16.1.1 Protocol and Protocol Amendments

This section contains the following documents:

Original protocol version 1.0 dated 24 June 2014

Protocol Amendment 1 version 2.0 dated 11 March 2015

Protocol Amendment 2 version 3.0 dated 02 June 2016

CLINICAL PROTOCOL

Protocol Number:	**TR03ext**
Version Number:	**1.0**
Version Date:	**24 June 2014**
EudraCT No.	**2013-005628-41**
Protocol Title:	**An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients**
Study Sponsor:	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, Connecticut 06510 United States Phone: (203) 304-2499 www.trevitherapeutics.com

Investigators: Multicenter

Research Facilities: Multicenter

Institutional Review Board/ Independent Ethics Committee: Multicenter

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26 June 2014
Date

INVESTIGATOR SIGNATURE PAGE

I have read the attached protocol entitled A Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of the Safety and Anti-Pruritic Efficacy of nalbuphine HCl ER Tablets in Prurigo Nodularis Patients dated **24 JUNE 2014** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 of the CFR, Parts 11, 50, 54, 56, and 312 or equivalent regulatory body regulations/guidelines, as applicable.

I agree to ensure that Financial Disclosure Statements will be completed by:

- Myself (including, if applicable, my spouse [or legal partner], and dependent children)
- My subinvestigators (including, if applicable, their spouses [or legal partners], and dependent children)

The Financial Disclosure Statements will be completed before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Trevi Therapeutics, Inc.

Principal Investigator:

_____ _____
Name of Principal Investigator Date

_____
Institution or Clinical Practice

_____
Signature

1 STUDY SYNOPSIS

Title	An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients
Sponsor	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, Connecticut 06510 United States Phone: (203) 304-2499 www.trevitherapeutics.com
Protocol Number	TR03ext
Version and Date	Version 1.0 dated 23 JUNE 2014
Indication	Prurigo Nodularis (PN)
Investigational Product	nalbuphine hydrochloride (HCl) extended-release (ER) tablets
Active Ingredient	nalbuphine hydrochloride
Route of Administration	Oral
Duration of Study	The total study duration for any individual patient will be up to 52 weeks. Patients will receive drug treatment for up to 50 weeks.
Study Phase	Phase 2/3
Study Design	Open label
Planned Sample Size	No *a priori* planned sample size is designated for this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., up to 60 patients)
Total Number of Centers	Up to 7 sites in North America and Europe
Primary Objective	• To evaluate the safety and tolerability of nalbuphine HCL ER tablets during a drug treatment period of up to 50 weeks.
Secondary Objectives	• To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Period

	Week 4. • Assess skin lesion improvement using the metrics of the PAS • Changes in Patient-Reported Outcome measures (worst itch NRS, average daily itch intensity NRS, VRS (itchy, burning and stinging), ItchyQoL, MOS Sleep-R, HADS and PBI-P) during the Treatment Period • the percentage of patients utilizing various doses of nalbuphine ER tablets by Study Week • the frequency and reasons for down-titration and treatment discontinuation during the study • the changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets • the number of days of use of rescue medications for itching.
Exploratory Objectives	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) in skin biopsies taken at the last Treatment Period Visit when compared to biopsy material assessed during study TR03 (selected sites only).
Selection Criteria	**Inclusion Criteria:** Patients must meet all of the following criteria to be eligible: 1. Have been adequately informed of the nature and risks of the study and have given written informed consent at or prior to Visit 1a. 2. Have completed participation in the TR03 study. Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6. 3. Agree to comply with the contraception requirements as below: Female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation,

	Essure procedure, or spermicide). 4. Ability and acceptance to provide written informed consent. 5. Willing and able to comply with study requirements and restrictions 6. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.
Selection Criteria	**Exclusion Criteria:** If a patient meets any of the following criteria, he or she is *not* eligible: 1. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study. 2. Known hypersensitivity or allergy to nalbuphine or formulation components. 3. Is a pregnant or lactating female.
Study Treatment Allocation	All patients who are enrolled into the study will receive active treatment with nalbuphine HCl ER tablets.
Study Procedures	Visit 1a of the TR03ext study is temporally the same visit as TR03 Visit 6. Informed consent for this study will be obtained during Study TR03 Visit 6, or earlier. Subjects who do not consent by the end of the TR03 study visit 6 are no longer eligible for the extension study. Study TR03 Visit 6 procedures in common with Study TR03ext Visit 1a procedures do not have to be repeated. <u>For All Patients:</u> For all patients, TR03 extension study Visits (both during the Treatment Period and Observation Period) will include recording of vital signs, completion of PRO questionnaires, assessment of AEs, and recording of concomitant medications. On Visit 1a, patients will either enter directly into the drug Treatment Period or into a no-drug Observation Period based on their reported <u>worst</u> itch NRS scores on that Visit day. **<u>Patients with NRS >2 enter the Treatment Period:</u>** Patients with <u>worst</u> itch NRS > 2 at Visit 1a will start in the drug Treatment Period of the study and will receive Study Drug starting with an evening 30 mg dose (to be taken at home), after the Treatment Visit 1a procedures have been completed. Receipt of the first dose of study drug will define Treatment Period Day 1. Treatment Visit 1a for these patients is also Treatment visit 1 (TV1). Subsequent visits will be defined as TV2, TV3, etc. In addition, during the

	time period of dose titration, information will be obtained via telephone communication; these will be defined as TC1, and TC2. The dose will be titrated for up to 4 weeks, after which time the dose achieved (90mg BID, 120mg BID or 180 mg BID) as of the end of Treatment Week 4 will be maintained up to an additional 46 weeks (with the exception of a single allowable down titration permitted). Patients requiring a second down-titration after Treatment Period week 4 must be discontinued from the study (see Table 3 dosing schedule). For patients transitioning from the Observation period, the total time in the Treatment Period plus any time in the Observation Period will be a total of 50 weeks. Safety laboratory data and blood for PK, ECGs, and physical examinations including the PAS assessment will be performed periodically according to the Schedule of Events (See Appendix 1). Schematic descriptions of the study can be found in Appendix 2. All patients on drug treatment will enter a 2-week wash-out and safety follow up period following end of the Treatment Period with procedures conducted according to the Schedule of Events (See Appendix 1). **Patients with NRS ≤ 2** enter the Observation Period: Patients with NRS ≤ 2 at Visit 1a will enter into an extended screening period, the Observation Period (no drug treatment), of the study and will be followed for up to 12 weeks. Visit 1a for these patients is also Observational Visit 1 (OV1). Subsequent visits will be defined as OV2, OV3 and OV4 and will occur at approximately monthly intervals for the next 3 months. During this Observation period, patients who report NRS score increases to >2 at any one of their Observation Visits will be eligible to enroll immediately into the Treatment Period of the study and that same visit is now referred to as Visit1b. Patients will receive open-label Study Drug starting with an evening 30 mg dose (to be taken at home), after the Visit 1b procedures have been completed. Receipt of the first drug will indicate the start of their Treatment Period and enrollment into the study. The duration of the Treatment Period for such a patient will equal 50 weeks minus the number of weeks spent in the Observation Period (i.e., the sum of time in the Observation Period and Treatment Period will not exceed 50 weeks). Patients in the Observation Period whose NRS scores remain ≤2 over the 12 weeks will be screen failed from the study at the end of that time period.
Safety Assessments	Safety will be assessed based on adverse events (AEs), clinical laboratory measurements, 12-lead electrocardiogram

	(ECG), vital signs and physical examinations.
Efficacy Assessments	**Efficacy Measurements:** • worst itch intensity (from NRS) • average itch intensity (from NRS) • VRS (itchy, burning and stinging) • ItchyQoL • MOS Sleep-R • HADS • PAS • PBI-P • Frequency, pattern, and reasons for dose titration • Use of rescue medications for itching At selected sites: • Nerve fiber density (histology) at Baseline and at the final Treatment Period visit • MOR/KOR density (histology, Western Blot) at Baseline and at the final Treatment Period visit.
Pharmacokinetic Assessments	Blood samples for nalbuphine plasma concentration (and metabolites as needed) will be collected periodically according to the Schedule of Events (Appendix 1).
Study Endpoints	**Primary Endpoint:** • A description of the incidence and nature of TEAEs during Treatment Weeks 5- 50 **Secondary Endpoints** 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. Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time. • Assess skin lesion improvement using the metrics of the PAS • Change from Baseline in Patient-Reported Outcome measures (worst itch NRS, average daily itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS) by Treatment Period study visit and Baseline NRS score categories • Change between Baseline and 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 • To describe the changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets • The number of days of use of rescue medications for itching. **Exploratory Endpoint** Impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken at the last Treatment Period Visit when compared to biopsy material assessed during study TR03. (selected sites only).
Statistical Methodology	**Efficacy:** All efficacy endpoints will be evaluated through the generation of 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. **Safety:** The incidence of AEs will be summarized through the presentation of proportions by MedDRA body system classification and preferred term. Vital signs and laboratory data will be summarized using continuous-based descriptive statistics (n, mean, SD, median, minimum, maximum). The extent and duration of use of rescue medications will be similarly summarized using descriptive statistics. Summary statistics for AEs with onset during the Observation Period will be separately summarized. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomic and Therapeutic Class
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CNS	Central nervous system
CRF	Case report form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
e-diary	Electronic daily patient diary
ER	Extended release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&E	Hematoxylin and eosin
HADS	Hospital Anxiety and Depression Scale
HCG	Human chorionic gonadotropin
HCl	Hydrochloric acid
HD	Hemodialysis
H pylori	Helicobacter pylori
HR	Heart rate
ICF	Informed consent form
ICD-10	International Classification of Diseases, 10th revision
ICH	International Conference on Harmonization
IFSI	International Forum for the Study of Itch
IRB	Institutional Review Board

Abbreviation	Definition
IUD	Intra-uterine device
KOR	Kappa Opiate Receptor
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MOR	Mu Opiate Receptor
MOS	Medical Outcomes Study
MITT	Modified Intent-To-Treat
NONMEM	Non-linear mixed effects modeling
NRS	Numerical Rating Scale
OV	Observation Period Visit
OTC	Over-the-counter
PAS	Prurigo Activity Score
PBI-P	Patient Benefit Index, pruritus version
PD	Pharmacodynamic(s)
PK	Pharmacokinetic
PN	Prurigo Nodularis
PRO	Patient-Reported Outcome; In this study, PRO instruments administered at the site are as follows: NRS, VRS, ItchyQoL, PBI-P, MOS Sleep-R, HADS
QoL	Quality of Life
RR	Respiratory rate
SAE	Serious adverse event
SD	Standard deviation
TC	Telephone Call
TV	Treatment Period Visit
UP	Uremic Pruritus
VRS	Verbal Rating Scale
WHO	World Health Organization

3 INTRODUCTION

3.1 PRURIGO NODULARIS AND STUDY RATIONALE

3.1.1 General Information on Prurigo Nodularis

Prurigo Nodularis (PN) is an intensely pruritic dermatologic condition with the presence of papules as well as nodules with excoriations and ulcerations. The basis of PN is a pre-existing severe and chronic pruritus of various etiologies (see Table 1). The pruritus leads to scratching. However, the etiology or predisposing factors leading to the development of papules and nodules of PN are largely unknown (Eigelshoven et al 2009; Valdya and Schwartz 2008; Lee and Shumack 2005). Iking et al (2012) reports that in the past few years the hypothesis for the etiology of PN as being a reaction pattern due to a "vicious cycle of repeated itching and scratching" is gaining wider acceptance in the medical community.

With regard to the types of pre-existing chronic pruritus conditions that have been reported in PN patients, Table 1 summarizes data reported by Iking et al (2012) in their study of PN patients (N=108). Pruritus secondary to multi-factorial etiologies ("Mixed Origin") was the most common source attributed to the cause of the chronic pruritus. The majority of the "mixed origin" patients had a combination of dermatological and systemic diseases or a combination of several systemic disorders.

Iking et al (2012) did not attribute any cases of PN to an underlying diagnosis that was solely psychological in origin. In the subjects who were diagnosed with PN from mixed origin etiologies (summarized in Table 1), the authors attributed psychological factors related to chronic pruritus etiology to be present in 5.6% of the PN subjects categorized as having mixed (multi-factorial) origin pruritus. In a study focused on understanding psychosomatic/psychiatric dimensions related to chronic itch, Schneider et al (2006) reported on 44 PN patients. The authors stated that 34% of subjects had no accompanying psychiatric diagnosis and 46.8% were given a diagnosis of "psychological or behavioral factors associated with disorders classified elsewhere" (ICD-10 code F54) –indicating that psychological factors may play a role in the development and course of the condition. Payne et al (1985) reported psycho-social problems may have been relevant in about 33% of the studied 42 subjects that were adequately questioned.

Table 1: Etiology of Chronic Pruritus Reported in Prurigo Nodularis Patients (N=108)

Origin of Pruritus by Organ System	Number of Patients (%)	% Mixed with Organ Category Contribution to Chronic Pruritus	Most Common Disease
Mixed (pruritus of multi-factorial etiologies)	64 (59.3%)	Dermatological Disease (19.4%)	Atopic diathesis
		Systemic Diseases (70.9%)	Sorbitol Intolerance
			Lactose Intolerance
			Iron Deficiency
			H pylori Infection
			Diabetes Mellitus
			Renal Failure
		Neurological Disease (4.1%)	Chronic pain Syndrome
			Neuropathy
			PUVA-pain
		Psychological Factors (5.6%)	Psychological Factors (non-specific)
Origin of Pruritus by Organ System	Number of Patients (%)	Most Common Disease	
Dermatological	20 (18.5%)	Atopic diathesis/dermatitis	
Systemic	8 (7.4%)	Sorbitol Intolerance	
		Lactose Intolerance	
		Hepatitis C	
		H pylori infection	
		Iron Deficiency	
		Diabetes Mellitus	
Unknown	14 (13%)	-	
Neurological	2 (1.9%)	Brachio-radial Pruritus	
Psychological	0 (0%)	-	

Source: Iking et al (2012)

Iking et al (2012) reported that the median value of the NRS average intensity pruritus measured 8 on a rating scale with anchor points of zero (no pruritus)-10 (worst imaginable pruritus). Itch intensity scores ≥ 7 are considered severe in terms of itch intensity and itch intensity scores ≥ 3 are considered moderate in terms of itch intensity (Stander et al 2013). Accioly-Filho et al (2000) reports that once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop as PN is very resistant to therapeutic intervention strategies. Papoiu et al (2013) report a central nervous system relationship to the itch-scratch cycle.

The authors showed that there is a complex interaction of sensory, motor and emotional components based on their investigation of using real-time flare brain MRI imaging and psychophysical ratings of itch relief or pleasurability of scratching conducted in healthy volunteer experimental subjects.

Eigelshoven et al (2009) reports that patients present with excruciating pruritus that is usually anatomically symmetrical and mainly involves the extensor aspects of the extremities, the shoulders, chest and sacral regions with the appearance of typical lesions. Payne et al (1985) reported in a study of 46 subjects that the patients came from all social classes and racial groups, almost equally divided by gender and with a mean age of 39.5 years at the time of PN onset. Iking et al (2012) reported in their study that the patients were distributed in age between 11.9 years - 95.6 years with a median age of 61.9 years and there were more females than males affected by the disease.

Weigelt et al (2010) summarized the characteristic histological findings in PN that include the presence of thick compact orthohyperkeratosis; folliculosebaceous units in nonvolar skin in conjunction with a thick and compact cornified layer; irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils.

In terms of treatment options for PN, there have been a variety of medical interventions discussed. Hogan et al (2012) recently reviewed the therapies discussed in the literature that included topical, systemic and intra-lesion steroids administration; antihistamines; anxiolytics; opiate receptor antagonists; thalidomide; gabapentin; capsaicin cream; topical anesthetics; occlusive therapies; ultraviolet light; and reports that they had "mild to moderate success at best". The authors also comment on the potential imbalance in the mu-kappa opiate receptor system and mention the possibility of studying the kappa agonist nalfurafine (see section 3.1.3.1, where nalfurafine was used as a positive control in Sponsor's preclinical substance P mouse model of itch investigation). Spring et al (2014) reported on the use of methotrexate and the need for chemotherapeutic related regular medical monitoring. Liu et al (2013) and Kanavy (et al 2012) both reported on lenalidomide is case reports, but the drug led to side effect of a reversible myopathy in one of the subjects. Accioly-Filho (2000) reported the condition is "notoriously resistant to therapy". Iking et al (2012) and Valdya and Schwartz (2008) reported a significant impact on the patient's quality of life (2008). Spring et al (2014) report PN to be debilitating condition and a therapeutic challenge where conventional treatments with steroids, standard anti-pruritic agents, phototherapy and immune-suppressors often fail.

3.1.2 Potential Mechanism of Prurigo Nodularis Pathophysiology

3.1.2.1 Opiate Neurobiology

The initiating biological event in the skin is unclear but assumed to patho-physiologically result from a complex cross talk of different skin cells. The neurobiology of opioid peptides may be involved at the peripheral level as part of a reaction to the skin tissue injury. Therapeutic intervention at the peripheral level through opioid pharmacology to

break the scratch-itch cycle via interrupting positive feedback loops that have developed between elements of the peripheral nervous system, immune system and various skin cell interactive dynamics may be possible. In addition, central nervous system opiate neurobiology may be involved in a positive feedback loop between the tremendous urge to scratch and the pleasurable anti-pruritic relief gotten from scratching that could also be a level of therapeutic intervention using opioid pharmacology.

3.1.2.2 Systems Biology Hypothesis to Prurigo Nodularis Etiology

Diseases that arise from an abnormal interaction between integrated body system networks and exhibit the concept of a positive feedback cycle which lead to an amplification of a biological signal can be discussed using concepts from systems biology (Kitano 2004). The physiological phenomena of a "scratch-itch cycle" ("positive feedback loop") underlying the patient's behavior, the intense ("amplified") nature of the pruritus and the large areas of body surface involvement in the absence of an active dermatosis suggest a "generalized" process either potentially due to central nervous system circuitry pathophysiology and/or widespread derangement of the dermal-immune-nervous system component interactions. PN may be analogous to chronic regional pain syndrome – a condition where there may or may not be an initiating etiological event, the intensity of pain is severe, the sensation of pain spreads to wide areas of the body surface and the condition is regarded as a systemic disease that involves both the central and peripheral components of the nervous system along with interactions with the immune system (Schwartzman et al 2009). Complex regional pain syndrome is completely independent of any potential nociceptive initiating event. Schmelz (2005) reviewed the literature on the evidence of similar biological patterns occurring in chronic pain and chronic itch conditions. Iking et al (2012) reported that on onset, PN was localized in 68.5% of patients with only 31.5% having generalized PN. In the majority of patients (56.5%), a secondary generalization of PN was observed. In the course of PN, only 12.0% still suffered from a localized form of PN.

3.1.2.3 Relevant Cutaneous Peripheral Neurobiology in the Skin

The complex neurochemical/neurohumoral interactions between the cutaneous resident mast cells and epidermal keratinocytes with peripheral non-myelinated type C nerve endings responsible for initiating the behavior of scratching as an evolved protective response to exogenous invading skin irritants is well summarized by Raap et al (2011) and the current understanding of the peripheral neuroanatomy-spinal cord synaptic connections underlying itch is well summarized by Dhand et al (2014). Selected aspects of this neurobiology as they relate to the development of some specifics of the known pathology in PN will be summarized.

The cellular initiation of itch can begin with the mast cell release of histamine that binds to H1 receptors on nerve fibers (Raap et al 2011). Endorphins and other opiate peptides are known to cause histamine mast cell release (Barke et al 1993). Endorphin itch initiation biology may be more direct. Bigiliardi and Bigliardi-Qi (2004) observed that while histamine interaction with nerve fibers may be a source of itch sensation, they summarize evidence for direct opiate peptide interaction with nerve fiber endings expressing endorphin receptors as a contributor to itch sensation initiation.

With regard to the skin cells themselves, keratinocytes are known to produce different neuropeptides that include proopiomelanocortin (POMC), which is a precursor for the opiate peptide beta-endorphin (Bigliardi et al 1998). In addition, mast cell activation can initiate the itch process via non-histamine mediated processes that that lead to substance P presence in the interstitium (Raap et al 2011). Substance P, a neuropeptide member of the tachykinin family, is thought to induce itching in humans via histamine degranulation from mast cells (Potenzieri et al 2012). Keratinocytes are known to express Substance P receptors (Peters et al 2006) and opiate receptors (Bigliardi et al 1998).

There is also a close link between endorphins and substance P in nerve fibers innervating the epidermis. Opioid receptors destined for insertion onto the distal portions of Type C cutaneous nerve fiber membrane and the neuropeptides (such as substance P) that are capable of release into the interstitium are both synthesized in the same dorsal root ganglion nerve cells and transported to the peripheral nerve processes in the skin (Stein et al 2003).

3.1.2.4 Abnormal endogenous opiates in the skin of PN patients:

Bigiliardi and Bigliardi-Qi (2004) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor expression in the epidermis compared to normal skin. The down regulation was thought to be a biological response to abnormal tissue exposure to large amounts of endogenous opioid ligands such as endorphins. The authors comment that the epidermal skin cells such as the keratinocytes that are no longer binding the opioid ligands possibly leave the ligands available to bind to epidermal nerve endings and thus induce a nerve transmission mediated signal to the CNS resulting in a pruritus sensation.

3.1.2.5 Abnormal substance P level in the skin of PN patients:

Haas et al (2010) reported data showing significantly increased density of dermal substance P nerve fibers both in lesion skin samples as well as normal appearing skin samples from PN patients. The authors concluded that the hyper-innervation by substance P containing sensory nerves may have a role in the itch sensation found in these patients. Molina et al (1992) reports increased nerve fibers containing substance P in PN subjects compared to control group that could be related to the intense pruritus.

3.1.2.6 Inflammatory Component to PN Histology:

Neurogenic inflammation refers to the manifestation of skin diseases related to the malfunctioning of the nervous system – immune system interaction (Steinhoff et al 2003, Peters et al 2006, and Potenzieri et al 2012). Bigliardi et al (1998) conclude that the presence of receptor systems for endorphins and substance P molecules is evidence of an interaction between skin, immune and nervous system. Given the abnormal biology of substance P and endorphins in the skin of PN patients just discussed above, the hypothesis that the induction of an inflammatory component in PN is etiologically related to endorphin-substance P pathobiology is based on the following biological facts:

In addition to being a pruitogen, substance P also has pro-inflammatory and immune-stimulatory activity (Peters et al 2006). Steinhoff et al (2003), Peters et al (2006), and

Potenzieri et al (2012) state that substance P may be an important mediator of cutaneous neurogenic inflammation. T he immune cells that migrate under a pro-inflammatory signal from released substance P are an important source of opioid ligands. The opioid ligand containing immune cells consist of T and B lymphocytes, granulocytes, and monocytes/macrophages (Sehgal et al 2011). As noted by Weigelt et al (2010), part of the characteristic PN histological findings is a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils (granulocytes). The opioid ligands released by immune cells interact with peripheral opioid receptors located on t he cutaneous nerves (Stein et al 2003). Otherwise stated, the cutaneous nerve induced signaling from opioid ligands released by immune cells may be a source of the pruritic signal to the brain.

3.1.3 Rationale for Investigating Nalbuphine HCl ER in Prurigo Nodularis

3.1.3.1 Pre-clinical Animal Data

A preclinical investigation (Covance Study No. 8265903) was undertaken to demonstrate the effects of nalbuphine HCl on substance-P (SubP) induced scratching behavior in the mouse, a standard animal model (Kuraishi et al. 1995). Scratching behavior induced by peripheral stimulation by the pruritogen SubP mimics the characteristics of itch-related scratches in humans (Kuraishi et al. 1995) and Andoh et al 1998). In addition, the SubP induced scratching behavior is not inhibited by the histamine H1 receptor antagonist and elicits responses even in mast cell-deficient mice. Thus, SubP-induced scratches are likely to represent antihistamine-resistant pruritus. The model is relevant to antihistamine-resistant pruritus (Togashi et al 2002 and references cited therein).

The SubP itch mouse model was successfully established and its viability confirmed by assessing the responses using vehicle (phosphate buffered saline, PBS) only group (VEH/VEH) and nalfurafine HCl, a positive comparative control group (PCC/SubP) relative to untreated group (VEH/SubP) group. Briefly, studies were conducted in male C57BL/6 mice. Animals were acclimated to the facility at least three days prior to dosing. On the test day, mice were acclimated to the observation cages for one hour prior to dosing. Mice were then randomly assigned to treatment groups and subcutaneously (SC) dosed with vehicle (PBS), PCC (0.01 or 0.02mg/kg), or the test article nalbuphine (10 or 30mg/kg) (NAL/SubP group), and video recorded for 30 minutes to establish baseline scratching behavior. After the 30-minute baseline recording, mice received either vehicle (0.05 mL PBS) or SubP (250 nM in 0.050 mL) injected intradermally (ID) into the rostral part of the back and video recording continued immediately for an additional hour.

Itching was scored by reviewing the recording and counting the number of scratches over 30 minute periods following SubP (or vehicle) challenge. Itching was defined as scratching with the hind paw at the intradermal injection site (upper right shoulder area). Continuous scratching over one second was counted as one scratch event and paused scratches were considered separate scratching events. Scratching of other sites such as ears and face were not recorded.

Baseline scratching (pre-SubP) was similar for all treatment groups. Following SubP administration in the untreated mice, itching began within 3-5 minutes from administration of the pruritogen. The itch intensity was the highest in the first 30 minutes post-dose. By 60 minutes post-dose, the effect of the SubP injection began to wear off as scratching returned towards baseline levels.

As expected, PCC significantly ($p< 0.001$) decreased the SubP-induced scratching supporting the validity of the itch model. Subcutaneous pre-treatment with PCC resulted in a reduction of 42 and 63% reduction at the 0.01 and 0.02mg/kg dose (from 107 to 62 or 40 scratches, respectively).

Significant reduction in itch ($p< 0.001$) was noted following nalbuphine SC administration with about 43% reduction in itch at the 10 mg/kg dose (from 107 to 61 scratches) and 52% at the 30 mg/kg dose (from 107 to 52 scratches). Though there was a trend for a dose dependence on itch reduction, there was no statistical difference between the tested nalbuphine doses.

In this study, nalbuphine was as effective as PCC (nalfurafine) at reducing SubP-induced itch with no statistical difference between nalbuphine and PCC effect, regardless of the dose.

Ambulation was not suppressed in mice injected with nalbuphine dosed at 10 or 30 mg/kg indicating that attenuation of the scratching was not due to decreased locomotor activity.

3.1.3.2 Neuropharmacologic Basis of the Rationale of Investigating Nalbuphine for the Treatment of Prurigo Nodularis

Gutstein et al (2001) reports that nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor and simultaneously acting as an agonist at the opioid κ-receptor, and thus is a member of the "opioid agonist-antagonist" class of drugs that mechanistically work through this dual pharmacologic process. There is no published literature on the use of the moiety nalbuphine in PN. Nalbuphine was shown to be effective in reducing morphine induced pruritus, a well-known clinical pruritic condition induced by morphine administration. In several published clinical well controlled studies (which are reviewed in detail in the Investigator Brochure Section 5.8), nalbuphine was either equally effective or superior in efficacy when compared to naltrexone or naloxone (both are pure u-antagonists) for the management of morphine induced pruritus.

