The use of placebo is necessary because there is no alternative method for establishing the efficacy of TV-45070 for chronic pain. Pain is a subjective condition, and there is no gold standard treatment for PHN that provides universally effective pain relief. The risk to patients for withholding alternative therapies for pain relief is negligible, and patients are free to withhold their consent for doing so and may withdraw from the study at any time. Rescue medication will be permitted once the subject has completed their baseline period.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the Sponsor and other forms as required by national authorities.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background and requirements of the study and the properties of the study drug(s) as described in the Investigator's Brochure or prescribing information.

The principal investigator at each study site has the overall responsibility for the conduct and administration of the study at that site and for contacts with study management, the Institutional Review Board (IRB), and local authorities.

1.7. Population To Be Studied and Justification

The study population will comprise approximately 330 patients (men and women) 18 years of age or older and with chronic PHN. Approximately 330 patients (110 per treatment group) will be randomly assigned to 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo to ensure that up to approximately 88 patients per group complete the treatment period, ie, have the week 4 visit (visit 5, day 29).

Patients must have chronic PHN according to the definition of pain present for more than 6 months and less than 6 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. The patient's average daily pain must be at least 4 on the 11-point NRS at screening and during the baseline pain assessment interval (days –7 to –1)

immediately before study randomization. Patients with PHN involving trigeminal dermatomes are excluded from the study.

Detailed inclusion and exclusion criteria are listed in Section 4.

1.8. Location and Timing of Study

The study is expected to start in March 2015 (first patient randomly assigned to treatment) and be completed in late 2016 up to mid 2017 (last patient last visit), with a duration of approximately 14 to 22 months.

Approximately 330 patients from up to approximately 70 study sites are planned to be enrolled in the study. The study is planned to be conducted in the US.

1.9. Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

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 in patients with PHN.

2.2. Study Objectives

2.2.1. 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% w/w ointment) compared with placebo for the relief of pain due to PHN, as assessed by 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 in the evening) of average pain, defined as the patient-reported average pain intensity over the prior 12 hours.

2.2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- to evaluate the efficacy of topical TV-45070 (4% and 8% w/w 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) score
  - patients' 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:
  - 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 clinically relevant covariates (eg, age, body weight, gender, and indication) affecting the pharmacokinetics of TV-45070 using the population pharmacokinetics model
- to evaluate the safety of topical TV-45070 (4% and 8% w/w 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 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
  - ECG findings
  - physical examination findings
  - dermal irritation findings
  - concomitant medication usage throughout the study

2.2.3. Exploratory/Other Efficacy Objectives

[redacted]

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

3. STUDY DESIGN

3.1. 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. The study schema is diagramed in Figure 1.

For each patient, there will be a total of 6 visits to the study site and 1 telephone contact as follows:

- screening period
  - visit 1: screening (up to 28 days before randomization/first administration of study drug)
  - washout phone contact (approximately 1 week after visit 1 for screening)
  - washout interval (if needed) of variable/flexible length during which the patient will discontinue oral analgesic therapy, topical pain therapy, and/or non-pharmacologic therapies before initiation of the baseline period (Appendix A, Table 2)
  - 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)
- treatment period
  - visit 3: randomization (day 1 [this is the day after day –1 and the first day of study drug application])
  - visit 4: day 15 ±1, week 2
  - visit 5: day 29, week 4
- follow-up period
  - visit 6: follow-up (day 57 ±3) or early termination (ET)

The screening period consists of a screening visit (informed consent and preliminary eligibility assessment are obtained); a washout phone contact during which eligibility based on laboratory test results will be reviewed and, as needed, patients will be given instructions to washout (discontinue) oral analgesic or topical pain therapy; a washout interval (if needed) of variable/flexible length during which appropriate patients will discontinue oral analgesic therapy, topical pain therapy, and/or non-pharmacologic therapies; and a baseline pain assessment interval, when each eligible patient will be given an electronic diary (eDiary) to record pain intensity from days –10 to –1. (To allow for training in the use of eDiaries, patients will use eDiaries from day –10, but baseline pain assessment will be defined as the last 7 days prior to randomization, ie, calculated from the values recorded from days -7 through –1.) During the baseline pain assessment interval, rescue medications for PHN pain will not be allowed. Rescue

medication will also not be allowed during the last 7 days of treatment. Starting with the baseline pain assessment interval, patients will use eDiaries to record pain, using an 11-point NRS each morning (0700 ±2 hours) and evening (1900 ±2 hours), and any rescue pain medication usage. [redacted]

At visit 3 (day 1, randomization), visit 4 (day 15 ±1, week 2), and visit 5 (day 29, week 4), the NPSI and the DSIS will be administered, and the results will be recorded. On the same visit days, the results of maximal intensity evoked allodynia and maximal intensity evoked hyperalgesia will be recorded. The NePIQoL will be evaluated at visit 3 (day 1, randomization) and visit 5 (day 29, week 4). The PGIC will be evaluated at visit 4 (day 15 ±1, week 2) and visit 5 (day 29, week 4). Efficacy measures are not collected at visit 6, except for ET visits.

At visit 1 (screening), the patient will identify the location of his/her most severe allodynia, and this location will be used for assessments at all subsequent visits. If allodynia or hyperalgesia is not present at screening, it will not be tested at subsequent visits. The investigator will establish normal sensation by using a standardized 1-inch foam brush (light pressure just sufficient to bend the tip of the brush) to stroke an area of skin that is unaffected by pain. The region of allodynia will then be mapped by applying brush strokes moving from normal skin toward the painful region. A felt-tip pen will be used to mark the point where sensation changes from normal to painful. This process will be repeated until 8 to 10 points are marked in a radial fashion to define the area of allodynia. The marks will then be connected with a continuous line. To assess the intensity of allodynia, the investigator will use the brush to perform 3 brush strokes within the mapped area of allodynia. The patient will then assess pain intensity using an 11-point NRS to answer the question “Please rate the intensity of pain caused by brushing the area of skin where 0=not painful at all and 10=worst pain possible.” The pain will be rated for intensity (using the highest pain rating reported) both at prebrush testing and during application of the brush and recorded; additionally, the difference between the 2 scores will be calculated and recorded.

In addition, at visit 1 (screening), the patient will identify the location of his/her most severe hyperalgesia, and this location will be used for assessments at all subsequent visits. To assess the intensity of punctate hyperalgesia, a Medipin will be applied in 3 successive applications to the area of skin identified at screening. The tip of the Medipin rests upon a flange, and the examiner should apply the pin so that the flange rests upon the skin without indenting it. The patient will then assess the pain intensity using an 11-point NRS to answer the question “Please rate the intensity of pain caused by application of the Medipin where 0=not painful at all and 10=worst pain possible.” The highest pain rating will be recorded.

Patients will be provided with acetaminophen (TYLENOL®, McNeil Consumer Healthcare Division of McNEIL-PPC, Inc) as 325-mg tablets in bottles of 100 tablets and allowed to take 1 to 2 tablets per dose every 6 hours, as needed, and up to 6 tablets or 1950 mg per day (over a 24-hour period) for rescue relief of PHN pain. Rescue medication will be provided at the screening visit. Rescue medication compliance will be checked at all visits until used rescue medication is collected after the baseline pain assessment interval or at randomization for patients not continuing in the study, at visit 5 (day 29, week 4) for patients who complete the treatment period, or at the ET visit for patients who prematurely discontinue study drug.

No other rescue medications will be provided or allowed from the washout phone contact through visit 5 (day 29, week 4) or the ET visit. Patients will not be permitted to use rescue

medication during the baseline pain assessment interval (days –10 through –1) and during the final week of treatment (the 7-day period before visit 5). During the washout interval, rescue medication use (dates of use and dose taken) will be recorded as concomitant medication. During the baseline period and the treatment period, rescue medication use will be recorded using the eDiary.

At the randomization visit (visit 3, day 1), eligible patients will be randomly assigned via interactive response technology (IRT) in a 1:1:1 fashion to 1 of 3 treatment groups: 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo ointment. Randomization will be stratified by test results of the pharmacogenomic sample collected at the screening visit (homozygous minor allele [positive, AA], heterozygous [positive, AG], and homozygous common allele [negative, GG]) for R1150W polymorphism in the *SCN9A* gene. The patient will be instructed on how to apply the study drug. Under study site staff supervision, the area affected by PHN pain will be carefully defined by mapping the area of pain, and dosing will be prescribed to fully cover the affected area.

Efficacy assessments of pain NRS, NPSI, NePIQoL, and DSIS scores will be conducted at visit 3 (day 1) to establish baseline measurements. The site staff will apply the first dose of blinded study drug and the patient will record the date/time in the eDiary. Subsequent study drug applications will be performed by the patient at home. (If the affected area is not within reach of application by the patient [such as the posterior thoracic region], the patient's designated caregiver will apply the ointment, but the patient will record the time of application in the eDiary.)

During the 4-week treatment period, patients will apply double-blind study drug to the area of PHN pain twice daily in the morning (0700 ±2 hours) and again in the evening (1900 ±2 hours). The first dose of study drug will be applied at the clinic on day 1 (visit 3). Regardless of the clock time of the first dose application at visit 3, the evening dose for day 1 should be applied at 1900 ±2 hours. The last dose of study drug will be applied at home on the evening of day 28, which is the day before visit 5. In the event that the patient cannot keep the scheduled appointment on day 29, it is nevertheless important for the patient to stop dosing on the evening of day 28. The morning and evening drug applications will be done after recording the response for the NRS pain score. At the start of the baseline pain assessment interval when the eDiary is provided, the eDiary will be used to record the NRS responses, PHN rescue medication use, and then, after randomization, the dates/times of study drug administration.

Patients will return to the study site for visit 4 (day 15 ±1, week 2) and again for visit 5 (day 29, week 4). Routine efficacy evaluations (including pain NRS, NPSI, DSIS, and PGIC scores) and safety assessments will be obtained at visit 4 (day 15±1, week 2) and visit 5 (day 29, week 4).

At visit 4 (day 15 ±1, week 2), 2 blood samples will be taken from each patient for pharmacokinetics analysis: the first sample within approximately 1 to 4 hours after the dose of study drug in the morning and the second sample approximately 2 hours after collection of the first sample. The date and time of the morning dose and the date and exact time for each of the 2 pharmacokinetics samples will be recorded.

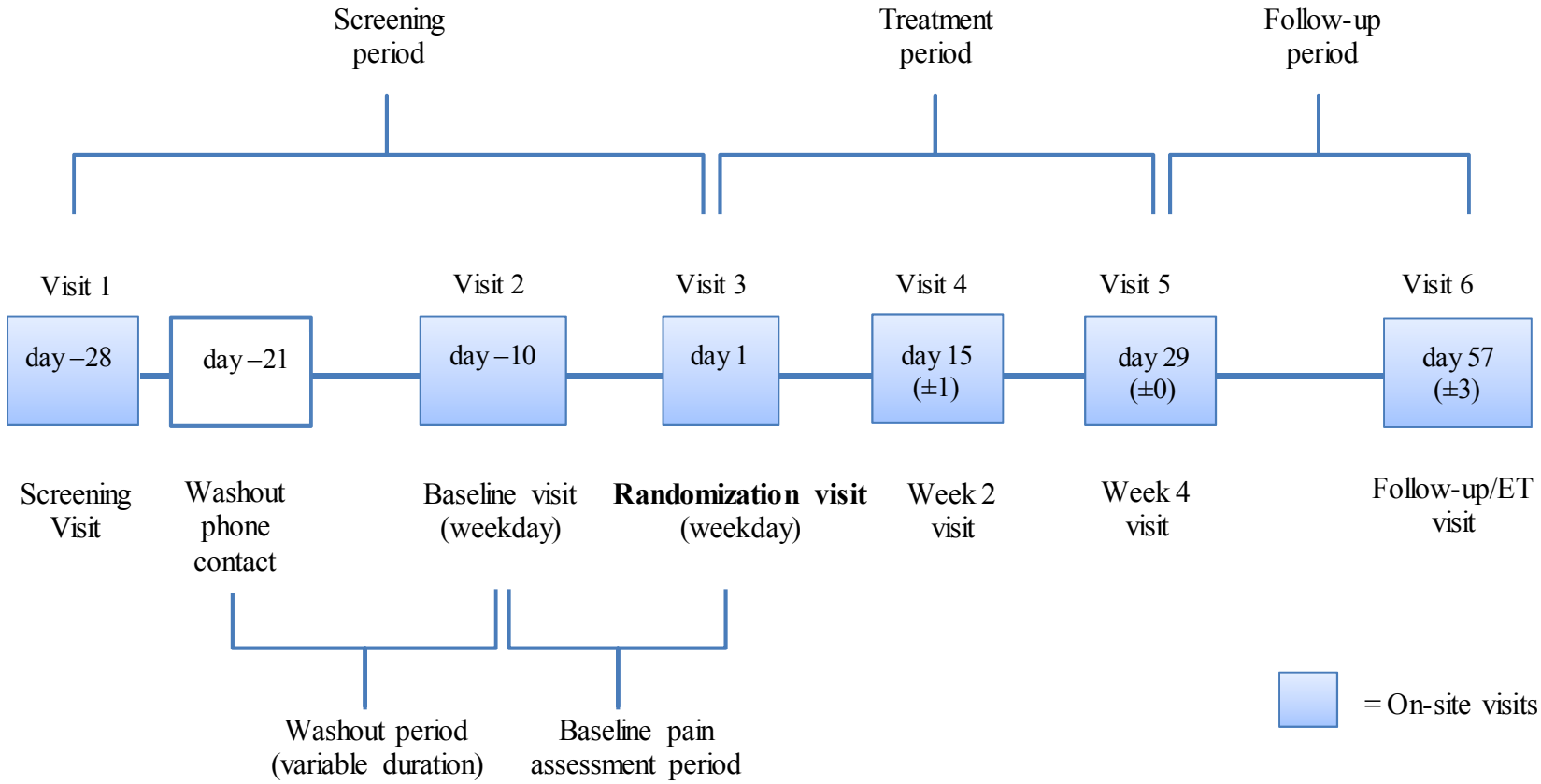
At visit 5 (day 29, week 4), the efficacy evaluation NePIQoL will also be performed, and the eDiary will be collected along with the tubes of study drug and bottles of rescue medication.

