Trevi Therapeutics, Inc.

Protocol TR03ext

An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients

Statistical Analysis Plan

Version 1.0

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Approval Signature Page:

Statistical Analysis Plan for Protocol TR03ext

An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients

Protocol Version 3.0 (Amendment 2), 02 June 2016

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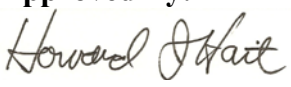
Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved By:



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List of Abbreviations

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic and Therapeutic Class
BID	Twice daily
BUN	Blood urea nitrogen
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Extended release
H&E	Hematoxylin and eosin
HADS	Hospital Anxiety and Depression Score
HCG	Human chorionic gonadotropin
HCl	Hydrochloride
HR	Heart rate
IFSI	International Forum for the Study of Itch
KOR	Kappa opiate receptor
LDH	Lactate dehydrogenase
LOV	Last observed value
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MOR	Mu opiate receptor
MOS	Medical Outcomes Study
NRS	Numerical Rating Scale
OV	Observation Period Visit
PAS	Prurigo Activity Score
PBI-P	Patient Benefit Index, pruritus version
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient-Reported Outcome
PT	Preferred term
QoL	Quality of life
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	SAS® statistical software
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment-emergent adverse events
TV	Treatment Period Visit

US	United States
UV	Ultraviolet light
UV-B	Ultraviolet light – B
VRS	Verbal Rating Scale
WHO	World Health Organization

1. Introduction

Protocol TR03ext is being conducted to examine the safety and anti-pruritic efficacy of nalbuphine hydrochloride (HCl) extended release (ER) tablets in prurigo nodularis patients. The purpose of this statistical analysis plan (SAP) is to provide specific guidelines from which the analysis will proceed. It will describe in detail the algorithms and conventions to be used in the analysis and presentation of the efficacy and safety data for protocol TR03ext. Any deviations from these guidelines will be documented in the clinical study report (CSR). In the event where discrepancies in statistical analysis may be encountered between the SAP and what is described in the study protocol, the SAP will take precedence.

2. Objectives

2.1. Primary Objectives

The primary objective of the study is to evaluate the safety and tolerability of nalbuphine HCl ER tablets during a treatment period of up to 50 weeks.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Week 4,
- To assess skin lesion improvement using the metrics of the Prurigo Activity Score (PAS),
- Change from Baseline in Patient-Reported Outcome (PRO) measures Worst (i.e. most severe itching over the past 24 hours) itch Numerical Rating Scale (NRS), average itch intensity NRS, Verbal Rating Scale (VRS) (itchy, burning and stinging), Medical Outcomes Scale (MOS) Sleep-R, ItchyQol, and Hospital Anxiety and Depression Score (HADS) by the final Treatment Period Visit,
- Change between Baseline and the final Treatment Period Visit in Patient Benefit Index, pruritus version (PBI-P),
- A description of the percentage of patients utilizing various doses of nalbuphine HCl ER tablets by Study Week,
- A description of the frequency and reasons for dose up-and down-titration and treatment discontinuation during the study,

- Frequency and distribution by time on study of patients determined to meet failure-to-improve criteria,
- Changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets,
- Time to first use of rescue medications and the number of days of use of rescue medications for itching,
- To evaluate the daily changes in the Subjective Opiate Withdrawal Scale (SOWS) during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets.

2.3. Exploratory Objectives

The exploratory objective of the study is to evaluate the potential of nalbuphine HCl ER tablets impact on the measurement of nerve fiber density (histology) and mu opiate receptor (MOR)/kappa opiate receptor (KOR) density (histology, Western Blot), as well as histological hematoxylin and eosin (H&E) changes in skin biopsies taken at Baseline and by the final Treatment Period Visit to investigate possible correlation with any clinical response and also compared to biopsy material assessed during study TR03 (optional procedures at select sites only).

3. Investigational Plan

3.1. Overall Study Design and Plan

This is an open label safety and tolerability extension study for patients who have completed the TR03 study. Patients will either enter directly into a drug Treatment Period (Worst Itch NRS ≥ 5) or enter an extended screening period of a no-drug Observation Period (Worst Itch NRS < 5) based on their reported NRS scores on the first Visit (Visit 1a). For up to 12 extended screening weeks, patients in the no-drug Observation Period may also transition into the drug Treatment Period if their Worst Itch NRS increases to ≥ 5.

To allow for various starting levels of pruritus intensity, patients who have a Worst Itch NRS that is ≥ 5 will enter the Treatment Period upon completion of Visit 1a. Patients whose Worst Itch NRS score is < 5 will be entered into an extended screening period, no-treatment criteria Observation Period for up to 12 weeks or until they develop a higher level of pruritus (i.e., Worst Itch NRS ≥ 5), at which point they will transition to the Treatment Period upon completion of Visit 1b. All patients entering the Treatment Period, whether immediately upon study entry or following a period of time in the Observation Period, will initially be titrated to a dose that can be as high as 180 mg twice daily (BID) during the first 4 weeks of the Treatment Period. Patients who continue in the Observation Period and maintain a Worst Itch NRS score of < 5 will be screen failed from the study at the end of the 12-week period. For enrolled patients whose Visit 1a worst itch NRS score satisfies the ≥ 5 enrollment criterion and for whom treatment is initiated, the screening visit Visit 1a will also be designated as the baseline visit. For enrolled patients who must continue into the Observation Period, the first visit during that period when the worst itch NRS ≥ 5 criterion is satisfied will be designated as Visit 1b and that visit will serve as the baseline visit.

The total study duration for any individual patient will be up to 53 weeks. For patients who enter directly into the Treatment Period, the total amount of time on drug will not exceed 50 weeks. Patients who enter the Treatment Period from the Observation Period, the total amount of time spent in the combined two periods of the study cannot exceed 50 weeks. All patients who received drug treatment will have a 2-week Washout and Safety Follow-up period at the end of the dosing period, unless consent is withdrawn.

The total amount of time in the Observation Period cannot exceed 12 weeks. After these 12 extended screening weeks, patients not eligible for the Treatment Period are screen failed from the study. The study periods are summarized below.

Study Period	Study Weeks	Duration
Observation Period	Patients who do not meet the criteria to start Treatment are followed in Observation Period visits (OV) for up to 12 extended screening weeks. During this time, the patient may meet criteria and become eligible to enter the Treatment Period. If the patient does not meet the criteria to enter the Treatment Period by the end of 12 extended screening weeks (OV12), participation in the study ends and the patient is screen failed	Up to 12 Extended Screening weeks
Treatment Period	For patients directly entering the Treatment Period as of Visit 1a, the Treatment Period begins with Study Week 1 (Visit 1a) and ends with Study Week 50. For patients entering the Treatment Period after being followed in the Observation Period, the number of weeks on treatment and the end of the Treatment Period varies. (See Table 8 in the study protocol for the details of which treatment visits are to take place). The End of Treatment Visit will take place after the patient completes the last week of study drug.	Up to 50 weeks
Washout and Safety Follow-Up Period	The Washout and Safety Follow-up Period is two (2) weeks in duration. For patients directly entering the Treatment Period as of Visit 1a and completing 50 weeks of study drug treatment, the Washout and Safety Follow-up Period should take place during weeks 51 and 52. For patients entering the Treatment Period after being followed in the Observation Period, the number of weeks on treatment and the end of the Treatment Period varies; Table 8 in the Study Protocol calculates the Treatment Visit assignments for any patient entering the Treatment Period from the respective Observation Period visits. The Washout and Safety Follow-up Period will take place during the two (2) weeks after the patient completes the last week of study drug. The Washout and Safety Follow-up Period Visit will take place in the week following the completion of the two (2) week Washout and Safety Follow-up Period.	2 weeks

3.2. *Premature Discontinuation of Study Drug Treatment*

3.2.1. Premature Discontinuation of Study Drug Treatment Associated with Failure-to-Improve Criterion

Patients who meet failure-to-improve criterion during the conduct of the study, will stop taking study medication.

The Failure-to-Improve criteria are as follows: Beginning on Treatment Period Visit 3 (TV3), and at every subsequent Treatment visit, patients with a worst itch NRS score ≥ the worst itch NRS score at Visit 1a (or at Visit 1b in the case of patients who require the OV period) will be discontinued from study drug. Patients discontinued from study drug are to undergo the End of Treatment Visit (TV14), the Washout/Safety Follow-up Period assessment in two weeks, and receive a follow-up telephone contact 30 days following end of study drug dosing for final safety assessment.