Neurogenic inflammation (as discussed in Section 3.1.2.6) may induce the secondary phenomena of "central sensitization" (Woolf et al 2011). Central sensitization is a central nervous system pathologic neurobiology change in cell circuitry that results from abnormal peripheral nerve signaling and/or peripheral nerve injury. The net effect of central sensitization is that there is a lowering of neural excitation threshold to external stimulus whereby either nociceptive or low intensity pruritogen cutaneous stimuli induce a high intensity sensation of pruritus (Paus et al 2006). Schmelz (2005) reports on the evidence that there is a mu-kappa opiate gating circuitry in the spinal cord whereby kappa agonist activity would inhibit mu opiate receptor containing cell activation mediated signaling that brings to consciousness the sensation of pruritus. The analysis by Schmelz may be an

example of what Pan (1998) reports as a potentially very general opioid μ-receptor antagonizing function by the opioid κ-receptor. The author reviews the literature on central neural networks where the opioid κ-receptors are located in cell groups that are distinct from the cell groups that contain the opioid μ-receptors and summarizes the evidence that agonism at the pharmacological level of the opioid κ-receptor antagonizes various opioid μ-receptor agonist mediated actions in the brain. This central gating mechanism could be important in countering any potential pruritogenic induced sensation from a peripheral neurogenic inflammatory initiating event in PN.

As discussed in Section 3.1.2.5, there is histological evidence of abnormal substance P presence in skin samples of PN patients. In that regard, an experiment conducted by Trevi Therapeutics indicated that nalbuphine administered subcutaneously significantly ($p<0.001$) suppressed the substance P induced scratching in mice (see Section 3.1.3.1 study summary).

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%. Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. This clinical observation potentially has different anatomical locations for the mechanistic drug effect. S ince Stein et al (2003) reported that inflammation increases both the number of sensory nerve terminals ("sprouting") and disrupts the perineural barrier –thus facilitating opioid access to receptors, there is the possibility that peripherally acting mu antagonist naltrexone action reduced the neural membrane excitation by blocking actions of endogenous endorphins reported by Bigiliardi and Bigliardi-Qi (2004) to be present in the epidermis. In fact, Bigiliardi and Bigliardi-Qi (2004) suggest an opiate antagonist be therapeutically investigated for this reason and also comment on the evidence that mu opiate receptors on epidermal cells may be have a role in skin healing.

However, consideration must also be given to central nervous system opioid pharmacology as a contributing antipruritic effect elicited by naltrexone. At the spinal cord level, Schmelz (2005) commented that the explanation for opiate mu antagonists being capable of reversing experimentally induced itch may be related to the neurobiology of spinal cord level neuronal kappa-mu opioid gating circuits where either a mu antagonist or kappa agonist drug may act to have a pruritus suppressing effect. Supraspinal brain level action related to interference of the circuits related to reward behavior cannot be excluded given that it is known that naltrexone, like nalbuphine, can abolish morphine induced pruritus from morphine administered intrathecally. In addition, opiate receptor neuronal systems are known to be related to the physiological psychology of human reward behaviour and mu antagonist opioid class drugs are known to block the phenomena (Le Merrer et al 2009). Nalbuphine is known to block the effects of mu agonist drugs and induce the opioid withdrawal syndrome (Nubain® label).

3.1.3.3 Nalbuphine Clinical Data in Uremic Pruritus

Mannenti et al (2009) summarized potential pathophysiologic mechanisms for the etiology of uremic pruritus. Included among the postulated uremia induced mechanisms to explain uremic pruritus is neurophysiologic central sensitization "wind up" phenomena related to

immune-inflammatory skin pathology. Mettang and Kremer (2014) in their review of uremic pruritus comment on the recent focus given to the mechanistic hypothesis related to peripheral neuropathic changes and central nervous system pathobiology along with evidence for cutaneous micro-inflammation. The authors state that a therapeutic option may be systemic treatment with mu-opioid receptor antagonist and kappa-opioid receptor agonist. The proposed etiology of uremic pruritus pathobiology may be similar in origin to the neuroinflammatory process discussed in Section 3.1.2.6 as part of the mechanism postulated for the underlying process involved in inducing PN. In should be noted that Lee and Shumack (2005) reported prurigo nodularis occurring in patients with renal failure and Iking et al (2012) report renal failure as a contributing source of chronic pruritus with PN that was attributed to mix origin chronic pruritic conditions (see Table 1).

In clinical study TR01, the effect of oral nalbuphine on pruritus in hemodialysis (HD) patients with uremic pruritus was explored. The results indicated that nalbuphine HCl ER tablets demonstrated ability to suppress itch in a dose response fashion (see Figure 1)

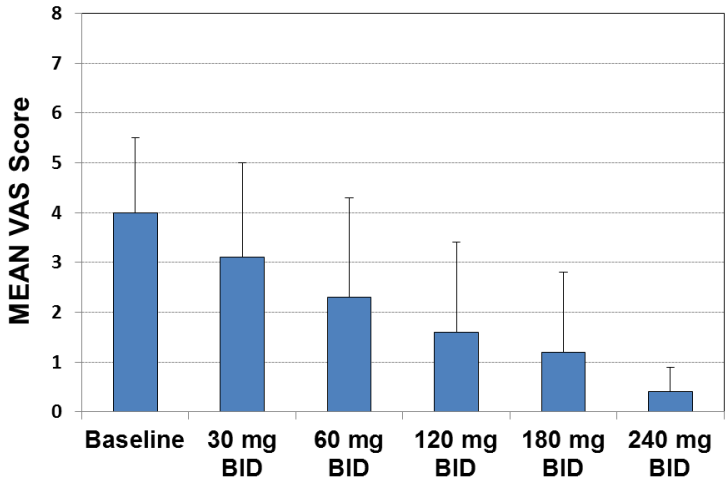

Figure 1: Mean VAS score (SD) for all patients as a function of nalbuphine HCl dose administered as nalbuphine HCl ER tablets. N= 14 except for 180 mg (N=13) and 240 mg (N=4). Source: NAL.001.TR01.PD

The TR01 study is summarized in the Investigator Brochure Section 5.4.3.

Considering the potential similarity in the underlying postulated mechanism between uremic pruritus and PN, nalbuphine would also be expected to be therapeutic in PN patients. As such, Study TR01 in HD patients can be regarded as a proof of concept study for PN.

Based on the clinical evidence of nalbuphine to suppress itch in uremic pruritus, morphine induced pruritus, the substance P induced itch in a pre-clinical study, results and the mechanistic link between the opioid receptors and substance P with the pathophysiology of PN, a clinical investigation of efficacy of nalbuphine on itch in the PN population is justified.

3.2 NALBUPHINE

Nalbuphine HCl is currently available only as a generic medication in an injectable form. An injectable form of nalbuphine is a commercially available approved drug product in the United States since 1979 and originally marketed as Nubain®, on which the presently sold generic injectable formulations are based. It is currently approved for use in the United States for the relief of moderate to severe pain, a supplement to balanced anesthesia, for pre-operative and post-operative analgesia and obstetrical analgesia during labor and delivery. The European Union marketing experience with the injectable form of nalbuphine dates back to 1986 and this was recently reviewed (Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report 2010).

Nalbuphine is not a controlled drug in the United States. An oral dosage form of the drug is not commercially available. Nalbuphine HCl ER is an extended release oral tablet that is currently being developed for the treatment of pruritus.

Nalbuphine is a synthetic opioid with mixed μ antagonist/κ agonist opioid properties. Structurally, nalbuphine is a derivative of 14-hydroxymorphine and is related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone. Nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor while simultaneously acting as an agonist at the opioid κ-receptor (Gutstein 2001; Gharagozlou 2003 and 2006).

3.3 NALBUPHINE HCL ER TABLET CLINICAL DEVELOPMENT

3.3.1 Overall Summary

The safety, tolerability and pharmacokinetics of nalbuphine HCl ER tablets have been characterized following single and multiple ascending dose studies in healthy male and female human subjects, in a single dose study conducted in a dental pain patient population, a multi-dose study conducted in a patient population experiencing osteoarthritic related joint pain and in a multi-dose study conducted in both hemodialysis (HD) population experiencing uremic pruritus and healthy subjects. Studies were conducted with nalbuphine HCl ER tablets or oral solution following single dose administration from 30 mg up to 180 mg and multiple doses ranging between 30 mg BID and 180 mg BID in subjects with normal renal function (up to 3 weeks) and in the hemodialysis population in multiple doses ranging from 30 mg BID to 240 mg BID (up to 15 days).

In subchronic and chronic dose toxicology studies, the CNS was identified as the only target organ when unformulated (neat) nalbuphine was given to dogs at high doses. High systemic drug exposures in dogs caused CNS toxicity (tremors and convulsions) leading to deaths in some cases. It should be noted that the convulsions at high doses of nalbuphine in dogs were most likely Cmax-related. In toxicology studies in which dogs were given high doses of nalbuphine formulated with release-rate controlling excipients that blunt the Cmax, no CNS signs of toxicity were observed. Using the most conservative (lowest) margin of safety determined in all toxicity studies, a minimum 12.4-fold safety margin was calculated respectively for the mean plasma Cmax in subjects with normal renal function at the highest projected clinical dose of nalbuphine (180 mg BID) relative to the plasma Cmax at the lowest NOAEL in dogs given unformulated nalbuphine. Convulsions were

not observed in any of the clinical trials conducted with nalbuphine HCl ER oral tablets in subjects with normal renal function at doses up to 180 mg BID (360 mg daily dose) or in HD patients at doses up to 240 mg BID (480 mg daily dose).

In the course of development, 355 subjects received at least one dose of oral nalbuphine HCl. The most frequently reported adverse events were primarily in the Central Nervous System (CNS) and Gastrointestinal (GI) organ system categories. All these side effects are known to occur with drugs with opioid pharmacologic properties. Most of the side effects noted in the study program were mild to moderate in severity. Initiating drug dosing in both HD patients and healthy subjects at the 30 mg BID dose resulted in good tolerability for subsequent titration related dose escalation.

No drug abuse issues were reported during any of the investigations. The incidence of opiate withdrawal effects noted at drug discontinuation in the patients was investigated in the osteoarthritis pain treatment study when nalbuphine dosing was abruptly stopped following the end-of-study participation. There was an absence of any objective evidence of physical withdrawal symptoms in 85% of the patients and only mild evidence of physical withdrawal symptoms in the remainder of the patients.

3.3.2 Clinical Study TR01 in Hemodialysis Patients and Healthy Volunteers

Pruritus is a frequently identified sign and symptoms of uremia ("uremic pruritus") and is thus a common symptom in patients receiving hemodialysis (Pisoni et al 2006 and Narita et al 2006). Study TR01 was undertaken to assess the safety, PK, and the open label effects on pruritus intensity in hemodialysis subjects. PK and safety was compared to matched healthy control subjects.

Study TR01 was a single site, open label, non-randomized, parallel group, escalating dose study in hemodialysis patients with pruritus of at least mild intermittent intensity receiving intermittent hemodialysis three times a week compared to matched healthy control patients. All subjects were in house during the entire dosing period. Nalbuphine HCl ER tablets were administered orally for up to a 15 day period in hemodialysis patients and 13 days in healthy subjects. Doses were sequentially escalated from 30 mg QD on Day 1 to 30mg BID then to 60 mg BID, 120 mg BID, 180 mg BID and 240 mg BID with dose escalation predicated on PK, safety, and tolerability of the preceding dose. HD Patients remained at each dose level for 2-3 days for a minimum of 4-5 consecutive doses. Healthy subjects remained at each dose level for 3-4 days for a minimum of 5 consecutive doses.

Study subjects were separated into 2 cohorts: Of the 15 hemodialysis patients in Cohort 1, 11 were assigned to dose escalate up to 180 mg BID and 4 were assigned to dose escalate up to 240 mg BID. 13 patients (11 males and 2 females) completed the study. One male patient discontinued secondary to non-drug related disease progression diagnosis of pleural effusion at the 30 mg BID dose level and a female patient discontinued following a Grade 3 AE of vertigo at the 240 mg BID dose level. Cohort 2 were healthy subjects who were assigned to dose escalate up to 180 mg BID. Cohort 2 consisted of 8 healthy subjects (6 males and 2 female) who completed the study and one male subject who discontinued at the 120 mg BID dosing level with only Grade 1 intensity AEs. All study subjects were closely monitored for AEs throughout the study.

In healthy subjects, the dosing regimen resulted in mainly Grade 1 AEs and the dose escalation was tolerable in 8/9 subjects dosed. Of the nine healthy subjects enrolled, one subject withdrew from the study secondary to AE Grade 1 level gastrointestinal reflux, nausea/vomiting and vertigo symptoms at the 120 mg BD dosing level. The subject recovered from the AE following drug discontinuation. AEs that occurred in greater than two subjects were somnolence (N=2), headaches (N=2), flatulence (N=2) and constipation (N=3).

In the HD subjects, there were no deaths or drug-related serious AEs. There were no dose-limiting AEs reported as defined as two hemodialysis patients experiencing a drug-related AE of Grade 3. A total of 72 AEs were reported in the 15 dialysis patients of Cohort 1. The nervous and gastrointestinal organ systems had the highest incidence of AEs. The most frequently occurring AEs were nausea and somnolence. Of the 13 hemodialysis patients who completed the study (10 HD patients assigned to dose up to 180 mg BID and 3 HD patients assigned to dose up to 240 mg BID), 12 patients completed the trial per protocol and 1 patient completed the study but did not dose titrate beyond 120 mg BID.

With regard to the gastrointestinal organ system, of the 14 hemodialysis patients who completed 13 days of dosing (1 patient at 120 mg BID and 13 patients at 180 mg BID), 4/14 (29%) experienced no nausea during the study and 7/14 (50%) experienced Grade 1 intensity nausea that was self-limited and only occurred at the initiation dose of 30 mg. One patient (1/14, 7%) experienced Grade 2 nausea starting from the 60 mg BID through the 180 mg BID dose. Three patients (3/14, 21%) only developed nausea at the 180 mg dose level.

With regard to the nervous system AEs, of the 14 subjects who completed the 13 days of dosing, 5/14 (36%) did not experience somnolence, 4/14 (29%) experienced somnolence that was self-limited and only occurred at the initiation dose of 30 mg. With regard to AE intensity, two patients (2/14, 14%) experienced somnolence of Grade 2 intensity at dosing levels above 30 mg BID. Only one drug-related Grade 3 AE (vertigo) was reported in one patient at the 240 mg dose which resolved completely following drug termination. No clinically relevant findings in vital signs, blood pressure (BP), ECGs or physical examinations were noted during the study. Oxygen saturation was also monitored via pulse oximetry as a safety precaution. The oximetry readings were taken at regular intervals during the daytime and continuously monitored during the nighttime hours over the 15 days of drug dosing and up to a maximal dose of 240 mg BID. No clinically significant decrease in daytime readings were recorded in the oximetry readings except in the one male HD subject previously mentioned who discontinued from the study at the time of the development of a pleural effusion. There was no clinically significant decrease in the nocturnal oxygen saturation level below the pre-dosing baseline nocturnal oxygen saturation level in any HD subject.

The Investigator Brochure and Section 5.4.4.4; Table 21 and Section 5.4.4.2.2; Table 17 summarize the AE profile of the TR01 HD subjects and healthy subjects respectively.

During the course of TR01, the 15 HD subjects that were enrolled were on multiple concomitant medications. Common concomitant medications included heparin, vitamin D, aspirin, iron, hyperphosphatemia management with sevelemar, erythropoiesis-stimulating agent, secondary hyperparathyroidism management with cinacalcet, neuropathic pain management with gabapentin; antihypertensive medications such as amlodipine (calcium

channel blocker), carvedilol (beta and alpha-1 blocker), metoprolol (beta blocker), linosopril (ACE inhibitor); gastrointestinal medications: omeprazole, pantoprazole, ranitidine and renal vitamins and supplements. These medications seem to be commonly used by HD patients both in the US and the EU (Schmid et al 2010). There was no clinically significant difference in the adverse event profile observed based on concomitant medication use or obvious pharmacodynamic interaction over the course of the study.

Data on Itch Intensity was obtained in an unblinded fashion from the hemodialysis patients enrolled in the open-label single arm Study TR01 using a 0 (none) to 10 mm (maximal possible intensity) itch Visual Analogue Scale (VAS) recording "worst itch" intensity. From a baseline mean daytime VAS of 4.4±2.3 mm and nighttime of 2.8±2. mm, the mean VAS decreased over a 13-day dosing period by -3.6±2.5 mm and by -1.8±2.1 mm, respectively.

Please see the Investigator Brochure for more details on the TR01 study.

3.3.3 Additional Nalbuphine HCl ER Tablet Clinical Data

In addition to the subjects in the TR01 study, a total of 331 subjects have been exposed to nalbuphine HCl during the course of 8 previous clinical studies.

Four Phase 1 studies were early biopharmaceuticals studies conducted in healthy subjects mainly for formulation selection and as such they support the safety of the drug product. In addition, two Phase 1 studies were conducted with the current clinical formulations and each consisted of a single dose study assessing the safety, tolerability, and PK of the current tablet formulations in the 30mg -180 mg range.

A safety and efficacy analgesic study was conducted in subjects with dental-pain following third molar extractions following a single dose (placebo or 60 mg or 120 mg). The subjects were otherwise healthy male and female subjects. The study also contained PK-PD analysis demonstrating an analgesic dose-response relationship, with clear differentiation between the nalbuphine dose groups and placebo group.

Oxygen saturation was monitored via pulse oximetry as a safety precaution during Phase 1 studies and in the single dose third molar extraction dental pain treatment study. All subjects who received the drug had oxygen saturation levels within the 90%-100% range during the studies.

A safety and efficacy analgesic study was conducted in a patient population experiencing osteoarthritic related joint pain using the current nalbuphine HCl ER 60 mg tablet. The population was demographically older with the mean age of 57 years and a range extending from age 40-70 years. Patients were dosed continuously for up to 3 weeks starting at 60 mg BID up to a dose of 180 mg BID. Patients who tolerated the initial dosing were titrated up in weekly increments of 60 mg BID to the maximal dose of 180 mg BID. The AEs that developed mainly had their onset at the initiation of dosing with no new type of AE developing in any statistically significant incidence during the course of dose escalation.

In these eight clinical studies overall, the most frequently reported AEs in the single dose and multi-dose studies were CNS events, namely dizziness, headache, and somnolence.

Gastrointestinal system AEs were mainly nausea and vomiting. Most of the AEs noted in the clinical study program were mild to moderate in severity.

In the case of single dose Phase 1 nalbuphine HCl ER tablet administration, there was a dose relationship to the incidence of AEs and there was minimal AEs observed at the 30 mg dose compared to initiating dosing at the higher doses. As a result, a titration to higher doses from a starting dose of 30 mg was selected for subsequent studies that also included TR01 in order to improve the tolerability of the drug.

Section 5 of the Investigator Brochure summarizes the results of the clinical development program in detail.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To evaluate the safety and tolerability of nalbuphine HCL ER tablets during a drug treatment period of up to 50 weeks.

4.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to evaluate the effect of two doses of nalbuphine HCl ER tablets on:

- To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Period Week 4.
- Assess skin lesion improvement using the metrics of the PAS
- Changes in Patient-Reported Outcome measures (worst itch NRS, average daily itch intensity NRS, VRS (itchy, burning and stinging), ItchyQoL, MOS Sleep-R, HADS and PBI-P) during the Treatment Period
- The percentage of patients utilizing various doses of nalbuphine HCl ER tablets by Study Week
- The frequency and reasons for down-titration and treatment discontinuation during the study
- The changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets
- The number of days of use of rescue medications.

4.3 EXPLORATORY OBJECTIVES

- The potential of nalbuphine HCl ER tablets to impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken at the last Treatment Period Visit when compared to biopsy material assessed during study TR03 (selected sites only).

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINT

- A description of the incidence and nature of TEAEs during Treatment Weeks 5-50

5.2 SECONDARY ENDPOINTS

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. Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time.

- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in Patient-Reported Outcome measures (worst itch NRS, average daily itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS) by Treatment Period visit and Baseline NRS score categories
- Change between Baseline and final Treatment Period visit in PBI-PA 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
- To describe the changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets
- A description of the number of days of use of rescue medications for itching.

5.3 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) in skin biopsies taken at the last Treatment Period Visit when compared to biopsy material assessed during study TR03 (selected sites only).

6 NUMBER OF SITES AND PATIENTS

Up to 7 sites in the North America and Europe are planned to participate in this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., up to 60 patients).

7 ESTIMATED STUDY DURATION

The total study duration for any individual patient will be up to 52 weeks. Patients will receive drug treatment for up to 50 weeks. Followed by two week washout period.

8 SELECTION CRITERIA

8.1 STUDY POPULATION

Patients with prurigo nodularis who completed the TR03 study and have met Inclusion/Exclusion eligibility requirements for TR03ext (see Section 8.2).

8.2 INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible:

1. Have been adequately informed of the nature and risks of the study and have given written informed consent at or prior to Visit 1a.
2. Have completed participation in the TR03 study.

   Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6.

3. Agree to comply with the contraception requirements as below:

   Female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, Essure procedure, or spermicide).

4. Ability and acceptance to provide written informed consent.
5. Willing and able to comply with study requirements and restrictions
6. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.

8.3 EXCLUSION CRITERIA

If a patient meets any of the following criteria, he or she is *not* eligible:

1. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study
2. Known hypersensitivity or allergy to nalbuphine or formulation components
3. Is a pregnant or lactating female.

9 STUDY PLAN

9.1 GENERAL STUDY DESIGN

This is an open label extension study for patients who have completed the TR03 study.

9.2 RATIONALE FOR STUDY DESIGN

The primary objective of this TR03ext study is to evaluate the safety of nalbuphine HCL ER tablets in patients with prurigo nodularis for up to 50 weeks on drug. The TR03ext study is 52 weeks in duration. The open label design allows all patients who have completed the parent study TR03, an opportunity to receive active treatment for the assessment of the safety of nalbuphine HCl ER tablets over a longer term. A maximum of 50 weeks on study drug was chosen as a reasonable time frame that would add substantially to the understanding of nalbuphine ER HCl tablets chronic use in prurigo nodularis.

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%. Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. Based on these clinical observations, TR03ext was designed to be of sufficient duration in order to observe any possible effects that potential anti-pruritic suppressive effects of study drug may have on impacting scratching behavior and thus potentially skin lesion healing. Furthermore, the TR03ext study design anticipates potential sustained anti-pruritic effect that may outlast the actual dosing of study drug in TR03. Thus there is an Observation Period incorporated into TR03ext to follow patients for up to 12 weeks in order to measure the duration of any possible sustained anti-pruritic effect and to allow patients to receive study drug if pruritus returns within the 12 week time period.

This study will allow evaluation of a titration algorithm that mimics the manner in which opioid medications are often used in clinical practice (i.e., stepwise, titration to effect). To facilitate evaluation by achieved dose, the dose to which the patient has been titrated at the end of Treatment Period week 4 will be maintained through Study Week 50, with the exception of one allowable down-titration (See Table 3 for dosing schedule). Patients who require a second down-titration after Treatment Period week 4 must be discontinued from the study.

Patients can enroll into TR03ext and receive drug as early as approximately 2 weeks following their last dose of study drug in the parent study TR03. Approximately one-third of patients are expected to enter the study after having received placebo in TR03. These patients are expected to have a high level of pruritus intensity. On the other hand, patients who have received active treatment in TR03 may still have residual anti-pruritic effects from active arm drug treatment as they enter the TR03ext study at the time of the last TR03 study visit when a signed informed consent for TR03ext is required. To allow for various starting levels of pruritus intensity, patients who have an NRS that is > 2 will enter the Treatment Period upon completion of Visit 1a. Patients whose NRS scores are ≤ 2 will be entered into an extended screening period, no-treatment Observation Period for up to 12

weeks or until they develop a higher level of pruritus (i.e., NRS >2), 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 BID during the first 4 weeks of the Treatment Period (See Table 3 for dosing schedule). Patients who continue in the Observation Period and maintain an NRS score of ≤ 2 will be screen failed from the study at the end of the 12-week period. While patients remain in the Observation Period, they will not be considered as enrolled into the study, but as participating in an extended screening process until they are eligible for treatment.

In the parent study, TR03, the two target doses (90 mg and 180 mg) of nalbuphine HCl are both within the dose range that was well tolerated in hemodialysis patients and healthy volunteers subjects from study TR01 (30 mg to 240 mg BID for up to 15 days). Additionally, data from TR01 suggested a decrease in itching intensity in this dose range. Further, the safety profile of nalbuphine following injection is well documented. Injectable nalbuphine has been commercially available in the United States since 1979 and there has been marketing experience within the European Union dating back to 1986 (See Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report (2010) for a recent review).

In order to facilitate analysis of the clinical safety data and efficacy data, patients in the present study will begin titration at the 30 mg QD dose and titrate to only one of three maintenance doses: 90 mg BID, 120 mg BID or 180 mg BID. The 60 mg BID dose is believed to be only a marginally effective dose based on available TR01 data. However since there is a one time dose reduction permitted in all subjects during Treatment Period weeks 5-50 (see Table 3) to the next lower allowed dose, a subject at the 90 mg BID maintenance dose will be permitted a dose reduction to 60 mg BID and maintained at that dose level for the remainder of the study.

The study population being evaluated is an intended target population for oral nalbuphine HCl ER tablets: prurigo nodularis patients.

Patients will be closely monitored for safety. All patients will be seen at the Investigator site (See Schedule of Events in Appendix 1). Adverse events and vital signs will be recorded. Additionally, 12-lead ECGs, physical examinations, and clinical laboratory testing will be conducted to monitor safety on patients receiving study drug. Safety monitoring will be done to address the primary objective of evaluating the longer term safety of study drug exposure. The primary endpoint is a description of adverse events during up to 50-weeks of treatment with nalbuphine HCl ER tablets. An important secondary endpoint objective of the study is to use recorded PAS metrics to assess the potential of any possible study drug anti-pruritic suppression to affect scratching behavior of the subject and result in skin lesion improvement. Changes in patient-reported outcome measures: Worst itch NRS, Average daily itch intensity NRS, VRS (itchy, burning and stinging), ItchyQoL, MOS Sleep-R, HADS and PBI-P will be explored.

9.3 SAFETY MONITORING PLAN

All the clinical studies conducted with nalbuphine HCl ER oral tablets to date have indicated that the most common AEs are gastrointestinal and nervous system-related.

To mitigate opioid-related side effects, nalbuphine will be titrated over 4 weeks based on a combination of efficacy and tolerability to a dose that is between 90 mg BID to 180 mg BID (see Table 3). Titration is a clinical management strategy consistent with dosing of opioids in general (Jovey 2003). The titration regimen planned in this study is similar to the regimen used in study TR01, in which doses in the planned range were well tolerated (Section 3.3.2). In this study, the combination of a low starting dosing (30 mg on the first day) followed by a relatively slow titration (dose escalation after six consecutive doses over approximately 3 days) is expected to minimize treatment-limiting opioid adverse effects. See Table 3 for the drug titration scheme. The time interval between dose escalations is consistent with the "three day tolerance check" suggested by the National Opioid Use Guideline Group of Canada (2010) for outpatient clinical practice management of opioid drug titration as part of monitoring patient side effects.

Nalbuphine has μ-opioid antagonist pharmacological properties. To minimize the possibility of acute opiate withdrawal occurring at drug initiation in a physically dependent subject, patients receiving daily doses of opiates are excluded from the study. Patients who require ongoing non-daily opiates concurrently with nalbuphine should be monitored carefully for additive opiate effects. If patients develop a new need for daily opiates during the study, the Investigator is required to contact the Medical Monitor to discuss the specifics of the situation.