Patients will be instructed to return to their primary care physician to resume therapy deemed appropriate for their PHN.

Four weeks after visit 5 (day 29, week 4), the patients who completed the double-blind treatment period will return to the study site for a follow-up (visit 6, day 57 ±3). Activities will include safety assessments for all patients.

Patients who prematurely discontinue study drug will have an ET visit within 2 weeks after the last study drug administration. During the ET visit, the same activities will be conducted as those administered for follow-up at visit 6, the eDiary and any unused study drug/rescue medication will be collected, and compliance checks will be performed. Any treatment-emergent adverse event or serious adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; until the patient is referred to the care of a health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made during the study period. For adverse event recording, the study period is defined for each patient as that time period from signature of the Informed Consent Form (ICF) through the end of the follow-up period, day 57 (±3). For patients who prematurely discontinue study drug and do not have a treatment-emergent adverse event or serious adverse event, the ET visit will be the last study visit.

Figure 1: Study Design



eDiary = electronic diary; ET = early termination
Notes: The screening visit should take place within 28 days of randomization, thus, day –28 is the earliest that it can occur.
The washout phone contact should occur approximately 1 week after the screening visit, thus, day –21 is the earliest it can occur.
The length of the washout period will vary from patient to patient depending on what, if any, treatments (analgesic therapy, topical pain therapy, and/or non-pharmacologic therapy) need to be discontinued.
Patients who discontinue study drug prematurely (any time after randomization and before visit 5) will have an ET visit with the same procedures as those scheduled for the follow-up visit plus eDiary and unused study drug/rescue medication collection (and compliance checks). Depending on when the patient stops taking study drug, the patient may proceed directly from visit 3 or visit 4 to the ET visit.

3.2. Justification for Study Design

TV-45070 has previously been studied in a 2-period crossover study (each period lasting 3 weeks) in 62 PHN patients who received 1 or more TV-45070 doses. Although it did not meet the primary endpoint (change in mean daily pain score during the last week compared to baseline as measured by the NRS), a significantly larger percentage of patients with 50% reductions in pain were seen during the TV-45070 treatment period in the efficacy evaluable and per protocol (PP) analysis groups. The current study is designed to more definitively evaluate the efficacy of TV-45070 in a larger, parallel-group study design.

3.3. Primary and Secondary Measures and Endpoints

3.3.1. 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 in the evening) of average pain, defined as the patient-reported average pain intensity over the prior 12 hours.

3.3.2. Secondary Efficacy Measures and Endpoints

The secondary efficacy measures and endpoints for this study are as follows:

- 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 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
- time to reach ≥30% improvement from baseline (randomization visit) in the weekly average of the daily average NRS scores
- change from baseline to weeks 2 and 4 in maximal intensity of patients' brush-evoked allodynia, as measured on the 11-point NRS

- change from baseline to weeks 2 and 4 in maximal intensity of patients' punctate-evoked hyperalgesia, as measured on the 11-point NRS using a Medipin

3.3.3. Exploratory Efficacy Measures and Endpoints

[redacted]

3.3.4. Safety Measures and Endpoints

The safety of TV-45070 (4% and 8% w/w ointment) will be assessed throughout the study by evaluating adverse events, clinical safety laboratory test results, vital signs measurements, ECG and physical examination results, dermal irritation, 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 [±30 minutes] after application of study drug), week 2, week 4, and week 8 for follow-up.

3.3.5. Tolerability Measures and Endpoints

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

3.3.6. Pharmacokinetic Measures and Endpoints

Two blood samples will be collected from each subject 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. Patients will go to the study center after applying study drug at home so that the 2 pharmacokinetic samples can be taken. The first sample will be taken within approximately 1 to 4 hours of the morning dose of study drug and the second sample taken approximately 2 hours after collection of the first sample. The date and time of the morning dose and the date and exact time for each of the 2 pharmacokinetic samples will be

recorded. Plasma samples will be analyzed for TV-45070. Population pharmacokinetic parameters, such as CL/F and V/F, following topical TV-45070 administration to patients with PHN, will be estimated when the sparse data from this study are combined with enriched pharmacokinetic data from other studies with topical TV-45070. Clinically relevant covariates affecting the pharmacokinetics of TV-45070 will be identified as data permit. These results will be reported separately from the main study results.

3.3.7. 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, as presented in Section 3.3.2.

3.3.8. Pharmacogenomic Analyses

Two blood samples (approximately 10 mL total) for pharmacogenomic analyses will be taken from all patients at the screening visit (visit 1) at approximately the same time as the clinical safety laboratory samples are collected. Patients who refuse to give these blood samples will be excluded from the study. One sample will be analyzed to identify the nucleotide (G or A) underlying the R1150W polymorphism in the *SCN9A* gene and may identify whether there are any other sequence variants in the *SCN9A* gene region. All samples will be retained for a maximum of 15 years after completion of the study [redacted] A pharmacogenomic blood sample may be used to assess the polymorphisms of the *CYP3A4* and *CYP2C19* genes. Depending on the distribution of allelic variations for CYP3A4 and CYP2C19, these results may be incorporated as covariates in the current or future population pharmacokinetic analyses. [redacted]

3.4. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. All tubes of the study drug will be identical, and the ointments will be indistinguishable. Patients, investigators, and all clinical study site staff will remain blinded to treatment assignment during the study. Eligible patients will be randomly assigned via 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).

The randomization code will be generated by a qualified service provider, following specifications from the Biostatistics Department.

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 reviewing 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 site.

All patients will be provided with tubes of blinded study drug ointment (4% w/w TV-45070, 8% w/w TV-45070, or placebo) to be applied twice daily to area of PHN pain during the 4-week treatment period. Placebo ointment is a vehicle-only ointment with identical excipients, content (other than the active pharmaceutical ingredient), appearance, packaging, and labeling to the active treatments.

The clinical study site 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 site staff, who will remain blinded to the treatment assignments, will dispense the kits to the patients based on the kit numbers assigned to patients by the IRT system. In case of emergency, the investigator and designated study site staff can call the IRT system to unblind the treatment for a specific patient. Details related to maintenance of blinding for study conduct, including pharmacokinetic analysis, and the unblinding process are in Section 3.5.

3.5. Maintenance of Randomization and Blinding

3.5.1. Randomization

The randomization code will be maintained in a secure location by a qualified service provider. At the time of analyses, when treatment codes are revealed, the service provider will provide the randomization code to the statistician assigned to this study.

3.5.2. Blinding/Unblinding

Pharmacokinetic data may be assessed during the study. For patients who have pharmacokinetic sample bioanalysis and/or population pharmacokinetic analysis conducted, the individuals responsible for these analyses will receive the randomization allocation and will know who received study drug and who received placebo during the study. Staff responsible for bioanalysis and pharmacokinetic data analysis will not directly interact with clinical study sites and will not have direct involvement in study conduct. All other study team members will remain blinded. Pharmacokinetic analyses performed during the conduct of the study will be provided to the clinical pharmacologist and other staff members in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data).

For information on other personnel who may be aware of treatment assignments, see Section 3.4. These individuals will not be involved in the conduct of any study procedures or assessment of any adverse events.

For a serious adverse event considered related (ie, reasonable possibility; see Section 7.1.4) to the study drug, the Sponsor's Global Patient Safety & Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment, but the Sponsor's clinical project physician (CPP)/clinical leader (CL) may be unblinded to treatment in order to decide on the action to be taken, as described in Section 3.9.

In the event of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment using IRT after consulting the Sponsor. In an extreme emergency, if the investigator is unable to contact the Sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. When this occurs, the investigator must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol immediately; the patient will be withdrawn from the study, and the event will be recorded on the study completion record. Proper documentation must be maintained when a treatment code is revealed. For a serious and unexpected adverse event considered related to the study drug or study procedure, the Sponsor's Global Patient Safety & Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, personnel involved in the conduct, analysis, and reporting of the data will remain blinded to treatment.

3.6. Drugs used in the Study

3.6.1. Investigational Product

The study drug is a double-blind TV-45070 ointment (4% or 8% w/w) or placebo ointment for topical administration. TV-45070 and matching placebo ointments are unscented, off-white to yellowish, opaque ointments with a smooth texture. The ointments contain the same excipients (described in Section 4 of the Investigator's Brochure) and differ only in the amount of active pharmaceutical ingredient. (The matching placebo ointment contains only the excipients.) They will be supplied to the study sites as 50-g fills in 60-mL plastic laminate tubes with tamper-evident seals. The tubes will be stored at ambient room temperature (15°C to 25°C).

Blinded study drug will be given to the patients as described in Section 3.4. Study drug will be applied twice daily to the painful area in the morning (0700 ±2 hours) and again in the evening (1900 ±2 hours) from days 1 through 28. Study drug will be applied at approximately 3 $\mu L/cm^2$ per application. The actual amount (mg of ointment) of study drug per application will be measured (as length of ointment) using one or more dosing cards based upon the area of pain determined at randomization (visit 3, day 1).

Patients will be provided with a laminated instruction sheet, including pictures, that will both describe and illustrate how the ointment is to be spread over the entire area of PHN pain in a thin layer that fully covers the area. The ointment should be lightly massaged into the skin to cover the entire area of PHN pain.

The first application of study drug will occur at the study site on the day of the randomization visit (visit 3, day 1). The study coordinator or designated site staff member will apply blinded study drug and will define the amount of ointment to be used for all subsequent treatment applications for that patient. Dosing cards and instructions will be provided on how to measure the appropriate amount of ointment for each application. Caretakers will be provided instructions at the randomization visit on how to apply ointment to areas inaccessible to the study patient.

The patients will apply blinded study drug twice daily (morning [0700 ±2 hours] and evening [1900 ±2 hours]) on the target area for 4 weeks from days 1 through 28. On day 1, the morning dose might not be applied at 0700 ±2 hours because the first dose of study drug will be applied at the randomization visit (visit 3, day 1). 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. Details about the timing of study drug applications are provided in Section 3.11.3.

Compliance will be assessed by weighing tubes at visit 3 (baseline), visit 4 (day 15 ±1, week 2), and visit 5 (day 29, week 4), or ET visit. A patient will be considered compliant during the interval between the previous 2 visits if the tube weighs between 70% and 120% of the expected weight.

A more detailed description of administration procedures is provided in Section 5.1.