3.2.2. Premature Discontinuation of Study Drug Treatment For Reasons Other Than Failure-to-Improve

Patients who complete Study Drug treatment through the End of Treatment Visit 14 (TV14) (even if some doses have been missed or if the patient was followed in the Observation Period before receiving study drug treatment) are considered to have completed Study Drug treatment. Patients discontinuing Study Drug treatment prior to the maximum allowable number of Treatment Weeks (based on their entry into the study at either Visit 1a or Visit 1b) will also be considered to have prematurely discontinued Study Drug treatment. Patients discontinuing Study Drug treatment prior to End of Treatment Visit 14 will be considered to have prematurely discontinued Study Drug treatment and will be asked to complete the End of Treatment Visit (TV14) regardless of where they were in the study visit schedule, the Washout and Safety Follow-up Period Visit and the Premature Discontinuation of Study Drug Telephone Contact visit. Patients removed from the study after enrollment and who have received a dose of study drug will not be replaced.

Some reasons for premature discontinuation of Study Drug treatment include:

- Intercurrent illness
- Any intolerable Adverse Event (AE) that cannot be ameliorated or safely managed with medical intervention or one that poses undue risk to the subject if Study Drug treatment were continued in the opinion of the Medical Monitor or Investigator
- Electrocardiogram (ECG) changes summarized in protocol Section 17.4
- Opioid medication is introduced in anticipation for chronic use of greater than 2 weeks
- Any medication prescribed for chronic anti-pruritic use of greater than 2 weeks
- Development of substance abuse as determined by the Investigator.

3.3. Study Endpoints

3.3.1. Primary Endpoint

The primary endpoint is a description of the overall incidence and nature of treatment-emergent adverse events (TEAEs) during treatment weeks 5-50.

3.3.2. Secondary Endpoints

Visit 1a or Visit 1b will serve as the baseline visit for efficacy endpoints. Visit 1a will be the Baseline for patients directly entering the Treatment Period as of Visit 1a. Visit 1b will be the Baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time.

The secondary endpoints are:

- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in PRO measures Worst itch NRS, average itch intensity NRS, VRS (itchy, burning and stinging), MOS-Sleep-R, ItchyQoL, HADS by Treatment Period study visit and Baseline NRS score
- Change between Baseline and the final Treatment Period visit in PBI-P
- A description of the percentage of patients utilizing various doses of nalbuphine HCl ER tablets by study week
- A description of the frequency and reasons for dose up-and down-titration and treatment discontinuation during the study
- Frequency and distribution by time on study of patients determined to meet failure-to-improve criterion
- Changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets
- Time to first use of rescue medications and the number of days of use of rescue medications for itching
- To evaluate the daily changes in the SOWS during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets.

3.3.3. Exploratory Endpoints

The exploratory objectives of the study are to evaluate the effect of nalbuphine HCl ER tablets on:

- The potential of nalbuphine HCl ER tablets to impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot), as well as histological (H&E) changes in skin biopsies taken at Baseline and the final TV when compared to biopsy material assessed during study TR03 (optional procedure at select sites only).

3.3.4. Safety Assessments

Safety assessments include the following:

- AEs
- Vital signs
  - Weight
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - Heart rate (HR)
  - Respiration rate (RR)
  - Body temperature
- Physical examination
  - Clinically significant abnormalities pre-dose are reported as part of medical history
  - Clinically significant abnormalities representing a worsening from baseline, subsequent to dosing, are reported as AEs
- Neurological examination
- Clinical laboratory tests
  - Blood chemistry
  - Hematology
  - Urinalysis
  - Serum Pregnancy
- Investigator reviewed ECG and central cardiac core laboratory read 12 Lead-ECG cardiovascular grading, and/or cardiovascular related prohibited medications
- SOWS.

3.4. Treatments

Following enrollment, the patient will receive 30 mg open-label tablets. At each visit at which study drug is to be dispensed, enough drug should be supplied to ensure a sufficient number of tablets available for dosing until the next visit plus an additional 8 tablets to allow for visit windows and/or possibility of a missed visit.

Study drug can be taken with or without food. Patients will be instructed to take the AM and PM Study Drug tablets at the same times of the day, approximately 12 hours apart, preferably with 240 milliliters (mL) (approximately 8 ounces) of water. If the patient does not take a particular dose at the planned time he or she may take it up to 2 hours later. For example, if a patient is taking the Study Drug at 9 AM and 9 PM but forgets to take the 9 AM dose, the patient may take the 9 AM dose as late as 11 AM. After that time, the patient should skip the 9 AM dose and, instead, take the regularly scheduled next dose at 9 PM.

The first dosing day will be on either Visit 1a or Visit 1b. Titration will be based on tolerability. If the patient is experiencing a study-drug related AE or an AE that may be aggravated by study drug up-titration, the study drug dose should not be increased, regardless of the NRS score.

The Study Drug will be titrated during the Treatment Period Weeks 1 - 4, according to the schedule in Table 3 in the study protocol to a final dose of 30 mg BID up to 180 mg BID. The dosing for Treatment Week 1 is further described in Section 9.6.1 (Visit 1a) and Section 9.6.4 (Visit 1b) of the study protocol. Patients should only ever be dispensed a single strength of the study drug (e.g. 30 mg bottle(s) or 60 mg bottle(s)) at a visit.

Patients will titrate to tolerability beginning with a 30 mg dose on Day 1 (Visit 1a or Visit 1b) with a dose increase of 30 mg BID not more often than every 3 to 4 days in order to attain steady-state plasma concentrations of nalbuphine at each dose.

Patients should be instructed to up-titrate beginning with a single 30 mg dose in the evening (PM) and then begin dosing with an increased 30 mg BID dose the following day. Dose titrations should be maintained for 3-4 days before further up-titration of the patient's dose is attempted

The maximum dose the patient should reach at the end of Week 1 is 60 mg BID. If this dose is tolerated (as determined by the Telephone Contact 1 (TC1) assessment), an additional up-titration may be attempted during Week 2.

The maximum dose the patient should reach at the end of Week 2 is 120 mg BID. If this dose is tolerated (as determined by the TC2 assessment), an additional up-titration may be attempted during Week 3.

The maximum dose the patient should reach at the end of Week 3 is 180 mg BID. If this dose is tolerated, it should be maintained throughout Week 4.

The dose achieved as of the end of Treatment Week 4 will be maintained throughout the rest of the Treatment Period. This dose will be defined as the patient's "maintenance dose".

During Treatment Weeks 1-4, the decision to up-titrate the patient's dose should be made based on tolerance to study drug. If the tolerance level becomes unacceptable to either the patient or the Investigator, the dose should be reduced incrementally until tolerance is stabilized (reduce dose by 30 mg BID if at the 30 mg, 60 mg, 90 mg or 120 mg dose level and reduce by 60 mg BID if the patient is at the 180 mg dose level). Patients who do not tolerate the 180 mg BID should be down titrated to the 120 mg BID dose level and maintained there if stabilized.

Two single dose reductions or dose holds per patient is permitted during Treatment Period at the Investigator's discretion. If subsequent dose reductions or dose interruptions are needed, the Medical Monitor must be contacted. The duration of any dose hold must be discussed with the Medical Monitor.

4. Statistical Considerations

4.1. General Methodology

Continuous data will be described using descriptive statistics including patient count (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be described using the patient count and percentage in each category. The percentage will be suppressed when the count is zero for a category in order to draw attention to the non-zero counts. Where specified on the table shells, a row denoted "Missing" is to be included in count tabulations to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment arm within the analysis population of interest, unless otherwise specified.

Patients will be identified in the listings by the patient identification number concatenated with the investigator/site number. Data will be displayed in all listings sorted by patient identification number concatenated with the investigator/site number. Data listings, unless otherwise specified, will include all patients who provide consent to participate in the study.