It is known from prior studies, that gastrointestinal opioid-like adverse effects (e.g., nausea, vomiting, and constipation) occur early and can be treatment-limiting. In anticipation of the possible occurrence of these effects, pre-medications for nausea will be permitted and Investigators will be advised to use pharmacologic or non-pharmacologic means to avoid constipation as clinically indicated. In anticipation of the possible occurrence of central nervous system (CNS) AEs such as somnolence, patients will be instructed to be aware of possible CNS AEs that may occur. The evening doses during the Titration Period should be taken at home. The first dose of any new titration step will occur with an evening dose (see Table 3). Patients will be additionally instructed that if any significant CNS AEs occur, they are to avoid activities such as driving and operation of dangerous machinery until the effect of the Study Drug can be assessed by the Investigator. Additionally, concomitant use of daily opioids during the course of the study, other than for short-term use, can be undertaken with the approval of the Medical Monitor. Overdoses or opioid-related significant central nervous system adverse effects may be reversed with opioid antagonists if clinically indicated.

Although psychological dependence or abuse can develop to chronically administered opioid drugs, the risk for psychological dependence or abuse in this study is judged to be low based on previous clinical studies with nalbuphine HCl ER oral tablets. To date, there have been no reported cases of psychological dependence or abuse reported following dosing for 3 weeks up to 180 mg BID and dosing for 15 days up to 240 mg BID. See the Investigator Brochure for details. Nevertheless, the nalbuphine HCl injection package insert for the product sold in the United States states that "*individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk for the development of drug abuse and dependence"*.

9.4 RISK-BENEFITS

The selected doses for study in TR03ext of 90 mg BID, 120 mg BID and 180 mg BID were chosen given the safety profile summarized in Section 3.3.2 and discussed further in Section 9.2 as well as detailed in the Investigator Brochure. As summarized in, Section 3.1.3.3, open label data from the TR01 study showed that pruritus suppression in the HD patients was noted with drug administration within the dose range that is planned for the current study.

Data obtained from a previous study in osteoarthritis patients dosed up to 180 mg BID with nalbuphine HCl ER tablets showed that objective opioid withdrawal symptoms at the termination of 3 weeks of therapy were absent or mild in degree (See the Investigator Brochure Section 5.4.4.5 for details).

It should be noted that the commercially available nalbuphine HCl for Injection product in the United States (Nalbuphine HCl package insert) has a usual recommended dose of 10 mg for a 70 kg adult, administered subcutaneously, intramuscularly, or intravenously, which may be repeated every 3 to 6 hours as necessary (ie, up to a daily dose of 40-80 mg IV); and, in non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg. Exposure following IV administration is approximately 6-fold higher than following oral administration (estimated oral bioavailability of nalbuphine HCl = 16%). Therefore, a 10-mg, 20-mg, or 160-mg IV dose would correspond to approximately 60 mg, 120 mg, and 960 mg oral nalbuphine, respectively. The highest dose proposed in the TR03 study is 180 mg BID (360 mg daily dose), and this oral dose is well below the highest recommended daily treatment of 160 mg IV (equivalent to 960 mg oral) for the current marketed product.

The risk for patients participating in the study is judged to be low based on previous experience with nalbuphine oral tablets. In addition, in the current study, there will be a low initiation dose of 30 mg, a slow dose titration rate, and careful safety monitoring of patients during the clinical study.

There is no approved therapy for prurigo nodularis related pruritus in the United States or Europe. Should nalbuphine prove effective, patients with purigo nodularis could potentially see benefit.

9.5 STUDY OVERVIEW

This is an open label safety and tolerability extension study for patients who have completed study TR03. Patients will either enter directly a drug Treatment Period (NRS >2) or a enter an extended screening period of a no-drug Observation Period (NRS $\leq$ 2) based on their reported NRS scores on the first Visit (Visit 1a). For up to 12 study weeks, patients in the no-drug Observation Period may also transition into the drug Treatment Period if their NRS increases to NRS>2.

The total study duration for any individual patient will be up to 52 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 on drug treatment will have a 2-week washout and safety follow-up period at the end of the dosing period.

The total amount of time in the Observation Period cannot exceed 12 weeks. After 12 weeks, subjects not eligible for the Treatment Period are screen failed from the study. The study periods are summarized below in Table 2.

Table 2: TR03ext Study Periods

Study Period	Study Weeks	Duration
Observation Period	Patients followed in Observation Period visits for up to 12 weeks. During this time, the patient either enters the Treatment Period or screen fails for entry to the Treatment Period at 12 weeks and participation in the study ends.	Up to 12 weeks
Treatment Period	For patient 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 Treatment Period still ends at Study Week 50, thus Table 8 calculates the TV assignment for any patient entering the Treatment Period from the respective Observation Period visits.	Up to 50 weeks
Washout and Safety Follow-Up Period	Weeks 51-52	2 weeks

9.6 STUDY PROCEDURES

Before the initiation of study-specific procedures the patient must be given a complete explanation of the purpose of the study, evaluations to be conducted, and risks/benefits for study participation. Patients must understand the requirements of the study, provide informed consent (See Section 9.6.1 and Section 20.3), agree to the study restrictions, and agree to return for the required assessments. After review of the informed consent is documented, the patient must give witnessed verbal and written consent. For this study, patients will retain their study number from study TR03.

With the exception of Visits 1a and 1b, windows for all visits will be +/-3 Days. Please see the Schedule of Events in Appendix 1 for details of the Titration Period assessments and the Study Schematics Flow Charts in Appendix 2. See Section 9.7.1 for details of Study Drug administration and Section 9.7.5.4 for information on the use of pre-medications with the Study Drug.

Visit 1a has procedures to be done as summarized in Section 9.6.1 regardless of the patient's pruritus intensity score. Following a set of common procedures, only patients who qualify for the Treatment Period based on meeting the pruritus intensity criteria will be eligible to receive study drug; Visit 1a corresponds to TV1. For patients who during the final visit of TR03 did not meet the pruritus intensity criteria to enter the TR03ext Treatment Period, Visit 1a corresponds to OV1, the first visit of the Observation Period. If during a subsequent observation period visit to the site, the patient meets the pruritus intensity criteria, then that observation visit immediately transitions into Visit 1b (it also corresponds to TV1 since it is now the first Treatment Period visit) – See Section 9.6.5.3.

For subjects who transition to the Treatment Period from the Observation Period, Table 8 provides details on the treatment visit schedule based on the study week that the subject transitioned from the Observation Period to the Treatment Period. The subject will follow the treatment visit schedule until they reach Study Week 50, at which time they will skip to the last treatment visit TV14 described in Section 9.6.2.2.4.

Figure 2 and Figure 3 visually display the relationship between TR03ext study weeks, Treatment Period weeks and Observation Period weeks.

9.6.1 Visit 1a (Day 1 of Study Week 1)

See Table 4 for summary of Visit 1a procedures.

Study TR03 Visit 6 procedures in common with Study TR03 extension Visit 1a procedures do not have to be repeated.

- obtain informed consent
- confirm eligibility
- obtain vital signs
- conduct a physical examination
- collect central laboratory samples (hematology and chemistry)
- collect serum pregnancy sample in women of childbearing potential (done at the central laboratory)*
- collect urine for central lab urinalysis
- collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)*

  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
  - instruct the patient to discontinue taking study drug
  - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.
- obtain blood for PK
- obtain a 12-lead ECG
- record AEs

- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins; also obtain the TR03 re
- retrieve any remaining study drug from the parent study TR03
- administer Worst itch NRS and **review score for eligibility to either enter the Treatment Period or to continue in screening under the Observation Period**

    a) If NRS scores are ≤ 2 (Worst Itch NRS), start the Observation Period. Do NOT initiate study drug treatment at this visit

    b) If NRS scores is >2 (Worst Itch NRS) start Treatment Period immediately

  The Worst Itch NRS must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)

For patients qualifying for drug Treatment Period only (Visit 1a is also study visit TV1):

- complete PAS
- administer PRO measurements:
    - Average daily itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS
    - PBI-P

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)
- dispense Study Drug to the patient required until return at TV2.
- instruct patients to self-administer the first dose on the evening of Visit 1a at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- instruct the patient to take the Study Drug twice daily at approximately the same times of day and how to escalate from 30mg to 60mg BID.
- instruct patients to bring all remaining Study Drug to the Investigator site for each study visit.

For patients starting the Treatment Period, the next visit will be TV2.

For patients not qualifying for drug Treatment Period only (Visit 1a is also study visit OV1), the patient will enter the Observation Period and the next visit will be OV2.

9.6.2 Treatment Period (Study Weeks 1-50)

Patients who enter the Treatment Period on Visit 1a will be in the Treatment Period for 50 weeks and thus are eligible to receive study drug for up to 50 weeks.

Patients who enter the Treatment Period from the Observation Period will be in the Treatment Period anywhere from 38-46 study weeks. Patients enter the Treatment Period from an Observation Visit (OV) when their worst itch NRS >2.

Regardless of how many treatment weeks the patient was on study drug, for all patients study week 50 will coincide with TV14 when end of study drug procedures are conducted. Since all patients must titrate to their maintenance dose over the first four weeks of the Treatment Period, Visits 1a/Visits 1b (TV 1) and TV 2 over the first four weeks of the Treatment Period will be common to all subjects in TR03ext regardless of the study week entry into the Treatment Period. Patients who transition from the Observation Period to the Treatment Period at a respective OV will follow a TV schedule outlined in Table 8 in order for the patient to complete the TV 14 visit during week 50.

9.6.2.1 Treatment Period Weeks 2-4 (Titration Phase of Study Drug)

The first week in the Titration phase is initiated as part of Visit 1a/1b (Day 1 Treatment period Week 1, see Section 9.6.1 above). Subsequently, the following events TC1, TV2 and TC2 will be conducted during the remainder of the titration phase. See Table 5 for the Schedule of Events during the titration phase.

9.6.2.1.1 Telephone Contact Number 1 (TC1, Treatment Period Week 2)

The patient is to be contacted by phone and the following are to take place:

- Record AEs
- Reinforce compliance
- Confirm that patient has titrated drug up to 60 mg BID following the dosing schedule of Table 3
- Document tolerability/intolerability to study drug and decision to continue dose escalation following the dosing schedule of Table 3
- Discontinue patients who could not tolerate 60 mg dose and schedule patients for an Early Termination Visit (See Section 9.6.4).

9.6.2.1.2 Treatment Visit 2 (TV2, Treatment Period Week 3)

The following procedures are to take place at this visit:

- obtain vital signs
- collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
- collect blood for PK
- administer PRO measurements:
  - Worst itch NRS

- Average daily itch intensity NRS
- VRS
- ItchyQoL
- MOS Sleep-R
- HADS.

The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs (including tolerability to study drug)
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform Study Drug accountability, retrieve previously dispensed Study Drug
- dispense the Study Drug to the patient required until return at TV3 (Treatment Week 5)
- Document tolerability/intolerability to study drug and decision to maintain dose at 180 mg or decrease dose to either 120 mg or 90 mg BID following the dosing schedule of Table 3.

9.6.2.1.3 Telephone Contact Number 2 (TC2, Treatment Period Week 4)

The patient is to be contacted by phone and the following are to take place:

- record AEs
- reinforce compliance
- for patients who report intolerable side effects at the 180 mg BID decrease dose to either 120 mg BID or 90 mg BID
- for Patients who report intolerable side effects at the 120 mg BID decrease dose to 90 mg BID
- record patient dose as maintenance dose
- patients dosed at 90 mg BID for the previous week and report intolerable AEs, the subject is to be discontinued and scheduled for an Early Termination Visit (See Section 9.6.4).

9.6.2.2 Treatment Period Weeks 5-50

During this period of the study, the patient continues on the maintenance dose established by the end of Treatment Period week 4 for the remainder of the study with the exception of a single allowable dose reduction is permitted during Treatment Period Weeks 5 – 50 (a patient at 90 mg BID can be reduced to 60 mg BID). If a second dose reduction is needed, the patient should be discontinued from the study (See Table 3).

See Table 6 for the Schedule of Events for Treatment Period weeks 5-50.

9.6.2.2.1 Treatment Visits 3-7 (TV3-TV7, Treatment Period Weeks 5-21)

The following procedures are to take place at these visits:

- obtain vital signs
- collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
- collect blood for PK
- administer PRO measurements:
  - Worst itch NRS
  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed Study Drug
- Dispense the study drug to the patient required until next TV

9.6.2.2.2 Treatment Visit 8 (TV 8, Treatment Period Week 26)

The following procedures are to take place at this visit:

- obtain vital signs
- perform physical examination
- complete the PAS
- perform 12-lead ECG
- collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
- collect urine for urinalysis for central lab
- collect blood for central laboratory (hematology and chemistry) and for PK
- administer PRO measurements:
  - Worst itch NRS
  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense study drug to the patient required until next TV

9.6.2.2.3 Treatment Visits 9-13 (TV 9-TV13, Treatment Period Weeks 30-46)

The following procedures are to take place at this visit:

- obtain vital signs
- collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
- collect blood for PK
- administer PRO measurements:
  - Worst itch NRS
  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until next TV

9.6.2.2.4 Treatment Visit 14 (TV 14, Last Treatment Period Visit – Study Week 50)

The following procedures are to take place at this visit:

- obtain vital signs

- perform physical examination
- complete the PAS
- perform 12-lead ECG
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test for central laboratory
- collect urine for urinalysis at the central laboratory
- collect blood for PK
- perform skin biopsy for histological studies (selected sites only)
- administer PRO measurements:
    - Worst itch NRS
    - Average daily itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any dispensed study drug

9.6.3 Washout and Safety Follow-Up Period (Week 52)

All patients on Treatment will have a 2-week Washout and Safety Follow-Up Period following TV14. During this visit, the PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual). Please see the Schedule of Events in Appendix 1 for details of the Washout and Safety Follow-Up Period assessments. Additional information for this visit is provided below.

The following procedures are to take place at this visit:

- obtain vital signs
- perform 12-lead ECG
- collect blood for central laboratory measurements and PK
- administer PRO measurements:
    - Worst itch NRS
    - Average daily itch intensity NRS
    - VRS
    - ItchyQoL

- MOS Sleep-R
- HADS

The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- AEs and concomitant medications (including rescue medications) will be recorded
- collect the Rescue Medication Log will be collected from the patient at this visit
- retrieve any remaining study drug that the patient did not previously turn in

9.6.4 Early Termination Visit

The following procedures are to take place at this visit:

- obtain vital signs
- perform physical examination
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test at the central laboratory
- collect blood for PK
- perform 12-lead ECG
- collect urine for urinalysis at central lab
- administer PRO measurements:
  - Worst itch NRS
  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any dispensed study drug

9.6.5 Observation Period (Study Weeks 1-12)

Only patients with Visit 1a worst itch NRS score of ≤2 (Visit 1a for these patients is considered OV1) should enter the Observation Period, which includes subsequent study visits OV 2-4 at approximately one month intervals over the next 12 study weeks (See Table 7). While patients remain in the Observation Period, they will not be considered enrolled into the study, but as participating in an extended screening process until they are eligible for enrollment. Patients evaluated at OV 2-4 and who record worst itch NRS>2 and

are otherwise eligible can immediately begin Visit 1b and transition into the Treatment Period.

For these patients, the sum of time in the Observation Period and Treatment Period will not exceed 50 weeks. As a result, both the Observation Period and Treatment Period will differ in length for different patients. To ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug up to the assessment of TV 2 during Treatment Period Week 3, and that the final Treatment Period visit is always TV14, multiple interim Treatment Visits will be skipped as indicated in Table 8.

9.6.5.1 Observation Visit 2 at Study Week 4 and Observation Visit 3 at Study Week 8

The following procedures are to take place at this visit:

- administer the Worst itch NRS; if >2, patient must undergo Visit 1b procedures
- obtain vital signs
- record AEs
- record concomitant medications

9.6.5.2 Observation Visit 4 at Study Week 12

The following procedures are to take place at this visit:

- administer the Worst itch NRS; if >2, patient must undergo Visit 1b procedures
- obtain vital signs
- record AEs
- record concomitant medications

If subject screen fails and does not transition to Visit 1b, conduct the following:

  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

9.6.5.3 Visit 1b

See Table 4 for summary of Visit 1b procedures.

Patients evaluated at OV 2-4 who record worst itch NRS>2 and are otherwise eligible can immediately begin Visit 1b. This patient then transitions into the Treatment Period and will undergo the following procedures:

- obtain vital signs
- conduct a physical examination
- collect central laboratory samples (hematology and chemistry)

- collect serum pregnancy sample in women of childbearing potential (done at the central laboratory)*
- collect urine for central lab urinalysis
- urine for pregnancy (must be confirmed negative prior to dispensing study drug)*

  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
    - instruct the patient to discontinue taking study drug
    - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.

- obtain blood for PK
- obtain a 12-lead ECG
- administer PRO measurements:

  - Worst itch NRS
  - Average daily itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS
  - PBI-P

  The PRO questionnaires must be administered at the study site under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- complete the PAS
- dispense Study Drug to the patient required until return at TV2
- instruct patients to self-administer the first dose on the evening of Visit 1b at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- instruct the patient to take the Study Drug twice daily at approximately the same times of day
- instruct patients to bring all remaining Study Drug to the Investigator site for each study visit.

The next study visit will be Treatment Visit 2 (TV2). However, to ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug and that the final Treatment Period visit is always TV14, multiple interim Treatment Visits will be skipped as indicated in Table 8.

9.6.6 Unscheduled Visits

If a patient needs to be evaluated in relation to the study on a day other than one of the study visit days, that day will be considered an Unscheduled Visit. The reason for each unscheduled visit will be recorded and the following procedures will be performed: vital signs (BP, HR, RR, temperature), assessment for AEs, review of concomitant medications, and Study Drug accountability. Additional procedures such as central or local laboratory sample collection may also take place, if clinically indicated. All unscheduled visits will be recorded on the Unscheduled Visit CRF.

9.6.7 Schedule of Events

The Schedule of Events is shown in Appendix 1 and is described in Section 9.6.

9.7 Study Drug Treatment and Drug Accountability

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

9.7.1 Study Drug Dosing

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 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, he 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 Study Drug will be titrated to their maintenance dose during the titration phase of the Treatment Period according to the schedule in Table 3 below and graphically displayed in Figure 4.

Table 3: Dosing Schedule for TR03ext

Week of Treatment Period[1] (TV or TC)	**Tolerance**	**Day**	**Dose[2]**
Week 1 (TV1/Visit1a or 1b)	N/A	Day 1	30 mg (PM dose)
		2	None (0 mg) AM; 30 mg PM
		3-4	30 mg BID
		5	30 mg AM; 60 mg PM
		6-7	60 mg BID
Week 2[2] (TC #1)	Unacceptable[3]	1	Discontinue Patient
	Acceptable	1	60 mg AM; 90 mg PM
		2-3	90 mg BID
		4	90 mg AM 120 mg PM
		5-6	120 mg BID
		7	120 mg BID
Week 3[2] (TV2)	Acceptable	1	120 mg AM; 180 mg PM
		2-7	180 mg BID
	Unacceptable[3]	1-7	Reduce dose and maintain at 90 mg BID
Week 4[2] (TC#2)	Uncceptable[3]	1-7	Decrease dose to either 120 mg BID or 90 mg BID[4]
	Acceptable	1-7	Maintain dose (either 90 mg BID, 120 mg BID or 180 mg BID)
Treatment Period Week 5[5] up to Treatment Period Week 50 (TV3-TV 14)	Acceptable[5]	1-7	Maintain dose at either 90 mg BID; 120 mg BID or 180 mg BID through TV14[6]

[1]The decision to enter the patient into the Titration Period is based on Worst Itch NRS score NRS >2 obtained from the patient on Visit 1a or 1b

[2]The titration decision will be made based on tolerance to study drug

[3]Tolerance level is unacceptable to either the patient and/or investigator.

[4]Patients who were dosing at 90 mg BID for the previous week and could not tolerate the study drug are to be discontinued

[5] The number of Treatment Period weeks prior to TV 14 will vary for patients previously in the Observation Period depending upon the number of weeks spent in the Observation Period. See Table 8

[6]The achieved dose attained as of the end of Treatment Period Week 4 will be maintained throughout the rest of the Treatment Period. This dose will be defined as the patient's "maintenance dose". A one time dose reduction to the next lower allowed dose is permitted during Treatment Period Weeks 5 – 50 (a patient at 90 mg BID can be reduced to 60 mg BID). If a second dose reduction is needed, the patient should be discontinued from the study.

9.7.2 Down-Titration

Down-titration is not permitted except as discussed in Section 9.7.1

9.7.3 Overdose

The effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Please see Guidance to the Investigator section of the Investigator Brochure for additional information.

9.7.4 Treatment Compliance

Returned study drug tablets will be used to assess compliance at each visit. Medication compliance will be recorded on the CRF for each designated visit (See Appendix 1). Patient compliance with the study dosing schedule will be assessed as part of the planned study analyses.

9.7.5 Rescue Medications, Concomitant Medications, Prohibited Medications, and Pre-Medications

9.7.5.1 Rescue Medications

A secondary objective of the study is to quantitate the number of days of rescue medication use for itching during the course of nalbuphine HCl ER treatment. 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 (See Table 9). For the purposes of this study, any UV light treatment received will also be defined as a rescue medication.

9.7.5.2 Concomitant Medications

Any medication taken by a patient following the signing of informed consent during the course of the study and the reason for use of the medication will be recorded on the case report form (CRF). Each patient will be instructed to report the use of all medication to the Investigator, including over-the-counter [OTC] medications, herbal medications, vitamins, and nutritional supplements. Patients will also be instructed about the importance of not

taking any new medications during the study (including OTC medications) without consulting the Investigator.

9.7.5.3 Prohibited Medications

Initiating use of opiate medications during the study should be done with caution with assessment of the patient for potential additive opiate AEs. If an enrolled patient requires daily treatment with opioid medications during the study (e.g., for post-surgical pain), please contact the Medical Monitor. Use of acetaminophen, non-steroidal anti-inflammatory medications, and aspirin is permitted.

Concomitant use of opioid antagonists (e.g. naloxone, naltrexone) are also prohibited during the study, unless required for urgent reversal of opioid adverse effects or opioid overdose.

Use of all other investigational drugs are prohibited during the study. A subject who initiates an investigational drug during the study should be discontinued.

9.7.5.4 Pre-Medications

Nalbuphine use may be associated with nausea, vomiting, and/or constipation, particularly as the dose is escalated or upon initiation of treatment. At the Investigator's discretion, anti-emetics such as ondanestron may be administered prophylactically, prior to taking the Study Drug or, as needed, for treatment. Dietary and other prophylactic measures to avoid constipation should also be considered as clinically indicated.

9.7.6 Efficacy Assessments

The below PRO instruments will be administered at the site at the site and under supervision by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual) according the Schedule of Events (see Appendix 1).

9.7.6.1 Numerical Rating Scale (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 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).

In this study, patients will be asked to record two NRS values:

- rate itching on average over the past 24 hours
- rate most severe itching over the past 24 hours

This instrument can be found in Appendix 4.

9.7.6.2 Verbal Rating Scale (VRS)

The VRS scale to be used in this study has three dimensions, each dimension coded with graduated adjectives (from 0 = none; to 5 = very severe) for the skin sensations of itchy, burning and stinging.

In this study, patients will be asked to record the VRS value:

- How is your skin sensation today?

This instrument can be found in the Appendix 4.

9.7.6.3 Hospital Anxiety and Depression Scale (HADS)

The HADS instrument includes 14 multiple-choice questions, each with 4 possible choices, scored between 0 and 3. This instrument can be found in Appendix 4.

9.7.6.4 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, all the time=5. The instrument can be found in Appendix 4.

9.7.6.5 Medical Outcomes Sleep Scale –Revised (MOS Sleep-R)

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).

Additionally, a 9-item Sleep Problems Index ("Sleep Problem Index I") can be generated which assesses overall sleep problems that includes the 4 sleep disturbance and the 2 sleep adequacy items, 2 of the somnolence items, and awakening short of breath/headache; higher scores indicate greater sleep impairment, and this index is often used in clinical trials as an indication of sleep quality. The instrument can be found in Appendix 4.

9.7.6.6 Patient Benefit Index (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". The instrument can be found in Appendix 4.

9.7.6.7 Prurigo Activity Score (PAS)

The PAS consists of 7 quantitative 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 percentages based on their stage (0-4). Photographs of the body are conducted with monitored lesions marked. The instrument can be found in Appendix 4.

9.7.6.8 Exploratory Histological Endpoints (at selected sites)

Punch biopsy skin material for measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) analysis was obtained during TR03 (at selected sites). Punch biopsy will be obtained (at selected sites) during TV 14 for a comparative analysis with the results of the histological results of pre-dosing TR03 and end of study TR03 results.

9.7.6.8.1 **MOR/KOR density and Nerve Fiber Density**

The potential of nalbuphine HCl ER tablets to impact on the Measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken at Baseline visit and the Evaluation visit will be investigated at selected sites.

In addition to skin biopsy tissue obtained prior to drug treatment for H&E and analysis by a central reading dermatopathologist, at selected sites additional skin biopsy material obtained before and at the end of drug treatment will be compared to investigate, in an exploratory manner, any evidence of change in expression of MOR and KOR and nerve fiber density in relation to any noted changes in clinical study endpoints.

Bigliardi et al (2007) reports that in normal skin, keratinocytes express high amounts of MOR and it is therefore concluded that endogenous ligands are bound primarily to opioid receptors on keratinocytes and thus the endogenous opiate ligands are not binding to opioid receptors located on nerve endings –the net result is at most a weak itch signal to the central nervous system in the normal state. In chronic pruritic skin disorders, most opioid receptors on keratinocytes are reported as internalized; therefore there are many opioid ligands available to bind to opioid receptors on sensory nerve endings. This state leads, together with the changed morphology of the epidermal nerve endings, to a strong itch signal to the CNS. The authors reported that topical administration of the opioid mu receptor antagonist naltrexone in subjects with atopic dermatitis, lichen simplex chronicus or prurigo simplex showed an antipruritic effect. In addition, there was also an upregulation of epidermal MOR expression following two weeks of treatment, but no MOR upregulation in subjects who did not experience an antipruritic response. Bigiliardi and Bigliardi-Qi (2004) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor (MOR) expression in the epidermis compared to normal skin.

Bigliardi-Qi et al (2009) reports that while it is widely accepted that KOR signaling

suppresses itch, there is currently no animal, behavioral or human data relating the regulation of skin KOR expression to pruritus. Salemi et al 2007 however reported high upregulation of KOR in the skin of fibromyalgia subjects that was thought to correlate with reported complaints of pain symptoms.

With regard to peripheral sensory nerve fiber density in the skin, Bigliardi et al (2009, 2007) report that epidermal nerve endings of pruritic skin in prurigo are thinner when compared to normal skin. In addition, the nerve fibers have a different morphology which may relate to initiating the sensation of pruritus because of the altered anatomical relationship to the various cellular elements of the skin.

9.7.7 Safety Assessments

Safety will be determined by evaluation of the following:

- AEs
- Vital signs including weight, BP, heart rate (HR), respiratory rate (RR), and body temperature
- Physical examination
- Clinical laboratory data (see Appendix 3 for list of analytes)
- 12 Lead-ECG.

10 STUDY DRUG

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

10.1 Formulation, Packaging and Labeling

The Study Drug in this trial is nalbuphine HCl ER tablets. Nalbuphine HCl ER tablets are white to off white film-coated round tablet containing either 30 mg or 60 mg nalbuphine HCl.

All study medication will be supplied by the Sponsor. Following confirmation of eligibility to start the Treatment Period, the patient will receive bottles of study drug tablets containing 60 tablets each. Bottles will be labeled with at minimum: contents, storage conditions, expiration date, clinical trial statement, and the name and lot number of the study drug Sponsor (Trevi Therapeutics).