3.6.2. Placebo

The placebo control for this study is placebo ointment for topical administration. The matching placebo ointment is an unscented, off-white to yellowish, opaque ointment with a smooth texture. The placebo ointment contains the same excipients (described in Section 4 of the Investigator's Brochure) as TV-45070, and differs only in that it contains no active pharmaceutical ingredient. The placebo ointment will be supplied to the study sites as 50-g fills in 60-mL plastic laminate tubes with tamper-evident seals. The tubes will be stored at ambient room temperature (15°C to 25°C).

3.7. Drug Supply and Accountability

3.7.1. Drug Storage and Security

Topical TV-45070 (4% and 8% w/w) and matching placebo ointment will be supplied as 50-g fills in 60-mL plastic laminated tubes with tamper-evident seals. The tubes must be stored at ambient room temperature (15°C to 25°C) both at the study site and at the patient's home.

Only authorized personnel will have access to the study drug at the study sites. The authorized study site personnel at each study site will be responsible for the proper storage and handling of the study drug products. Study site personnel will acknowledge receipt of the study drug using the IRT.

3.7.2. Drug Accountability

Each study drug shipment will include a packing slip that lists the contents of the shipment. Study drug accountability records must be maintained at the study site at all times. A record of study drug accountability (ie, study drug and other materials received, used, or retained) with accounts/explanations given for any discrepancies should be documented in the IRT and signed by the principal investigator or designee.

At each study site, the investigator is responsible for ensuring that deliveries of study drug and other study materials from the Sponsor are correctly received and recorded, handled and stored safely and properly in accordance with applicable regulations, and used in accordance with this protocol.

At each study site, a record of study drug accountability (ie, study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies so that possible diversions, abuse, and loss of study drug are documented. Empty/partially used/unused tubes of study drug, upon the Sponsor's approval, will either be destroyed by the study sites or will be returned to a

depot for destruction, according to local and national regulations at specified time intervals as described in the Study Pharmacy Manual. Documented evidence of destruction should be made available to the Sponsor and/or its designees. The investigator or designee will prepare an overall summary of all drug supplies received and used for the study. The investigator, pharmacist, or drug administrator and monitor must verify that no drug supplies remain in the study site's possession.

3.8. Duration of Patient Participation and Justification

This study will consist of a screening period of up to 4 weeks, including a variable-length washout of oral analgesic therapy or topical pain therapy if needed, a 4-week double-blind treatment period, and a 4-week follow-up period. Patients are expected to participate in this study for about 12 weeks. This duration is needed to allow the therapeutic properties of TV-45070 to take effect and to be assessed as part of a controlled clinical trial.

3.9. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the study site to identify safety concerns.

In prior clinical studies with topical TV-45070, skin irritation was seen in some patients exposed to either TV-45070 or vehicle, as described in the Investigator Brochure (Appendix A, also Sections 7.2.2 and 7.11.1). These skin reactions included pain, pruritus, exfoliation, rash, and erythema; were nearly all mild to moderate in severity; and showed complete resolution after cessation of dosing. Skin reactions are evaluated using the dermal irritation evaluation (modified Draize scale) as described in Section 7.9 at visits 2 (baseline visit), 3 (randomization visit, 1 hour [±30 minutes] after application of the ointment), 4 (day 15 ±1, week 2 visit), 5 (day 29, week 4 visit), and 6 (follow-up or ET visit). Good clinical judgment is advised in evaluating skin reactions. In the event that a patient develops progressive or severe skin reaction, the Investigator should carefully evaluate the patient and decide whether or not to stop dosing. The Investigator is reminded to follow the adverse event reporting practices described in the protocol (Section 7.1) when recording and reporting any adverse events, including dermal findings.

A patient may withdraw participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, or adverse event). The investigator and/or Sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event).

Also, the Sponsor may terminate the study for any reason and at any time.

3.10. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the case report form (CRF). Data may not be recorded directly onto the CRF and considered as source data unless the study site obtains written documentation from the Sponsor before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

If data are processed from other institutions (eg, clinical laboratory, central image center, or eDiary), the results will be sent to the study site where they will be retained but not entered into the CRF unless otherwise noted in the protocol. These data may also be sent electronically to the Sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator(s).

The CRFs are filed in the Sponsor's central file.

3.11. Study Procedures

Study procedures and assessments with their timing are summarized in Table 1.

Table 1: Study Procedures and Assessments

Study period	**Screening Period**			**Randomization**	**Double-blind treatment period**		**Follow-up/ET**	
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**[f] **phone contact**	**Baseline**[g] **visit**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**ET**
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 medications	X[i]	X	X	X[h]	X	X	X	X
Start 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 signs 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 samples for pharmacogenomics assessments	X							

Table 1: Study Procedures and Assessments (Continued)

Study period	**Screening Period**			**Randomization**	**Double-blind treatment period**		**Follow-up/ET**	
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**[f] **phone contact**	**Baseline**[g] **visit**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**ET**
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 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							
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 in the evening using eDiary[s]			X[t]	X[h,u]	X[v]	X[v]		

Table 1: Study Procedures and Assessments (Continued)

Study period	**Screening Period**			**Randomization**	**Double-blind treatment period**		**Follow-up/ET**	
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**[f] **phone contact**	**Baseline**[g] **visit**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**ET**
[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)

Table 1: Study Procedures and Assessments (Continued)

Study period	**Screening Period**			**Randomization**	**Double-blind treatment period**		**Follow-up/ET**	
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**[f] **phone contact**	**Baseline**[g] **visit**	**Day of first dose**	**Week 2 visit**	**Week 4 visit**	**Follow-up**	**ET**
Blood samples (including recording of sampling dates/times) for PK assessments[ii]					X[ij]			
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 tracings taken at least 1 minute apart (with an upper limit of 5 minutes apart) 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 Section 3.6.
[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 (±30 minutes) 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 site 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.

3.11.1. Procedures for the Screening Period (Day –28 to Day –1)

3.11.1.1. Screening Visit (Visit 1, Day –28)

The screening visit will be no more than 28 days before randomization/first dose of study drug. A signed and dated ICF will be obtained before screening procedures commence.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each study site are given consecutive identification numbers in successive order of inclusion. The first 2 digits of this screening number will be the number assigned to the country where the study site is located, the next 3 digits will be the designated study site number, and the last 3 digits will be assigned at the study site (eg, if the number assigned to the country is 01, the third patient screened at study site 5 would be given the number of 01005003).

A patient who is screened and does not meet study entry criteria will not be considered for screening again, except that patients who were excluded from enrollment under inclusion or exclusion criteria that have since been revised may be rescreened to determine their eligibility under these criteria as amended. However, a patient taking prohibited concomitant medications may be allowed to continue with study procedures if the investigator or designee believes that the patient can discontinue the prohibited medications during the 4-week screening period and remain off the prohibited medications through the week 4 (visit 5, day 29) or the ET visit.

The screening visit (visit 1) will take place ≤28 days before the first dose (application) of study drug scheduled to be given in the clinic at the randomization visit (visit 3) on day 1. The following procedures to determine patient eligibility for the study will be performed at the screening visit:

- obtain written informed consent before any other study-related procedures are performed
- review inclusion/exclusion criteria
- review medical history and demography
- review prior medication history and concomitant medications
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine drug screen
- perform vital signs measurements
- perform physical examination (including body weight and height)
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)
- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia

- obtain NRS, NPSI, DSIS, and NePIQoL assessments
- dispense rescue medication

In addition, at visit 1 (screening), the patient will identify the location of his/her most severe hyperalgesia, and this location will be used for assessments at all subsequent visits.

Patients will also be informed of all study restrictions and compliance requirements at visit 1.

Two blood samples will be collected for pharmacogenomic analysis. A patient's refusal to provide the pharmacogenomic blood samples will disqualify the patient from participation in the study.

3.11.1.2. Washout Phone Contact (Approximately 1 Week After the Screening Visit)

The washout phone contact will be no more than 21 days before randomization/first dose of study drug, since it takes place 1 week after visit 1. During the washout phone contact, study eligibility based on laboratory test results will be reviewed, the initial adverse event inquiry will be performed, rescue medication use (if any) will be reviewed and recorded as concomitant medication, prior/concomitant medications will be reviewed, and as needed, patients will be given instructions to washout (discontinue) oral analgesic therapy, topical pain therapy, or non-pharmacologic therapy.

For patients who do not need medication washout, this phone contact will be used for other activities needed at this point in the study (review of eligibility based on laboratory test results, initial inquiry for adverse events, review and recording of any rescue medication use, review of prior/concomitant medications as needed, and scheduling the baseline visit).

3.11.1.3. Washout Period (Variable Duration Period Between the Washout Phone Contact and the Baseline Visit)

If needed, a washout period of variable/flexible length will take place, during which the patient will discontinue oral analgesic therapy, topical pain therapy, and/or non-pharmacologic therapies before initiation of the baseline period. The duration of the washout interval will vary from patient to patient, depending on which (if any) medications need to be discontinued. Please refer to Appendix A.

Patients will be provided with acetaminophen (TYLENOL, McNeil Consumer Healthcare Division of McNEIL-PPC, Inc) as 325-mg tablets in bottles of 100 tablets and allowed to take 1 to 2 tablets per dose every 6 hours, as needed, and up to 6 tablets or 1950 mg per 24-hour day.

No other rescue medications will be provided or allowed from the washout phone contact through visit 5 (day 29, week 4) or the ET visit. During the washout interval, rescue medication use (dates of use and dose taken) will be recorded as concomitant medication.

3.11.1.4. Baseline Visit (Visit 2, Day –10, weekday)

All patients who successfully complete the washout period or who did not need the washout period will return to the study site for a baseline visit (visit 2). The baseline visit marks the beginning of the baseline period, and must be confirmed as a weekday upon scheduling. Activities at this visit will include the following:

- review inclusion/exclusion criteria
- perform adverse event inquiry
- review prior/concomitant medications
- perform vital signs measurement
- dispense/collect rescue medication (collect rescue medication from patients not eligible to continue in the study), perform accountability, and return unused portion to patients continuing in the study
- provide eligible patient with an eDiary and instruct patient on its use
- review rescue drug compliance
- evaluate area of PHN pain for dermal irritation

A patient who does not meet study entry criteria on the basis of results of baseline assessments and is not randomly assigned to treatment/enrolled in the study will not be considered for screening again.

At the baseline visit, patients should be instructed to:

- record average daily pain intensity (over the previous 12 hours [NRS]), in the morning and in the evening using eDiary
- record rescue pain medication usage for PHN via eDiary *(patients will be reminded of the restrictions on rescue medication use during the baseline period, and will be instructed to record any use of rescue medications in the eDiary)*
- after the baseline visit, record worst daily pain intensity (NRS) in the evening using eDiary

3.11.2. Randomization Visit (Visit 3, Day 1, weekday)

Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number using an IRT. These 2 newly assigned numbers will be entered into the CRF, and study drug will be dispensed.

The randomization visit occurs on the same day as the start of study drug treatment. This visit must be confirmed as a weekday upon scheduling.

At the randomization visit (visit 3, day 1), eligible patients will be randomly assigned via IRT in a 1:1:1 fashion to 1 of 3 treatment groups: 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo ointment. Randomization will be stratified by test results of the pharmacogenomic sample collected at the screening visit (homozygous minor allele [positive, AA], heterozygous [positive, AG], and homozygous common allele [negative, GG]) for R1150W polymorphism in the *SCN9A* gene.