Unscheduled results will not be included in the summary tables except for determining Baseline values for efficacy and safety evaluations and the handling of laboratory data both at Baseline and during treatment (see Section 4.2). For patients discontinuing from the study, planned study visit data that are collected at the early termination visit will be included in by-visit summaries in the summary tables or figures (e.g. PRO questionnaires) using the serial next visit number associated with what would have been the patient's next scheduled visit. Thus, for example, a patient discontinuing from the study after Treatment Visit 2 would have efficacy and safety data obtained at the study termination visit treated as Treatment Visit 3 results. Data listings will include all data from scheduled, repeated, unscheduled and early termination visits.

All p-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Point estimates of the parameter of interest will be generated along with, where appropriate, 95% confidence intervals.

All analyses will be conducted using SAS Version 9.2 or higher.

4.2. Baseline, Study Day and Analysis Visit Windows

Unless otherwise specified, "Baseline" for efficacy and safety information is defined as the last non-missing evaluation taken prior to the first dose of study medication during the TR03 extension study (including repeated and unscheduled assessments).

For variables that require the analysis of change from baseline, the post-baseline assessment value minus the baseline assessment value will be used to derive change from baseline value. If either value is missing then the change from baseline will also be missing.

When study day is used for display or in comparisons, the following algorithm will be used:

- Study day = date of assessment – date of first dose of study medication + 1, if the date of the assessment is on or after the date of first dose;
- Study day = date of assessment – date of first dose of study medication, if the date of the assessment is prior to the date of first dose.

No analysis visit windows will be defined for this study, i.e., by-visit assessments will be based on the designated scheduled visit number associated with the data recorded for the endpoint of interest.

4.3. Sample Size

As this is a safety extension study for which patients will be recruited from patients who have completed parent study TR03, the sample size cannot be predicted. No formal sample size

calculations have been performed and no inferential statistics are planned. The maximum number of patients will not exceed the number of patients who completed TR03.

4.4. Randomization, Stratification, and Blinding

Patients will not be randomized into this study. For this study, patients will retain their study number from the TR03 study.

4.5. Pooling of Study Sites

No *a priori* pooling of sites is planned for this study as no formal statistical testing is planned.

4.6. Analysis Populations

4.6.1. All Enrolled

An enrolled patient is one who provides consent to participate in the TR03ext study.

4.6.2. Safety

The Safety population will consist of all enrolled patients who have received a single dose of study medication in the TR03 extension study. The Safety population will be used to evaluate the safety and efficacy endpoints defined for this study.

Patients will be summarized in a single nalbuphine treatment group.

4.7. Methods for Handling Dropouts and Missing Data

No replacement or imputation of missing data will be conducted for this study.

4.8. Multiple Comparisons/Multiplicity Considerations

There will be no consideration for multiple comparisons/multiplicity for this study as no inferential analyses will be performed.

4.9. Examination of Subgroups

No *a priori* planned subgroup analyses are specified and none will be performed.

4.10. Data Display Treatment and Other Descriptors

Unless otherwise noted, TR03 extension study treatments will be presented in all tables, listings and figures (TLFs) as: All Patients. Additionally, TR03 core study randomized treatments will be presented as: Nalbuphine 90 mg, Nalbuphine 180 mg, and Placebo.

For measurements collected at multiple study visits, visit and week number will be used in all TLFs. Baseline results (as described in Section 4.2) will be displayed as “Baseline.”

4.11. Changes in the Planned Analysis

Section 9.7.7.5 of the protocol discusses a 9-item sleep problems index that can be generated for the MOS Sleep Scale-R. This, however, will not be implemented. SAP Section 8.1.6 describes the summaries that will be presented for the MOS Sleep Scale-R.

Section 19.6 of the protocol states that opioid medication usage will be tabulated separately from all other concomitant medications. Instead, opioid medication usage will be tabulated with all other concomitant medications as discussed in SAP Section 7.1.

Section 19.7 of the protocol states that mean dose during the treatment period will be summarized. Instead, as discussed in SAP Section 7.3.1, highest dose achieved during the treatment period will be summarized.

Section 8.6 of the SAP describes the summarization and graphical presentation of premature discontinuation due to lack of efficacy or adverse events. This is not included in the protocol but is desired for reporting purposes.

5. Patient Disposition

5.1. Disposition

The number of patients in the safety population will be summarized overall and percentages will be based on the number of enrolled patients.

The number and percentage of patients who consented to participate (i.e. enrolled patients), consented to participate but were not treated, were treated, completed the study, discontinued from the study and the primary reason for premature study and treatment discontinuation will be summarized for all patients who provided consent to participate in the TR03 extension study. Reason for screening failure for patients who discontinued during the Observation Period are not collected on the electronic case report form (eCRF) so will not be summarized. The number and percentage of patients who met failure to improve criterion at any time during the study will also be summarized.

Patient disposition will also be summarized by site.

Patient disposition data will be presented in a data listing.

Reason(s) for exclusion from the safety population will be presented in a data listing.

5.2. Protocol Deviations

Protocol deviations represent departures from protocol-specified procedures and practices. During the course of the study, protocol deviations will be tracked and entered into a single master database that captures the patient number, the type of protocol deviation, and detailed information surrounding the nature and/or circumstance for which the deviation may have occurred.

Protocol deviations will be identified and accounted for prior to database lock. The number and percentage of patients reporting any protocol deviations and the incidence of each deviation type will be summarized by treatment group and overall for the safety population and individual responses will be presented in a data listing for all enrolled patients.

5.3. Eligibility Criteria

For those patients who fail to fulfill any of the inclusion/exclusion criteria or fail to meet the NRS criteria, the criteria not met will be presented in a single data listing for all enrolled patients.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographics and baseline information will be summarized overall for the safety population.

The demographic characteristics consist of age (years), sex, race, ethnicity, and geographic region (United States (US) or Europe). A patient's age in years is calculated as FLOOR[(informed consent date for the TR03 extension study – date of birth)/365.25] expressed as an integer value. The baseline characteristics consist of baseline height (cm) and baseline weight (kg).

Baseline height (cm) and weight (kg) are obtained from the last non-missing evaluation taken prior to the first dose of study medication during the extension study. All other demographic and baseline characteristics (i.e. sex, race, ethnicity and geographic region) were obtained prior to first dose of study medication during the core TR03 study.

Age (years), baseline height (cm) and baseline weight (kg) will be summarized using descriptive statistics. The number and percentage of patients by race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino) will also be reported.

Patient demographics and baseline characteristics will be presented in a listing for the safety population.

6.2. *Medical History*

6.2.1. General Medical History

Past and present medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report) and presented in a data listing for the safety population.

For the patients who entered the TR03 Observation Period, medical history with an onset date on or after the TR03 core study randomization date will be presented in a data listing. The listing, thus, will include all TEAEs for the TR03 core study that were converted into medical history in

the TR03 extension study and the non-serious AEs that occurred in the Observation Period of TR03 extension study.

6.2.2. Prurigo Nodularis History

Prurigo nodularis history data for the subset of TR03 core study patients entering the TR03 extension study will be taken from the TR03 core study database as this history was not collected separately for the TR03 extension.

Patients' prurigo nodularis history, collected at the Screening visit during the TR03 core study and consisting of a multitude of categorical responses within various component sub-categories of interest, will be summarized using frequencies and percentages for the safety population.

Responses to all questions will be presented in a data listing for the safety population.

6.2.3. Neurological History

Primary cause of neurological history, collected at Visit 1a/Visit 1b, will be summarized using frequencies and percentages for the safety population. All neurological history information and neurological examination details regarding abnormal findings will be presented in data listings for the safety population.

7. Treatments and Medications

7.1. Concomitant Medications

Patients may receive all clinically indicated medications during the study with the exceptions noted in the study protocol.

A medication's usage will be considered concomitant if it was used by the patient at the time of informed consent or started and/or continued after administration of the study medication.

Concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins will be coded according to the World Health Organization (WHO) Drug Dictionary.

For the purpose of summarizing prior and concomitant medications, incomplete medication start and end dates for medications which are not ongoing will be imputed as follows:

- If the year and month are present and the day is missing, then the day is set to the first day of the month for the start date, and to the last day of the month for the end date.
- If the year and day are present and the month is missing, then the month is set to January for the start date, and to December for the end date.
- If the year is present and the month and day are missing, then the month and day are set to January 1 for the start date, and to December 31 for the end date.
- Data listings will include the recorded and imputed (as described above) start and end dates for each reported medication.