10.2 Shipping, Storage And Handling

The Investigator will ensure that the Study Drug is stored and dispensed in accordance with FDA and EU regulations concerning the storage and administration of investigational drugs. Nalbuphine HCl ER tablets should be stored at 20°C-25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (59° to 86°F). The Study Drug should be stored away from any extreme conditions of temperature, light, or excess humidity.

10.3 Unblinding

Not applicable. This is an open-label study.

10.4 DRUG ACCOUNTABILITY

The Investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all Study Drug shipped by the sponsor or the sponsor's representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all Study Drug. Current dispensing records will also be maintained including the date and amount of drug dispensed and the patient receiving the drug. All remaining drug not required by regulations to be held by the clinical facility will be destroyed on site at the end of the study.

11 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT

Patients who complete Study Drug treatment through Treatment Visit 14 (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 Treatment Visit 14 will be considered to have prematurely discontinued Study Drug treatment. 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:

- Withdrawal of consent to continue Study Drug treatment
- Intercurrent Illness
- Any intolerable 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.

12 PREMATURE WITHDRAWL OF PATIENTS FROM THE STUDY

Patients who complete study visits through the Evaluation visit of Week 10, even if there have been intervening missed visits, are considered to have completed the study.

All patients who receive study treatment should remain in the study whenever possible. Reasons for withdrawal of the patient from the study include:

- Withdrawal of consent for study participation
- Premature discontinuation of Study Drug treatment
- Sponsor terminates the study for any reason
- Investigator decision

  The Investigator may withdraw any patient from the study if, in the Investigator's opinion, it is not in the patient's best interest to continue on the study.
- Death of the patient
- Change in eligibility to participate in the study.

Any patient whose condition significantly changes after entering the study should be carefully evaluated by the Investigator and discussed with the Medical Monitor. Such patients should be withdrawn from the study if continuing would place them at risk or compromise the results of the study.

Patients who prematurely discontinue from the study will be asked to undergo and have completed all evaluations that may be necessary to ensure that the patient is free of untoward effects and to seek appropriate follow-up for any continuing problems. The date on which the patient is withdrawn from the study and the reason for discontinuation will be recorded on the CRF. When a patient is withdrawn prematurely from the study, (regardless of the reason), all evaluations required at the Early Termination visit will be performed. Patients who withdraw from the study will not be replaced.

13 WARNINGS AND PRECAUTIONS

Please refer to the accompanying Investigator's Brochure for more details summarizing the safety data on nalbuphine HCl ER tablets. In addition, see the Warnings and Precautions sections of the parenteral nalbuphine HCl package insert for safety-related information. The package insert is contained in the Study Reference Manual.

14 EFFICACY EVALUATIONS

Efficacy measurements will be evaluated as exploratory endpoints in this study. The measurements include:

- Worst itch intensity NRS
- Average daily itch intensity baseline.
- VRS (itchy, burning and stinging)
- ItchyQoL
- MOS Sleep-R
- HADS
- Prurigo Activity Score (PAS)
- Patient Benefit Index, pruritus version (PBI-P)
- Frequency, pattern, and reasons for dose titration
- Use of rescue medications.

14.1 EXPLORATORY

The potential of nalbuphine HCl ER tablets to impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken during TR03 and the the last week on study drug during TR03ext (at selected sites only).

15 COLLECTION, HANDLING, AND ANALYSIS OF PHARMACOKINETIC BLOOD SAMPLES

15.1 BLOOD SAMPLE COLLECTION

Blood samples will be collected for safety, pharmacokinetic and CYP analysis. At the time of sample collection and processing, study patient information will be anonymized. Only the patient's identification number, assigned by an IVR/IWR system, and a sample barcode aligned to the lab requisition form will be noted on the tube/vial.

See the study Laboratory Manual for specimen collection, handling and shipping details.

15.2 CENTRAL LABORATORY

Blood samples, including chemistry, serum pregnancy test, and hematology, and urine for urinalysis obtained for the study will be analyzed at a central laboratory.

Urine pregnancy testing will be conducted at the site.

The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment should the urine and serum pregnancy test results differ. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.

15.3 PHARMACOKINETIC SAMPLES

To determine Study Drug content in plasma, blood samples will be collected at various time intervals over the duration of the study.

15.4 PREPARATION, STORAGE, AND HANDLING FOR PHARMACOKINETIC SAMPLES

Immediately after blood sample collection, the tubes will be gently inverted several times to mix the anticoagulant with the blood sample and placed on ice (4 to 8°C) until centrifuged.

The plasma fraction will be separated by centrifugation of the collection tube. It is preferable that a refrigerated (4 to 8°C) centrifuge be used. Centrifugation will be conducted in a manner to yield approximately 2 x1 mL of plasma (e.g., 10 minutes at 1,500 x g). The plasma fraction will be withdrawn by pipette and divided into 2 evenly proportioned aliquots in polypropylene freezing tubes. All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the patient identification number, the study dose, and the collection date and time.

Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be processed and placed into either a minus 70°C or minus 20°C refrigerator within 1 hour after collection. Tube labels for PK samples will be provided in the Central Laboratory kits. Each label will contain the study number, patient number, study day of sample, and time of sample. The actual date and time of blood collection will be recorded in the patient's CRF.

All plasma samples will be stored frozen (at either -70ºC or -20°C) until they are shipped for storage and analysis.

15.5 ANALYTICAL

Plasma samples will be analyzed for Study Drug using a validated liquid chromatography mass spectrometry (LC-MS/MS) method developed at Tandem Lab/s-RTP, Durham, North Carolina. The units for nalbuphine will be in ng/mL. In addition, metabolite concentrations will be assessed in these samples using an exploratory analytical LC-MS/MS method.

Analysis and reporting of results will be conducted according to the current Standard Operating Procedures for bioanalysis at Tandem labs Durham, North Carolina. Details of the sample analysis, including a bioanalytical study report, will be included with the final clinical study report.

16 TISSUE SAMPLES AND HISTOLOGY

At selected sites only, three 3 mm punch skin biopsy samples will be obtained at TV 14. One sample will be fixed in formalin and then paraffin for routine histology (H&E) and immunohistochemical examination of inflammatory cells and pro-inflammatory mediators. One sample will be fixed in 4% paraformaldehyde for 2 h to 5 days, and then kept in 5% sucrose overnight, buffered in 10% and 20% sucrose and after 6 h stored in liquid nitrogen. This tissue will serve for the determination of the nerve fiber density. One sample will be used for RNA and protein extraction for the quantification of MOR/KOR by PCR and western blot. Analysis will be performed at the University of Munster, Munster, Germany.

See the study Laboratory Manual for specimen collection, handling and shipping details.

17 SAFETY EVALUATIONS

Safety evaluations will include physical examination findings, changes in vital signs and ECGs, findings from clinical laboratory studies and the incidence of AEs

17.1 PHYSICAL EXAMINATION

A complete physical examination will be performed at the Screening Visit and subsequently according to the Schedule of Events (Appendix 1). Physical examinations may be performed by physicians or mid-level providers such as advanced practice nurses and physician assistants with the Sponsor's approval. 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.

17.2 VITAL SIGN MEASUREMENTS

Blood pressure and HR will be taken while sitting or semi-recumbent/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 (BP, HR, RR, body temperature, and weight will be obtained according to the Schedule of Events (Appendix 1). The height, weight and BMI will be recorded only on Visit 1.

17.3 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 (Appendix 1). The required clinical laboratory tests are listed in Appendix 3.

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.

17.4 ELECTROCARDIOGRAM

A standard 12-lead ECG will be obtained according to the Schedule of Events (Appendix 1). Electrocardiograms will be read locally for ECG intervals (PR, RR, QRS, and QT), 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.

17.5 ADVERSE EVENTS

Adverse events 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). Adverse events that have not been directly reported to the Investigator will be promptly conveyed to the Investigator by the study staff. Investigators will additionally review any AE source documents and the patient's medical records, on a regular basis during the course of the study.

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 adverse event has stabilized.

17.5.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation patient reported on or after the first screening date. A treatment-emergent AE (TEAE) is any untoward medical occurrence in a clinical investigation patient or patient administered a pharmaceutical product on or after the initial administration of study medication on the evening of Visit 7. An AE does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom whether or not related to the medicinal (investigational) product, or disease temporally associated with the use of a medicinal (investigational) product.

The AE may be any of the following:

- a new illness
- worsening of a pre-existing condition
- worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- an effect of the study medication, including comparator
- a combination of 2 or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "AE."

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Adverse events fall into the categories "non-serious" and "serious."

17.5.2 Serious Adverse Events

The reporting period for serious AEs is the same as for AEs. Serious AEs must be submitted to the Sponsor within 24 hours of their discovery, even if the full information about the event is not yet available. These events should also be reported to the IRB/IEC as needed based on local requirements. Fax SAE forms to the following number:

Serious AE Fax #: 888-529-3580

Also notify the PPD Medical Monitor at **(888) 483-7729.**

17.5.2.1 Serious Adverse Event Definition

An SAE is one that, at any dose, results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

A hospitalization is defined as an inpatient admission lasting 24 hours or more. Visits to urgent care centers and emergency departments that do not result in admission to a hospital for $\geq$24 hours will not be considered hospitalizations. Hospitalizations for elective procedures, defined as any procedure that was planned prior to signing of the informed consent will not, in and of themselves, be considered to fulfill criteria for an SAE. For example, for patients on the kidney transplant waiting list prior to signing the ICF who

subsequently are hospitalized for a transplant, the hospitalization would be considered elective.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the SAE. It does not refer to a SAE that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. 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 development of drug dependency or drug abuse.

Female patients who become pregnant should be immediately discontinued from the study if they have not yet received Study Drug. If a patient is found to be pregnant after they have received Study Drug, she should discontinue dosing, complete all end-of-study procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications or less than a healthy, normal outcome will be recorded as an AE or SAE.

Clarification on the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

17.5.3 Non-Serious Adverse Events

A non-serious AE is any AE not meeting the SAE criteria.

17.5.4 Definition of Relationship to Study Medication

Association or relatedness to the study medication will be graded as either "probably," "possibly," or "unlikely." Determination of relatedness includes:

PROBABLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- abates upon discontinuation of the drug;
- cannot be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.

UNLIKELY – The AE:

- does not follow a reasonable temporal sequence from drug administration;
- is readily explained by the patient's clinical state or by other modes of therapy administered to the patient.

17.5.5 Definition of Severity

All AEs will be graded, if possible, by the 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]. This is also provided in the Study Reference Manual for reference purposes.

The severity of AEs that cannot be graded by the most current version of CTCAE will be categorized as follows:

- **Grade 1** – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Grade 2** – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Grade 3** – Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
- **Grade 4** – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable.
- **Grade 5** – Death.

17.5.6 Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with the current Investigator Brochure, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

18 EMERGENCY PROCEDURES

In case of study-related medical questions, or if a pregnancy is confirmed in a trial patient, the Investigator should contact the designated Medical Monitor.

18.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the Investigator should contact the designated sponsor representative at the following address:

Thomas Sciascia, MD
Trevi Therapeutics, Inc.
195 Church Street, 14th Floor
New Haven, CT 06510 USA
Telephone: (203) 304-2499
Mobile: (617) 913-6808

19 CONSIDERATION, ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

19.1 GENERAL

As a companion to this protocol and in an effort to provide a more detailed explanation of the statistical methodology to be used for this study, which will consist of data summaries, a statistical analysis plan (SAP) will be developed prior to locking the data base.

No formal statistical testing is planned for this study. Data summaries will provide the basis for clinical interpretation of efficacy and safety outcomes

19.2 INTERIM ANALYSES

There is no interim analysis planned in this study.

19.3 METHODS FOR HANDLING MISSING DATA

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

19.4 PATIENT DISPOSITION

Patient disposition will be summarized, including the reasons for discontinuation. The number of patients in each analysis population will be displayed and an accounting of exclusions from each study population will be provided.

19.5 BASELINE CHARACTERISTICS

Demographics, medical history, laboratory data, and physical examination findings will be summarized.

19.6 CONCOMITANT MEDICATIONS

Concomitant medications will be tabulated by Anatomic and Therapeutic Class (ATC) of WHO drug, preferred term, and treatment group. A medication's usage will be considered concomitant if it was started or continued after administration of the study medication. If the start date is missing, it will be assumed that the medication was used concomitantly. Rescue and opioid medication usage will be tabulated separately from all other concomitant medications.

19.7 STUDY DRUG DOSING

The percentage of patients reaching various achieved doses at the end of Treatment Week 4 and through Study Week 50 will be summarized. The mean dose during the Treatment Period and the dose distribution by Treatment Period Visit will be reported. Descriptive statistics will be used to describe the mean daily dose by Visit.

19.8 EFFICACY ANALYSES

19.8.1 Efficacy Population

The Safety population, consisting of all enrolled patients who have received a single dose of study medication, 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 for the endpoint of interest, 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.

19.8.2 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 will be summarized. Patients who prematurely discontinue after having been followed in the Observation Period only will be also be summarized.

19.9 SAFETY ANALYSES

19.9.1 Safety Population

The Safety Population will consist of all patients who have received a single dose of study medication, i.e., this same population will be used both for the efficacy and safety evaluations. The Safety Population will be used in all safety analyses.

19.9.2 Adverse Events

All treatment emergent AEs will be summarized overall and for each body system and preferred term by treatment group, relationship to study medication, and severity. For tabulations by severity, only a patient's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. Adverse events will be dichotomized into "related" (probably and possibly) and "unrelated" (unlikely). "Treatment-emergent" will be defined as starting or worsening after the first dose of study medication. If the start date is missing, the event is assumed to be treatment emergent. All SAEs will be tabulated as well.

Although nalbuphine is not a controlled substance in the United States, adverse events of special interest that suggest a possible addiction or abuse potential or withdrawal will be specifically analyzed to screen for these effects. The list of MedDRA preferred terms for adverse events of special interest will be described in the Statistical Analysis Plan.

19.9.3 Vital Signs

Vital signs, including BP, HR, body temperature, and RR, and weight will be summarized by treatment group at Baseline and at each assessment time point during the post dosing period.

19.9.4 Laboratory Evaluations

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and at each scheduled visit. Summaries of safety laboratory parameters will include the first measurement of each scheduled assessment but repeat assessments done at the same study time point will not be included in summary calculations. Lab data will also be listed by treatment, patient, and visit. Listings will include scheduled, unscheduled, and

repeat evaluations. A listing of markedly abnormal values, as defined in the Statistical Analysis Plan, will additionally be generated.

19.9.5 Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening will be reported as AEs and analyzed as such. Clinically significant findings noted prior to start of Study Drug treatment will be recorded as medical history and analyzed as such.

19.9.6 Electrocardiograms

A standard 12-lead ECG will be obtained on Visit 1a/1b and subsequently, according to the Schedule of Events in Appendix 1. Electrocardiogram intervals (PR, RR, QTcF) will be summarized with descriptive statistics. All findings, including any follow-up ECGs as a result of any significant abnormal results, will be listed by treatment, patient, and visit.

19.10 Determination of 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 (i.e., up to 60 patients).

19.11 PHARMACOKINETIC AND PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The Study Drug plasma concentration data will be provided as data listings and will be summarized descriptively (mean, median, SD, minimum, and maximum) by collection time and nalbuphine dose. Additionally, these PK data may be analyzed through population, nonlinear mixed effects modeling (NONMEM), using the software package NONMEM (Version V, Level 1.1 or higher; GloboMax LLC, Hanover, MD).

20 ETHICS

20.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the study, the Investigator will submit the study protocol, sample ICF, and any other documents that pertain to patient information, recruitment methods such as patient diaries, and advertisements, to the Institutional Review Board/Independent Ethics Committee (IRB/ IEC). The Investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the Study Monitor prior to initiation of this study. This letter will be forwarded to the Sponsor prior to the initiation of the study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site, as well as other AE reports received the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study.

20.2 ETHICAL CONDUCT OF THE STUDY

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice [GCP], 1 May 1996), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations.

The Investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator should maintain a list of Subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties. Should the Investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

20.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An ICF that includes information about the study will be prepared and given to the patient.. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the patient and must specify who informed the patient.. Where required by local law, the person who informs the patient must be a physician.

After reading the ICF, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed ICFs must be given to the patient. The original signed ICFs will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

21 **STUDY ADMINISTRATION**

21.1 CLINICAL MONITORING

Monitoring and auditing procedures, developed or endorsed by Trevi Therapeutics will be followed to comply with GCP guidelines. Access to the on-site study documentation and medical records will be ensured.

The study will be monitored by Trevi Therapeutics or its designee. Throughout the course of the study, the Study Monitor will make frequent contact with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and adherence to the protocol. As part of the data audit, source

documents must be made available to the Study Monitor for review. The Study Monitor will also perform drug accountability checks and will request to perform a review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the Study Monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The Investigator, or appointed delegate, will meet with the Study Monitor during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of Trevi Therapeutics or the regulatory agencies.

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

21.2 DATA QUALITY ASSURANCE

The Investigator, or designee, will enter study data required by the protocol into an electronic data capture (EDC) system. The clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review the electronic CRF (eCRF) for completeness and accuracy. Any discrepancies found between source documents and completed eCRF will be entered as a discrepancy in the EDC system by the clinical research associate. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for eCRF correction (queries) will be discussed during the study site initiation visits and will be documented in the study operations manual.

Data from eCRF and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data from eCRF and data from other external sources for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be documented, and the study site should be requested to review and resolve the queries. Only authorized personnel can make corrections to the clinical database, and all corrections should be documented in an audit trail.

Adverse events will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

21.3 RETENTION OF STUDY RECORDS

The following records must be retained by the Investigator for a minimum of 2 years after the Sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed ICFs for all patients
- Patient identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of all communications between the Investigator and Sponsor (or Contract Research Organization [CRO])
- List of Subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all patients
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

However, because of international regulatory requirements, the Sponsor may request retention for a longer period of time. The Investigator must therefore obtain approval in writing from the Sponsor prior to destruction of any records.

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

21.4 CONFIDENTIALITY

Patient names will not be supplied to the Sponsor. Only the patient number and patient initials will be recorded in CRF (unless not allowed by local regulations), and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The will be told that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

21.5 DOCUMENTATION OF STUDY RESULTS

As part of the responsibilities assumed by participating in the study, the Investigator or Subinvestigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator or Subinvestigator agrees to maintain

accurate eCRF and source documentation as part of the case histories. These source documents may include laboratory reports and ECG recordings.

The Investigator or designees must enter all results collected during the clinical study into the eCRF. Guidelines for completion of the eCRF will be reviewed with study-site personnel at the site initiation visits. There is a 2-part process to review and collect the eCRF data. Study-site personnel will enter the data from each study visit. The Investigator is responsible for approval of the entered/corrected data. The eCRF responsibilities of the study team members will be documented on the site delegation log, which will be collected at the closeout visits.

The Investigator can authorize Sub-investigators to sign and approve the eCRF if they are designated on Form FDA 1572 as Sub-investigators, have been trained on the EDC system, and have their own user name and password. The Investigators or designees must review and approve the data before database lock.

21.6 USE OF STUDY RESULTS

All information concerning the product, as well as any matter concerning the operation of Trevi Therapeutics (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Trevi Therapeutics and are unpublished) are confidential and must remain the sole property of Trevi Therapeutics. The Investigator and participating vendors will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Trevi Therapeutics is obtained. The Sponsor has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Trevi Therapeutics. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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APPENDICES

Appendices 1 through 4 are provided on the following pages.

Appendix 1: Schedule of Events

Table 4: Schedule of Events for Visits 1a and 1b
(Day 1 of Week 1 of Treatment Period)

Visit	1a[1]	1b[4]
Informed Consent[2]	X	
Confirm Eligibility	X	
Vital Signs[3]	X	X
Physical Examination	X	X
Central Clinical Labs[5] & serum PregnancyTest[6]	X	X
Urinalysis	X	X
Urine for pregnancy test[11]	X	X
Blood for PK	X	X
12-lead ECG	X	X
Worst itch Numerical Rating Scale (NRS)[7]	X	X
Average daily itch intensity Numerical Rating Scale (NRS)[7]	X[9]	X
Verbal Rating Scale (VRS)[7]	X[9]	X
ItchyQoL[7]	X[9]	X
MOS Sleep-R[7]	X[9]	X
Hospital Anxiety and Depression Scales (HADS)[7]	X[9]	X
Patient Benefit Index Pruritus (PBI-P)[7]	X[9]	X
Prurigo Activity Score (PAS)	X[9]	X
Record AEs	X	X
Review Rescue Medications and Concomitant Medications	X[8]	X
Study Drug Retrieval and Accountability for TR03	X	
Dispense Study Drug for TR03ext	X[9]	X
First dose of Study Drug for TR03ext[10]	X[9]	X

[1]Study TR03 Visit 6 procedures in common with Study TR03 extension Visit 1a procedures do not have to be repeated.

[2] To be completed any time before start of Visit 1a procedures

[3]BP and HR (sitting or semi-recumbent), RR, temperature, and pre-dialysis weight

[4] Visit 1b is the first visit of the Treatment Period for patients transitioning from the Observation Period to the Treatment Period.

[5]Hematology and chemistry

[6]Females of Childbearing potential only

[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)

[8]Includes review of patient TR03 Rescue Medication Log

[9]Study procedures only conducted if patient qualifies to enter the Treatment Period based on worst itch NRS>2

[10]Titrate study drug according to the schedule in Table 3;

The first dose of study drug treatment will define enrollment into the study

[11] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing study drug.

Table 5: Treatment Period Weeks 2-4

	TC 1[1]	TV 2[1]	TC 2[1]
Treatment Period Week	**2**	**3**	**4**
Dispense Study Drug[3]		X	
Titrate Study Drug[2]	X	X	
Confirm Maintenance Dose			X[5]
Vital Signs[4]		X	
Urine pregnancy test[7]		X	
Blood for PK		X	
12-lead ECG			
Worst itch NRS[6]		X	
Average daily itch intensity NRS[6]		X	
VRS[6]		X	
MOS Sleep-R[6]		X	
HADS[6]		X	
ItchyQoL[6]		X	
PBI-P[6]			
PAS			
Study Drug BID		X	
Record AEs	X	X	X
Record Concomitant Medications		X	
Reinforce Compliance	X	X	X
Study Drug Accountability		X	

[1] The window for TC 1-2 and TV2 is +/-3 days
[2]Titrate study drug according to the schedule in Table 3 and assess tolerability/intolerability to study drug; determine if to continue dose escalation
[3]At TV 2 dispense a single 60 mg tablet bottle for the 120 mg BID and 180 BID dosing patients; Dispense 30 mg bottle for the 90 mg BID dosing patients.
[4] BP and HR (sitting or semi-recumbent), RR, temperature.
[5] Down titrate only if necessary and only down titration from the 180 mg BID and 120 mg BID groups are allowed. If 90 mg BID is intolerable, the subject is discontinued. See Table 3.
[6]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[7] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.

Table 6: Treatment Period Visits[12] During Study Weeks 5-50 and Washout/Safety Follow-up Visit or Treatment Period Early Termination Visit

Treatment Period Weeks 5-52[1,3]	**TV 3**	**TV 4**	**TV 5**	**TV 6**	**TV 7**	**TV 8**	**TV 9**	**TV 10**	**TV 11**	**TV 12**	**TV 13**	**TV 14**	**Washout / Safety Follow-up Period**	**ET[9]**
Treatment Period Week	5	9	13	17	21	26	30	34	38	42	46	50[2]	52	
Physical Examination						X						X		X
Central Clinical Labs[6]						X						X	X	X
Serum pregnancy test to central lab[11]												X		X
Urinalysis to central lab						X						X		X
PAS						X						X		
PBI-P[7]												X		
12-lead ECG						X						X	X	X
Skin biopsy												X[10]		
Blood for PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X			
Urine pregnancy test[5]	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Worst itch NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Average daily itch intensity NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ItchyQoL	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MOS Sleep-R[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		X
Reinforce Compliance	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Accountability	X	X	X	X	X	X[8]	X	X	X	X	X	X		X[8]
Study Drug BID	X	X	X	X	X	X	X	X	X	X	X			

[1]Patients who were previously in the Observation Period should start the Treatment Period at Visit 1b and continue in the study for 38-46 weeks; the total number of weeks in the combined Observation and Treatment Periods is no more than 50 weeks. The last scheduled visit on study drug for patients previously in the Observation Period should be TV 14 regardless of the study week.

[2] The number of Treatment Period weeks prior to TV 14 will vary for patients previously in the Observation Period depending upon the number of weeks spent in the Observation Period. See Table 8

[3]A single allowable dose reduction is permitted during Treatment Period Weeks 5 – 50 (a patient at 90 mg BID can be reduced to 60 mg BID). If a second dose reduction is needed, the patient should be discontinued from the study.

[4] BP and HR (sitting or semi-recumbent), RR, temperature

[5]For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.

[6] Hematology and chemistry.