The following procedures/assessments will be performed at visit 3 prior to study drug dose:

- review inclusion/exclusion criteria
- perform adverse event inquiry

- review prior/concomitant medications
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine drug screen
- perform vital signs measurements
- perform physical examination
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)
- obtain NPSI, DSIS, and NePIQoL assessments
- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia
- review rescue drug compliance, perform accountability, and return unused portion to patient if continuing
- review eDiary and review eDiary data via website *(for patients not eligible to be randomly assigned to treatment, collect eDiary)*
- weigh tube of study drug ointment, to obtain baseline tube weight prior to study drug dispensing for study drug compliance checks at subsequent visits
- [redacted]

[redacted]

At visit 3 (day 1), the area affected by PHN pain will be carefully defined by the investigator and the patient by mapping the area of pain. Dosing of TV-45070 ointment will be prescribed to fully cover the affected area. [redacted] The following procedures/assessments will be performed at visit 3 immediately prior to or at the time of the first study drug dose:

- instruct the patient to apply study drug twice daily to area of PHN pain, with the first dose administered by site staff
- provide patient with instructions on how to apply study drug
- dispense study drug
- record date and time of study drug application using eDiary

The following procedures/assessments will be performed at visit 3 after the first study drug dose:

- evaluate area of PHN pain for dermal irritation 1 hour (±30 minutes) after first dose

At the randomization visit, patients should be instructed to perform the following procedures in the evening at 1900 ±2 hours:

- apply study drug
- record date/time of study drug application using eDiary
- record rescue pain medication usage for PHN via eDiary
- record worst daily pain intensity (NRS) in the evening using eDiary
- record average daily pain intensity (over the previous 12 hours [NRS]) in the evening using eDiary

Patients should also be instructed to record average daily pain intensity (over the previous 12 hours [NRS]) in the morning at 0700 ±2 hours using eDiary.

3.11.3. Procedures During Double-Blind Treatment Period (Day 1 Through Day 29 Visit)

The start of study drug treatment occurs on the randomization visit (visit 3, day 1), as detailed in Section 3.11.2. Study drug treatment continues until the evening of day 28.

3.11.3.1. Daily Routine

During this treatment period (and after the morning study drug application at the clinic on day 1), patients will self-administer topical study drug (4% or 8% w/w TV-45070 ointment or placebo ointment) according to the instructions provided by the study site. Study drug will be applied twice daily (in the morning [0700 ±2 hours] and again in the evening [1900 ±2 hours]). The first dose of study drug will be applied at the clinic on day 1 during 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. The last dose of study drug will be applied at home on the evening of day 28. No study drug will be applied on day 29, the day of visit 5 (week 4).

Patients who participate in the study in compliance with the protocol from the screening visit through the week 4 visit (visit 5, day 29) will be considered to have completed the study for statistical purposes.

3.11.3.2. Week 2 Visit (Visit 4, Day 15 [±1])

On day 15 (±1 day), patients will visit the study site (visit 4) in addition to the normal at-home routine (Section 3.11.3.1). Activities at this visit will include the following:

- perform adverse event inquiry
- review prior/concomitant medications
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform vital signs measurements
- perform physical examination
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)

- obtain NPSI, DSIS, and PGIC assessments
- evaluate area of PHN pain for dermal irritation
- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia
- dispense/collect rescue medication, perform rescue medication accountability, and return unused portion to patients continuing in the study
- review patient eDiary and review eDiary data via website
- review study drug compliance and rescue drug compliance
- dispense/collect study drug
- obtain 2 blood samples (with recording of sampling dates/times) for pharmacokinetics assessments (the first sample taken within approximately 1 to 4 hours after morning study drug and the second sample taken approximately 2 hours after collection of the first sample)

At visit 4, patients should be instructed to continue to:

- record average daily pain intensity (over the previous 12 hours [NRS]) in the morning and in the evening using eDiary
- apply study drug twice daily to area of PHN pain
- record date/time of study drug application using eDiary
- record rescue pain medication usage for PHN via eDiary
- record worst daily pain intensity (NRS) in the evening using eDiary

3.11.3.3. Week 4 Visit (Visit 5, Day 29 [±0])

The following procedures/assessments will be performed:

- perform adverse event inquiry
- review prior/concomitant medications
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform urine drug screen
- perform vital signs measurements
- perform physical examination
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)
- obtain NPSI, DSIS, NePIQoL, and PGIC assessments
- evaluate area of PHN pain for dermal irritation

- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia
- collect rescue medication and review accountability
- review eDiary and review eDiary data via website, including the following data recorded by the patient at home:
  - average daily pain intensity (over the previous 12 hours [NRS]) through the morning of day 29
  - date/time of study drug application through the evening of day 28
  - rescue pain medication usage for PHN
  - worst daily pain intensity (NRS) through the evening of day 28
- collect eDiary
- review study drug compliance and rescue drug compliance
- collect study drug

3.11.3.4. Early Termination Visit

For patients who discontinue the study drug prematurely (do not complete the per protocol treatment period), there will be an ET visit as soon as possible after the last study drug administration. General procedures for patients who withdraw prematurely from the study are described in Section 4.3.

The follow-up visit activities (Section 3.11.4.2) plus eDiary and unused study drug/rescue medication collection (and compliance checks) will be conducted at the ET visit, for ET visits occurring prior to visit 5 (day 29, week 4). (An ET visit may also occur after visit 5 but before the day that visit 6 would normally be scheduled, on day 57 ±3.) If adverse events or other safety findings are present at the ET visit, the clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. Otherwise, the ET visit will be the last study visit for these patients.

Because premature discontinuations of treatment may occur at any time between randomization and the week 4 visit (visit 5, day 29), patients will be permitted to proceed directly from either visit 3 (day 1, randomization), visit 4 (day 15 ±1, week 2), or visit 5 (day 29, week 4) to the ET visit. For example, a patient who discontinues study drug on day 20 will have visit 4 (day 15 ±1, week 2) followed by visit 6 (ET) as soon as possible after day 20 with no visit 5 (day 29, week 4) in between.

The following procedures/assessments will be performed at the ET visit:

- perform adverse event inquiry
- review prior/concomitant medications

- review and record rescue medication use (if any) as concomitant medication, not using eDiary
- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform vital signs measurements
- perform physical examination (including body weight)
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)
- obtain NPSI, DSIS, NePIQoL, and PGIC assessments
- evaluate area of PHN pain for dermal irritation
- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia
- collect rescue medication (if prior to visit 5) and review accountability
- review eDiary and review eDiary data via website, including the following data recorded by the patient the previous evening (if prior to visit 5):
  - date/time of study drug application
  - rescue pain medication usage for PHN
  - worst daily pain intensity (NRS) in the evening
- collect eDiary (if prior to visit 5)
- review study and rescue drug compliance
- collect study drug (if prior to visit 5)

3.11.4. Procedures After Study Drug Treatment

3.11.4.1. Follow-up Period (After the Week 4 Visit)

At the week 4 visit (visit 5, day 29), patients who completed the double-blind treatment period will enter a 4-week follow-up period, during which they will not use study drug. They should be instructed to return to their primary care physician to resume therapy deemed appropriate for their PHN.

3.11.4.2. Follow-up Visit or ET visit (Visit 6, Day 57 [±3])

At the end of the follow-up period (visit 6, day 57 ±3), patients will return to the study site for the follow-up visit. This visit will be the final visit of the study. Activities at the follow-up visit will include the following:

- perform adverse event inquiry
- review medications taken since previous visit

- perform clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- perform vital signs measurements
- perform physical examination (including body weight)
- perform 12-lead ECG (all ECGs taken in triplicate tracings obtained at least 1 minute apart [with an upper limit of 5 minutes apart])
- obtain urine pregnancy test (women of child-bearing potential only)
- evaluate area of PHN pain for dermal irritation

Activities performed at the ET visit only will include the following:

- obtain NPSI, DSIS, NePIQoL, and PGIC assessments
- measure maximal intensity of brush-evoked allodynia and maximal intensity of punctate-evoked hyperalgesia
- collect rescue medication (if prior to visit 5)
- review and record rescue medication use (if any) as concomitant medication, not using eDiary
- review eDiary and review eDiary data via website, including the following data recorded by the patient the previous evening (if prior to visit 5):
  - date/time of study drug application
  - rescue pain medication usage for PHN
  - worst daily pain intensity (NRS) in the evening
- collect eDiary (if prior to visit 5)
- review study and rescue drug compliance
- collect study drug (if prior to visit 5)

3.11.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

Patients may be included in the study only if they meet all of the following criteria:

a. **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than 10 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.

b. Patient has average daily pain of at least 4 on the 11-point NRS at screening and during the baseline pain assessment interval (days –7 to –1) immediately before randomization.

c. Patient must properly assess and record pain intensity in an eDiary for at least 5 of the 7 daily morning measurements and at least 5 of the 7 daily evening measurements during the 7 days immediately before randomization.

d. **[Revision 1**] Patient is ≥18 years of age, with a body mass index (BMI) between 18 and 34 kg/m^2, inclusive, at screening visit.

e. If the patient is a woman:

   – The patient cannot become pregnant because she is surgically sterile (hysterectomy or tubal ligation) or postmenopausal for at least 6 months.

     OR

   – If fertile, the patient is not pregnant and has negative pregnancy tests at both the screening and randomization visits and agrees to use an acceptable method of contraception (ie, oral contraceptives, hormone implant, intrauterine device, spermicide with barrier method, surgically sterile male sexual partner[s], or no sexual partners) for the duration of the study, including follow-up.

f. If the patient is a man:

   – The patient is surgically sterile.

     OR

   – If capable of producing offspring, the patient must agree to use a barrier method of contraception in combination with a spermicide with any female partner, unless the partner cannot become pregnant because she is surgically sterile (hysterectomy or tubal ligation), she has been postmenopausal for at least 6 months, or she is fertile but using an acceptable method of contraception (ie, oral contraceptives, hormone implant, or intrauterine device) for the duration of the study, including follow-up.

g. Patient must sign the written ICF for the study and be willing to comply with all study procedures and restrictions.

h. Patient must be judged by the investigator to be medically healthy (except for PHN) and able to participate in the study.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet 1 or more of the following criteria:

a. Patient has any other severe pain that might confound assessment or self-evaluation of pain due to PHN.

b. Patient has PHN affecting the face (trigeminal nerve distribution).

c. **[Revision 1]** Patient has a history, in the judgment of the investigator, of inadequate response to more than 3 adequate courses of treatment with other medications used to treat neuropathic pain (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.

d. Patient is taking oral analgesics (either opioid or non-opioid) or is receiving topical therapy such as the 5% topical lidocaine patch for the treatment of pain and is unwilling or unable to complete a washout period during which the patient will discontinue analgesic therapy or topical pain therapy.

e. Patient has been treated with topical capsaicin at any time in the past 6 months for neuropathic pain.

f. Patient has an NRS score of 10 on 1 or more occasions during the baseline pain assessment interval (days –7 to –1) immediately before randomization or NRS scores of 9 on 3 or more occasions during the same time frame

g. Patient used rescue medication during the 7-day baseline period

h. Patient has a history of fibromyalgia.

i. Patient has uncontrolled cardiac, renal, hepatic, or other systemic disorders that, in the opinion of the investigator, may jeopardize the patient.

j. Patient uses Class Ic anti-arrhythmic drugs such as flecainide or propafenone.

k. Patient has a resting heart rate <45 or >100 beats per minute (bpm), QRS ≥120 milliseconds (including complete left and/or right bundle branch block), QT interval corrected for heart rate by Fridericia's formula (QTcF) ≤320 milliseconds or ≥470 milliseconds, and, for patients in sinus rhythm, PR <120 milliseconds or ≥220 milliseconds. (These numerical exclusion criteria will be applied using the mean values of 3 ECGs.)

l. Patient has second- or third-degree atrioventricular block unless treated with a permanent pacemaker.

m. Patient has uncontrolled atrial fibrillation or flutter (ventricular rate >100 bpm).

n. Patient has a congenital arrhythmia syndrome (eg, Brugada syndrome or long or short QT syndrome).

o. Patient has had myocardial infarction within the past 12 months or current unstable angina, coronary ischemia, or heart failure

p. . Patient has significant edema or loss of skin integrity (including sores or ulcers) other than healed herpes zoster skin rash affecting the region of pain and surrounding area.

q. Patient is intolerant to study drug, its excipients, and/or acetaminophen.

r. Patient uses any over-the-counter (OTC) analgesic medication/topical therapy for the duration of the study except for permitted rescue (for PHN pain) medications. Stable therapy of more than 30 days for aspirin (up to 81 mg/day) is allowed as cardiovascular prophylaxis.

s. Patient uses any non-pharmacologic pain management techniques (eg, physical techniques, physiotherapy, massage therapy, acupuncture, biofeedback, and/or psychological support) and is unable or unwilling to discontinue prior to baseline pain assessment.

t. [**Criterion Removed**]

u. Patient uses any topical/cosmetic products (eg, lotions and tanning products) on the skin in the painful region of PHN.

v. Patient has a history of alcohol or drug abuse within 1 year before the screening visit, or a positive urine drug test at the screening visit for cocaine, marijuana, opioids, amphetamines, methamphetamines, benzodiazepines, barbiturates, methadone, and/or tricyclic antidepressants unless explained by the use of prescription medication. (The use of medical marijuana is not permitted and excludes the patient from the study.)

w. Patient is pregnant or breast-feeding at the time of the screening visit.

x. Patient has findings in laboratory data, vital signs measurements, or physical examination at the screening, baseline pain assessment interval, or randomization visit that, in the opinion of the investigator, may pose undue risk to the patient or may interfere with study data interpretation.

y. Patient was previously randomly assigned to treatment in this study and received/subsequently discontinued study drug.

z. Patient used another investigational drug within 30 days or 5 half-lives (whichever is longer) before the planned first day of study drug application (day 1) in this study.

aa. Patient refuses to provide 2 blood samples at the screening visit for pharmacogenomic analyses.

bb. Patient is a study site or Sponsor employee who is directly involved in the study or the relative of such an employee.

cc. There is any other reason that would make the patient, in the opinion of either the investigator or the Sponsor, unsuitable for the study.