If the medication start date is completely missing and the end date is after the first dose of study drug, then the medication will be classified as concomitant. If the end date is missing, then the medication will be classified as ongoing (concomitant). Medications for which the start and end dates are missing will be classified as concomitant.

The total number of concomitant medications and the number and percentage of patients using at least one concomitant medication will be summarized overall for the safety population.

The number and percentage of all concomitant medications will be summarized by Anatomic and Therapeutic Class (ATC) of WHO drug and preferred term overall for the safety population. Patients will be counted only once within a medication category. If a patient reports taking the same medication more than once, as determined by WHO Drug name, then the medication will be counted only once for that WHO Drug name and patient.

Concomitant medications will be presented in a data listing for the safety population.

Opioid medication usage is summarized and listed with all other concomitant medications. Rescue medications, as described in Section 7.2, will be summarized and listed separately from concomitant medications.

7.2. Rescue Anti-Pruritic Medications

Rescue medications will be defined as those drugs, when used for the purpose of treating itch, that were required to be washed out prior to entry into TR03 as described in the protocol. For the purposes of this study, any ultraviolet (UV) light treatment received will also be defined as a rescue medication. If a medication is prescribed for chronic anti-pruritic use of greater than 2 weeks, the patient should be discontinued as described in the protocol.

Concomitant use of medications for pruritus is not prohibited except as described in the protocol. Details pertaining to the use of opiate medications are also discussed in the protocol. The list of protocol-defined rescue medications for itching is presented in Table 1.

For drugs that may be used for multiple indications including pruritus, a drug is only considered a rescue medication if taken for pruritus. Use of rescue medications will not preclude continuation in the study; however, all uses of such medication along with their indication for use will be recorded. Patients will be provided a log on which to record use of rescue medications.

Table 1: List of Rescue Medications for Itching

Table 1: Rescue Medications for Itching		
Rescue Medication	**Only intended for anti-pruritic treatment**	**Examples**
Opioid receptor antagonists		naltrexone, naloxone
Antihistamines	✓	topical or systemic
Topical calcineurin inhibitors	✓	tacrolimus
Topical antibiotics	✓	---
Topical steroids	✓	---
Topical capsaicin	✓	---
Anti-septic baths and anti-septic cleansing lotions	✓	---
Anti-convulsant class drugs	✓	gabapentin or pregabalin
Systemic Steroids	✓	---
cyclosporin A and other immunosuppressants	✓	---
antidepressant medications	✓	paroxetine, fluvoxamine, amitriptyline
Malignant tumor related active treatment with a systemic drug	✓	---
UV Therapy	✓	---

The total number of rescue medications subsequent to the first dose of treatment with study medication and the number and percentage of patients using at least one rescue medication subsequent to the first dose of treatment with study medication will be summarized overall for the safety population.

Incidence of concomitant rescue medication use will be summarized for the safety population. For incidence of use, patients will be counted only once within a medication category. In addition, for incidence of use calculations, if a patient reports taking the same medication more than once, as determined by WHO Drug name, then the medication will be counted only once (incidence of use) for that WHO Drug/medication name and patient.

The prevalence of use of rescue medications will also be summarized for rescue medications for the safety population. In this construct, multiple, distinct instances when a particular rescue medication was required will be counted as the number of times reported.

Antihistamine use across ATC classifications (a list to be furnished prior to data base lock) will also be summarized by incidence and prevalence for the safety population.

Rescue medication use will be presented separately in a data listing for the safety population.

The number and proportion of patients with rescue medication use at each visit and within ATC classification will be presented. This will be obtained by comparing the rescue medication onset date to the patient's visit dates and slotting the rescue medication accordingly. The number of days of rescue medication use will also be evaluated using descriptive statistics. Details regarding the analysis of number of days of rescue medication use are presented in Section 8.5.

7.3. Study Treatments

7.3.1. Study Drug Dosing

The number and percentage of patients reaching various achieved doses (30, 60, 90,120, 150, 180 and 210 mg BID) will be summarized at each study visit beginning at the Visit 3/Week 5 study visit for the safety population. In addition, the number of percentage of patients will be presented for the highest dose achieved during the entire 50 weeks of active treatment.

Patient study drug dispensing/return and missed doses information will be presented in data listings for the safety population.

7.3.2. Extent of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug and will be presented as the total number of days from the first dose date to the last dose date: (date of last dose of study medication - the date of first dose of study medication + 1). The date of first dose and date of last dose are reported in the eCRF on the dosing history and study completion pages, respectively. If the last dose date on the study completion page is missing, or if a patient is lost to follow-up, the visit date at which drug was last returned will be used as the date of last dose.

The duration of exposure to study drug will be summarized using descriptive statistics for the safety population.

Patient exposure information will be presented in a listing for the safety population.

It should be noted that duration of exposure calculated in this fashion does not account for missing individual doses or dosing interruptions as recorded in the eCRF.

7.3.3. Treatment Compliance

On the date of the first dose of study medication, the patient is expected to take only one dose (3 tablets) of study medication (in the evening). For the remainder of the study, patients should take two doses (6 tablets) of study medication each day (one in the morning and one in the evening).

At designated visits (i.e. Weeks 1, 3, 5, 9, 13, 17, 21, 26, 30, 34, 38, 42 and 46) patients will be distributed bottles containing study medication. Patients will return the bottles at a subsequent study visit, as instructed.

The number of tablets taken will be derived as: (total tablets dispensed across visits – total tablets returned across visits) and will be used to assess overall study compliance.

The total number of tablets planned will be derived as:
3 + (number of days between day after first dosing day and last dosing day, inclusive)*6.

Patient compliance over the entire time interval from first day of treatment until the last reported dosing date will be derived as: (number of tablets taken/number of tablets planned) * 100%. Patient study compliance will be summarized using descriptive statistics overall for the safety population.

Patient compliance information will be presented in a data listing for the safety population.

8. Secondary Endpoint Analysis

Efficacy measurements will be evaluated as secondary endpoints in this study. The safety population will be used to evaluate the efficacy endpoints defined for this study. Eligibility for analysis of a particular endpoint will require only that the patient have a baseline value and at least one post-baseline value so that a change from baseline calculation can be obtained. All efficacy endpoints will be evaluated through the generation of descriptive summary statistics. For continuous variables, the mean, standard deviation, median, minimum, and maximum will be presented for a particular visit and for the change from baseline (Visit 1a or 1b). For categorical variables, the number and percentage of patients within each category of classification will be summarized by study visit. No formal statistical testing will be conducted.

Visit 1a or 1b will serve as the baseline visit for efficacy endpoints. Visit 1a will be the baseline for patients directly entering the Treatment Period as of Visit 1a and Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time.

Last observed value (LOV) is defined as the values at the last post-baseline visit, up to and including the Safety and Washout Period visit.

8.1. Change from Baseline in PRO Measures

For the PRO measures detailed in the subsections below, change from baseline analysis will be performed.

Summary statistics will be generated for each PRO measure for total patients and for patients by their TR03 core study treatment at Baseline, each Treatment Period study visit, the Washout and Safety Follow-up visit and LOV and for change from baseline in each PRO measure at each Treatment Period study visit, the Washout and Safety Follow-up visit and LOV.

Means and change from baseline means for each PRO with a continuous response will be presented in bar charts for all patients by study visit.

Values from all PRO measures will be presented in data listings.

8.1.1. Change from Baseline in Worst Itch Intensity NRS

The NRS is a patient-reported outcome instrument, designed to quantify the intensity of worst itching experienced during a 24-hour period. The scale is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). The NRS is a widely used instrument recommended by International Forum for the Study of Itch (IFSI) for quantifying itch intensity as well as a useful instrument for grouping patients into categories of itch intensity described as mild, moderate or severe (Stander et al 2013). The itch NRS has been investigated in patients with chronic pruritus of a variety of origins and has a high reliability and concurrent validity was found (Phan et al 2012). The patient is to check the number that best reflects the worst itching during the prior 24 hours.

Summaries and bar charts of the worst itch intensity NRS scores will be presented as detailed in Section 8.1.

Worst itch intensity NRS values will be presented in a data listing.

8.1.2. Change from Baseline in Average Itch Intensity NRS

In addition to worst itch intensity, the patient is also to rate average itch intensity during the prior 24 hours.

Summaries and bar charts of the average itch intensity NRS scores will be presented as detailed in Section 8.1.

Average itch intensity NRS values will be presented in a data listing.