[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)

[8] Retrieve remaining study drug at TV 14 or ET Visit

[9] ET Visit is conducted within 2 weeks of study drug termination

[10] Skin biopsy material for nerve fiber density (histology) and MOR/KOR density to be performed only at select sites

[11]Females of Childbearing potential only

[12] Visit windows will be +/-3 Days

Table 7: Observation Period Visits[5]

Observation Visit	OV 2	OV 3	OV 4
Observation Study Week	4	8	12[1]
Check Worst itch NRS[2]: If >2, patient must undergo Visit 1b	X[4]	X[4]	X[4]
Vital Signs[3]	X	X	X
Average daily itch intensity NRS[2]			X
VRS[2]			X
MOS Sleep-R[2]			X
HADS[2]			X
ItchyQoL[2]			X
Record AEs	X	X	X
Record concomitant medications	X	X	X

[1]Patients whose NRS is ≤2 at OV 4 should be screen failed from the study.
[2] Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[3]BP and HR (sitting or semi-recumbent), RR, temperature
[4]If patient's NRS>2 proceed to Visit1b procedures and no need to record any further data under OV visit procedures
[5]Visit windows will be +/-3 Days

Table 8: Schedule of Next Treatment Period Visits for Patients Transitioned from the Observation Period and who complete titration

	Study Week of Visit 1b	Study Week of TV2	Next Treatment Period Visit[1,2,3]
OV2	Week 4	Week 6	TV4, Week 9
OV3	Week 8	Week 10	TV5, Week 13
OV4	Week 12	Week 14	TV6, Week 17

[1] See Table 6

[2] Schedule modifications will take place for patients entering the Treatment Period from the Observation Period. These patients will not have specific visits depending on when they enter the Treatment Period

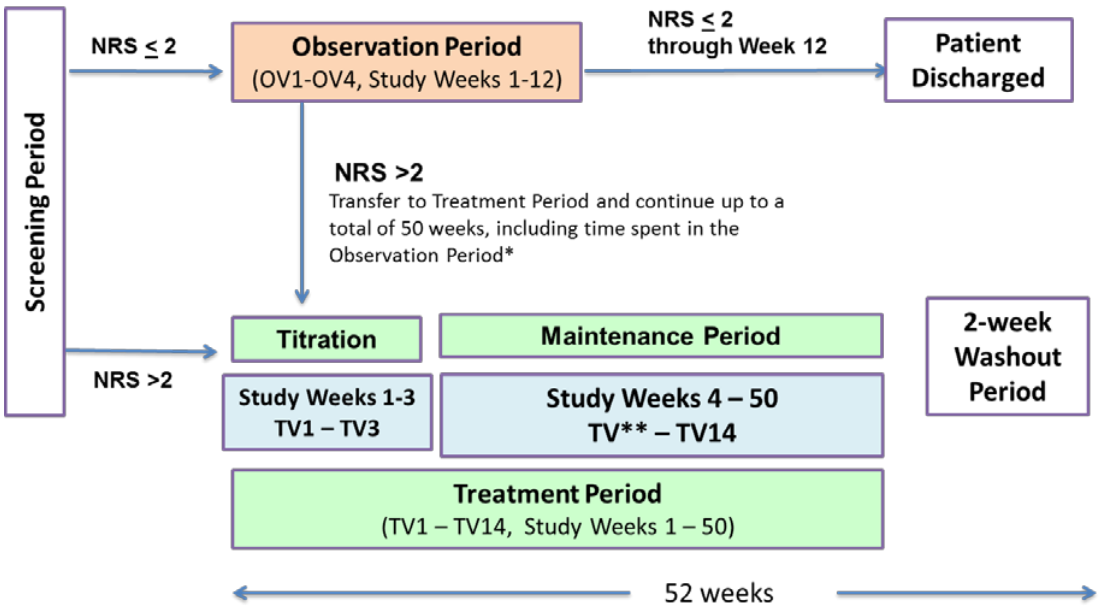
- For patients entering at OV2, TV3 will not take place
- For patients entering at OV3, TV4 will not take place
- For patients entering at OV4, TV5 will not take place

[2] Patients will be provided with adequate study drug to take them from TV2 to the next Treatment Period visit listed

Table 9: 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	✓	---

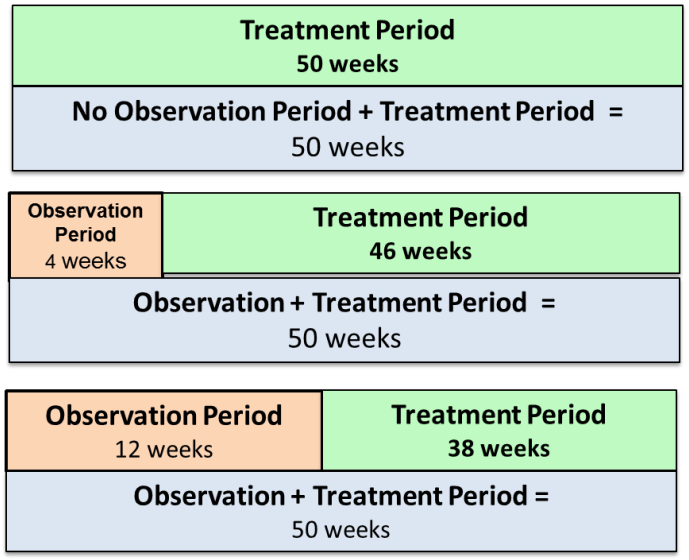
Appendix 2: Study Schematic Flow Charts

Figure 2: Overview of TR03-EXT Study Design



*Patients transferring from the Observation Period will start with Visit 1b/TV1.
Their follow-up in the Observation + Treatment Period will be 50 weeks in total.
** See Table 8

Figure 3: Examples illustrating possible Observation and Treatment periods Scenarios in TR03-Ext



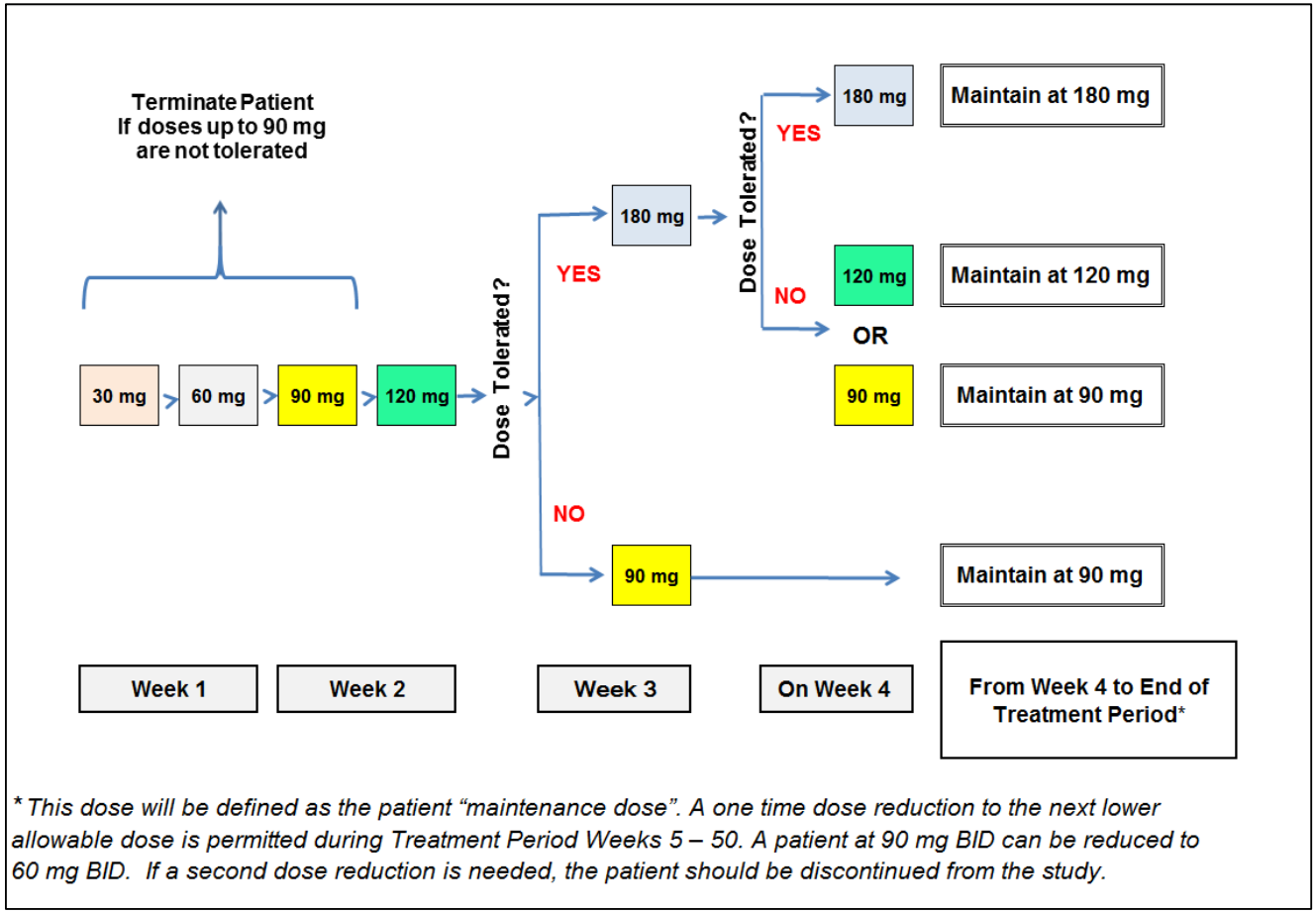
Example of patient who qualifies to start treatment based on screening NRS scores

Example of patient who does not qualify to start treatment until Observation Period Week 4

Example of patient who does not qualify to start treatment until Observation Period Week 12

- Some patients will not be followed in the Observation Period (Top Scenario).
- For patients followed in the Observation Period, the total duration of time in the Observation and Treatment Periods will be up 50 weeks, regardless of when they transfer from the Observation Period to the Treatment Period (Middle and Bottom Scenarios)
- The first Observation Period visit at which the patient qualifies for treatment (see Table 1) will also be defined as Visit Ib/TV1.

Figure 4: Dosing Schedule in TR03ext



** This dose will be defined as the patient "maintenance dose". A one time dose reduction to the next lower allowable dose is permitted during Treatment Period Weeks 5 – 50. A patient at 90 mg BID can be reduced to 60 mg BID. If a second dose reduction is needed, the patient should be discontinued from the study.*

Appendix 3: Clinical Laboratory Tests

Hematology:

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

Urine:

Urinalysis
Pregnancy

Serum Pregnancy:

β-Human Chorionic Gonadotropin (HCG) (women of childbearing potential)

Serum Chemistry:

Potassium
Chloride
Carbon Dioxide
Blood Urea Nitrogen (BUN)
Creatinine
Calcium
Phosphorus
Total Protein
Albumin
Total Bilirubin
AST
ALT
Alkaline Phosphatase
LDH
Glucose

Appendix 4: Patient Reported Outcomes

The Patient Reported Outcomes are provided on the subsequent pages.

Medical Outcomes Sleep Scale (Revised MOS Sleep-R)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Your Sleep

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. How long did it usually take for you to <u>fall asleep</u> during the <u>past 4 weeks</u>?

0-15 minutes	16-30 minutes	31-45 minutes	46-60 minutes	More than 60 minutes
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. On the average, how many hours did you sleep <u>each night</u> during the <u>past 4 weeks</u>?

Write in number of hours per night: ☐☐

3. How often during the <u>past 4 weeks</u> did you…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	get enough sleep to feel rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	awaken short of breath or with a headache?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	have trouble falling asleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

MOS 12-Item Sleep Scale – Revised 2010
United States (English)

Medical Outcomes Sleep Scale (Revised MOS Sleep-R) (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

How often during the <u>past 4 weeks</u> did you…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
f	awaken during your sleep time and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	snore during your sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	take naps (5 minutes or longer) during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	get the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ItchyQoL™

Sample – actual assessment scale will be provided to the patient at appropriate visits

ITCHING QUALITY OF LIFE SURVEY

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My itchy skin condition bleeds.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. My skin hurts because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. My itchy skin condition burns or stings.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. I get scars from my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. I need to scratch my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. I spend a lot of money treating my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Updated 06 August 2013
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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
10. My itchy skin condition affects how well I sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. My itchy skin condition often makes it difficult to concentrate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. My itchy skin condition limits the types of clothes I can wear.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. I am frustrated by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I am embarrassed by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Updated 06 August 2013
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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

	How often during the past week do these statements apply to you?				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. My itchy skin condition drives me crazy/nuts.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. My itchy skin condition makes me angry or irritable.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. My itchy skin condition makes me feel depressed or sad.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. I worry about what other people think about me because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I worry that the itching will last forever.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. I feel self-conscious because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. My personality has changed because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Subject signature Date

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Prurigo Activity Score (PAS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

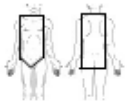
1. Type
a) Which efflorescences do you see?
□ papules
□ nodules
□ plaques
□ umbilicated ulcers
□ hypo-/hyperpigmented maculae

b) Which type of prurigo is predominant?
□ Prurigo papular type
□ Prurigo nodular type
□ Prurigo plaques type
□ Prurigo umbilicated "Kyrle" type
□ completely healed

2. Number
a) How many Prurigo lesions do you see? (do not count scars)
□ 0
□ 1 - 19
□ 20 – 100
□ > 100

3. Distribution:
□ disseminated
□ localized (only 1 or 2 areas affected)
□ neither of them

4. Please mark the affected area(s) (for definition of trunk see image).
whole body except head □
whole body head included □



or

forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal
head	□ capillitium	□ face

5. Please choose a representative area:

forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal

Number of prurigo lesions in representative area (do not count scars):_____

6. Monitor lesions. Please mark the biggest (B) and a representative (R) prurigo lesion (remains the same in every visit).

	Highest elevation [mm]	Biggest diameter [mm]	
		longitudinal	crosswise
biggest prurigo lesion			
representative prurigo lesion			

7. Activity. Please mark the stage.

	stage 0	**stage 1**	**stage 2**	**stage 3**	**stage 4**
Prurigo lesions with excoriations/crusts compared to all prurigo lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
Healed prurigo lesions compared to all prurigo lesions	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

8. Take photos of the patient: Overview front and back, area(s) of marked monitor lesions to recognize on next visit

SST-Pr-10-2007, Amendment 9, PAS, Version 0.7; 11.09.2013

Patient Benefit Index, Pruritus Version (PBI-P)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Importance of Treatment Goals

With the help of the following questions, we'd like to know how important the goals mentioned below are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you.
If a statement does not apply to you, for example because you are not experiencing pain, please mark "*does not apply to me*".

	As a result of therapy, how important is it for you to ...	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on your skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...concentrate better	O	O	O	O	O	O
6	...be less nervous	O	O	O	O	O	O
7	...be able to wear all types of clothing	O	O	O	O	O	O
8	...be able to bathe and shower normally	O	O	O	O	O	O
9	...sleep better	O	O	O	O	O	O
10	...feel less depressed	O	O	O	O	O	O
11	...experience greater enjoyment of life	O	O	O	O	O	O
12	...have no fear that the disease will get worse	O	O	O	O	O	O
13	...lead a normal everyday life	O	O	O	O	O	O
14	...be more productive in everyday life	O	O	O	O	O	O
15	...be less of a burden to relatives and friends	O	O	O	O	O	O
16	...engage in normal leisure activities	O	O	O	O	O	O
17	...be able to lead a normal working life	O	O	O	O	O	O
18	...be able to have more contact with other people	O	O	O	O	O	O
19	...be more comfortable showing yourself in public	O	O	O	O	O	O
20	...be less burdened in your partnership	O	O	O	O	O	O
21	...be able to have a normal sex life	O	O	O	O	O	O
22	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	...need less time for daily treatment	O	O	O	O	O	O
24	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	...have fewer side effects	O	O	O	O	O	O
26	...find a clear diagnosis and therapy	O	O	O	O	O	O
27	...have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

PBI-P (Cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Treatment Benefits

When the treatment began, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent to which those treatment goals **were achieved**, indicating if the treatment has benefited you. If a statement did not apply to you, for example because you did not experience any pain, please mark "*did not apply to me*".

	The current treatment has helped me to …	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*did not apply to me*
1	…be free of pain	O	O	O	O	O	O
2	…be free of itching	O	O	O	O	O	O
3	…no longer have burning sensations on my skin	O	O	O	O	O	O
4	…be healed of all skin defects	O	O	O	O	O	O
5	…concentrate better	O	O	O	O	O	O
6	…be less nervous	O	O	O	O	O	O
7	…be able to wear all types of clothing	O	O	O	O	O	O
8	…be able to bathe and shower normally	O	O	O	O	O	O
9	…sleep better	O	O	O	O	O	O
10	…feel less depressed	O	O	O	O	O	O
11	…experience greater enjoyment of life	O	O	O	O	O	O
12	…have no fear that the disease will get worse	O	O	O	O	O	O
13	…lead a normal everyday life	O	O	O	O	O	O
14	…be more productive in everyday life	O	O	O	O	O	O
15	…be less of a burden to relatives and friends	O	O	O	O	O	O
16	…engage in normal leisure activities	O	O	O	O	O	O
17	…be able to lead a normal working life	O	O	O	O	O	O
18	…be able to have more contact with other people	O	O	O	O	O	O
19	…be more comfortable showing myself in public	O	O	O	O	O	O
20	…be less burdened in my partnership	O	O	O	O	O	O
21	…be able to have a normal sex life	O	O	O	O	O	O
22	…be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	…need less time for daily treatment	O	O	O	O	O	O
24	…have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	…have fewer side effects	O	O	O	O	O	O
26	…find a clear diagnosis and therapy	O	O	O	O	O	O
27	…have confidence in the therapy	O	O	O	O	O	O

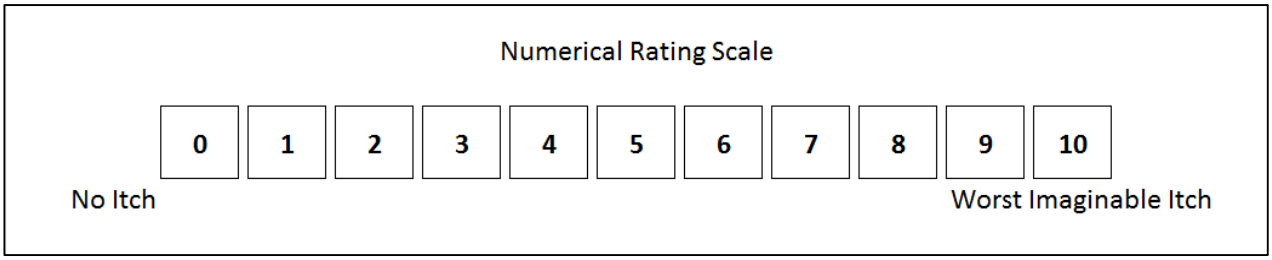
Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

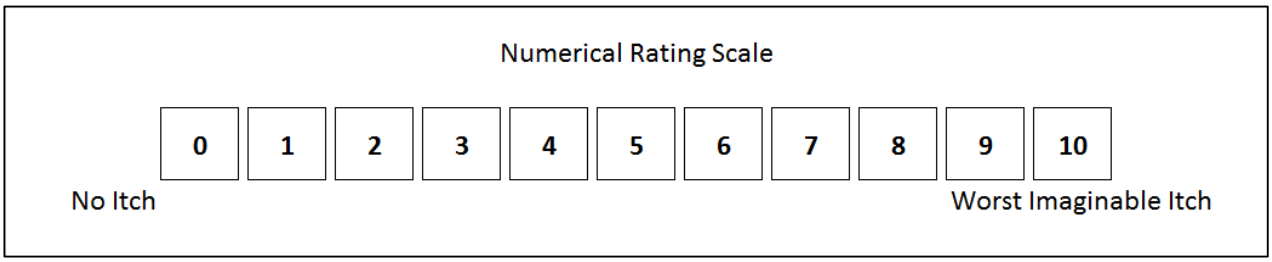
Numerical Rating Scale (Worst Itch)

How would you rate your most severe itching over the past 24 hours?



Numerical Rating Scale (Average-Itch)

How would you rate your itching on average over the past 24 hours?



Verbal Rating Scale

How is your skin sensation today?

	0: not present	**1:** mild present	**2:** moderately present	**3:** severely present	**4:** very severely present
Itchy					
Burning					
Stinging					

Hospital Anxiety and Depression Scale (HADS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A D

I feel tense or 'wound up'
- 3 Most of the time
- 2 A lot of the time
- 1 From time to time, occasionally
- 0 Not at all

I still enjoy the things I used to enjoy
- 0 Definitely as much
- 1 Not quite so much
- 2 Only a little
- 3 Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
- 3 Very definitely and quite badly
- 2 Yes, but not too badly
- 1 A little, but it doesn't worry me
- 0 Not at all

I can laugh and see the funny side of things
- 0 As much as I always could
- 1 Not quite so much now
- 2 Definitely not so much now
- 3 Not at all

Worrying thoughts go through my mind
- 3 A great deal of the time
- 2 A lot of the time
- 1 Not too often
- 0 Very little

I feel cheerful
- 3 Never
- 2 Not often
- 1 Sometimes
- 0 Most of the time

I can sit at ease and feel relaxed
- 0 Definitely
- 1 Usually
- 2 Not often
- 3 Not at all

I feel as if I am slowed down
- 3 Nearly all the time
- 2 Very often
- 1 Sometimes
- 0 Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach
- 0 Not at all
- 1 Occasionally
- 2 Quite often
- 3 Very often

I have lost interest in my appearance
- 3 Definitely
- 2 I don't take as much care as I should
- 1 I may not take quite as much care
- 0 I take just as much care as ever

I feel restless as if I have to be on the move
- 3 Very much indeed
- 2 Quite a lot
- 1 Not very much
- 0 Not at all

I look forward with enjoyment to things
- 0 As much as I ever did
- 1 Rather less than I used to
- 2 Definitely less than I used to
- 3 Hardly at all

I get sudden feelings of panic
- 3 Very often indeed
- 2 Quite often
- 1 Not very often
- 0 Not at all

I can enjoy a good book or radio or television programme
- 0 Often
- 1 Sometimes
- 2 Not often
- 3 Very seldom

Now check that you have answered all the questions

A D

TOTAL

CLINICAL PROTOCOL

Protocol Number:	**TR03ext**
Version Number:	**2.0**
Version Date:	**11 March 2015**
EudraCT No.	**2013-005628-41**
Protocol Title:	**An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients**
Study Sponsor:	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, Connecticut 06510 United States Phone: (203) 304-2499 www.trevitherapeutics.com

CONFIDENTIAL

Investigators: Multicenter

Research Facilities: Multicenter

Institutional Review Board/ Independent Ethics Committee: Multicenter

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Signature Date 11 MARCH 2015

INVESTIGATOR SIGNATURE PAGE

I have read the attached protocol entitled A Randomized, Double-Blind, Placebo-Controlled, Parallel, 3-Arm Study of the Safety and Anti-Pruritic Efficacy of nalbuphine HCl ER Tablets in Prurigo Nodularis Patients dated **11 MARCH 2015** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 of the CFR, Parts 11, 50, 54, 56, and 312 and European Union Directive 2001/20/EC or equivalent regulatory body regulations/guidelines, as applicable.

I agree to ensure that Financial Disclosure Statements will be completed by:

- Myself (including, if applicable, my spouse [or legal partner], and dependent children)
- My subinvestigators (including, if applicable, their spouses [or legal partners], and dependent children)

The Financial Disclosure Statements will be completed before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Trevi Therapeutics, Inc.

Principal Investigator:

_____ _____
Name of Principal Investigator Date

_____
Institution or Clinical Practice

_____
Signature

1 STUDY SYNOPSIS

Title	An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients
Sponsor	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, Connecticut 06510 United States Phone: (203) 304-2499 www.trevitherapeutics.com
Protocol Number	TR03ext
Version and Date	Amendment 1: Version 2.0 dated 11 MARCH 2015 Version 1.0 dated 24 JUNE 2014
Indication	Prurigo Nodularis (PN)
Investigational Product	nalbuphine hydrochloride (HCl) extended-release (ER) tablets
Active Ingredient	nalbuphine hydrochloride
Route of Administration	Oral
Duration of Study	The total study duration for any individual patient will be up to 53 weeks. Patients will receive drug treatment for up to 50 weeks.
Study Phase	Phase 2/3
Study Design	Open label
Planned Sample Size	No *a priori* planned sample size is designated for this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., up to 60 patients)
Total Number of Centers	Up to 10 sites in North America and Europe
Primary Objective	• To evaluate the safety and tolerability of nalbuphine HCl ER tablets during a drug treatment period of up to 50 weeks.

Secondary Objectives	• To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Week 4. • Assess skin lesion improvement using the metrics of the PAS • Change from Baseline in Patient-Reported Outcome measures Worst (i.e., most severe itching over the past 24 hours) itch NRS, average itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS by the final Treatment Period Visit • Change between Baseline and the final Treatment Period Visit in PBI-P • 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.
Exploratory Objectives	A single exploratory objective of the study is to evaluate: • 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 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).
Selection Criteria	**Inclusion Criteria:** Patients must meet all of the following criteria to be eligible: 1. Have been adequately informed of the nature and risks of the study and have given written informed

	consent at or prior to Visit 1a. 2. Have completed participation in the TR03 study. Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6. 3. Agree to comply with the contraception requirements as below: Female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, Essure procedure, or spermicide). For the purpose of this study, all females are considered to be of childbearing potential unless they are post-menopausal (i.e., at least 1 year since last menses and age >50 years) or surgically sterile (i.e., tubal ligation, hysterectomy and/or bilateral oophorectomy). 4. Ability and acceptance to provide written informed consent. 5. Willing and able to comply with study requirements and restrictions 6. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.
Selection Criteria	**Exclusion Criteria:** If a patient meets any of the following criteria, he or she is *not* eligible: 1. Patients with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association scale (scale provided in Appendix 5) 2. Patients with a history of angina pectoris grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale (scale provided in Appendix 5) 3. History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the patient. 4. Serum potassium below the laboratory lower limit of normality. Potassium supplementation can be prescribed and the serum potassium level repeated 5. QTcF interval >450ms on screening EKG 6. Heart rate <50 BPM on screening

	7. Use of a medication known to be associated with risk of torsade de pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes) 8. History of substance abuse within the past year as determined by the Investigator 9. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study 10. Known hypersensitivity or allergy to nalbuphine or formulation components 11. Is a pregnant or lactating female
Study Treatment Allocation	All patients who are enrolled into the study will receive active treatment with nalbuphine HCl ER tablets.
Study Procedures	Visit 1a of the TR03ext study is temporally the same visit as TR03 Visit 6. Subjects who do not consent by the end of the TR03 study visit 6 are no longer eligible for the extension study. Study TR03 Visit 6 procedures in common with Study TR03ext Visit 1a procedures do not have to be repeated. **For All Patients:** For all patients, TR03ext Visits (both during the Treatment Period and Observation Period) will include recording of vital signs, completion of PRO questionnaires, assessment of AEs, and recording of concomitant medications. On Visit 1a, patients will either enter directly into the drug Treatment Period or into a no-drug Observation Period based on their reported Worst itch NRS scores (defined as most severe itching over the past 24 hours) on that Visit day. **Patients with a Worst Itch NRS score greater than or equal to 5 (≥) 5 enter the Treatment Period:** Patients with Worst itch NRS ≥ 5 at Visit 1a will start in the drug Treatment Period of the study and will receive Study Drug starting with an evening 30 mg dose (to be taken at home), after the Treatment Visit 1a procedures have been completed. Receipt of the first dose of study drug will define Treatment Period Day 1. Treatment Visit 1a for these patients is also Treatment Visit 1 (TV1). Subsequent visits will be defined as TV2, TV3, etc. In addition, during the time period of dose titration, information will be obtained via telephone communication; these will be defined as TC1, and TC2. The dose will be titrated for up to 4 weeks based on tolerability, after which time the dose achieved (as of the end of Treatment Week 4) will be maintained up to an additional 46 weeks (with the exception of permitted down titrations);

	see Table 3 Study Drug Dosing schedule. For patients transitioning from the Observation period, the total time in the Treatment Period plus any time in the Observation Period will be a total of 50 weeks. Safety laboratory data and blood for PK, ECGs (locally and centrally read), and physical examinations including the PAS assessment will be performed periodically according to the Schedule of Events (See Appendix 1). Schematic descriptions of the study can be found in Appendix 2. All patients on drug treatment will enter a 2-week wash-out and safety follow up period following end of the Treatment Period with procedures conducted according to the Schedule of Events (See Appendix 1). **Patients with a Worst Itch NRS score less than 5 (< 5) enter the Observation Period:** Patients with a Worst Itch NRS score < 5 at Visit 1a will enter into an extended screening period, Observation Period (no drug treatment), of the study and will be followed for up to 12 weeks (extended screening weeks). Visit 1a for these patients is also Observational Visit 1 (OV1). Subsequent visits will be defined as OV2, OV3 and OV4 and will occur at approximately monthly intervals for the next 3 months. During this Observation period, patients who report an increase in their Worst Itch NRS with a score of ≥ 5 at any one of their Observation Visits and meet all other eligibility criteria will be able to enroll immediately into the Treatment Period of the study and Visit1b procedures are to be performed. Patients will receive open-label Study Drug starting with an evening 30 mg dose (to be taken at home), after the Visit 1b procedures have been completed. Receipt of the first drug will indicate the start of their Treatment Period and enrollment into the study. The duration of the Treatment Period for such a patient will vary depending upon the visit at which they transition from the Observation Period to the Treatment Period. Patients in the Observation Period whose Worst Itch NRS score remains <5 over the 12 extended screening weeks will be screen failed from the study at the end of that time period. **Failure to Improve Criteria:** Beginning on TV 3 and at every subsequent Treatment Visit, patients with a Worst itch NRS equal to or greater than (≥) the Worst Itch NRS at Visit 1a (or at Visit 1b in the case of patient who require the Observation Visit period) will be discontinued from taking study drug. Subjects discontinued from taking 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 for final safety

	assessment.
Safety Assessments	Safety will be assessed based on adverse events (AEs), clinical laboratory measurements, Investigator review and central cardiac core laboratory read-12-lead electrocardiogram (ECG), vital signs and physical examinations. An unblinded, independent Data Safety Monitoring Board (DSMB) will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter.
Efficacy Assessments	**Efficacy Measurements:** • Worst itch intensity (from NRS) • Average itch intensity (from NRS) • VRS (itchy, burning and stinging) • ItchyQoL • MOS Sleep-R • HADS • PAS • PBI-P • Frequency, pattern, and reasons for dose titration • Use of rescue medications for itching At selected sites (optional procedures): • Nerve fiber density (histology) at Baseline and the final Treatment Period Visit • MOR/KOR density (histology, Western Blot) at Baseline and the final Treatment Period Visit • Histological analysis (H&E) at Baseline and the final Treatment Period Visit
Pharmacokinetic Assessments	Blood samples for nalbuphine plasma concentration (and metabolites as needed) will be collected periodically according to the Schedule of Events (Appendix 1).
Study Endpoints	**Primary Endpoint:** • A description of the incidence and nature of TEAEs during Treatment Weeks 5- 50 **Secondary Endpoints** 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. Visit 1b will be the baseline for patients entering the

	Treatment Period after participating in the Observation Period for any length of time. • Assess skin lesion improvement using the metrics of the PAS • Change from Baseline in Patient-Reported Outcome 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 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 criteria • Changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets • Time to the 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 **Exploratory Endpoint** • 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 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).
Statistical Methodology	**Efficacy:** All efficacy endpoints will be evaluated through the generation of 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. **Safety:** The incidence of AEs will be summarized through the presentation of proportions by MedDRA body system classification and preferred term. Vital signs and laboratory data will be summarized using continuous-based descriptive statistics (n, mean, SD, median, minimum, maximum). The extent and duration of use of rescue medications will be similarly summarized using descriptive statistics. Summary statistics for AEs with onset during the Observation Period will be separately summarized. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomic and Therapeutic Class
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CNS	Central nervous system
CRF	Case report form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Extended release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&E	Hematoxylin and eosin
HADS	Hospital Anxiety and Depression Scale
HCG	Human chorionic gonadotropin
HCl	Hydrochloric acid
HD	Hemodialysis
H pylori	Helicobacter pylori
HR	Heart rate
ICF	Informed consent form
ICD-10	International Classification of Diseases, 10th revision

Abbreviation	Definition
ICH	International Conference on Harmonization
IFSI	International Forum for the Study of Itch
IRB	Institutional Review Board
IUD	Intra-uterine device
KOR	Kappa Opiate Receptor
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MOR	Mu Opiate Receptor
MOS	Medical Outcomes Study
MITT	Modified Intent-To-Treat
NONMEM	Non-linear mixed effects modeling
NRS	Numerical Rating Scale
NYHA	New York Heart Association
OV	Observation Period Visit
OTC	Over-the-counter
PAS	Prurigo Activity Score
PBI-P	Patient Benefit Index, pruritus version
PD	Pharmacodynamic(s)
PK	Pharmacokinetic
PN	Prurigo Nodularis
PRO	Patient-Reported Outcome; In this study, PRO instruments administered at the site are as follows: NRS, VRS, ItchyQoL, PBI-P, MOS Sleep-R, HADS, SOWs
QoL	Quality of Life
RR	Respiratory rate
SAE	Serious adverse event
SD	Standard deviation
SOWS	Subjective Opiate Withdrawal Scale
TC	Telephone Call
TdP	Torsade de Pointes
TV	Treatment Period Visit
UP	Uremic Pruritus
VRS	Verbal Rating Scale
WHO	World Health Organization

3 INTRODUCTION

3.1 PRURIGO NODULARIS AND STUDY RATIONALE

3.1.1 General Information on Prurigo Nodularis

Prurigo Nodularis (PN) is an intensely pruritic dermatologic condition with the presence of papules as well as nodules with excoriations and ulcerations. The basis of PN is a pre-existing severe and chronic pruritus of various etiologies (see Table 1). The pruritus leads to scratching. However, the etiology or predisposing factors leading to the development of papules and nodules of PN are largely unknown (Eigelshoven et al 2009; Valdya and Schwartz 2008; Lee and Shumack 2005). Iking et al (2012) reports that in the past few years the hypothesis for the etiology of PN as being a reaction pattern due to a "vicious cycle of repeated itching and scratching" is gaining wider acceptance in the medical community.