4.3. Justification of Key Inclusion and Exclusion Criteria

The inclusion criteria for this study have been selected to identify an appropriate patient population to evaluate the efficacy of topical TV-45070 in PHN. The exclusion criteria have been selected to exclude patients with characteristics that would put them at risk if they participated in the study, and to exclude patients with potentially confounding characteristics that would make data interpretation difficult.

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (and/or with the applicable country's acceptance), each patient is free to withdraw from the study and/or study drug treatment at any time. The investigator also has the right to withdraw a patient from the study and/or study drug treatment in the event of intercurrent illness, adverse events, pregnancy (see Section 7.3.4.1), other reasons concerning the health or well-being of the patient, or lack of cooperation. In addition, a patient may be withdrawn from the study and/or drug treatment as described in Sections 3.9, 3.5, and 7.1.7.

Should a patient decide to withdraw (from either the study or study drug treatment) after starting study drug or should the investigator decide to withdraw the patient at such time, all reasonable efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, and an explanation given as to why the patient is withdrawing or being withdrawn from the study and/or study drug treatment.

The reason for and date of withdrawal from study and/or study drug treatment must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of another health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event(s) or test result(s) must be recorded on the source documentation and transcribed onto the CRF. In addition, a blood sample will be obtained for the measurement of study drug concentrations. The sample date and time will be recorded on the source documentation and transcribed onto the CRF.

An ET visit should be conducted within 2 weeks after the last study drug administration. The activities for the ET visit are described in Section 3.11.3.4. Because premature discontinuations of treatment may occur at any time between randomization and the week 4 visit (visit 5, day 29), patients will be permitted to proceed directly from either visit 3 (day 1, randomization) or visit 4 (day 15 ±1, week 2) to the ET visit. For example, a patient who discontinues study drug on day 20 will have visit 4 (day 15 ±1, week 2) followed by visit 6 (ET) within 2 weeks after day 20 with no visit 5 (day 29, week 4) in between.

Data from any efficacy evaluations performed after the specified time will not be collected on the CRF; in the event, however, if such data are collected, these data will not be analyzed.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.3, respectively.

A patient who is randomly assigned to treatment (enters the double-blind treatment period) but fails to complete the double-blind treatment period will not be replaced. Measures will be taken to increase the recruitment rate, as needed, to ensure that a minimum of 330 patients (110 patients per treatment arm) are randomly assigned to treatment and 264 patients (up to approximately 88 patients per treatment arm) complete the double-blind treatment period and are evaluable for the primary efficacy analysis.

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

At the baseline/randomization visit, eligible patients will be randomly assigned to 1 of 3 treatment groups (4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or placebo ointment) as described in Section 3.4. Blinded study drug will be applied twice daily to the area of PHN pain during the treatment period from days 1 through 28, as described in Sections 3.6 and 3.11.3.

Study drug will be packaged in tubes and provided for patients to apply at home (see Section 3.6). Patients will be instructed to store the tube of ointment at ambient room temperature (15°C to 25°C) at home. Study drug exposure will be measured, and compliance to study drug administration will be monitored. Compliance will be assessed by weighing tubes at visit 3 (baseline), visit 4 (day 15 ±1, week 2), and visit 5 (day 29, week 4) or ET visit. A patient will be considered compliant during the interval between the previous 2 visits if the tube weighs between 70% and 120% of the expected weight.

Each patient will be given an eDiary and instructions on using it to record daily pain (11-point NRS), the date/time of study drug applications, and rescue medication usage. The eDiary will be used to record responses to an 11-point NRS before applying the study drug twice daily. Patients will apply the study drug in the morning after recording the morning responses to the 11-point NRS at 0700 ±2 hours, and in the evening after recording the responses to the 11-point NRS at 1900 ±2 hours.

Patients (and caregivers, as applicable) will receive instructions on how to apply the study drug. Under study site staff supervision, the area affected by PHN pain will be carefully defined by mapping the area of pain, and dosing will be prescribed to fully cover the affected area. Dosing cards and instructions will be provided on how to measure the appropriate amount of ointment for each application. A laminated instruction sheet, including pictures, will describe and illustrate how the ointment is to be spread over the entire area of PHN pain in a thin layer that fully covers the area and gently massaged into the skin.

The first application of study drug will occur at the study site on the day of the randomization visit (visit 3, day 1). The study coordinator or designated site staff member will apply blinded study drug and will define the amount of ointment to be used for all subsequent treatment applications for that patient. Subsequent study drug applications will be performed by the patient at home. (If the affected area is not within reach of application by the patient [such as the posterior thoracic region], the patient's designated caregiver will apply the ointment, but the patient will record the time of application in the eDiary.)

Patients will return to the study site for visit 4 (day 15 ±1, week 2) and again for visit 5 (day 29, week 4). At visit 4, 2 blood samples will be taken from each patient for pharmacokinetic analysis: the first sample taken within approximately 1 to 4 hours after the dose of study drug in the morning and the second sample taken approximately 2 hours after collection of the first sample. Patients will go to the study site after applying study drug at home so that the 2 pharmacokinetic samples can be taken.

At visit 5, the eDiary will be collected along with the tubes of study drug and bottles of rescue medication. Patients will be instructed to return to their primary care physician to resume therapy deemed appropriate for their PHN.

5.2. Restrictions

Patients will be required to comply with the following restrictions with respect to activity:

- After applying ointment, patients should wait for 10 minutes before covering the area with clothing, to allow the ointment to be absorbed by the skin. After the ointment has fully penetrated the skin, the area will be dry.
- After applying ointment, patients must not apply pressure to the area of skin treated with ointment by leaning against surfaces, such as furniture, for 10 minutes, to allow the ointment to be absorbed by the skin. After the ointment has fully penetrated the skin, the area will be dry.

In addition, patients must maintain (hold constant) their current level of physical activity from the baseline visit through the end of treatment (visit 5, day 29, week 4).

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy or medication that a patient has had within 90 days before study drug administration and up to the end of the study period, including follow-up, will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The Sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug).

The following medications will not be allowed during this study:

- Oral analgesics
- Topical analgesics, including lidocaine (gels, creams and patches) and capsaicin patches
- Rescue pain medication except permitted acetaminophen rescue
- Class Ic anti-arrhythmic drugs such as flecainide or propafenone

At each clinic visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than study drug), including OTC medications, vitamins, or herbal or nutritional supplements, since the previous visit. Indication, dosage, and start and end dates should be entered on the CRF.

5.4. Rescue Medications for PHN Pain

Patients will be provided with acetaminophen (TYLENOL, McNeil Consumer Healthcare Division of McNEIL-PPC, Inc) as 325-mg tablets in bottles of 100 tablets and allowed to take 1 to 2 tablets per dose every 6 hours, as needed, and up to 6 tablets or 1950 mg per day (over a 24-hour period) for rescue relief of PHN pain. Rescue medication will be provided at the screening visit. Rescue medication compliance will be checked at all visits until used rescue medication is collected after the baseline pain assessment interval for patients not continuing in

the study, at visit 5 (day 29, week 4) for patients who complete the treatment period, or at the ET visit for patients who prematurely discontinue study drug.

No other rescue medications will be provided or allowed from the washout phone contact through visit 5 (day 29, week 4) or the ET visit. Patients will not be permitted to use rescue medication during the baseline pain assessment interval (days –10 through –1) and during the final week of treatment (the 7-day period before visit 5). During the washout interval, rescue medication use (dates of use and dose taken) will be recorded as concomitant medication. During baseline and the treatment period, rescue medication use will be recorded using the eDiary.

5.5. Procedures for Monitoring Patient Compliance

Each investigator or designee will be responsible for monitoring patient compliance. Study drug exposure will be measured, and compliance to study drug administration will be monitored by weighing the tubes of blinded study drug at the week 2 (visit 4, day 15 ±1) and week 4 (visit 5, day 29) or ET visits. (At visit 3, the tubes will be weighed to obtain a baseline weight.) A patient will be considered compliant during the interval between the previous 2 visits if the tube weighs between 70% and 120% of the expected weight. Also, study drug accountability records will be completed. Patients will not be discontinued for noncompliance at week 2 (visit 4, day 15 ±1); however, they will be retrained in proper medication dispensing.

5.6. Total Blood Volume

The total amount of blood drawn during the study from each patient will be approximately 50 mL.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Variable

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 daily morning and evening patient-reported measurements) of average pain intensity over the prior 12 hours.

The NRS is a widely-used, standard one-dimensional scale from 0 to 10 for patient self-reporting of pain.

6.2. Secondary Efficacy Variables

The secondary efficacy endpoints, including those defined using the NePIQoL, DSIS, NPSI, and PGIC, are listed in Section 3.3.2.

6.3. Exploratory Efficacy Variables

The exploratory efficacy endpoints are described in Section 3.3.3.

6.4. Methods and Timing of Assessing, Recording, and Analyzing Efficacy and Clinical Pharmacology Data

Methods for assessing efficacy data are described in Section 3.3. Methods for obtaining samples for pharmacokinetic analyses are described in Section 3.3.6. Methods for obtaining samples for pharmacogenomic analyses are described in Section 3.3.8. Timing of assessing efficacy, pharmacokinetic, and pharmacogenomic data are discussed in Section 3.11. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses of the efficacy data are discussed in Section 9.6. Procedures for obtaining pharmacokinetic and pharmacogenomic assay results and analyzing the data are described in separate documents. The population pharmacokinetic analyses results (including analyses of the effects of allelic variants of CYP3A4 and/or CYP2C19, if performed) will be reported separately from the main study results.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study staff by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight measurements), dermal irritation findings, and concomitant medication usage.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

In this study, any adverse event occurring after the clinical study patient has signed the ICF should be recorded and reported as an adverse event. Any adverse event occurring after the first application of study drug is considered a treatment-emergent adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered adverse events.

Worsening of the disease under study will be measured by increased PHN pain scores. Worsening of PHN should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

Accordingly, an adverse event can include any of the following:

- Intercurrent illnesses.
- Physical injuries.
- Events possibly related to concomitant medication.
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. Note: A condition recorded as pre-existing that is intermittently symptomatic (eg, headache) and that occurs during the study should be recorded as an adverse event.
- Drug interactions.
- Events occurring during diagnostic procedures or during any washout phase of the study.
- Laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work-up, or are considered

by the investigator to be clinically significant. Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events but will be evaluated to monitor data from patients who do not meet screening criteria.

- All events of possible drug-induced liver injury with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN] plus either bilirubin ≥2 times the ULN or International Normalized Ratio [INR] >1.5) or Hy's Law events require immediate study treatment cessation and reporting as a serious adverse event.

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the ICF through the end of the follow-up period. For this study, the follow-up period ends with the day 57 (±3) follow-up visit (visit 6) or ET visit, or it ends when a patient is confirmed as lost to follow-up. A patient is confirmed as lost to follow-up after all reasonable efforts to locate the patient have failed.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed, and the serious adverse event must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a patient after the follow-up period should be reported to the Sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open-ended question such as "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates and times, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- Death.

- A life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions).
- A congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in reference safety information for topical TV-45070 by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is located in the TV-45070 Investigator's Brochure.