8.1.3. Change from Baseline in the VRS

The VRS scale to be used in this study has three dimensions, each dimension is coded with graduated adjectives (from 0 = none; to 5 = very severe) for the skin sensations of itchy, burning and stinging. Patients will be asked to record the VRS value: “How is your skin sensation today?”

Summaries of each of the three skin sensations will be presented as detailed in Section 8.1. In addition, for each of the three skin sensations, patients’ change between baseline and LOV will be summarized using frequencies and percentages for the following categories: 4 grades better, 3 grades better, 2 grades better, 1 grade better, no change (VRS change of < abs(1)), 1 grade worse, 2 grades worse, 3 grades worse and 4 grades worse. The summary will be presented for all patients, patients with at least 6 months of treatment, patients with at least 9 months of treatment and patients who have completed the treatment period. Patients will be counted in each treatment duration category whose criteria they have met (i.e. A patient who has completed the treatment period will be included in the denominator for all patients, patients with at least 6 months of treatment, patients with at least 9 months of treatment and patients who have completed the treatment period.).

All VRS data will be presented in a data listing for the safety population.

8.1.4. Change from Baseline in the HADS

The HADS instrument includes 14 multiple-choice questions, each with 4 possible choices, scored between 0 and 3.

Separate anxiety and depression subscale scores will be derived, each with a possible value of 0-21 with higher scores indicating worse impairment.

The HADS anxiety subscale score will be derived as the sum of the responses to the following items:

- I feel tense or wound up
- I get a sort of frightened feeling as if something bad is about to happen
- Worrying thoughts go through my mind
- I can sit at ease and feel relaxed
- I get a sort of frightened feeling like butterflies in the stomach
- I feel restless and have to be on the move
- I get sudden feelings of panic.

The HADS depression subscale score will be derived as the sum of the responses to the following items:

- I still enjoy the things I used to enjoy
- I can laugh and see the funny side of things
- I feel cheerful
- I feel as if I am slowed down
- I have lost interest in my appearance
- I look forward with enjoyment to things
- I can enjoy a good book or radio or TV program.

In the event of a single missing item from a subscale, the missing value will be derived as the mean of the remaining six items. If more than one item is missing, then the subscale score will not be derived.

Summaries for the anxiety and depression scales will be will be presented as detailed in Section 8.1.

Responses to each of the 14 individual HADS items will be summarized at the baseline visit, Visit 14/End of Treatment visit and at the Washout and Safety Follow-up visit using descriptive statistics.

Individual HADS items and anxiety and depression subscale scores will be presented in a data listing for the safety population.

8.1.5. Change from Baseline in the ItchyQoL

The ItchyQoL consists of 22 pruritus-specific items measuring how pruritus affects patients' QOL in the area of symptoms related to the itch condition (6 questions), functional limitations (7

questions), and emotions (9 questions). The subject scores each question never =1, rarely=2, sometimes=3, often=4 and all the time=5.

Individual scores for each of the 22 items will be summarized categorically using frequencies and percentages at each study visit.

The ItchyQoL total score will be obtained as the sum of the 22 items. If no more than three items are missing, each missing item will be estimated as the mean of the remaining items. If more than three items are missing, the ItchyQoL total score will be set to missing.

Summaries for ItchyQol total score will be presented as detailed in Section 8.1. In addition, change in ItchyQoL total score between baseline and LOV will be summarized using frequencies and percentages for the following categories: very good improvement, marked improvement, some improvement, no change, slightly worse, markedly worse and much worse. The magnitude of ItchyQoL change associated with each category is taken from Siebenhaar et al., 2013: Very good improvement: > 50% to 100% reduction; Marked improvement: > 20% to 50% reduction; Some improvement: > 5% to 20% reduction; No change: 5% reduction to 5% increase; Slightly worse: > 5% to 20% increase; Markedly worse: > 20% to 50% increase; Much worse: > 50% increase. The summary will be presented for all patients, patients with at least 6 months of treatment, patients with at least 9 months of treatment and patients who have completed the treatment period. Patients will be counted in each treatment duration category whose criteria they have met (i.e. A patient who has completed the treatment period will be included in the denominator for all patients, patients with at least 6 months of treatment, patients with at least 9 months of treatment and patients who have completed the treatment period.).

Individual ItchyQoL item scores as well as the calculated total score for each patient will be presented in a data listing for the safety population.

8.1.6. Change from Baseline in the MOS Sleep Scale-R

The MOS Sleep Scale-R measure is a 12-item self-report sleep measure that was developed to assess sleep quality and quantity. It is a multi-dimensional assessment of sleep parameters with scoring results in six subscales or domains: sleep disturbance (4 items), snoring (1 item), awaken short of breath or with headache (1 item), quantity of sleep (1 item), optimal sleep (1 item), sleep adequacy (2 items), and daytime somnolence (3 items). There are three question types with the third type consisting of 10 sub-questions. The first question pertains to how long it takes for a patient to get to sleep: 0-15 minutes, 16-30 minutes, 31-45 minutes, 46-60 minutes and >60 minutes. The second question asks how many hours of sleep per night the patient reports getting. The third question (consisting of 10 sub-questions) categorically evaluates sleep quality and sleep disturbance. Categories of response are 1="all of the time", 2="most of the time", 3="some of the time", 4="a little of the time", and 5="none of the time."

Question 1, having to do with sleep onset, will be summarized by creating a crosstabulation table of the baseline vs. post-baseline visit categorical distributions for each post-baseline visit up to and including the Washout and Safety Follow-up visit, and LOV.

Question 2, number of hours per night of sleep, will be summarized as detailed in Section 8.1.

Individual sub-question scores for Question 3 will be summarized categorically using frequencies and percentages.

MOS Sleep Scale-R questions will be presented in a data listing for the safety population.

8.1.7. Change from Baseline in the PBI-P

The PBI-P questionnaire assesses the importance of treatment objectives to the individual. Before, and at the end of drug treatment in this study, the patient completes the same questionnaire and rates the extent to which the treatment objectives have been achieved. The instrument consists of 27 multiple choice questions that can be answered “not at all”, “somewhat”, “moderately”, “quite” and “very”.

At baseline and at the end of treatment visit, the total PBI-P summed across 27 items will be calculated and a mean total score will be obtained. For mean score calculation, responses of “does not apply” and “question unanswered” will be treated as missing values. Mean score will be derived as (sum of all non-missing items)/(number of non-missing items).

PBI-P mean score and each of the 27 individual PBI-P items will be summarized as detailed in Section 8.1.

Responses to each of the 27 individual PBI-P items will be summarized at baseline and the end of treatment visit using descriptive statistics.

Individual PBI-P item scores will be presented in a data listing for the safety population

8.1.8. Change from Baseline in PAS

The PAS consists of 7 qualitative and quantitative measurements related to the examination of the skin. Type, number, distribution, affected body parts, and quantitative number of lesions in a representative body part are documented. The biggest lesion and the most representative lesion are monitored with documentation of height and area measurements. Prurigo lesion activity is recorded as a percentage based on their stage (0-4).

Separate activity classification is provided for prurigo lesions with excoriations/crusts compared to all prurigo lesions and for healed prurigo lesions compared to all prurigo lesions. The proportion of patients with each stage of classification will be summarized at each visit for each of the two activity classifications (note that PAS is not completed at the Washout/Safety and Follow-up visit). Shift from baseline to LOV and the End of Treatment visit for all patients, patients with at least 6 months of treatment, patients with at least 9 months of treatment and patients who complete treatment will also be presented for each of the two activity classifications. Shift from baseline to Visit 5/Week 13, Visit 8/Week 26 and Visit 11/Week 38 for all patients will also be presented for each of the two activity classifications.

Classification is provided for total number of prurigo lesions (not including scars). The proportion of patients at each classification level (0, 1-19, 20-100 and >100) will be summarized at each visit (note that PAS is not completed at the Washout/Safety and Follow-up visit). Shift from baseline to LOV and the End of Treatment visit for all patients, patients with at least 6

months of treatment, patients with at least 9 months of treatment and patients who complete treatment will also be presented. Shift from baseline to Visit 5/Week 13, Visit 8/Week 26 and Visit 11/Week 38 for all patients will also be summarized.