With regard to the types of pre-existing chronic pruritus conditions that have been reported in PN patients, Table 1 summarizes data reported by Iking et al (2012) in their study of PN patients (N=108). Pruritus secondary to multi-factorial etiologies ("Mixed Origin") was the most common source attributed to the cause of the chronic pruritus. The majority of the "mixed origin" patients had a combination of dermatological and systemic diseases or a combination of several systemic disorders.

Iking et al (2012) did not attribute any cases of PN to an underlying diagnosis that was solely psychological in origin. In the subjects who were diagnosed with PN from mixed origin etiologies (summarized in Table 1), the authors attributed psychological factors related to chronic pruritus etiology to be present in 5.6% of the PN subjects categorized as having mixed (multi-factorial) origin pruritus. In a study focused on understanding psychosomatic/psychiatric dimensions related to chronic itch, Schneider et al (2006) reported on 44 PN patients. The authors stated that 34% of subjects had no accompanying psychiatric diagnosis and 46.8% were given a diagnosis of "psychological or behavioral factors associated with disorders classified elsewhere" (ICD-10 code F54) –indicating that psychological factors may play a role in the development and course of the condition. Payne et al (1985) reported psycho-social problems may have been relevant in about 33% of the studied 42 subjects that were adequately questioned.

Table 1: Etiology of Chronic Pruritus Reported in Prurigo Nodularis Patients (N=108)

Origin of Pruritus by Organ System	Number of Patients (%)	% Mixed with Organ Category Contribution to Chronic Pruritus	Most Common Disease
Mixed (pruritus of multi-factorial etiologies)	64 (59.3%)	Dermatological Disease (19.4%)	Atopic diathesis
		Systemic Diseases (70.9%)	Sorbitol Intolerance
			Lactose Intolerance
			Iron Deficiency
			H pylori Infection
			Diabetes Mellitus
			Renal Failure
		Neurological Disease (4.1%)	Chronic pain Syndrome
			Neuropathy
			PUVA-pain
		Psychological Factors (5.6%)	Psychological Factors (non-specific)
Origin of Pruritus by Organ System	Number of Patients (%)	Most Common Disease	
Dermatological	20 (18.5%)	Atopic diathesis/dermatitis	
Systemic	8 (7.4%)	Sorbitol Intolerance	
		Lactose Intolerance	
		Hepatitis C	
		H pylori infection	
		Iron Deficiency	
		Diabetes Mellitus	
Unknown	14 (13%)	-	
Neurological	2 (1.9%)	Brachio-radial Pruritus	
Psychological	0 (0%)	-	

Source: Iking et al (2012)

Iking et al (2012) reported that the median value of the NRS average intensity pruritus measured 8 on a rating scale with anchor points of zero (no pruritus)-10 (worst imaginable pruritus). Itch intensity scores ≥ 7 are considered severe in terms of itch intensity and itch intensity scores ≥ 3 are considered moderate in terms of itch intensity (Stander et al 2013). Accioly-Filho et al (2000) reports that once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop as PN is very resistant to therapeutic intervention strategies. Papoiu et al (2013) report a central nervous system relationship to the itch-scratch cycle. The authors showed that there is a complex interaction of sensory, motor and emotional

components based on their investigation of using real-time flare brain MRI imaging and psychophysical ratings of itch relief or pleasurability of scratching conducted in healthy volunteer experimental subjects.

Eigelshoven et al (2009) reports that patients present with excruciating pruritus that is usually anatomically symmetrical and mainly involves the extensor aspects of the extremities, the shoulders, chest and sacral regions with the appearance of typical lesions. Payne et al (1985) reported in a study of 46 subjects that the patients came from all social classes and racial groups, almost equally divided by gender and with a mean age of 39.5 years at the time of PN onset. Iking et al (2012) reported in their study that the patients were distributed in age between 11.9 years - 95.6 years with a median age of 61.9 years and there were more females than males affected by the disease.

Weigelt et al (2010) summarized the characteristic histological findings in PN that include the presence of thick compact orthohyperkeratosis; folliculosebaceous units in nonvolar skin in conjunction with a thick and compact cornified layer; irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils.

In terms of treatment options for PN, there have been a variety of medical interventions discussed. Hogan et al (2012) recently reviewed the therapies discussed in the literature that included topical, systemic and intra-lesion steroids administration; antihistamines; anxiolytics; opiate receptor antagonists; thalidomide; gabapentin; capsaicin cream; topical anesthetics; occlusive therapies; ultraviolet light; and reports that they had “mild to moderate success at best”. The authors also comment on the potential imbalance in the mu-kappa opiate receptor system and mention the possibility of studying the kappa agonist nalfurafine (see section 3.1.3.1, where nalfurafine was used as a positive control in Sponsor’s preclinical substance P mouse model of itch investigation). Spring et al (2014) reported on the use of methotrexate and the need for chemotherapeutic related regular medical monitoring. Liu et al (2013) and Kanavy (et al 2012) both reported on lenalidomide is case reports, but the drug led to side effect of a reversible myopathy in one of the subjects. Accioly-Filho (2000) reported the condition is “notoriously resistant to therapy”. Iking et al (2012) and Valdya and Schwartz (2008) reported a significant impact on the patient’s quality of life (2008). Spring et al (2014) report PN to be debilitating condition and a therapeutic challenge where conventional treatments with steroids, standard anti-pruritic agents, phototherapy and immune-suppressors often fail.

3.1.2 Potential Mechanism of Prurigo Nodularis Pathophysiology

3.1.2.1 *Opiate Neurobiology*

The initiating biological event in the skin is unclear but assumed to patho-physiologically result from a complex cross talk of different skin cells. The neurobiology of opioid peptides may be involved at the peripheral level as part of a reaction to the skin tissue injury. Therapeutic intervention at the peripheral level through opioid pharmacology to break the scratch-itch cycle via interrupting positive feedback loops that have developed between elements of the peripheral nervous system, immune system and various skin cell

interactive dynamics may be possible. In addition, central nervous system opiate neurobiology may be involved in a positive feedback loop between the tremendous urge to scratch and the pleasurable anti-pruritic relief gotten from scratching that could also be a level of therapeutic intervention using opioid pharmacology.

3.1.2.2 *Systems Biology Hypothesis to Prurigo Nodularis Etiology*

Diseases that arise from an abnormal interaction between integrated body system networks and exhibit the concept of a positive feedback cycle which lead to an amplification of a biological signal can be discussed using concepts from systems biology (Kitano 2004). The physiological phenomena of a "scratch-itch cycle" ("positive feedback loop") underlying the patient's behavior, the intense ("amplified") nature of the pruritus and the large areas of body surface involvement in the absence of an active dermatosis suggest a "generalized" process either potentially due to central nervous system circuitry pathophysiology and/or widespread derangement of the dermal-immune-nervous system component interactions. PN may be analogous to chronic regional pain syndrome – a condition where there may or may not be an initiating etiological event, the intensity of pain is severe, the sensation of pain spreads to wide areas of the body surface and the condition is regarded as a systemic disease that involves both the central and peripheral components of the nervous system along with interactions with the immune system (Schwartzman et al 2009). Complex regional pain syndrome is completely independent of any potential nociceptive initiating event. Schmelz (2005) reviewed the literature on the evidence of similar biological patterns occurring in chronic pain and chronic itch conditions. Iking et al (2012) reported that on onset, PN was localized in 68.5% of patients with only 31.5% having generalized PN. In the majority of patients (56.5%), a secondary generalization of PN was observed. In the course of PN, only 12.0% still suffered from a localized form of PN.

3.1.2.3 *Relevant Cutaneous Peripheral Neurobiology in the Skin*

The complex neurochemical/neurohumoral interactions between the cutaneous resident mast cells and epidermal keratinocytes with peripheral non-myelinated type C nerve endings responsible for initiating the behavior of scratching as an evolved protective response to exogenous invading skin irritants is well summarized by Raap et al (2011) and the current understanding of the peripheral neuroanatomy-spinal cord synaptic connections underlying itch is well summarized by Dhand et al (2014). Selected aspects of this neurobiology as they relate to the development of some specifics of the known pathology in PN will be summarized.

The cellular initiation of itch can begin with the mast cell release of histamine that binds to H1 receptors on nerve fibers (Raap et al 2011). Endorphins and other opiate peptides are known to cause histamine mast cell release (Barke et al 1993). Endorphin itch initiation biology may be more direct. Bigiliardi and Bigliardi-Qi (2004) observed that while histamine interaction with nerve fibers may be a source of itch sensation, they summarize evidence for direct opiate peptide interaction with nerve fiber endings expressing endorphin receptors as a contributor to itch sensation initiation.

With regard to the skin cells themselves, keratinocytes are known to produce different neuropeptides that include proopiomelanocortin (POMC), which is a precursor for the

opiate peptide beta-endorphin (Bigliardi et al 1998). In addition, mast cell activation can initiate the itch process via non-histamine mediated processes that that lead to substance P presence in the interstitium (Raap et al 2011). Substance P, a neuropeptide member of the tachykinin family, is thought to induce itching in humans via histamine degranulation from mast cells (Potenzieri et al 2012). Keratinocytes are known to express Substance P receptors (Peters et al 2006) and opiate receptors (Bigliardi et al 1998).

There is also a close link between endorphins and substance P in nerve fibers innervating the epidermis. Opioid receptors destined for insertion onto the distal portions of Type C cutaneous nerve fiber membrane and the neuropeptides (such as substance P) that are capable of release into the interstitium are both synthesized in the same dorsal root ganglion nerve cells and transported to the peripheral nerve processes in the skin (Stein et al 2003).

3.1.2.4 *Abnormal endogenous opiates in the skin of PN patients:*

Bigiliardi and Bigliardi-Qi (2004) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor expression in the epidermis compared to normal skin. The down regulation was thought to be a biological response to abnormal tissue exposure to large amounts of endogenous opioid ligands such as endorphins. The authors comment that the epidermal skin cells such as the keratinocytes that are no longer binding the opioid ligands possibly leave the ligands available to bind to epidermal nerve endings and thus induce a nerve transmission mediated signal to the CNS resulting in a pruritus sensation.

3.1.2.5 *Abnormal substance P level in the skin of PN patients:*

Haas et al (2010) reported data showing significantly increased density of dermal substance P nerve fibers both in lesion skin samples as well as normal appearing skin samples from PN patients. The authors concluded that the hyper-innervation by substance P containing sensory nerves may have a role in the itch sensation found in these patients. Molina et al (1992) reports increased nerve fibers containing substance P in PN subjects compared to control group that could be related to the intense pruritus.

3.1.2.6 *Inflammatory Component to PN Histology:*

Neurogenic inflammation refers to the manifestation of skin diseases related to the malfunctioning of the nervous system – immune system interaction (Steinhoff et al 2003, Peters et al 2006, and Potenzieri et al 2012). Bigliardi et al (1998) conclude that the presence of receptor systems for endorphins and substance P molecules is evidence of an interaction between skin, immune and nervous system. Given the abnormal biology of substance P and endorphins in the skin of PN patients just discussed above, the hypothesis that the induction of an inflammatory component in PN is etiologically related to endorphin-substance P pathobiology is based on the following biological facts:

In addition to being a pruitogen, substance P also has pro-inflammatory and immune-stimulatory activity (Peters et al 2006). Steinhoff et al (2003), Peters et al (2006), and Potenzieri et al (2012) state that substance P may be an important mediator of cutaneous neurogenic inflammation. The immune cells that migrate under a pro-inflammatory signal from released substance P are an important source of opioid

ligands. The opioid ligand containing immune cells consist of T and B lymphocytes, granulocytes, and monocytes/macrophages (Sehgal et al 2011). As noted by Weigelt et al (2010), part of the characteristic PN histological findings is a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils (granulocytes). The opioid ligands released by immune cells interact with peripheral opioid receptors located on the cutaneous nerves (Stein et al 2003). Otherwise stated, the cutaneous nerve induced signaling from opioid ligands released by immune cells may be a source of the pruritic signal to the brain.

3.1.3 Rationale for Investigating Nalbuphine HCl ER in Prurigo Nodularis

3.1.3.1 *Pre-clinical Animal Data*

A preclinical investigation (Covance Study No. 8265903) was undertaken to demonstrate the effects of nalbuphine HCl on substance-P (SubP) induced scratching behavior in the mouse, a standard animal model (Kuraishi et al. 1995). Scratching behavior induced by peripheral stimulation by the pruritogen SubP mimics the characteristics of itch-related scratches in humans (Kuraishi et al. 1995) and Andoh et al 1998). In addition, the SubP induced scratching behavior is not inhibited by the histamine H1 receptor antagonist and elicits responses even in mast cell-deficient mice. Thus, SubP-induced scratches are likely to represent antihistamine-resistant pruritus. The model is relevant to antihistamine-resistant pruritus (Togashi et al 2002 and references cited therein).

The SubP itch mouse model was successfully established and its viability confirmed by assessing the responses using vehicle (phosphate buffered saline, PBS) only group (VEH/VEH) and nalfurafine HCl, a positive comparative control group (PCC/SubP) relative to untreated group (VEH/SubP) group. Briefly, studies were conducted in male C57BL/6 mice. Animals were acclimated to the facility at least three days prior to dosing. On the test day, mice were acclimated to the observation cages for one hour prior to dosing. Mice were then randomly assigned to treatment groups and subcutaneously (SC) dosed with vehicle (PBS), PCC (0.01 or 0.02mg/kg), or the test article nalbuphine (10 or 30mg/kg) (NAL/SubP group), and video recorded for 30 minutes to establish baseline scratching behavior. After the 30-minute baseline recording, mice received either vehicle (0.05 mL PBS) or SubP (250 nM in 0.050 mL) injected intradermally (ID) into the rostral part of the back and video recording continued immediately for an additional hour.

Itching was scored by reviewing the recording and counting the number of scratches over 30 minute periods following SubP (or vehicle) challenge. Itching was defined as scratching with the hind paw at the intradermal injection site (upper right shoulder area). Continuous scratching over one second was counted as one scratch event and paused scratches were considered separate scratching events. Scratching of other sites such as ears and face were not recorded.

Baseline scratching (pre-SubP) was similar for all treatment groups. Following SubP administration in the untreated mice, itching began within 3-5 minutes from administration of the pruritogen. The itch intensity was the highest in the first 30 minutes post-dose. By

60 minutes post-dose, the effect of the SubP injection began to wear off as scratching returned towards baseline levels.

As expected, PCC significantly ($p< 0.001$) decreased the SubP-induced scratching supporting the validity of the itch model. Subcutaneous pre-treatment with PCC resulted in a reduction of 42 and 63% reduction at the 0.01 and 0.02mg/kg dose (from 107 to 62 or 40 scratches, respectively).

Significant reduction in itch ($p< 0.001$) was noted following nalbuphine SC administration with about 43% reduction in itch at the 10 mg/kg dose (from 107 to 61 scratches) and 52% at the 30 mg/kg dose (from 107 to 52 scratches). Though there was a trend for a dose dependence on itch reduction, there was no statistical difference between the tested nalbuphine doses.

In this study, nalbuphine was as effective as PCC (nalfurafine) at reducing SubP-induced itch with no statistical difference between nalbuphine and PCC effect, regardless of the dose.

Ambulation was not suppressed in mice injected with nalbuphine dosed at 10 or 30 mg/kg indicating that attenuation of the scratching was not due to decreased locomotor activity.

3.1.3.2 *Neuropharmacologic Basis of the Rationale of Investigating Nalbuphine for the Treatment of Prurigo Nodularis*

Gutstein et al (2001) reports that nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor and simultaneously acting as an agonist at the opioid κ-receptor, and thus is a member of the "opioid agonist-antagonist" class of drugs that mechanistically work through this dual pharmacologic process. There is no published literature on the use of the moiety nalbuphine in PN. Nalbuphine was shown to be effective in reducing morphine induced pruritus, a well-known clinical pruritic condition induced by morphine administration. In several published clinical well controlled studies (which are reviewed in detail in the Investigator Brochure Section 5.8), nalbuphine was either equally effective or superior in efficacy when compared to naltrexone or naloxone (both are pure u-antagonists) for the management of morphine induced pruritus.

Neurogenic inflammation (as discussed in Section 3.1.2.6) may induce the secondary phenomena of "central sensitization" (Woolf et al 2011). Central sensitization is a central nervous system pathologic neurobiology change in cell circuitry that results from abnormal peripheral nerve signaling and/or peripheral nerve injury. The net effect of central sensitization is that there is a lowering of neural excitation threshold to external stimulus whereby either nociceptive or low intensity pruritogen cutaneous stimuli induce a high intensity sensation of pruritus (Paus et al 2006). Schmelz (2005) reports on the evidence that there is a mu-kappa opiate gating circuitry in the spinal cord whereby kappa agonist activity would inhibit mu opiate receptor containing cell activation mediated signaling that brings to consciousness the sensation of pruritus. The analysis by Schmelz may be an example of what Pan (1998) reports as a potentially very general opioid μ-receptor antagonizing function by the opioid κ-receptor. The author reviews the literature on central neural networks where the opioid κ-receptors are located in cell groups that are distinct from the cell groups that contain the opioid μ-receptors and summarizes the evidence that

agonism at the pharmacological level of the opioid κ-receptor antagonizes various opioid μ-receptor agonist mediated actions in the brain. This central gating mechanism could be important in countering any potential pruritogenic induced sensation from a peripheral neurogenic inflammatory initiating event in PN.

As discussed in Section 3.1.2.5, there is histological evidence of abnormal substance P presence in skin samples of PN patients. In that regard, an experiment conducted by Trevi Therapeutics indicated that nalbuphine administered subcutaneously significantly ($p<0.001$) suppressed the substance P induced scratching in mice (see Section 3.1.3.1 study summary).

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%. Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. This clinical observation potentially has different anatomical locations for the mechanistic drug effect. Since Stein et al (2003) reported that inflammation increases both the number of sensory nerve terminals ("sprouting") and disrupts the perineural barrier –thus facilitating opioid access to receptors, there is the possibility that peripherally acting mu antagonist naltrexone action reduced the neural membrane excitation by blocking actions of endogenous endorphins reported by Bigiliardi and Bigliardi-Qi (2004) to be present in the epidermis. In fact, Bigiliardi and Bigliardi-Qi (2004) suggest an opiate antagonist be therapeutically investigated for this reason and also comment on the evidence that mu opiate receptors on epidermal cells may be have a role in skin healing.

However, consideration must also be given to central nervous system opioid pharmacology as a contributing antipruritic effect elicited by naltrexone. At the spinal cord level, Schmelz (2005) commented that the explanation for opiate mu antagonists being capable of reversing experimentally induced itch may be related to the neurobiology of spinal cord level neuronal kappa-mu opioid gating circuits where either a mu antagonist or kappa agonist drug may act to have a pruritus suppressing effect. Supraspinal brain level action related to interference of the circuits related to reward behavior cannot be excluded given that it is known that naltrexone, like nalbuphine, can abolish morphine induced pruritus from morphine administered intrathecally. In addition, opiate receptor neuronal systems are known to be related to the physiological psychology of human reward behaviour and mu antagonist opioid class drugs are known to block the phenomena (Le Merrer et al 2009). Nalbuphine is known to block the effects of mu agonist drugs and induce the opioid withdrawal syndrome (Nubain® label).

3.1.3.3 *Nalbuphine Clinical Data in Uremic Pruritus*

Mannenti et al (2009) summarized potential pathophysiologic mechanisms for the etiology of uremic pruritus. Included among the postulated uremia induced mechanisms to explain uremic pruritus is neurophysiologic central sensitization "wind up" phenomena related to immune-inflammatory skin pathology. Mettang and Kremer (2014) in their review of uremic pruritus comment on the recent focus given to the mechanistic hypothesis related to peripheral neuropathic changes and central nervous system pathobiology along with evidence for cutaneous micro-inflammation. The authors state that a therapeutic option may be systemic treatment with mu-opioid receptor antagonist and kappa-opioid receptor

agonist. The proposed etiology of uremic pruritus pathobiology may be similar in origin to the neuroinflammatory process discussed in Section 3.1.2.6 as part of the mechanism postulated for the underlying process involved in inducing PN. In should be noted that Lee and Shumack (2005) reported prurigo nodularis occurring in patients with renal failure and Iking et al (2012) report renal failure as a contributing source of chronic pruritus with PN that was attributed to mix origin chronic pruritic conditions (see Table 1).

In clinical study TR01, the effect of oral nalbuphine on pruritus in hemodialysis (HD) patients with uremic pruritus was explored. The results indicated that nalbuphine HCl ER tablets demonstrated ability to suppress itch in a dose response fashion (see Figure 1)

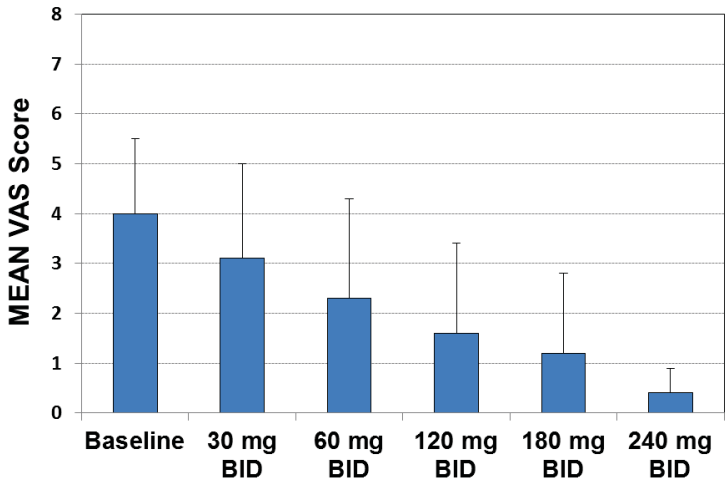

Figure 1: Mean VAS score (SD) for all patients as a function of nalbuphine HCl dose administered as nalbuphine HCl ER tablets. N= 14 except for 180 mg (N=13) and 240 mg (N=4). Source: NAL.001.TR01.PD

The TR01 study is summarized in the Investigator Brochure Section 5.4.3.

Considering the potential similarity in the underlying postulated mechanism between uremic pruritus and PN, nalbuphine would also be expected to be therapeutic in PN patients. As such, Study TR01 in HD patients can be regarded as a proof of concept study for PN.

Based on the clinical evidence of nalbuphine to suppress itch in uremic pruritus, morphine induced pruritus, the substance P induced itch in a pre-clinical study, results and the mechanistic link between the opioid receptors and substance P with the pathophysiology of PN, a clinical investigation of efficacy of nalbuphine on itch in the PN population is justified.

3.2 NALBUPHINE

Nalbuphine HCl is currently available only as a generic medication in an injectable form. An injectable form of nalbuphine is a commercially available approved drug product in the United States since 1979 and originally marketed as Nubain®, on which the presently sold

generic injectable formulations are based. It is currently approved for use in the United States for the relief of moderate to severe pain, a supplement to balanced anesthesia, for pre-operative and post-operative analgesia and obstetrical analgesia during labor and delivery. The European Union marketing experience with the injectable form of nalbuphine dates back to 1986 and this was recently reviewed (Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report 2010).

Nalbuphine is not a controlled drug in the United States. An oral dosage form of the drug is not commercially available. Nalbuphine HCl ER is an extended release oral tablet that is currently being developed for the treatment of pruritus.

Nalbuphine is a synthetic opioid with mixed μ antagonist/κ agonist opioid properties. Structurally, nalbuphine is a derivative of 14-hydroxymorphine and is related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone. Nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor while simultaneously acting as an agonist at the opioid κ-receptor (Gutstein 2001; Gharagozlou 2003 and 2006).