The Sponsor's Global Patient Safety & Pharmacovigilance Department will determine the expectedness for all serious adverse events.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period), regardless of judged relationship to treatment with the study drug, must be reported to the Sponsor by the investigator within 24 hours when the investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day. Completing the Serious Adverse Event Form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor subjects for adverse events once the study has ended. Serious adverse events occurring to a patient after the follow-up period should be reported to the Sponsor if the investigator becomes aware of them.

The Serious Adverse Event Form should be sent to the Sponsor's local safety officer (LSO); for this study, the LSO is the Teva USA Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- study number (Study TV45070-CNS-20013)
- investigator and study site identification
- patient number
- onset date and description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of the patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the Sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the study site within 24 hours when it becomes known to the same address as the initial report.

The LSO will be responsible for submission of the MedWatch form 3500/Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the regulatory authorities. In EU countries, the LSO will distribute for local submission to International Ethics Committees (IECs)/IRBs and investigators according to regulations. In non-EU countries, serious adverse events will be reported by the Sponsor or designee (contract research

organization [CRO]) to investigators. The investigators should report the serious adverse events to their local IRB as dictated by their board's policies and procedures.

The study drug blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a suspected unexpected serious adverse reaction (SUSAR), only the LSO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the Sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TV-45070 and the appropriate regulatory authorities.

In addition to notifying the investigators and regulatory authorities, other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to TV-45070

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting were identified for this study.

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from study drug treatment at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and the termination page of the CRF will be completed at that time. If possible, a blood sample will be obtained for the measurement of study drug concentrations.

The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the CPP/CL as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from study drug treatment and/or the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that, in the opinion of the investigator, is not severe enough to warrant

discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

7.1.8. Medical Emergencies

Medical emergencies must be reported to the individual identified in the Clinical Study Personnel Contact Information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an adverse event requiring immediate treatment. Any dose of study drug (whether the investigational product, reference therapy, or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the Sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.5.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the Sponsor, will decide whether the patient should continue to participate in the study. Any departures from the protocol because of adverse events must be noted on the CRF and in source documents, along with the reason for such departures.

7.2. Pregnancy

All pregnancies (pregnancies of women participating in the study and female partners of men participating in the study) that occur during the study, or within 30 days of completion of the study, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO with the Clinical Trial pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.1.5.3).

Any patient becoming pregnant during the study will be withdrawn from study drug treatment. All patients (or female partners of male patients) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications will be reported to the Sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.

- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

Clinical laboratory tests (serum chemistry and hematology) and urinalysis will be performed at the time points indicated in Table 1. The clinical laboratory tests will be performed using a central laboratory, with more details provided in the Laboratory Procedures Manual for this study. The urinalysis will be done macroscopically at the study site with a dipstick provided by the central laboratory. If any portion of the dipstick is positive, the urine sample will be sent to the central laboratory for microscopic evaluation. The dipstick results will be recorded in the CRF. Specific laboratory tests to be performed are listed below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- potassium
- chloride
- bicarbonate or carbon dioxide
- glucose
- blood urea nitrogen (BUN)
- creatinine
- cholesterol
- uric acid
- ALT
- AST

- lactic dehydrogenase (LDH)
- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase
- creatine phosphokinase
- total protein
- albumin
- total bilirubin
- direct bilirubin
- indirect bilirubin

7.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- platelet count
- absolute neutrophil count
- white blood cell (WBC) count and differential count
  - polymorphonuclear leukocytes (neutrophils)
  - lymphocytes
  - eosinophils
  - monocytes
  - basophils
  - atypical lymphocytes

7.3.3. Urinalysis

Urinalysis will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity

- microscopic, as needed
  - bacteria
  - RBCs
  - WBCs
  - casts
  - crystals

7.3.4. Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the patients but will not be used to assess the safety of the study drug.

7.3.4.1. Pregnancy Tests

Urine pregnancy tests will be performed at the study site (with test kits provided by a central laboratory) for all women of child-bearing potential at screening (visit 1), randomization (visit 3, day 1), visit 4 (day 15 ±1, week 2), visit 5 (day 29, week 4), and at the follow-up/ET visit (visit 6, day 57 ±3). Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.3.4.2. Urine Drug Screen

A urine drug screen will be performed at the time points indicated in Table 1. The urine drug screen includes a means to detect the presence of drugs prohibited according to the protocol, including cannabinoids, cocaine, amphetamines, barbiturates, benzodiazepine, and opiates. If a parameter noted above cannot be tested using urine, an alternative matrix (eg, serum) may be considered acceptable. The Sponsor's medical expert must be made aware in advance of, and provide approval for, drug screen parameters to which this will apply. A positive result for any of the above drugs or their metabolites, without medical explanation, will preclude the patient from enrollment or continued participation in the study.

7.4. Vital Signs

Vital signs will be measured at the time points indicated in Table 1. Vital signs include the following:

- heart rate
- respiration rate
- body temperature
- blood pressure

Before pulse and blood pressure are measured, the patient must be in a supine or seated position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse

event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.5. Electrocardiography

A 12-lead ECG will be conducted as triplicate tracings taken at least 1 minute apart (with an upper limit of 5 minutes apart) at the time points indicated in Table 1. To determine eligibility based upon numerical exclusion criteria of cardiac intervals, the investigator will use the mean values of 3 ECGs. A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. Any ECG finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.6. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight (screening and follow-up/ET visits only) will be performed at the time points indicated in Table 1. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.7. Other Safety Measures and Variables: Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3.

7.8. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

Methods and timing of assessing safety data are discussed in Section 3.11. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.8.2.

7.9. Dermal Irritation Evaluation

Dermal irritation will be evaluated at the time points indicated in Table 1 using the scale below (FDA 1999):

- 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 test site

8. ASSESSMENT OF PHARMACOKINETICS / PHARMACODYNAMICS / PHARMACOGENOMICS

8.1. Pharmacokinetic Variables

Samples (plasma) will be analyzed for TV-45070 using an appropriate validated method.

The dates and times of study drug administration and the date and time of each pharmacokinetic sample must be well documented on the source documentation and transcribed onto the CRF.

Samples will be collected into K_2EDTA VACUTAINER® (Becton, Dickinson and Company) tubes, inverted slowly 6 to 8 times to mix the contents, and placed on ice (0°C to 5°C). Blood samples will be centrifuged (1500 × g, approximately 10 minutes, 0°C to 5°C) within 1 hour after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. As needed, other measures should be taken to prevent samples from heating significantly during centrifugation. Separated plasma will be transferred in approximately equal portions into 2 opaque, labeled, polypropylene tubes (sets A and B).

Sample labels should include the study number, patient identification number, visit number, nominal collection time, set (A or B), and indication that they are pharmacokinetic samples. Plasma samples will be placed on ice (0°C to 5°C) in an upright position until they are frozen at –70°C within 1 hour of centrifugation.

Plasma samples for all patients will be shipped from the study site to the central laboratory upon the Sponsor's request and will be shipped in batch shipments to the central laboratory designated in the Study Laboratory Manual. Samples will be stored in an upright position at -70°C until assayed. The laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped.

Set A samples will be transported, frozen with sufficient dry ice for 4 days, by next day courier to Teva Pharmaceutical Works P.Ltd.Co. as described in the Study Laboratory Manual.

Set B samples will be shipped and stored as described in the Study Laboratory Manual.

Sample shipments should be sent no later in the week than Wednesday morning for next day delivery. Samples are not to arrive on the weekend.

Further details for sample collecting, handling, shipping, and storage are provided in the Study Laboratory Manual.

8.2. Pharmacodynamic Variables

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

8.3. Pharmacogenomic Variables

It is recognized that genomic variation within the population can be an important contributory factor to inter-individual differences in drug response. Pharmacogenomic analyses investigate

the association between genetic sequence polymorphisms and/or gene expression signatures and clinical response to a certain therapeutic intervention. Pharmacogenomic results may help explain inter-individual variability and subsequently identify population subgroups that respond differently to the drug. Furthermore, regulatory guidance and white papers indicate that pharmacogenomic analyses employing DNA collected from all study participants may support investigation of unexpected adverse events.

The objectives of the pharmacogenomic analyses in this study are as follows:

- To genotype the underlying R1150W polymorphism in the *SCN9A* gene so as to stratify patients according to R1150W polymorphism status (homozygous minor allele [positive, AA], heterozygous [positive, AG], and homozygous common allele [negative, GG]) in the randomization
- [redacted]
- To genotype polymorphisms of the *CYP3A4* and *CYP2C19* genes as potential covariates in the population pharmacokinetic analysis

Individual patients will be genotyped for the R1150W polymorphism for randomization allocation purposes. Pharmacogenomic samples will be stored for a period of up to 15 years after the last patient last visit in the study and then destroyed. [redacted]

Pharmacogenomic assessment will be performed using blood samples of 12 mL total volume, collected in 2 K_3EDTA Vacutainer plastic tubes for pharmacogenomic analysis (1 sample will be used for the R1150W randomization test and the other for further pharmacogenomic analyses). Pharmacogenomic samples will be collected from all patients at the screening visit (visit 1) because randomization will be stratified based on R1150W polymorphism status. The samples may also be examined for other sequence variations in the *SCN9A* gene region and/or other genes. [redacted] A patient's refusal to have this blood sample taken will exclude him/her from participation in this study.

Pharmacogenomic samples will be sent to the central laboratory within 72 hours after collection. Further details for sample collecting, handling, shipping, and storage will be provided in the Study Laboratory Manual.

The R1150W polymorphism test will be done at the central laboratory, a Clinical Laboratory Improvement Amendments-certified laboratory, and the exact genotyping assay will be selected in discussion with the laboratory staff. The laboratory for the testing of other genetic variations will be selected after the start of this study (TV45070-CNS-20013) and will be performed if and when required. The laboratory for these other analyses will be selected according to the nature of the analyses.

9. STATISTICS

9.1. Study Design and Randomization

This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of TV-45070 treatment in patients with PHN. Patients will be randomly assigned to receive treatment with 4% w/w TV-45070 ointment, 8% w/w TV-45070 ointment, or matching placebo ointment in a 1:1:1 ratio. Randomization will be as described in Section 3.4.

9.2. 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 (Rice et al 2001) to 1.3 (Dworkin et al 2003). For this decision-making, proof-of-concept study, it is reasonable to use a conservative estimate of 1.0. If we assume 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. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.

9.3. Analysis Sets/Populations

9.3.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

9.3.2. Safety Population

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

9.3.3. Full Analysis Set

The full analysis set (FAS), defined as all patients in the ITT population (all patients randomly assigned to 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.

9.3.4. Per Protocol Population

The PP population will include all subjects in the FAS who have not had major protocol deviations (ie, protocol violations). Protocol violations will be determined before unblinding. The PP Population will serve as the supportive population for efficacy analyses.

9.3.5. Additional Analysis Sets

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.

9.4. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the by-visit summaries. Data imputation rule(s) will be detailed in the Statistical Analysis Plan.

9.5. Study Population

The ITT population (see Section 9.3.1) will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients.

9.5.1. Patient Disposition

Data from patients screened, patients screened but not randomized and reason not randomized, patients who are randomized/enrolled, patients randomized/enrolled but not treated (and reason), patients in the safety set and FAS, 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 study will also be summarized by reason for withdrawal using descriptive statistics.

9.5.2. Demographic 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. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, 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.

The categorical variables of patient sex and race will be summarized using descriptive statistics for each variable category. Missing categories will be presented if necessary. Treatment groups will be compared for all categorical variables using a Pearson's chi-square (or Fisher's exact test if cell sizes are too small).

9.6. Efficacy Analysis

The primary, secondary, and exploratory efficacy variables and endpoints are described in Section 3.3.

9.6.1. Planned Method of Analysis

The FAS (see Section 9.3.3) will serve as the primary analysis set for all efficacy analyses. The PP population will be the supportive population for efficacy analyses.

9.6.1.1. Primary Efficacy Analysis

The primary efficacy variable, change from baseline to week 4 in the weekly average of the daily average NRS scores, 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 2 and

4 as the dependent variable; visit in weeks, treatment, and treatment by visit interaction as fixed factors; baseline weekly average of the daily average NRS scores as covariate; and patient as random effect. The unstructured covariance matrix for repeated observations within patients will be used. The primary treatment comparison will be conducted at week 4 in this model. All tests will be 2-sided at a significance level of 0.05. More details will be provided in the Statistical Analysis Plan.