All PAS data obtained in the study will be presented in a data listing for the safety population

8.2. Change during the Washout Period in PROs

Change during the Washout Period after cessation of treatment in the following PROs will be summarized using simple summary statistics generated for the End of Treatment visit and the Washout/Safety Follow-up visit and for change from the End of Treatment visit to the Washout/Safety Follow-up Visit.

- Worst itch intensity NRS
- Average itch intensity NRS
- VRS (itchy, burning, stinging)
- ItchyQoL Total Score
- MOS Sleep Scale-R Question 2
- HADS

No formal analysis of this presentation of data will be performed. Note that only patients who complete the study through the End of Treatment visit will be included in this evaluation.

8.3. Dose-Up and Down-Titration

The number and percentage of patients with any dosing change during the Treatment Period and for each Treatment Period visit will be presented by reason for dosing change.

Reasons for dosing changes will be presented in a data listing for the safety population.

8.4. Failure-to-Improve Criteria

Beginning with the TV3 visit and at each subsequent treatment visit (up to and including the TV13 visit) the number and percentage of patients who meet failure-to-improve criteria will be summarized.

The visit at which failure-to-improve criteria are met will be presented in a data listing for the safety population.

8.5. Rescue Medication Use

Details regarding the definition of and overall summary of rescue medications are presented in Section 7.2.

The number of days of use of rescue medications by study period (Pre-Treatment (after the date of last visit during the TR03 core study and prior to first dose during the TR03 extension study) and Treatment Period (Visits 2-14)) and by visit for the Treatment Period will be summarized

using descriptive statistics for both the overall number of days of use as well as for the number of days of rescue medication use for the drug classes presented in Table 1.

The number of days of rescue medication use between each visit will be presented graphically for overall rescue medication use as well as for each of the drug classes presented in Table 1.

The overall number of days of rescue medication use and number of days of rescue medication use for each of the drug classes presented in Table 1 will be summarized using descriptive statistics. For patients with >=1 day of rescue medication use, percentage of total time on study will be derived as: [(the number of days of rescue medication use)/[days from the informed consent date through the fixed dose period]]*100. The mean for all patients on-study during the time period will be presented.

Time to first new use of rescue medication (days) will be summarized using descriptive statistics. The earliest date on or after the date of first dose of study medication on which a patient begins new rescue medication use will be considered the date of first new use of rescue medication. Time to first new rescue medication use will be derived as: (date of first new use of rescue medication – date of first dose of study medication) + 1. For patients who have no new rescue medication use on or after the date of their first dose of study medication time to first new use of rescue medication is not calculated.

It is recognized, however, that all of these evaluations are potentially confounded with early discontinuation that may or may not be observed among patients reporting use of rescue medications. That is, the extent and duration of use of rescue medications may, at least in part, be a function of duration of participation in the study.

8.6. Premature Discontinuation Due to Lack of Efficacy or Adverse Events

The distribution of patients who prematurely discontinue due to lack of efficacy or adverse events during the Treatment Period and Washout Period will be summarized for the safety population across all Treatment Period visits, separately at each Treatment Period visit, and for the Washout Period. Date of discontinuation during the Treatment Period will be defined as the date of last dose of study medication. For patients who complete the Treatment Period, date of discontinuation during the Washout Period will be defined as the earliest non-missing of the date of last contact or the last observed visit date.

9. Safety Analysis

All analyses of safety will be conducted using the safety population.

No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

9.1. Adverse Events

Details regarding the definition and reporting of an AE or a serious adverse event (SAE) are provided in the study protocol. AEs will be recorded starting with the signing of the first

informed consent. All AEs will be collected through the Washout and Safety follow up visit (or Early Termination Visit). Following the Washout and Safety follow up visit (or Early Termination Visit), all unresolved AEs that were reported by the Investigator to be probably drug related should be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE has stabilized.

Non-serious AEs that begin during the Observation Period will be captured as medical history in the TR03 extension study; patients who never transition from the Observation Period to the Treatment Period are screening failures and did not complete the early termination or end of study CRFs. SAEs occurring during the Observation Period will be recorded as SAEs.

Also, AEs that were ongoing at the time of a patient's completion of the TR03 core study are recorded as medical history in the TR03 extension study.

A treatment-emergent AE (TEAE) will be defined as one starting or worsening on or after the first dose of study medication during the extension study. If the start date is missing, the event is assumed to be treatment emergent.

For patients who complete study treatment through the Visit 14/End of Treatment visit, Titration Period AEs are those with an onset date from first dose date of the extension study through (first dose date + 27 days). Treatment Period AEs are those with an onset date from first dose date of the extension study through (first dose date + 349 days). Washout and Safety Follow-up AEs are those with an extension study onset date of (first dose date + 350 days) through (first dose date + 363 days). For patients who are treated and who discontinue study drug use prior to the Visit 14/End of Treatment visit yet remain on-study, AEs with an onset date on or after the first dose date of the extension study will be considered Treatment Period AEs.

For the purpose of inclusion in TEAE table summaries, incomplete AE onset and end dates will be imputed as described below.

For incomplete AE onset dates:

- If the day is missing but the month and year are known:
    - If the month and year are different from the month and year of the first dose of study drug, then use the first day of the month as the imputed onset date.
    - If the month and year are the same as the month and year of the first dose of study drug, and the end date (after any imputation) is on or after the first dose of study drug, then use the date of the first dose of study drug as the imputed onset date.
    - If the month and year are the same as the month and year of the first dose of study drug, and the end date (after any imputation) is prior to the date of the first dose of study drug, then use the end date as the imputed onset date.
- If the month is missing but the year is known (day can be either missing or known):
    - If the year is different from the year of the first dose of study drug then use Jan. 1st of the reported year as the imputed onset date.

  - If the year is the same as the year of the first dose of study drug and the end date (after any imputation) is on or after the first dose of study drug then use the date of the first dose of study drug as the imputed onset date.
  - If the year is the same as the year of the first dose of study drug and the end date (after any imputation) is prior to the date of the first dose of study drug, then use the end date as the imputed onset date.
- If the start date is completely missing, the event is assumed to be treatment-emergent.

For incomplete AE end dates:

- If the day is missing but the month and year are known then use the last day of the month as the imputed end date.
- If the month is missing but the year is known (and the day is either missing or known) then use Dec. 31st of the year as the imputed end date.

Adverse events will be coded according to MedDRA (version to be delineated in the clinical study report).

All AE summary tables will present system organ class (SOC) and preferred term (PT), will include counts of patients, and will be based on TEAEs. SOC will be displayed in descending order of frequency overall and then alphabetically. PT will be displayed in descending order of frequency overall and then alphabetically within SOC. A patient with two or more AEs within the same level of summarization will be counted only once in that level using the most extreme incident. Percentages will be based on the number of patients in the safety population.

In all AE summary tables, TEAEs will be presented in descending order of incidence from the SOC with the highest total incidence to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal then the SOCs will be presented in alphabetical order. Within each SOC, the PTs will also be presented in descending order of total incidence among the active treatment arms with ties at the PT level being presented in alphabetical order. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the safety population.

9.1.1. Incidence of Adverse Events

An overview summary of the number and percentage of patients with any TEAE and the total number of TEAEs recorded will be presented for: patients experiencing any TEAE, any treatment-emergent SAE, any related TEAE, any TEAE by maximum intensity, and any TEAE by treatment period for the Treatment Period and Washout and Safety Follow-up Period.

The overview summary will be repeated for the Treatment Period and Washout and Safety Follow-up Period. For an AE that is reported during more than one of these periods, the earliest period of onset will be used in the incidence calculation. Additionally, the overview summary will be repeated for the Titration Period. Since the Titration Period is a subset of the Treatment Period, AEs will be reported in both periods, where applicable.

Summaries of the total number of TEAEs and the number and percentage of patients with at least one TEAE will be provided by SOC and PT.

A summary of the total number of AEs occurring during the Observation Period (captured in the TR03 extension study medical history form) and the number and percentage of patients with at least one AE during the Observation Period will be provided by body system and dictionary term. New medical history for the TR03 extension study (i.e. with an onset date on or after the signing of the informed consent for the TR03 extension study) is captured in the TR03 extension study medical history form.

All AEs will be presented in a data listing for the safety population.

9.1.2. Relationship of Adverse Events to Study Drug

Association or relatedness to the study medication will be graded as either "probably," "possibly," or "unlikely." For the purpose of summarization, AEs will be dichotomized into "related" (probably and possibly) and "unrelated" (unlikely).