3.3 NALBUPHINE HCL ER TABLET CLINICAL DEVELOPMENT

3.3.1 Overall Summary

The safety, tolerability and pharmacokinetics of nalbuphine HCl ER tablets have been characterized following single and multiple ascending dose studies in healthy male and female human subjects, in a single dose study conducted in a dental pain patient population, a multi-dose study conducted in a patient population experiencing osteoarthritic related joint pain and in a multi-dose study conducted in both hemodialysis (HD) population experiencing uremic pruritus and healthy subjects. Studies were conducted with nalbuphine HCl ER tablets or oral solution following single dose administration from 30 mg up to 180 mg and multiple doses ranging between 30 mg BID and 180 mg BID in subjects with normal renal function (up to 3 weeks) and in the hemodialysis population in multiple doses ranging from 30 mg BID to 240 mg BID (up to 15 days).

In subchronic and chronic dose toxicology studies, the CNS was identified as the only target organ when unformulated (neat) nalbuphine was given to dogs at high doses. High systemic drug exposures in dogs caused CNS toxicity (tremors and convulsions) leading to deaths in some cases. It should be noted that the convulsions at high doses of nalbuphine in dogs were most likely Cmax-related. In toxicology studies in which dogs were given high doses of nalbuphine formulated with release-rate controlling excipients that blunt the Cmax, no CNS signs of toxicity were observed. Using the most conservative (lowest) margin of safety determined in all toxicity studies, a minimum 12.4-fold safety margin was calculated respectively for the mean plasma Cmax in subjects with normal renal function at the highest projected clinical dose of nalbuphine (180 mg BID) relative to the plasma Cmax at the lowest NOAEL in dogs given unformulated nalbuphine. Convulsions were not observed in any of the clinical trials conducted with nalbuphine HCl ER oral tablets in subjects with normal renal function at doses up to 180 mg BID (360 mg daily dose) or in HD patients at doses up to 240 mg BID (480 mg daily dose).

In the course of development, 355 subjects received at least one dose of oral nalbuphine HCl. The most frequently reported adverse events were primarily in the Central Nervous

System (CNS) and Gastrointestinal (GI) organ system categories. All these side effects are known to occur with drugs with opioid pharmacologic properties. Most of the side effects noted in the study program were mild to moderate in severity. Initiating drug dosing in both HD patients and healthy subjects at the 30 mg BID dose resulted in good tolerability for subsequent titration related dose escalation.

No drug abuse issues were reported during any of the investigations. The incidence of opiate withdrawal effects noted at drug discontinuation in the patients was investigated in the osteoarthritis pain treatment study when nalbuphine dosing was abruptly stopped following the end-of-study participation. There was an absence of any objective evidence of physical withdrawal symptoms in 85% of the patients and only mild evidence of physical withdrawal symptoms in the remainder of the patients.

3.3.2 Clinical Study TR01 in Hemodialysis Patients and Healthy Volunteers

Pruritus is a frequently identified sign and symptoms of uremia ("uremic pruritus") and is thus a common symptom in patients receiving hemodialysis (Pisoni et al 2006 and Narita et al 2006). Study TR01 was undertaken to assess the safety, PK, and the open label effects on pruritus intensity in hemodialysis subjects. PK and safety was compared to matched healthy control subjects.

Study TR01 was a single site, open label, non-randomized, parallel group, escalating dose study in hemodialysis patients with pruritus of at least mild intermittent intensity receiving intermittent hemodialysis three times a week compared to matched healthy control patients. All subjects were in house during the entire dosing period. Nalbuphine HCl ER tablets were administered orally for up to a 15 day period in HD subjects and 13 days in healthy subjects. Doses were sequentially escalated from 30 mg QD on Day 1 to 30mg BID then to 60 mg BID, 120 mg BID, 180 mg BID and 240 mg BID with dose escalation predicated on PK, safety, and tolerability of the preceding dose. HD subjects remained at each dose level for 2-3 days for a minimum of 4-5 consecutive doses. Healthy subjects remained at each dose level for 3-4 days for a minimum of 5 consecutive doses.

Study subjects were separated into 2 cohorts: Of the 15 HD subjects in enrolled into Cohort 1, 11 were assigned to dose escalate up to 180 mg BID and 4 were assigned to dose escalate up to 240 mg BID. 13 subjects (11 males and 2 females) completed the study. One male subject discontinued secondary to non-drug related disease progression diagnosis of pleural effusion at the 30 mg BID dose level and a female subject discontinued following a Grade 3 AE of vertigo at the 240 mg BID dose level. Cohort 2 were healthy subjects who were assigned to dose escalate up to 180 mg BID. Cohort 2 consisted of 8 healthy subjects (6 males and 2 female) who completed the study and one male subject who discontinued at the 120 mg BID dosing level with only Grade 1 intensity AEs. All study subjects were closely monitored for AEs throughout the study.

In healthy subjects, the dosing regimen resulted in mainly Grade 1 AEs and the dose escalation was tolerable in 8/9 subjects dosed. Of the nine healthy subjects enrolled, one subject withdrew from the study secondary to AE Grade 1 level gastrointestinal reflux, nausea/vomiting and vertigo symptoms at the 120 mg BD dosing level. The subject recovered from the AE following drug discontinuation. AEs that occurred in greater than two subjects were somnolence (N=2), headaches (N=2), flatulence (N=2) and constipation (N=3).

In the HD subjects, there were no deaths or drug-related serious AEs. There were no dose-limiting AEs reported as defined as two HD subjects experiencing a drug-related AE of Grade 3. A total of 72 AEs were reported in the 15 HD subjects of Cohort 1. The nervous and gastrointestinal organ systems had the highest incidence of AEs. The most frequently occurring AEs were nausea and somnolence. Of the 13 HD subjects who completed the study (10 HD patients assigned to dose up to 180 mg BID and 3 HD subjects assigned to dose up to 240 mg BID), 12 subjects completed the trial per protocol and 1 subject completed the study but did not dose titrate beyond 120 mg BID.

With regard to the gastrointestinal organ system, of the 14 HD subjects who completed 13 days of dosing (1 subject at 120 mg BID and 13 subjects at 180 mg BID), 4/14 (29%) experienced no nausea during the study and 7/14 (50%) experienced Grade 1 intensity nausea that was self-limited and only occurred at the initiation dose of 30 mg. One subject (1/14, 7%) experienced Grade 2 nausea starting from the 60 mg BID through the 180 mg BID dose. Three subjects (3/14, 21%) only developed nausea at the 180 mg dose level.

With regard to the nervous system AEs, of the 14 HD subjects who completed the 13 days of dosing, 5/14 (36%) did not experience somnolence, 4/14 (29%) experienced somnolence that was self-limited and only occurred at the initiation dose of 30 mg. With regard to AE intensity, two subjects (2/14, 14%) experienced somnolence of Grade 2 intensity at dosing levels above 30 mg BID. Only one drug-related Grade 3 AE (vertigo) was reported in one subject at the 240 mg dose which resolved completely following drug termination. No clinically relevant findings in vital signs, blood pressure (BP), ECGs or physical examinations were noted during the study. Oxygen saturation was also monitored via pulse oximetry as a safety precaution. The oximetry readings were taken at regular intervals during the daytime and continuously monitored during the nighttime hours over the 15 days of drug dosing and up to a maximal dose of 240 mg BID.

In both the HD and healthy subjects, no clinically significant decrease in daytime readings were recorded in the oximetry readings except in the one male HD subject previously mentioned who discontinued from the study at the time of the development of a pleural effusion. There was no clinically significant decrease in the nocturnal oxygen saturation level below the pre-dosing baseline nocturnal oxygen saturation level in any HD subject.

The Investigator Brochure and Section 5.4.4.4; Table 21 and Section 5.4.4.2.2; Table 17 summarize the AE profile of the TR01 HD subjects and healthy subjects respectively.

During the course of TR01, the 15 HD subjects that were enrolled were on multiple concomitant medications. Common concomitant medications included heparin, vitamin D, aspirin, iron, hyperphosphatemia management with sevelemar, erythropoiesis-stimulating agent, secondary hyperparathyroidism management with cinacalcet, neuropathic pain management with gabapentin; antihypertensive medications such as amlodipine (calcium channel blocker), carvedilol (beta and alpha-1 blocker), metoprolol (beta blocker), linosopril (ACE inhibitor); gastrointestinal medications: omeprazole, pantoprazole, ranitidine and renal vitamins and supplements. These medications seem to be commonly used by HD patients both in the US and the EU (Schmid et al 2010). There was no clinically significant difference in the adverse event profile observed based on concomitant medication use or obvious pharmacodynamic interaction over the course of the study.

Data on Itch Intensity was obtained in an unblinded fashion from the HD subjects enrolled in the open-label single arm Study TR01 using a 0 (none) to 10 cm (maximal possible

intensity) itch Visual Analogue Scale (VAS) recording "worst itch" intensity. From a baseline mean daytime VAS of 4.4±2.3 cm and nighttime of 2.8±2. cm, the mean VAS decreased over a 13-day dosing period by -3.6±2.5 cm and by -1.8±2.1 cm, respectively.

Please see the Investigator Brochure for more details on the TR01 study.

3.3.3 Additional Nalbuphine HCl ER Tablet Clinical Data

In addition to the subjects in the TR01 study, a total of 331 subjects have been exposed to nalbuphine HCl during the course of 8 previous clinical studies.

Four Phase 1 studies were early biopharmaceuticals studies conducted in healthy subjects mainly for formulation selection and as such they support the safety of the drug product. In addition, two Phase 1 studies were conducted with the current clinical formulations and each consisted of a single dose study assessing the safety, tolerability, and PK of the current tablet formulations in the 30 mg -180 mg range.

A safety and efficacy analgesic study was conducted in subjects with dental-pain following third molar extractions following a single dose (placebo or 60 mg or 120 mg). The subjects were otherwise healthy male and female subjects. The study also contained PK-PD analysis demonstrating an analgesic dose-response relationship, with clear differentiation between the nalbuphine dose groups and placebo group.

Oxygen saturation was monitored via pulse oximetry as a safety precaution during Phase 1 studies and in the single dose third molar extraction dental pain treatment study. All subjects who received the drug had oxygen saturation levels within the 90%-100% range during the studies.

A safety and efficacy analgesic study was conducted in a patient population experiencing osteoarthritic related joint pain using the current nalbuphine HCl ER 60 mg tablet. The population was demographically older with the mean age of 57 years and a range extending from age 40-70 years. Subjects were dosed continuously for up to 3 weeks starting at 60 mg BID up to a dose of 180 mg BID. Subjects who tolerated the initial dosing were titrated up in weekly increments of 60 mg BID to the maximal dose of 180 mg BID. The AEs that developed mainly had their onset at the initiation of dosing with no new type of AE developing in any statistically significant incidence during the course of dose escalation.

In both genders, the most frequently reported adverse events were primarily in the Central Nervous System and Gastrointestinal organ system categories. A higher incidence of AEs was noted in females during week one of dosing with the gender asymmetry in AE generation lessening as a function of time. This difference in AE incidence may be related to the tendency of females to have higher plasma levels than males (about 1.7 and 1.3 fold higher for Cmax and AUC, respectively).

In these eight clinical studies overall, the most frequently reported AEs in the single dose and multi-dose studies were CNS events, namely dizziness, headache, and somnolence. Gastrointestinal system AEs were mainly nausea and vomiting. Most of the AEs noted in the clinical study program were mild to moderate in severity.

In the case of single dose Phase 1 nalbuphine HCl ER tablet administration, there was a dose relationship to the incidence of AEs and there was minimal AEs observed at the 30 mg dose compared to initiating dosing at the higher doses. As a result, a titration to higher

doses from a starting dose of 30 mg was selected for subsequent studies that also included TR01 in order to improve the tolerability of the drug.

Section 5 of the Investigator Brochure summarizes the results of the clinical development program in detail.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To evaluate the safety and tolerability of nalbuphine HC1 ER tablets during a drug treatment period of up to 50 weeks.

4.2 SECONDARY OBJECTIVES

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

- To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Week 4
- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in Patient-Reported Outcome measures Worst (i.e., most severe itching over the past 24 hours) itch NRS, average itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS by the final Treatment Period Visit
- 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 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

4.3 EXPLORATORY OBJECTIVES

- The potential of nalbuphine HCl ER tablets to impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) and Histological (H&E) changes in skin biopsies taken Baseline and the final Treatment

Period Visit to investigate possible correlation with any clinical response and also compared to biopsy material assessed during study TR03 (optional period at select sites only).

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINT

- A description of the incidence and nature of TEAEs during Treatment Weeks 5-50

5.2 SECONDARY ENDPOINTS

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. Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time.

- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in Patient-Reported Outcome 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 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.

5.3 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 Treatment Period Visit when compared to biopsy material assessed during study TR03 (optional procedure at select sites only).

6 NUMBER OF SITES AND PATIENTS

Up to 10 sites in the North America and Europe are planned to participate in this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., up to 60 patients).

7 ESTIMATED STUDY DURATION

The total study duration for any individual patient will be up to 53 weeks. Patients will receive drug treatment for up to 50 weeks, followed by a two week washout period.

8 SELECTION CRITERIA

8.1 STUDY POPULATION

Patients with prurigo nodularis who completed the TR03 study and have met Inclusion/Exclusion eligibility requirements for TR03ext (see Section 8.2 and Section 8.3).

8.2 INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible:

1. Have been adequately informed of the nature and risks of the study and have given written informed consent by Visit 1a.
2. Have completed participation in the TR03 study.

   Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6.

3. Agree to comply with the contraception requirements as below:

   Female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, Essure procedure, or spermicide).

   For the purpose of this study, all females are considered to be of childbearing potential unless they are post-menopausal (i.e., at least 1 year since last menses and age >50 years) or surgically sterile (i.e., tubal ligation, hysterectomy and/or bilateral oophorectomy).

4. Ability and acceptance to provide written informed consent.
5. Willing and able to comply with study requirements and restrictions
6. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.

8.3 EXCLUSION CRITERIA

If a patient meets any of the following criteria, he or she is *not* eligible:

1. Patients with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association scale (scale provided in Appendix 5)
2. Patients with a history of angina pectoris grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale (scale provided in Appendix 5)
3. History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the patient.
4. Serum potassium below the laboratory lower limit of normality. Potassium supplementation can be prescribed and the serum potassium level repeated
5. QTcF interval >450ms on screening EKG
6. Heart rate <50 BPM on screening
7. Use of a medication known to be associated with risk of torsade de pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes)
8. History of substance abuse within the past year as determined by the Investigator
9. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study
10. Known hypersensitivity or allergy to nalbuphine or formulation components
11. Is a pregnant or lactating female.

9 STUDY PLAN

9.1 GENERAL STUDY DESIGN

This is an open label extension study for patients who have completed the TR03 study.

9.2 RATIONALE FOR STUDY DESIGN

The primary objective of this TR03ext study is to evaluate the safety of nalbuphine HCl ER tablets in patients with prurigo nodularis for up to 50 weeks on drug, followed by a two week washout period for a total of up to 53 weeks of study duration. The open label design allows all patients, who have completed the parent study TR03, an opportunity to receive active treatment for the assessment of the safety of nalbuphine HCl ER tablets over a longer term and follow the effect of skin lesion healing in addition to reducing itch. A maximum of 50 weeks on study drug was chosen as a reasonable time frame that would add substantially to the understanding of chronic use of nalbuphine HCl ER tablets chronic use in prurigo nodularis.

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%.

Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. Based on these clinical observations, TR03ext was designed to be of sufficient duration to observe potential anti-pruritic suppressive effects of study drug on scratching behavior and thus potentially skin lesion healing. Furthermore, the TR03ext study design anticipates potential sustained anti-pruritic effect that may outlast the actual dosing of study drug in TR03. Thus an Observation Period has been incorporated to follow patients whose Worst Itch NRS has been significantly reduced for up to 12 weeks in order to measure the durability of the anti-pruritic effect and to allow patients to receive study drug if pruritus intensity increases within the 12 week time period.

This study will also allow evaluation of a titration algorithm that mimics the manner in which opioid medications are often used in clinical practice (i.e., stepwise titration) to a tolerable dose with an improvement in worst itch intensity. To facilitate evaluation by achieved dose, the dose to which the patient has been titrated at the end of Treatment Week 4 will be maintained through Study Week 50, with the exception of two allowable down-titration (See Table 3 for dosing schedule). Patients who require a third down-titration after Treatment Week 4 must be discontinued from the study.

Patients can enroll into TR03ext and receive drug as early as approximately 2 weeks following their last dose of study drug in the parent study TR03. Approximately one-third of patients are expected to enter the study after having received placebo in TR03. These patients are expected to have a high level of pruritus intensity. On the other hand, some patients who have received active treatment in TR03 may still have either reverted to their original pruritic conditions or may have a residual anti-pruritic effects from the drug treatment even following the 2-week wash out period. To allow for various starting levels of pruritus intensity, patients who have 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 BID during the first 4 weeks of the Treatment Period (See Table 3 for dosing schedule). 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. While patients remain in the Observation Period, they will not be considered as enrolled into the study, but as participating in an extended screening process until they are eligible for treatment.

Patients who fail to improve, as defined by the failure-to-improve criteria, will be taken off study drug treatment. A failure-to-improve criteria is implemented beginning on TV 3 and at every subsequent Treatment Visit, and is described in Section 11.1. The rationale for the failure-to-improve criteria is based on the following: Following a maximal titration period of up to 3-weeks, an approximate 2-week window on stable drug dose should be sufficient for the drug to start eliciting a beneficial effect. The subject's self-reporting of pruritus intensity at each visits beginning at TV 3 will be compared to the baseline value of the patient's pruritus intensity upon entry to TR03ext. The premise of the failure-to-improve criteria is that patients will not be allowed to continue to receive study drug for an extended

period of time if there is no demonstration of diminishment in pruritus intensity. Subjects discontinued from treatment are to participate in the Washout and Safety Follow-up Period, unless consent is withdrawn. These patients will also receive a Telephone Contact 30 days (+2 weeks) post the completion of study drug to collect safety information related to previous drug exposure.

In the parent study, TR03, the two target doses (90 mg and 180 mg) of nalbuphine HCl ER are both within the dose range that was well tolerated in HD subjects and healthy volunteers subjects from study TR01 (30 mg to 240 mg BID for up to 15 days). Additionally, data from TR01 suggested a decrease in itching intensity in this dose range. Further, the safety profile of nalbuphine following injection is well documented. Injectable nalbuphine has been commercially available in the United States since 1979 and there has been marketing experience within the European Union dating back to 1986 (See Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report (2010) for a recent review).

In order to facilitate analysis of the clinical safety data and efficacy data, patients in the present study will begin titration at the 30 mg QD dose and titrate to only a maintenance dose ranging between 30 mg BID and 180 mg BID. The 30 mg BID and 60 mg BID doses are believed to be only marginally effective doses based on available TR01 data. However there is a two time dose reduction permitted for all subjects during Treatment Weeks 5-50 (see Table 3) to the next lower allowed dose (e.g., a subject at the 90 mg BID maintenance dose will be permitted a dose reduction to 60 mg BID or subsequently to 30 mg BID and then be maintained at that dose level for the remainder of the study).

The study population being evaluated is an intended target population for oral nalbuphine HCl ER tablets: prurigo nodularis patients.

Patients will be closely monitored for safety. All patients will be seen at the Investigator site (See Schedule of Events in Appendix 1). Adverse events and vital signs will be recorded. Additionally, 12-lead ECGs (locally and centrally read), physical examinations, and clinical laboratory testing will be conducted to monitor safety on patients receiving study drug. Safety monitoring will be done to address the primary objective of evaluating the longer term safety of study drug exposure. The primary endpoint is a description of adverse events during up to 50-weeks of treatment with nalbuphine HCl ER tablets. An important secondary endpoint objective of the study is to use recorded PAS metrics to assess the study drug anti-pruritic suppression of the scratching behavior of the subject and impact on skin lesion improvement. Changes in patient-reported outcome measures: Worst itch NRS, Average itch intensity NRS, VRS (itchy, burning and stinging), ItchyQoL, MOS Sleep-R, HADS and PBI-P will be explored.

9.3 SAFETY MONITORING PLAN

Patients will be closely monitored for safety. Adverse events will be continuously evaluated throughout the study (and in particular AEs of special interest: nausea, vomiting, constipation, somnolence, sedation, dizziness, and vertigo) and vital signs, locally and central cardiac core laboratory read 12-lead ECGs, physical examinations, and clinical laboratory testing will be conducted to monitor patient safety.

An independent Data Safety Monitoring Board (DSMB) will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter.

Patients with apparent failure-to-improve to a stable dose of study drug will be taken off study drug.

As with all subjects 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. The SOWS is a self-administered scale for grading opioid withdrawal symptoms. If the subject is experiencing any symptoms on the SOW scale to a moderate degree, the subject will be instructed to contact the site. If a subject is determined to be experiencing significant subjective withdrawal symptoms (at the Investigator's discretion), the subject will be offered treatment.

As summarized in Section 6.2.7 of the Investigator Brochure, the CNS has been identified as the only target organ when nalbuphine was given to animals at high doses. In addition, the most frequently reported adverse events reported in the nalbuphine HCl ER tablet dosing studies were primarily in the nervous system and gastrointestinal organ system categories. .

To mitigate opioid-related side effects, nalbuphine will be titrated over 4 weeks based on tolerability to a dose that is between 30 mg BID to 180 mg BID (see Table 3). Titration is a clinical management strategy consistent with dosing of opioids in general (Jovey 2003). The titration regimen planned in this study is similar to the regimen used in study TR01, in which doses in the planned range were well tolerated (Section 3.3.2) except uptitration is not a forced titration. This will provide flexibility for each patient to assess tolerability. In this study, the combination of a low starting dosing (30 mg on the first day) followed by a relatively slow titration (dose escalation after a minimum of six consecutive doses over approximately 3 days) is expected to minimize treatment-limiting opioid adverse effects. See Table 3 for the drug titration scheme. The time interval between dose escalations is consistent with the "three day tolerance check" suggested by the National Opioid Use Guideline Group of Canada (2010) for outpatient clinical practice management of opioid drug titration as part of monitoring patient side effects.

Nalbuphine has μ-opioid antagonist pharmacological properties. To minimize the possibility of acute opiate withdrawal occurring at drug initiation in a physically dependent subject, patients receiving daily doses of opiates are excluded from the study. Patients who require ongoing non-daily opiates concurrently with nalbuphine should be monitored carefully for additive opiate effects. If patients develop a new need for daily opiates during the study, the Investigator is required to contact the Medical Monitor to discuss the specifics of the situation.

It is known from prior studies, that gastrointestinal opioid-like adverse effects (e.g., nausea, vomiting, and constipation) occur early and can be treatment-limiting. In anticipation of the possible occurrence of these effects, pre-medications for nausea will be permitted and Investigators will be advised to use pharmacologic or non-pharmacologic means to avoid constipation as clinically indicated. In anticipation of the possible occurrence of central nervous system (CNS) AEs such as somnolence, patients will be instructed to be aware of possible CNS AEs that may occur. The evening doses during the Titration Period should

be taken at home. The first dose of any new titration step will occur with an evening dose (see Table 3). In order to monitor any potential CNS related side effects, a brief neurological assessment will be conducted at each study visit as well as a focused neurological medical history will be obtained at enrollment.

Patients will be additionally instructed that if any significant CNS AEs occur, they are to avoid activities such as driving and operation of dangerous machinery until the effect of the Study Drug can be assessed by the Investigator. Additionally, concomitant use of daily opioids during the course of the study, other than for short-term use, can be undertaken with the approval of the Medical Monitor. Overdoses or opioid-related significant central nervous system adverse effects may be reversed with opioid antagonists if clinically indicated.

Although psychological dependence or abuse can develop to chronically administered opioid drugs, the risk for psychological dependence or abuse in this study is judged to be low based on previous clinical studies with nalbuphine HCl ER oral tablets. To date, there have been no reported cases of psychological dependence or abuse reported following dosing for 3 weeks up to 180 mg BID and dosing for 15 days up to 240 mg BID. See the Investigator Brochure for details. Nevertheless, the nalbuphine HCl injection package insert for the product sold in the United States states that "*individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk for the development of drug abuse and dependence"*.

9.4 RISK-BENEFITS

The selected dose range for study in TR03ext of 30 mg BID to 180 mg BID were chosen given the safety profile summarized in Section 3.3.2 and discussed further in Section 9.2 as well as detailed in the Investigator Brochure. As summarized in, Section 3.1.3.3, open label data from the TR01 study showed that pruritus suppression in the HD patients was noted with drug administration within the dose range that is planned for the current study.

Data obtained from a previous study in osteoarthritis patients dosed up to 180 mg BID with nalbuphine HCl ER tablets showed that objective opioid withdrawal symptoms at the termination of 3 weeks of therapy were absent or mild in degree (See the Investigator Brochure Section 5.4.4.5 for details).

It should be noted that the commercially available nalbuphine HCl for Injection product in the United States (Nalbuphine HCl package insert) has a usual recommended dose of 10 mg for a 70 kg adult, administered subcutaneously, intramuscularly, or intravenously, which may be repeated every 3 to 6 hours as necessary (i.e., up to a daily dose of 40-80 mg IV); and, in non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg. Exposure following IV administration is approximately 6-fold higher than following oral administration (estimated oral bioavailability of nalbuphine HCl = 16%). Therefore, a 10-mg, 20-mg, or 160-mg IV dose would correspond to approximately 60 mg, 120 mg, and 960 mg oral nalbuphine, respectively. The highest dose proposed in the TR03 study is 180 mg BID (360 mg daily dose), and this oral dose is well below the highest recommended daily treatment of 160 mg IV (equivalent to 960 mg oral) for the current marketed product.

The risk for patients participating in the study is judged to be low based on previous experience with nalbuphine oral tablets. In addition, in the current study, there will be a low initiation dose of 30 mg, a slow dose titration rate, and careful safety monitoring of patients during the clinical study.

There is no approved therapy for prurigo nodularis related pruritus in the United States or Europe. Should nalbuphine prove effective, patients with prurigo nodularis could potentially see benefit.

9.5 STUDY OVERVIEW

This is an open label safety and tolerability extension study for patients who have completed study TR03. Patients will either enter directly a drug Treatment Period (Worst Itch NRS greater than or equal to 5 (≥ 5)) or enter an extended screening period of a no-drug Observation Period (Worst Itch NRS less than 5 (<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 greater than or equal to 5 (≥ 5).

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. For 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 12 extended screening weeks, subjects not eligible for the Treatment Period are screen failed from the study. The study periods are summarized below in Table 2.

Table 2: TR03ext Study Periods

Study Period	Study Weeks	Duration
Observation Period	Patients who do not meet the criteria to start Treatment are followed in Observation Period visits 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 patient 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; Table 8 calculates the Treatment Visit assignments for any patient entering the Treatment Period from the respective Observation Period visits. 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 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 patients 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

9.6 STUDY PROCEDURES

Before the initiation of study-specific procedures the patient must be given a complete explanation of the purpose of the study, evaluations to be conducted, and risks/benefits for study participation. Patients must understand the requirements of the study, provide informed consent (See Section 9.6.1 and Section 20.3), agree to the study restrictions, and agree to return for the required assessments. After review of the informed consent is documented, the patient must give witnessed verbal and written consent. For this study, patients will retain their study number from study TR03.

With the exception of Visits 1a and 1b, windows for all visits will be +/-3 Days. Please see the Schedule of Events in Appendix 1 for details of the Titration Period assessments and the Study Schematics Flow Charts in Appendix 2. See Section 9.7.1 for details of Study Drug Dosing and Section 9.7.6.4 for information on the use of pre-medications with the Study Drug. Visit 6 of TR03 will serve as TR03ext Visit 1a.