9.6.1.2. Sensitivity Analysis

Sensitivity analysis on the primary efficacy variable, while taking discontinuation reason and rescue medication usage into consideration, may be performed.

9.6.1.3. Secondary Efficacy Analysis

The continuous secondary efficacy variables will be analyzed in a similar way as the primary efficacy variable.

The percentages of patients with ≥30% and ≥50% improvement from baseline in weekly average NRS scores at week 4 will be summarized using descriptive statistics. The time to reach ≥30% improvement in weekly average NRS scores from baseline will also be summarized using descriptive statistics.

PGIC scores will be analyzed using a MMRM model with 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.

NePIQoL score will be analyzed using an analysis of covariance (ANCOVA) model with effects due to baseline and treatment, imputing missing data via last observation carried forward (LOCF).

9.6.1.4. Exploratory Efficacy Analysis

9.7. Multiple Comparisons and Multiplicity

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

9.8. Safety Variables and Analysis

9.8.1. Safety Variables

The overall safety and tolerability of topical TV-45070 (4% and 8% w/w ointment) treatment will be assessed throughout the study by evaluating adverse events and the following additional safety variables at the time points specified in Section 3.11:

- clinical laboratory tests
- vital signs
- physical examination
- dermal irritation
- 12-lead ECGs
- concomitant therapy or medication usage

9.8.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (ie, reasonable possibility; see Section 7.1.4) (adverse events defined as related or with missing relationship will be summarized overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

9.9. Pharmacokinetic Analysis

The population pharmacokinetic analyses will be detailed in a population pharmacokinetic analysis plan for this study. Results will be reported separately from the main study results.

9.10. Pharmacodynamic Analysis

The pharmacodynamic analysis plan will be detailed in the Statistical Analysis Plan for this study. Exploratory analyses may be reported separately from the main study results.

9.11. Pharmacogenomic Analysis

The objectives of the pharmacogenomic analyses in this study are provided in Section 8.3. Exploratory analyses may be reported separately from the main study results.

9.12. Planned Interim Analysis

No interim analysis is planned for this study.

9.13. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report (CSR), or any combination of these, as appropriate, and in accordance with applicable local and regional requirements and regulations.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol required worksheets, and CRFs that are used as the source (see Section 3.10).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IRB, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator and the Sponsor will sign the protocol amendment.

11.1.2. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Important protocol deviations, referred to as protocol violations, are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Protocol violations include enrolling patients in violation of key eligibility criteria designed to ensure a specific subject population; failing to collect data necessary to interpret primary endpoints; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients or compromise the scientific value of the trial. Protocol violations will be identified and recorded by study site personnel on the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the Sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical representative. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are **not** prospectively granted by the Sponsor. If study site personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the Sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded. If such patient is still participating in the study, a determination will be made by the sponsor and the investigator as to whether it is in the best interest of the patient to continue in the study.

11.2. Information to Study Personnel

Each investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). Each investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study site

authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including each investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the ICF and the study is conducted according to applicable standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the Sponsor and each investigator. The main responsibilities of the study monitor are to visit each investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact each investigator and visit the study site at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, to include specific electronic source documentation [see Section 3.10]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification (SDV) flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other Sponsor personnel may, on request, accompany the study monitor on visits to the study site. Each investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components
- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)

- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated odor

Each study site will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed from the Study Site

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- study site number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, container, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling the Study Drug at the Study Site

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the study site must return all of the study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event, the protocol should be followed.

11.4.4. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the study site where the complaint originated or to all study sites using the product.

11.5. Audit and Inspection

The Sponsor may audit the study site to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The Sponsor Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) a study site audit.

Each investigator must accept that regulatory authorities and Sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

Details of compliance with regulatory guidances and applicable laws are provided in Section 1.6.

12.1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documentation.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The patient's willingness to participate in the study will be documented in a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

12.2. Health Authorities and Institutional Review Boards

Before this study starts, the protocol will be submitted to the FDA and to each IRB for review. As required, the study will not start at a given study site before the IRB and health authority (where applicable) for the study site give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

Each investigator must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, patients will be identified not by their names, but by an identification code (eg, identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the Sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

The end of this clinical study is defined as the date of the last visit of the last study patient.

12.5. Registration of the Clinical Study

This clinical study was registered on clinical trials registry websites according to Teva standard procedures.

13. DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the study site by appropriately designated and trained personnel, and CRFs must be completed for each screened patient who provided informed consent according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the study site. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, and eDiary data), the results will be sent to the study site. At the study site, the data will be retained but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the Sponsor (or organization performing data management) for direct entry into the clinical database (see Section 3.10). Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigator(s).

For patients who enter a study but do not meet screening criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.2. Data Quality Assurance

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a data management plan.

The CRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see Section 3.10], data results from other sources [see Section 13.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed ICFs, and other essential documents) must be retained until the Sponsor notifies the institution, in writing, that records may be destroyed.

If the Sponsor has not provided written notification of records destruction after 15 years from study completion (or earlier in the event of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the Sponsor at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the Sponsor and the investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the Sponsor.

13.3.2. Sponsor Responsibilities

The Sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the Sponsor's SOPs for clinical studies.

If data management and filing of documents for this study are delegated to a contract organization, these functions will be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the Sponsor before the start of data management and filing activities. The original CRFs will be archived by the Sponsor. Site-specific CRFs will be provided to the respective study sites for archiving.

14. FINANCING AND INSURANCE

A separate financial agreement will be made between each principal investigator and the Sponsor before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the study sites by the Sponsor.

For covered clinical studies (see 21CFR54), each investigator will provide the Sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the Sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. REPORTING AND PUBLICATION OF RESULTS

The Sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration and posting of results.

The Sponsor is responsible for preparing a CSR, in cooperation with the principal investigator. The final report is signed by the Sponsor and, if applicable, by the principal investigator.

When the Sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the principal investigator for comments and suggestions. An endorsement of the final report will be sought from the principal investigator.

All unpublished information given to any investigator by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor. The primary publication from this study will report the results of the study in accordance with the current "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the Sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent application(s) based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the Sponsor.

16. REFERENCES

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Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP, et al. Pain perception is altered by a nucleotide polymorphism in *SCN9A*. Proc Natl Acad Sci USA 2010;107(11):5148-53.

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 03 Dated 21 April 2016

The primary reason for amendment 03 is to facilitate timely enrollment of patients by broadening the inclusion criterion for the maximum duration of PHN and the exclusion criterion for the number of adequate courses of treatment with other medications for which response was inadequate; by allowing rescreening of patients excluded under these criteria before implementation of amendment 03; and by increasing the number of study sites. These changes are not anticipated to affect potential risks to patients or the statistical power of the study.

Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Personnel Contact Information		
[redacted] INC Research, LLC Role in the Study: Project Manager [redacted]	[redacted] INC Research, LLC Role in the Study: Project Manager [redacted]	This revision reflects a change in contact information for operational support at INC Research LLC
Synopsis: Number of Study Sites Planned		
Up to approximately ~~55~~**70** study sites	Up to approximately 70 study sites	The number of study sites was increased to improve the timely enrollment of patients.
Synopsis: Planned Study Period:		
March 2015 (first patient randomly assigned to treatment) to ~~the third quarter of~~ late 2016 up to mid 2017 (last patient last visit)	March 2015 (first patient randomly assigned to treatment) to late 2016 up to mid 2017 (last patient last visit)	The planned study period was extended to allow recruitment of the needed number of patients.
Synopsis: Diagnosis and Criteria for Inclusion		
a. **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than ~~6~~**10** years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	**a.** **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than 10 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	This criterion was broadened to improve the timely enrollment of patients.
Synopsis: Exclusion criteria		
c. **[Revision 1]** Patient has a history, in the judgment of the investigator, of inadequate response to more than ~~2~~**3** adequate courses of treatment with other medications used to treat neuropathic pain (eg,	a. **[Revision 1]** Patient has a history, in the judgment of the investigator, of inadequate response to more than 3 adequate courses of treatment with other medications used to treat	This criterion was broadened to improve the timely enrollment of patients.

Original text with changes shown	New wording	Reason/Justification for change
tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	neuropathic pain (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	

Original text with changes shown	New wording	Reason/Justification for change
Synopsis: Sample Size Rationale		
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 (Rice et al 2001) to 1.3 (Dworkin et al 2003). For this decision-making, proof-of-concept study, it is reasonable to use a conservative estimate of 1.0. If we assume a standard deviation of 2.35, a sample size of up to approximately 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. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.	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 (Rice et al 2001) to 1.3 (Dworkin et al 2003). For this decision-making, proof-of-concept study, it is reasonable to use a conservative estimate of 1.0. If we assume a standard deviation of 2.35, a sample size of up to approximately 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. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.	
No previous text	**Amendment 03:** The primary reason for amendment 03 is to facilitate timely enrollment of patients by broadening the inclusion criterion for the maximum duration of PHN and the exclusion criterion for the number of adequate courses of treatment with other medications for which response was inadequate; by allowing rescreening of patients excluded under these criteria before implementation of amendment 03; and by increasing the number of study sites.	The justification for amendment 03 has been added.
Section 1.8.		
The study is expected to start in March 2015 (first patient randomly assigned to treatment) and be completed in ~~the third quarter of~~late 2016 up to mid	The study is expected to start in March 2015 (first patient randomly assigned to treatment) and be completed in late 2016 up to mid 2017 (last patient	The planned study period was extended to allow recruitment of the needed number of patients.

Original text with changes shown	New wording	Reason/Justification for change
2017 (last patient last visit), with a duration of approximately 14 to 22 months.	last visit), with a duration of approximately 14 to 22 months.	
Approximately 330 patients from up to approximately ~~55~~**70** study sites are planned to be enrolled in this study. The study is planned to be conducted in the US.	Approximately 330 patients from up to approximately 70 study sites are planned to be enrolled in this study. The study is planned to be conducted in the US.	The number of study sites was increased to improve the timely enrollment of patients.
Section 3.11.1.1.		
A patient who is screened and does not meet study entry criteria will not be considered for screening again, except that patients who were excluded from enrollment under inclusion or exclusion criteria that have since been revised may be rescreened to determine their eligibility under these criteria as amended.	A patient who is screened and does not meet study entry criteria will not be considered for screening again, except that patients who were excluded from enrollment under inclusion or exclusion criteria that have since been revised may be rescreened to determine their eligibility under these criteria as amended.	Text was added to allow the rescreening of patients excluded under inclusion or exclusion criteria that have since been revised.
Section 4.1.		
a. **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than ~~6~~10 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	a. **[Revision 1]** Patient has chronic PHN, defined as pain present for more than 6 months and less than 10 years after onset of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. Patients excluded under this criterion before implementation of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	This criterion was broadened to improve the timely enrollment of patients.
Section 4.2.		
c. [Revision 1] Patient has a history, in the judgment of the investigator, of inadequate response to more than ~~2~~**3** adequate courses of treatment with other medications used to treat neuropathic pain (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation	**c. [Revision 1]** Patient has a history, in the judgment of the investigator, of inadequate response to more than 3 adequate courses of treatment with other medications used to treat neuropathic pain (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical lidocaine, and/or topical capsaicin). Patients excluded under this criterion before implementation	This criterion was broadened to improve the timely enrollment of patients.

Original text with changes shown	New wording	Reason/Justification for change
of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	of Amendment 03 may be rescreened to determine eligibility under the revised criterion.	
9.2 Sample Size and Power Considerations		
Assuming an approximately 20% dropout rate, 110 patients per arm (a total of 330 patients) will be randomly assigned to each treatment group. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.	Assuming an approximately 20% dropout rate, 110 patients per arm (a total of 330 patients) will be randomly assigned to each treatment group. During the study, the ultimate sample size may be adjusted on the basis of the actual dropout rate.	

17.2. Administrative Letter Dated 28 September 2015

September 28, 2015

RE: 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

Subject: Update to Operational Contact

The purpose of this administrative letter is to communicate a change in the Operational Contact for this study.

The Operational Contact is:

[redacted]
INC Research, LLC
Role in the Study: Project Manger
[redacted]

Please file this correspondence with your protocol in your Regulatory Binder.