A summary of TEAEs by relationship ("related", "unrelated") to study drug will be presented in a table by incidence of occurrence. A patient with two or more AEs within the same level of summarization will be counted only once in that level using the most related category. TEAEs that are missing a relationship will be presented in the summary table as "related" but will be presented in the data listing with a missing relationship.

9.1.3. Severity of Adverse Events

The severity of all AEs will be graded by the investigator as Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A summary of TEAEs by severity will be presented. The severity that will be presented represents the most extreme severity captured on the eCRF page (Grade 1 through Grade 5 with Grade 5 being the most severe). A patient with two or more AEs within the same level of summarization will be counted only once in that level using the most severe incident. TEAEs that are missing severity will be presented in tables as "Severe" (i.e. Grade 3) but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of patients in the safety population.

The summary of TEAEs by severity will be repeated for the Treatment Period and Washout and Safety Follow-up Period. For an AE that is reported during more than one of these periods, the earliest period of onset will be used in the incidence calculation. Additionally, the summary will also be repeated for the Titration Period. Since the Titration Period is a subset of the Treatment Period, AEs will be reported in both periods, where applicable.

9.1.4. AEs Leading to Treatment Discontinuation

The incidence of AEs leading to study drug discontinuation will be summarized by SOC and PT and will be presented in a data listing. This listing will be a subset of the full listing of all AE information.

9.1.5. SAEs and Deaths

A summary of the total number of treatment-emergent SAEs and the number and percentage of patients with at least one treatment-emergent SAE will be provided by SOC and PT. An additional summary of all SAEs will be provided, broken down by the AE severity grade and investigator assessment of relationship to treatment. The summaries will also be presented separately for the Treatment Period and the Washout and Safety Follow-up Period.

A summary of the total number of SAEs during the Observation Period and the number and percentage of patients with at least one SAE during the Observation Period will be provided by SOC and PT. An additional summary of all SAEs during the Observation Period will be provided, broken down by the AE severity grade and investigator assessment of relationship to treatment.

All SAEs and fatal AEs will be presented in data listings for the safety population. These listings will be subsets of the full listing of all AE information.

9.1.6. AEs of Special Interest

The following AEs of special interest are noted: nausea, vomiting, constipation, somnolence, sedation, dizziness and vertigo. For each of these AEs, summary tables of incidence and prevalence will be prepared that look at the number of days from the start of treatment until first onset and duration of the AE in days for all patients and by gender.

The summary of TEAEs by severity will be repeated for each AE of special interest overall and for the Treatment Period and Washout and Safety Follow-up Period. The severity that will be presented represents the most extreme severity captured on the eCRF page (Grade 1 through Grade 5 with Grade 5 being the most severe). A patient with two or more AEs within the same level of summarization will be counted only once in that level using the most severe incident. TEAEs that are missing severity will be presented in tables as “Severe” (i.e. Grade 3) but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of patients in the safety population. For an AE that is reported during more than one of these periods, the earliest period of onset will be used in the incidence calculation. Additionally, the summary will also be repeated for the Titration Period. Since the Titration Period is a subset of the Treatment Period, AEs will be reported in both periods, where applicable.

9.1.7. Abuse-Potential Related AEs

Although nalbuphine is not a controlled substance in the US or Europe, AEs of special interest that suggest a possible addiction or abuse potential or withdrawal will be specifically analyzed to screen for these effects. These AEs, obtained from the list provided by Love et al (2013) [see Section 13.2] will be designated as such in the study data base.

The overview AE summary will be repeated for abuse-potential related AEs. Summary tables of incidence and prevalence for these events will be prepared that look at the number of days from the start of treatment until first onset and duration of the AE in days for all patients and by gender.

The summary of TEAEs by severity will be repeated for abuse-potential related AEs overall and for the Treatment Period and Washout and Safety Follow-up Period. The severity that will be

presented represents the most extreme severity captured on the eCRF page (Grade 1 through Grade 5 with Grade 5 being the most severe). A patient with two or more AEs within the same level of summarization will be counted only once in that level using the most severe incident. TEAEs that are missing severity will be presented in tables as "Severe" (i.e. Grade 3) but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of patients in the safety population. For an AE that is reported during more than one of these periods, the earliest period of onset will be used in the incidence calculation. Additionally, the summary will also be repeated for the Titration Period. Since the Titration Period is a subset of the Treatment Period, AEs will be reported in both periods, where applicable.

9.2. Other Safety Assessments

9.2.1. SOWS

The SOWS is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the patient classifies as: 0="not at all", 1="a little", 2="moderately", 3="quite a bit", and 4="extremely". In this study, patients will complete the SOWS daily, starting at the TV14, End of Treatment visit through to the Washout and Safety Follow-up Period visit. The SOWS will also be completed at the Premature Discontinue of Study Drug Treatment visit. As with all patients who are discontinued from study drug, the patient will complete a daily SOWS scale for the two weeks following the last dose of study drug (unless consent is withdrawn).

To evaluate the daily changes in the SOWS during the Washout Period after cessation of treatment, each of the 16 symptom items will be summarized for each of the first 14 days beginning with the End of Treatment visit as frequencies and percentages of patients. No formal analysis will be undertaken. Additionally, the sum of all non-missing responses for the 16 items (SOWS total score) will be derived and similarly presented for each of those 14 days.

The change from the End of Treatment visit (defined as the maximum SOWS total score across days from the End of Treatment visit date to 7 days following the End of Treatment visit date), to the Washout and Safety Follow-up visit (defined as the SOWS total score on the date of the Washout and Safety Follow-up Period or the latest date following the End of Treatment Visit and before the Washout and Safety Follow-up visit) will be summarized using descriptive statistics for each treatment group.

A categorical summary will also be provided for the number and percentage of patients by their highest observed SOWS total score during the 14-day (washout) period already defined. The categories will be: $\leqslant$10, 11-20, 21-30, 31-40, 41-50, 51-60, >60. No formal analysis will be undertaken.

Maximum SOWS symptom score (defined for each patient for each day of the Washout and Safety Follow-up Period as the maximum (i.e. worst) non-missing score across all 16 symptom items) will be summarized using descriptive statistics for each treatment group.

9.2.2. Neurological Examination

A categorical summary of the number and percentage of patients by result (normal, abnormal-NCS, abnormal-CS, not done) will be presented for each neurological condition by study visit. No formal analysis will be undertaken.

9.3. Clinical Laboratory Evaluations

A complete series of laboratory evaluations (including hematology, serum chemistry, serum pregnancy and urine pregnancy (both if applicable) and urinalysis will be obtained according to the Schedule of Events. The required clinical laboratory tests are listed in Section 13.1.
Clinically-significant worsening in laboratory findings following start of Study Drug treatment will be recorded as AEs and these will be repeated for verification. Clinically-significant findings noted prior to the start of Study Drug treatment will be recorded as Medical History. The recorded AE will indicate the underlying abnormality or diagnosis as opposed to the observed deviation in laboratory results if the diagnosis is known (e.g. “acute Hepatitis A” is preferable to “ALT increased”).
Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE will be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, tests will be repeated to document resolution or stability of the abnormality.

All summaries will be based on the conventional units of measurements.

Clinical safety laboratory data will be summarized descriptively at baseline and all post-baseline visits as detailed in the Schedule of Events. Change from baseline summary statistics (n, mean, SD, median, minimum, maximum) will also be provided for all post-baseline visits. Summaries of safety laboratory parameters will include the first measurement of each scheduled assessments but repeat assessments (except as already described for the determination of the Baseline value of interest) done at the same study time point will not be included in summary calculations.

Laboratory data will also be listed by patient, and visit. Listings will include scheduled, unscheduled, and repeat evaluations.

9.3.1. Hematology

All hematology lab tests with a numerical result will be summarized and listed as described in Section 9.3.

9.3.2. Serum Chemistry

All chemistry lab tests with a numerical result will be summarized and listed as described in Section 9.3.

9.3.3. Urinalysis

All urinalysis lab tests with a numerical result will be summarized and listed as described in Section 9.3.

9.3.4. Serum Pregnancy

Serum pregnancy test results will be presented in a data listing.