Sincerely,

[redacted]

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | [redacted] | www.tevapharm.com

17.3. Amendment 02 Dated 09 September 2015

The primary reason for amendment 02 is to remove the stipulation in exclusion criterion t that excludes patients from participating in the study if they used any of the CYP3A4 or CYP2C19 inhibitors or substrates that were previously listed in Table 2 under Appendix A to this protocol. Related editorial changes have been made are as a result of this removal, including 1) replacement of the previous Table 2 (CYP3A4 and CYP2C19 Substrates and Inhibitors with Documented Clinically Significant Interactions) in Appendix A with a new Table 2 entitled Washout Periods for Specific Drugs, and 2) revision of any statement(s) and cross-references within the protocol referring to information previously provided in Table 2 of Appendix A.

An additional reason for amendment 02 is to revise inclusion criterion d to broaden the recruitment criterion for BMI by increasing the upper limit of the range for BMI from 32 to 34 kg/m2.

Amendment 02 also serves to correct the list of drugs as described in Section 7.3.4.2 that are detected by the urine drug screen performed to detect the presence of drugs prohibited by protocol. Alcohol was incorrectly listed in Section 7.3.4.2 as a substance detected by the drug screen, and has been deleted from Section 7.3.4.2 as part of this amendment.

Time windows have been added for the timing of the dermal irritation test and for the triplicate ECGs to allow for natural variability in timing and to avoid unnecessary protocol deviations.

Minor editorial changes for improved text flow and clarity have been incorporated into the protocol text as part of this amendment.

Finally, the protocol is now presented in an updated protocol template maintained by the Sponsor. The change to an updated template is an administrative change per Sponsor policy, and is not intended to alter the clinical conduct of the study.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.1.		
TV-45070 is a novel, potent, voltage-dependent sodium channel (Na_V) blocker being developed for the treatment of patients with various neuropathic pain indications~~, including neuropathic and nociceptive pain.~~	TV-45070 is a novel, potent, voltage-dependent sodium channel (Na_V) blocker being developed for the treatment of patients with various neuropathic pain indications.	This change was made as an update.
Section 1.3.2.		
Additionally, ~~evaluation of~~ topical TV-45070 has been evaluated ~~is currently underway~~ in a Phase 2 study in patients with osteoarthritis (OA) of the knee, ~~and in~~ a Phase 1 dose-escalation study in healthy volunteers, and a Phase 1 DDI study with midazolam and omeprazole. Final data are not yet available from these ~~ongoing~~ studies.	Additionally, topical TV-45070 has been evaluated in a Phase 2 study in patients with osteoarthritis (OA) of the knee, a Phase 1 dose-escalation study in healthy volunteers, and a Phase 1 drug-drug interaction study with midazolam and omeprazole. Final data are not yet available from these studies.	This change was made as an update.
The clinical conduct of ~~all studies except for~~ the ~~ongoing~~ OA study, ~~and~~ the ~~ongoing~~ dose-escalation study, and the DDI study have been completed, but analysis is ongoing.	The clinical conduct of the OA study, the dose-escalation study, and the DDI study have been completed, but analysis is ongoing	This change was made as an update.
Section 1.4., 1.4.1., 1.4.2.		
1.4. Known and Potential Risks and Benefits to Human Subjects 1.4.1. Risks of TV-45070 Following topical administration, […] 1.4.2. Benefits of TV-45070	1.4. Known and Potential Risks and Benefits to Human Subjects 1.4.1. Risks of TV-45070 Following topical administration, […] 1.4.2. Benefits of TV-45070	This change is shown as representative of a change based on presentation of the protocol in the updated template.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.4.1.		
In vitro data using human cryopreserved hepatocytes have also shown that TV 45070 metabolite (M3) is an inhibitor of CYP3A4 and CYP2C19, which indicates a potential DDI risk between TV 45070 and medications that are primarily metabolized by CYP3A4 or CYP2C19. However, the preliminary results of a clinical study designed to assess the risk of these DDIs revealed no significant risk of an interaction. ~~Therefore, certain medications that undergo major metabolism by CYP3A4 and CYP2C19 are excluded as concomitant medications during this study (Appendix A, Table 2).~~	In vitro data using human cryopreserved hepatocytes have also shown that TV 45070 metabolite (M3) is an inhibitor of CYP3A4 and CYP2C19, which indicates a potential DDI risk between TV 45070 and medications that are primarily metabolized by CYP3A4 or CYP2C19. However, the preliminary results of a clinical study designed to assess the risk of these DDIs revealed no significant risk of an interaction.	The rationale for this change is that new data from a clinical study designed to assess the risk of DDI between TV-45070 and medications that are primarily metabolized by CYP3A4 and CYP2C19 revealed no significant risk of an interaction.
Section 2.2., 2.2.1.		
2.2. Study Objectives 2.2.1. Primary Objective The primary objective of this study is to […]	2.2. Study Objectives 2.2.1. Primary Objective The primary objective of this study is to […]	This change is shown as representative of a change based on presentation of the protocol in the updated template (heading added).

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1. (and others, for consistency)		
Appendix A~~3~~, ~~Table 3~~Table 2	Appendix A, Table 2	This change was made as an update and correction to Appendix numbering, and an update to Table numbering related to the exclusion criterion being removed from the protocol
Section 3.3.4. (and others for consistency)		
Skin rashes or skin irritation in the area of ointment application will be evaluated using a dermal irritation evaluation (modified Draize scale) at day 1 (at 1 hour [±30 minutes] after application of study drug), week 2, week 4, and week 8 for follow-up.	Skin rashes or skin irritation in the area of ointment application will be evaluated using a dermal irritation evaluation (modified Draize scale) at day 1 (at 1 hour [±30 minutes] after application of study drug), week 2, week 4, and week 8 for follow-up.	This change was made to allow for natural variability in timing and to avoid unnecessary protocol deviations.
Section 4.1.		
d. Patient is ≥18 years of age, with a body mass index (BMI) between 18 and ~~32~~34 kg/m2, inclusive, at screening visit.	d. [**Revision 1]** Patient is ≥18 years of age, with a body mass index (BMI) between 18 and 34 kg/m2, inclusive, at screening visit.	This update was made to broaden the recruitment criteria.
Section 4.2. and synopsis		
s. Patient uses any non-pharmacologic pain management techniques […] t. [Criterion removed]~~ Patient uses any CYP3A4 or CYP2C19 inhibitors or substrates listed in Appendix B.~~	s. Patient uses any non-pharmacologic pain management techniques […] t. [**Criterion removed**]	Criteria t was removed as new data demonstrate that TV-45070 does not interact with CYP3A4 and CYP2C19 and therefore medications metabolized via these pathways no longer need to be excluded for safety reasons.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.5.1.		
Inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event or that they occurred as a consequence of the event.	Inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event or that they occurred as a consequence of the event.	This change is shown as representative of a minor editorial change for clarity.
Section 7.3.4.2.		
A urine drug screen will be performed at the time points indicated in Table 1. The urine drug screen includes a means to detect the presence of drugs prohibited according to the protocol, including cannabinoids, ~~alcohol,~~ cocaine, amphetamines, barbiturates, benzodiazepine, and opiates.	A urine drug screen will be performed at the time points indicated in Table 1. The urine drug screen includes a means to detect the presence of drugs prohibited according to the protocol, including cannabinoids, cocaine, amphetamines, barbiturates, benzodiazepine, and opiates.	This change was made as a correction to the list of substances detected by the urine drug screen.
Section 7.5; 3.11.1; 3.11.2; 311.3.2; 311.3.3; 311.3.4 and Table 1 (footnote l)		
A 12-lead ECG will be conducted as triplicate tracings taken at least 1 minute apart (with an upper limit of 5 minutes apart) at the time points indicated in Table 1.	A 12-lead ECG will be conducted as triplicate tracings taken at least 1 minute apart (with an upper limit of 5 minutes apart) at the time points indicated in Table 1.	This change was made to allow for natural variability in timing and to avoid unnecessary protocol deviations.

17.4. Amendment 01 Dated 18 February 2015

The primary reason for this amendment is to update the name and contact numbers and email address for the Medical Monitor to the correct information. Additional reasons are to update the protocol wording to reflect the planned location of study sites in one country (the United States), and to correct a typographical error in the corporate name of the CRO providing monitoring and other services for Study TV45070-CNS-20013.

The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are not considered substantial by the Teva Authorized Representative.

Original text with changes shown	**New wording**	**Reason/ Justification for change**
TITLE PAGE		
Monitor INC Research, LL~~P~~C	**Monitor** INC Research, LLC	Correcting typographical error in CRO name
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
For medical issues, contact the physician listed below: [redacted] INC Research, LL~~P~~C Role in the Study: Medical Monitor [redacted] INC Emergency Hotline: [redacted] **For operational issues, contact the operational lead listed below:** [redacted] INC Research, LL~~P~~C Role in the Study: Project Manager [redacted]	**For medical issues, contact the physician listed below:** [redacted] INC Research, LLC Role in the Study: Medical Monitor [redacted] INC Emergency Hotline: [redacted] **For operational issues, contact the operational lead listed below:** [redacted] INC Research, LLC Role in the Study: Project Manager [redacted]	Updating name and contact information for Medical Monitor Correcting typographical error in CRO name

Original text with changes shown	New wording	Reason/ Justification for change
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
For serious adverse events: The serious adverse event form should be sent to the Sponsor's local safety officer (LSO). The LSO will forward the report to the Sponsor's Global Patient Safety & Pharmacovigilance Department. For this study, the e mail address for the USA LSO is [redacted] ([redacted]). ~~The e-mail address for the LSO in Canada is:~~ [redacted]~~:~~ In the event of difficulty transmitting the form, contact the Sponsor's study personnel identified above for further instruction.	**For serious adverse events:** The serious adverse event form should be sent to the Sponsor's local safety officer (LSO). The LSO will forward the report to the Sponsor's Global Patient Safety & Pharmacovigilance Department. For this study, the e-mail address for the USA LSO is: [redacted] ([redacted]). In the event of difficulty transmitting the form, contact the Sponsor's study personnel identified above for further instruction.	Deleting reference to Canada since study sites will not be located in Canada, but in the United States only (based on a site feasibility search that revealed insufficient numbers of patients with post-herpetic neuralgia to support study activities in Canada).
Section 3.10 (Other section affected by this change: Protocol Synopsis)		
Approximately 330 patients from up to approximately 55 investigational centers are planned to be enrolled in the study. The study is planned to be conducted in the US~~ and Canada~~.	Approximately 330 patients from up to approximately 55 study sites are planned to be enrolled in the study. The study is planned to be conducted in the US.	Deleting reference to Canada since study sites will not be located in Canada, but in the United States only (see above).

17.5. Administrative Letter Dated 17 December 2014

December 17, 2014

RE: 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

Subject: Correct CRO corporate name: INC Research, LLC

The purpose of this administrative letter is to correct a typographical error in the corporate name of the contract research organization (CRO) providing monitoring and other services for Study TV-45070-CNS-20013. The correct corporate name for this CRO is:

INC Research, LLC

For example, the name should appear as INC Research, LLC on the title page (page 1) of the protocol, under Monitor. It should also appear as INC Research, LLC on page 4 of the protocol, under Clinical Study Personnel Contact Information, as the corporate affiliation of the physician (Medical Monitor) and operational lead (Project Manager) listed.

This administrative letter will be an addendum to Protocol TV-45070-CNS-20013 and is not considered a substantial amendment.

If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

[redacted]

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | [redacted] | www.tevapharm.com

APPENDIX A. WASHOUT PERIODS FOR COMMON MEDICATIONS TAKEN BY PATIENTS WITH POSTHERPETIC NEURALGIA

Table 2: Washout Periods for Specific Drugs

Name of Drug	Half-life	Recommended Washout Period
Patches		
Lidocaine	~ 6 – 12 hours (topical administration)	7 days
Anticonvulsants		
Gabapentin	5 – 7 hours	7 days
Pregabalin	~ 6 hours	7 days
Antidepressants		
Duloxetine	8 – 17 hours	7 days
Venlafaxine	5 – 11 hours (active metabolite)	7 days
Amitriptyline	10 – 50 hours	14 days
Nortriptyline	16 to >90 hours	21 days
Opioid Analgesics		
Morphine	12 – 24 hours (ER formulation)	7 days
Oxycodone	12 – 24 hours (ER formulation)	7 days
Tramadol	6 – 18 hours	7 days
Methadone	13 – 47 hours	14 days