9.4. Vital Sign Measurements

Blood pressure and HR will be taken while sitting or semi-recumbent for at least 5 minutes. Temperature may be taken by any standard method (e.g., oral, tympanic, rectal, etc.), but the method must be recorded. Vital signs will be obtained according to the Schedule of Events presented in the protocol.

Vital signs will be summarized during the Observation Period, at Baseline and at each assessment time point during the post dosing periods.

All vital sign data will be presented in a data listing.

9.5. Physical Examination

A complete physical examination will be performed according to the Schedule of Events as described in the protocol. Any clinically significant worsening after the start of Study Drug treatment will be reported as an AE. Clinically significant findings observed prior to start of Study Drug treatment will be recorded as part of the medical history.

Physical examination details regarding abnormal findings will be summarized and listed with the AE and medical history information.

9.6. Electrocardiogram

A standard 12-lead ECG will be obtained according to the Schedule of Events as detailed in the protocol. ECGs will be read locally for clinical significance and centrally for ECG intervals (PR, RR, QRS, QT and QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities such as left ventricular hypertrophy, pathological Q-waves, etc. Clinically significant worsening in ECG findings following start of study drug treatment will be recorded as AEs. Clinically significant findings noted prior to the start of study drug treatment will be recorded as Medical History.

ECG summaries and listings will be provided by a core cardiac laboratory and will be described further in a separate ECG analysis plan.

10. Pharmacokinetic (PK) and Pharmacokinetic (PK)/Pharmacodynamic (PD) Analyses

All PK and PD analyses will be performed by PPD's PK group. The PK/PD analyses will be described further in a separate PK/PD analysis plan.

11. Interim Analyses and Data Monitoring

No interim analyses or data monitoring committee meetings are planned for this study.

12. References

1. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf].
2. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, Augustin M, Szepietowski JC, Ständer S. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol. 2012 Sep;92(5):502-7.
3. Siebenhaar F, Fortsch A, Krause K, Weller K, Metz M, Magerl M, Martus P, Church MK, Maurer M. Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial. Allergy 2013; 68: 949-952.
4. Stander S, Augustin M, Reich A, Blome C, Ebata T, Phan NQ, Szepietowski JC; International Forum for the Study of Itch Special Interest Group Scoring Itch in Clinical Trials. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. Acta Derm Venereol. 2013 Sep 4;93(5):509-14.

13. Appendices

13.1. Clinical Laboratory Tests

Hematology:
Hemoglobin
Hematocrit
Red Blood Cell Count
White Blood Cell Count
Platelet Count
White Blood Cell Differential

Urine:
Urinalysis
Pregnancy

Serum Pregnancy:
β-Human Chorionic Gonadotropin (HCG) (women of childbearing potential regardless of sexual activity)

Serum Chemistry:
ALT
Albumin
Alkaline Phosphatase
AST
Bicarbonate
Blood Urea Nitrogen (BUN)
Carbon Dioxide
Calcium
Chloride
Creatinine
Gamma-glutamyl transferase
Glucose
LDH
Phosphorus
Potassium
Sodium
Total Bilirubin
Total Protein
Uric acid

13.2. List of Abuse-Potential Associated Adverse Events

From Love et al (2013): "Proposed Query to Capture Abuse-Associated Adverse Events," College on Problems of Drug Dependence, 75th Annual Meeting, San Diego, CA

******** SELECTED ABUSE-RELATED ADVERSE EVENTS ********;
"Abnormal behaviour", "Abnormal dreams", "Abnormal sleep-related event", "Accidental death", "Accidental overdose", "Accidental poisoning", "Acute psychosis", "Affect lability", "Affective disorder", "Aggression", "Agitation", "Alice in wonderland syndrome", "Altered state of consciousness", "Altered visual depth perception", "Amnesia", "Amnestic disorder", "Amphetamines", "Amphetamines positive", "Analgesic therapy", "Anger", "Anhedonia", "Anterograde amnesia", "Antisocial behaviour", "Antitussive therapy", "Anxiety", "Anxiolytic therapy", "Apathy", "Asocial behaviour", "Asthenia", "Attention-seeking behaviour", "Balance disorder", "Belligerance", "Benzodiazepine drug level", "Blunted affect", "Bradyphenia", "Central nervous system stimulation", "Cognitive disorder", "Completed suicide", "Compulsions", "Confabulation", "Confusional arousal", "Confusional state", "Consciousness fluctuating", "Coordination abnormal", "Deja vu", "Delirium", "Delusion", "Delusion of grandeur", "Delusion of reference", "Delusion of replacement", "Delusional perception", "Delusional disorder, erotomatic type", "Delusional disorder, grandiose type", "Delusional disorder, jealous type", "Delusional disorder, mixed type", "Delusional disorder, persecutory type", "Delusional disorder, somatic type", "Delusional disorder, unspecified type", "Delusions, mixed", "Dependence", "Depersonalization", "Depressed level of consciousness", "Depressive delusion", "Derailment", "Derealisation", "Disinhibition", "Disorientation", "Dissociation", "Dissociative amnesia", "Dissociative identity disorder", "Disturbance in attention", "Disturbance in social behaviour", "Dopamine dysregulation syndrome", "Dopaminergic drug therapy", "Drug abuse", "Drug abuser", "Drug dependence", "Drug dependence, antpartum", "Drug dependence, postpartum", "Drug detoxification", "Drug diversion", "Drug screen positive", "Drug tolerance increased", "Dyslogia", "Dysphoria", "Elevated mood", "Emotional disorder", "Emotional distress", "Energy increased", "Erotomanic delusion", "Euphoric mood", "Executive dysfunction", "Fear", "Feeling abnormal", "Feeling drunk", "Feeling jittery", "Feeling of despair", "Feeling of relaxation", "Flashback", "Flat affect", "Flight of ideas", "Formication", "Hallucination", "Hallucination, auditory", "Hallucination, gustatory", "Hallucination, olfactory", "Hallucination, synaesthetic", "Hallucination, tactile", "Hallucination, visual", "Hallucinations, mixed", "Hangover", "Homicidal ideation", "Homicide", "Hostility", "Hypervigilance", "Hypnagogic hallucination", "Hypnopompic hallucination", "Ideas of reverence", "Illogical thinking", "Illusion", "Impaired driving ability", "Impaired reasoning", "Impulsive behaviour", "Inappropriate affect", "Incoherent", "Intentional drug misuse", "Intentional overdose", "Intentional self-injury", "Irritability", "Jamais vu", "Jealous delusion", "Judgement impaired", "Loose associations", "Magical thinking", "Mania", "Maternal use of illicit drugs", "Memory impairment", "Mental disability", "Mental disorder", "Mental impairment", "Mental status changes", "Miosis", "Mood altered", "Multiple drug overdose", "Multiple drug overdose accidental", "Multiple drug overdose intentional", "Muscle relaxant therapy", "Mydriasis", "Nasal necrosis", "Nasal septum perforation", "Nasal septum ulceration", "Needle track marks", "Neonatal complications of substance abuse", "Overdose", "Panic attack", "Panic reaction", "Paramnesia",

"Paranoia", "Parasomnia", "Paroxysmal perceptual alteration", "Persecutory delusion", "Personality change", "Personality disorder", "Physical assault", "Poisoning", "Polysubstance dependence", "Prescription form tampering", "Product tampering", "Product used for unknown indication", "Psychomotor hyperactivity", "Psychomotor retardation", "Psychomotor skills impaired", "Psychotic behaviour", "Psychotic disorder", "Reactive psychosis", "Restlessness", "Retrograde amnesia", "Sedation", "Self-injurious behaviour", "Self-injurious ideation", "Sensory disturbance", "Sensory level abnormal", "Sleep sex", "Sleep terror", "Slow speech", "Somatic delusion", "Somatic hallucination", "Somnolence", "Staring", "Steroid withdrawal syndrome", "Stupor", "Substance abuse", "Substance abuser", "Substance use", "Substance-induced mood disorder", "Substance-induced psychotic relief", "Suicidal behaviour", "Suicidal ideation", "Suicide attempt", "Suspiciousness", "Tangentiality", "Thinking abnormal", "Thought blocking", "Thought broadcasting", "Thought insertion", "Thought withdrawal", "Toxicity to various agents", "Transient global amnesia", "Transient psychosis", "Treatment noncompliance", "Urine amphetamine", "Urine amphetamine positive", "Violence-related symptom"