Visit 1a has procedures to be done as summarized in Section 9.6.1 regardless of the patient's pruritus intensity score. Following a set of common procedures, only patients who qualify for the Treatment Period based on meeting the pruritus intensity criteria will be eligible to receive study drug; Visit 1a corresponds to TV1. For patients who, during the final visit of TR03, did not meet the pruritus intensity criteria to enter the TR03ext Treatment Period, Visit 1a corresponds to OV1, the first visit of the Observation Period. If during a subsequent observation period visit to the site, the patient meets the pruritus intensity criteria, then that observation visit immediately transitions into Visit 1b (it also corresponds to TV1 since it is now the first Treatment Period visit) – See Section 9.6.3.3 and Section 9.6.4.

For subjects who transition to the Treatment Period from the Observation Period, Table 8 provides details on the treatment visit schedule based on the study week that the subject transitioned from the Observation Period to the Treatment Period. The subject will follow the Treatment Visit schedule outlined on the Schedule of Events (Appendix 1).

For clarity,

Patients with a Worst Itch NRS greater than 5 (≥ 5) enter the Treatment Period and will receive Study Drug starting with an evening 30 mg dose (to be taken at home), after the Visit 1a (or Visit 1b) procedures have been completed.

Receipt of the first dose of study drug will define Day 1. Visit 1a or Visit 1b for these patients is also Treatment Visit 1 (TV1). Subsequent visits will be defined as TV2, TV3, etc.

Patients with a Worst Itch NRS less than 5 (<5) enter the Observation Period and will not receive study drug treatment. Visit 1a for these patients is also Observational Visit 1 (OV1). Subsequent visits will be defined as OV2, OV3, etc.

Patients in the observation period can be followed for up to 12 weeks.

If during the Observation Period, a patient's Worst Itch NRS increases to greater than or equal to 5 (≥ 5) and the patient meets all other eligibility criteria**,** Visit 1b

procedures are to be performed. The patient's next visit will be Treatment Visit 2 (TV2). Do not repeat the Worst Itch NRS during Visit 1b.

If, however, at Observation Visit 12 the patient does not have a Worst Itch NRS greater than or equal to 5 (≥ 5), the patient will be screen failed without having initiated treatment with nalbuphine.

Figure 2, Figure 3 and Figure 4 visually display the relationship between TR03ext study weeks, Treatment Period weeks and Observation Period weeks.

9.6.1 Visit 1a (Day 1 of Study Week 1)

See Table 4 for summary of Visit 1a procedures. See Section 20.3 regarding the informed consent process that must take place prior to any study procedures.

Study TR03 Visit 6 procedures in common with Study TR03 extension Visit 1a procedures do not have to be repeated.

- obtain informed consent
- confirm eligibility
- obtain vital signs
- conduct a physical examination
- conduct a neurological exam
- collect central laboratory samples (hematology and chemistry)
- collect serum pregnancy sample in women of childbearing potential (done at the central laboratory)*
- collect urine for central lab urinalysis
- collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)*
  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
    - instruct the patient to discontinue taking study drug
    - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.
- obtain blood for PK
- at select sites only, perform skin biopsy (optional). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins; also collect the TR03 rescue medication log

- retrieve any remaining study drug from the parent study TR03
- administer the Worst itch NRS and **review score for eligibility to either enter the Treatment Period or to continue in screening under the Observation Period**

    a) If the Worst Itch NRS score is < 5, start the Observation Period. Do NOT initiate study drug treatment at this visit

    b) If Worst Itch NRS score is ≥ 5, confirm eligibility and start the Treatment Period (see below, 'For patients qualifying for drug Treatment Period only').

  The Worst Itch NRS must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)

For patients qualifying for the drug Treatment Period only (Visit 1a is also study visit TV1):

- complete PAS
- administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS
    - PBI-P

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)
- At selected sites only, perform skin biopsy (optional). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- dispense Study Drug to the patient required until return at Treatment Visit 2, TV2
- dispense the Dosing Diary and instruct the patient on how to complete it
- dispense the Rescue Medication Log and instruct the patient on how to complete it
- instruct patients to self-administer the first dose on the evening of Visit 1a at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- instruct the patient to take the Study Drug twice daily at approximately the same times of day. All patients should be instructed to titrate to their most tolerated dose. See Table 3 Drug Dosing Schedule for more information. Here is the recommended Week 1 titration schedule for patients who tolerate study drug:

    Day 1 (the first day that study drug the patient receives a study drug dose): No dose in the AM and 30 mg in the PM

Day 2: No dose in the AM and 30 mg in the PM
Day 3: 30 mg in the AM and 30 mg in the PM
Day 4: 30 mg in the AM and 30 mg in the PM
Day 5: 30 mg in the AM and 60 mg in the PM
Day 6: 60 mg in the AM and 60 mg in the PM
Day 7: 60 mg in the AM and 60 mg in the PM

- instruct patients to bring all remaining Study Drug to the Investigator site for each study visit
- If a patient misses 3 or more consecutive doses, contact the Medical Monitor.

For patients starting the Treatment Period, the next visit will be TV2, Treatment Week 3.

For patients not qualifying for the drug Treatment Period only (Visit 1a is also study visit OV1), the patient will enter the Observation Period and the next visit will be OV2, Extending Screening Week 4 (see section 9.6.3 Observation Period (Extended Screening Weeks 1-12))

9.6.2 Treatment Period (Treatment Weeks 1-50)

Patients who enter the Treatment Period on Visit 1a will be in the Treatment Period for up to 50 weeks and thus are eligible to receive study drug for up to 50 weeks.

Patients who enter the Treatment Period from the Observation Period will be in the Treatment Period for up to 46 Treatment Weeks. Patients enter the Treatment Period from an Observation Visit (OV) when their Worst itch NRS is greater than or equal to 5 (≥ 5).

Regardless of how many treatment weeks the patient was on study drug, all patients who enter the Treatment Period will complete End of Treatment Visit TV14. Since all patients must titrate to their maintenance dose over the first four weeks of the Treatment Period, Visits 1a/Visits 1b (TV 1) and TV 2 over the first four weeks of the Treatment Period will be common to all subjects in TR03ext regardless of when they enter into the Treatment Period. Patients who transition from the Observation Period to the Treatment Period at a respective Observation Visit will follow the Treatment Visit schedule outlined in Table 8.

9.6.2.1 *Treatment Period Weeks 2-4 (Titration Phase of Study Drug)*

The first week in the Titration phase is initiated as part of Visit 1a/1b (Day 1 Treatment Week 1, see Section 9.6.1 and Section 9.6.4). Subsequently, the following events TC1, TV2 and TC2 will be conducted during the remainder of the titration phase. See Table 5 for the Schedule of Events during the titration phase.

9.6.2.1.1 Telephone Contact Number 1 (TC1, Treatment Week 2)

The patient is to be contacted by phone and the following are to take place:

- Record AEs
- Reinforce compliance
- Confirm that patient has titrated drug in accordance with the dosing schedule on Table 3

- Document tolerability/intolerability to study drug and decision to continue dose titration/maintenance following the dosing schedule of Table 3
- Discontinue study medication in patients who could not tolerate 30 mg BID dose and complete the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.1.2 TV 2 (Treatment Week 3)

The following procedures are to take place at this visit:

- obtain vital signs
- collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements:
  - Worst itch NRS
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS.

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs (including tolerability to study drug)
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform Study Drug accountability, retrieve previously dispensed Study Drug
- dispense the Study Drug to the patient required until return at TV3 (Treatment Week 5)
- Document tolerability/intolerability to study drug and titration decision based on Table 3
- Discontinue study medication in patients who could not tolerate 30 mg BID dose and complete the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.1.3 Telephone Contact Number 2 (TC2, Treatment Week 4)

The patient is to be contacted by phone and the following are to take place:

- record AEs

- reinforce compliance
- instruct the patient on dose titration/maintenance based on Table 3
- patients reporting intolerable side effects at their current dose should titrate down to a tolerable preceding dose and this should be record as the patient's maintenance dose
- patients at any dose who reported intolerable AEs for the previous week (Week 3 on drug) and continue to report intolerable AEs on this visit, should be discontinued from study drug and scheduled for the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.2 *Treatment Period Weeks 5-50*

During this period of the study, the patient continues on the maintenance dose established by the end of Treatment Week 4 for the remainder of the study with the exception of two allowable dose reductions permitted during Treatment Weeks 5 – 50 (e.g., a patient at 90 mg BID can be reduced to 60 mg BID and then subsequently to 30 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study (See Table 3, Section 9.6.2.2.12 and Section 11). Patients who are on the 30 mg BID dose will be discontinued if a dose reduction is required.

See Table 6 for the Schedule of Events for Treatment Weeks 5-50.

9.6.2.2.1 TV 3 (Treatment Week 5)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
    - Stop study medication
    - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve criteria, perform the following procedures
    - obtain vital signs
    - collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
    - collect blood for PK
    - perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
    - perform brief neurological assessment
    - administer PRO measurements:
        - Average itch intensity NRS

- VRS
- ItchyQoL
- MOS Sleep-R
- HADS

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.2 TV 4 (Treatment Week 9)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
  - collect blood for PK
  - perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
  - perform brief neurological assessment
  - administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

    The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed Study Drug
- dispense study drug required until the patient returns for the next Treatment Visit

9.6.2.2.3 TV 5 (Treatment Week 13)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
    - Stop study medication
    - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
    - obtain vital signs
    - collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
    - collect blood for PK
    - perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
    - perform brief neurological assessment
    - administer PRO measurements:
        - Average itch intensity NRS
        - VRS
        - ItchyQoL
        - MOS Sleep-R
        - HADS

      The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
    - record AEs
    - review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
    - reinforce compliance
    - perform study drug accountability, retrieve previously dispensed study drug
    - dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.4 TV 6 (Treatment Week 17)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
    - Stop study medication
    - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
    - obtain vital signs
    - collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
    - collect blood for PK
    - perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
    - perform brief neurological assessment
    - administer PRO measurements:
        - Average itch intensity NRS
        - VRS
        - ItchyQoL
        - MOS Sleep-R
        - HADS

      The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
    - record AEs
    - review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
    - reinforce compliance
    - perform study drug accountability, retrieve previously dispensed study drug
    - dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.5 TV 7 (Treatment Week 21)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
  - collect blood for PK
  - perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
  - perform brief neurological assessment
  - administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

    The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
  - record AEs
  - review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
  - reinforce compliance
  - perform study drug accountability,
  - retrieve previously dispensed Study Drug
  - dispense the study drug to the patient required until next Treatment Visit

9.6.2.2.6 TV 8 (Treatment Week 26)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs

- perform physical examination
- perform brief neurological assessment
- complete the PAS
- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect urine for pregnancy test (must be confirmed negative prior to dispensing study drug)
- collect urine for urinalysis for central lab
- collect blood for central laboratory (hematology and chemistry) and for PK
- administer PRO measurements:
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense study drug to the patient required until the next Treatment Visit

9.6.2.2.7 TV 9 (Treatment Week 30)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DID NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)

- collect blood for PK
- perform brief neurological assessment
- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.8 TV 10 (Treatment Week 34)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
    - Stop study medication
    - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
    - obtain vital signs
    - collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
    - collect blood for PK
    - perform brief neurological assessment
    - perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)

- administer PRO measurements:
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.9 TV 11 (Treatment Week 38)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
  - collect blood for PK
  - perform brief neurological assessment
  - perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
  - administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R

- HADS

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.10 TV 12 (Treatment Week 42)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
  - collect blood for PK
  - perform brief neurological assessment
  - perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
  - administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

  - record AEs

- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance
- perform study drug accountability, retrieve previously dispensed study drug
- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.11 TV 13 (Treatment Week 46)

The following procedures are to take place at this visit:

- Administer the Worst Itch NRS and evaluate against the Failure-to-Improve criteria (see Section 11.1)
- For patients who MEET the Failure-to Improve criteria
  - Stop study medication
  - Perform End of Treatment Visit (TV14) procedures
- For patients who DO NOT meet Failure-to-Improve perform the following procedures
  - obtain vital signs
  - collect urine for pregnancy (must be confirmed negative prior to dispensing study drug)
  - collect blood for PK
  - perform brief neurological assessment
  - perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
  - administer PRO measurements:
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

    The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
  - record AEs
  - review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
  - reinforce compliance
  - perform study drug accountability, retrieve previously dispensed study drug

- dispense the study drug to the patient required until the next Treatment Visit

9.6.2.2.12 TV 14 (End of Treatment Visit)

This visit applies to all patients who completed TV13; including patients who met Failure-to-Improve criteria at any Treatment Visit during the study.

For patients who DID NOT meet Failure-to-Improve criteria during the conduct of the study, this visit (TV14) takes place after the patient has completed study medication.

- For patients who entered the Treatment Period at Visit 1a, TV14 would take place during week 51; four (4) weeks after TV13, as these patients should complete 50 weeks of treatment prior to TV14
- For patients who entered the Treatment Period at Visit 1b see Table 8 for information on when TV14 is to take place

The following procedures are to take place at this visit:

- obtain vital signs
- perform physical examination
- perform brief neurological assessment
- complete the PAS
- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test for central laboratory
- collect urine for urinalysis at the central laboratory
- collect blood for PK
- at select sites only, perform skin biopsy (optional). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- administer PRO measurements:
  - Worst itch NRS
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS
  - SOWS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs

- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any dispensed study drug
- retrieve the Dosing Diary
- Dispense the 14 Day SOWS packet, instruct the patient on how to complete the scales and to complete the scales daily for 14 days
- Schedule the patient for the Washout and Safety Follow-up Period Visit

9.6.3 Observation Period (Extended Screening Weeks 1-12)

Only patients with Visit 1a Worst itch NRS score of less than 5 (<5) (Visit 1a for these patients is considered OV1) should enter the Observation Period, which includes subsequent study visits OV 2-4 at approximately one month intervals over the next 12 extended screening weeks (See Table 7). While patients remain in the Observation Period, they will not be considered enrolled into the study, but as participating in an extended screening process until they are eligible for enrollment. Patients evaluated at OV 2-4 and who record Worst itch NRS greater than or equal to 5 (≥ 5), and are otherwise eligible, can immediately begin Visit 1b and transition into the Treatment Period.

For these patients, the sum of time in the Observation Period and Treatment Period will not exceed 50 weeks. As a result, both the Observation Period and Treatment Period will differ in length for different patients. To ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug up to the assessment of TV 2 during Treatment Week 3, and that the final Treatment Period visit is always TV14, see Table 8 for visit details. As such, visits during this period are not equivalent to Treatment Weeks. During the Observation Period, patients are participating in Extended Screening Weeks.

9.6.3.1 *Observation Visit 2 at Extended Screening Week 4 and Observation Visit 3 at Extended Screening Week 8*

The following procedures are to take place at this visit:

- administer the Worst itch NRS
    - If the Worst Itch NRS is less than 5 (<5), perform the following Observation Visit procedures at any time during the visit
        - obtain vital signs
        - record AEs
        - record concomitant medications
    - If the Worst Itch NRS is greater than or equal to 5 (≥5), transition the patient to the Treatment Period and conduct Visit 1b procedures (described in Section 9.6.4) on the same day as this visit. See Table 8 for a summary related to future Treatment Period Visits.

9.6.3.2 *Observation Visit 4 at Extended Screening Week 12*

The following procedures are to take place at this visit:

- administer the Worst itch NRS
    - If Worst Itch NRS is less than 5 (<5), perform the following Observation Visit procedures at any time during the visit
        - obtain vital signs
        - administer the following
            - Average itch intensity NRS
            - VRS
            - ItchyQoL
            - MOS Sleep-R
            - HADS
        - record AEs
        - record concomitant medications
    - If the Worst Itch NRS is greater than or equal to 5 (≥5), transition the patient to the Treatment Period and conduct Visit 1b procedures (described in Section 9.6.4) on the same day as this visit. See Table 8 for a summary related to future Treatment Period Visits.

Patients whose Worst Itch NRS is less than 5 (<5) at the OV4 should be screen failed from the study. No Washout/Safety follow-up visit is to take place.

9.6.3.3 *Transitioning from the Observation Period to the Treatment Period*

- For patients who have a Worst NRS score that is greater than or equal to 5 (≥5) at Observation Visit 2, 3, or 4, complete Visit 1b procedures (see Section 9.6.4).
- These patients will receive up to 46 weeks of study medication treatment.
- See Table 8 for the Treatment Period Visits to be completed post Visit 1b, as well as the number of weeks of study drug to dispense at each Treatment Visit and when to schedule the End of Treatment Visit 14, TV14, to take place.
- See Section 9.6.2 and the Schedule of Events (Appendix 1) for procedures to be performed at each applicable Treatment Visit.

9.6.4 Transition to Treatment Period (Visit 1b)

Confirm each patient's eligibility (see Sections 8.2 and 8.3) prior to performing any Visit 1b procedures. If the patient does not meet eligibility requirements, do not perform any Visit 1b procedures; the patient is to be screen failed.

See Table 4 for summary of Visit 1b procedures.

Patients evaluated at OV 2-4 who record a Worst itch NRS greater than or equal to 5 (≥ 5) and, are otherwise eligible, can immediately begin Visit 1b. This patient then transitions into the Treatment Period and will undergo the following procedures:

- obtain vital signs
- conduct a physical examination
- collect central laboratory samples (hematology and chemistry)

- collect serum pregnancy sample in women of childbearing potential (done at the central laboratory)*
- collect urine for central lab urinalysis
- urine for pregnancy (must be confirmed negative prior to dispensing study drug)*

  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
    - instruct the patient to discontinue taking study drug
    - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.
- obtain blood for PK
- Perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements:
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS
  - PBI-P

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- complete the PAS
- dispense Study Drug to the patient required until return at Treatment Visit 2, TV2
- instruct patients to self-administer the first dose on the evening of Visit 1b at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- all patients should be instructed to titrate to their most tolerated dose. See Table 3 Drug Dosing Schedule for more information. Here is the recommended Week 1 titration schedule for patients who tolerate study drug:

  Day 1(the first day that study drug is dispensed to a patient on treatment): No dose in the AM and 30 mg in the PM
  Day 2: No dose in the AM and 30 mg in the PM
  Day 3: 30 mg in the AM and 30 mg in the PM

Day 4: 30 mg in the AM and 30 mg in the PM
Day 5: 30 mg in the AM and 60 mg in the PM
Day 6: 60 mg in the AM and 60 mg in the PM
Day 7: 60 mg in the AM and 60 mg in the PM

- Instruct patients to bring all remaining Study Drug to the dialysis unit for each subsequent treatment period study visits.
- If a patient misses 3 or more consecutive doses, contact the Medical Monitor.

The next study visit will be Treatment Visit 2 (TV2). However, to ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug and that the End of Treatment Visit is always TV14, see Table 8 for more information.

The next visit will be Treatment Visit 2 (Section 9.6.2.1.2). See Appendix 1, Schedule of Event and Table 8 for the Treatment Visit Schedule for Patients Entering Treatment via Visit 1b.

9.6.5 Washout and Safety Follow-Up Period

All patients who received Treatment, but did not withdraw consent, will have a 2-week Washout and Safety Follow-Up Period following TV14. During this visit, the PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual). Please see the Schedule of Events in Appendix 1 for details of the Washout and Safety Follow-Up Period assessments. Additional information for this visit is provided below.

For patients who entered the Treatment Period at Visit 1a, the Washout and Safety Follow-Up Period Visit would take place during week 53, post TV14. However, for a patient who enters the Treatment Period at Visit 1b, the Washout and Safety Follow-up Period Visit will take place 14 days (plus the visit window) post TV14.

For patients who met Failure-to-Improve criteria or who discontinue treatment for other reasons (see Section 11.1), this visit is to take place 14 days (+ 7 days) after TV14.

The following procedures are to take place at this visit:

- obtain vital signs
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- collect blood for central laboratory measurements and PK
- administer PRO measurements:
  - Worst itch NRS
  - Average itch intensity NRS
  - VRS
  - ItchyQoL

- MOS Sleep-R
- HADS

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- AEs and concomitant medications (including rescue medications) will be recorded
- collect the Rescue Medication Log will be collected from the patient at this visit
- retrieve any remaining study drug not previously returned by the patient
- retrieve the 14 day SOWS packet

For patients who prematurely discontinued study medication for reasons other than withdrawal of consent, schedule the Premature Discontinuation of Study Drug Follow-up Telephone Contact visit.

9.6.6 Premature Discontinuation of Study Drug Follow-up Telephone Contact Visit

Patients who prematurely discontinued study drug during the study, for reasons other than withdrawal of consent, will have completed TV14 and the Washout and Follow-up Safety Period Visit. These patients are to be contacted by telephone 30 days (+ 2 weeks) after the visit that the patient met the Failure-to-Improve criteria and stopped medication.

During this Telephone Contact, record AEs and changes in concomitant medications since the completion of the Washout and Follow-up Safety Period Visit.

Document any additional efforts that take place to reach a patient who is non-responsive to telephone contact.

9.6.7 Early Termination Visit for Patients who Withdraw Consent

Patients may withdraw consent from the study at any time. However, if feasible for the patient, the following procedures should take place as part of an Early Termination Visit:

- obtain vital signs
- perform physical examination
- complete the PAS
- perform brief neurological assessment
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test at the central laboratory
- collect blood for PK
- Perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect urine for urinalysis at central lab
- administer PRO measurements:
  - Worst itch NRS
  - Average itch intensity NRS

- VRS
- ItchyQoL
- MOS Sleep-R
- HADS
- SOWS
- PBI-P

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any dispensed study drug

9.6.8 Unscheduled Visits

If a patient needs to be evaluated in relation to the study on a day other than one of the study visit days, that day will be considered an Unscheduled Visit. The reason for each unscheduled visit will be recorded and the following procedures will be performed: vital signs (BP, HR, RR, temperature), assessment for AEs, review of concomitant medications (including rescue medications), and Study Drug accountability. Additional procedures such as central or local laboratory sample collection may also take place, if clinically indicated. All unscheduled visits will be recorded on the Unscheduled Visit CRF.

9.6.9 Schedule of Events

The Schedule of Events is shown in Appendix 1 and is described in Section 9.6.

9.7 STUDY DRUG TREATMENT AND DRUG ACCOUNTABILITY

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

9.7.1 Study Drug Dosing

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

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 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, he 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 uptitration, the study drug dose should not be increased, regardless of the NRS score.

The Study Drug will be titrated during the Treatment Weeks 1 - 4, according to the schedule in Table 3 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).

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.

The achieved dose attained 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". A single dose reduction or dose hold 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.

Table 3: Dosing Schedule for TR03ext

Week of Treatment Period[1] (TV or TC)	Day	Drug Tolerance		Discontinuation
		Acceptable	Unacceptable[3]	
Week 1 (TV1/Visit1a /1b)	1	30 mg (PM dose)	--	
	2	0 mg (AM dose) 30 mg (PM dose)	--	
TC#1	3-4	30 mg BID		
	5-7	Titrate patients to tolerability with dose increases of 30 mg BID. Maintain dose for at least 3 to 4 days up to next dose level	Reduce dose incrementally by 30 mg	NA
The highest possible titration dose by the end of Treatment Week 1 is 60 mg BID				
Week 2[2]	1-7	Continue incremental increase in dose and maintaining at each dosed level for 3 to 4 days	Reduce dose incrementally by 30 mg	If 30 mg BID is not tolerated within one week, discontinue subject
The highest possible titration dose by the end of Treatment Week 2 is 120 mg BID				
Week 3[2]	1-7	Continue dose increase	Reduce dose by 30 mg BID and maintain	If 30 mg BID is not tolerated within one week, discontinue subject
The highest possible titration dose by the end of Treatment Week 3 is 180 mg BID				
Week 4[2] (TC#2)	1-7	Maintain dose at highest dose level reached on Week 3 Day 7	Reduce dose reached on Week 3 Day 7 by either 30 or 60 mg and maintain	NA
Treatment Week 5[4] up to Treatment Week 50 (TV3-TV 14)	1-7	Maintain dose from Week 4 through TV14[5,6]	*Patient may down titrate twice over remaining duration of study*	Patient discontinued if a 3rd time down-titration is needed.

[1]The decision to enter the patient into the Titration Period is based on Worst Itch NRS score NRS ≥ 5 obtained from the patient on Visit 1a or 1b

[2]The titration decision will be made based on tolerance to study drug

[3]Tolerance level is unacceptable to either the patient and/or investigator.

[4] The number of Treatment Weeks prior to TV 14 will vary for patients previously in the Observation Period depending upon the number of weeks spent in the Observation Period. See Table 8

[5]The achieved dose attained 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". Two dose reductions to the next lower allowed dose are permitted during Treatment Weeks 5 – 50 (e.g., a patient at 90 mg BID can be reduced to 60 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study.

[6] Beginning on TV 3 and at every subsequent Treatment Visit, patients with a Worst itch NRS ≥ the Worst itch NRS at Visit 1a (or at Visit 1b in the case of patient who require the OV period) will be discontinued from study drug, complete the End of Treatment Visit 14, the Washout and Safety Follow-up Period and Visit, and a Telephone Contact Visit 30 days after the last dose of study drug.

9.7.2 Down-Titration

Down-titration is not permitted except as discussed in Section 9.7.1.

9.7.3 Multiple Missed Doses

If a patient misses multiple doses of the Study Drug, please follow the procedures below. In no case should patients take additional doses of Study Drug to make up for missed doses. If Study Drug is re-started after missed doses, the patient should be instructed to take Study Drug from the tablets designated for the visit during which Study Drug is being re-started rather than from the visits during which Study Drug doses were missed.

- **During the Titration Period**

If a patient misses 3 (or more) consecutive doses, please contact the study Medical Monitor.

- **During the Stable Dose Period**

If a patient misses 6 (or more) consecutive doses, please contact the study Medical Monitor. If authorized by the Medical Monitor, patients who miss more than 6 consecutive doses may be allowed to continue on study. In such situations, patients should receive the Study Drug only once daily (i.e., the AM or PM dose only) for the first 3 days before returning to the full (BID) target dose.

9.7.4 Overdose

The effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Please see Guidance to the Investigator section of the Investigator Brochure for additional information.

9.7.5 Treatment Compliance

Returned study drug tablets will be used to assess compliance at each visit. Medication compliance will be recorded on the CRF for each designated visit (See Appendix 1). Patient compliance with the study dosing schedule will be assessed as part of the planned study analyses.

9.7.6 Rescue Medications, Concomitant Medications, Prohibited Medications, and Pre-Medications

9.7.6.1 *Rescue Medications*

A secondary objective of the study is to quantitate the number of days of rescue medication use for itching during the course of nalbuphine HCl ER treatment. 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 (See Table 9). For the purposes of this study, any 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 subject should be discontinued (see Section 11.2).

9.7.6.2 *Concomitant Medications*

Any medication taken by a patient following the signing of informed consent during the course of the study and the reason for use of the medication will be recorded on the case report form (CRF). Each patient will be instructed to report the use of all medication to the Investigator, including over-the-counter [OTC] medications, herbal medications, vitamins, and nutritional supplements. Patients will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator.

9.7.6.3 *Prohibited Medications*

Initiating use of opiate medications during the study should be done with caution with assessment of the patient for potential additive opiate AEs. If an enrolled patient requires daily treatment with opioid medications during the study (e.g., for post-surgical pain), please contact the Medical Monitor. Use of acetaminophen, non-steroidal anti-inflammatory medications, and aspirin is permitted. If an opioid medication is introduced in anticipation for chronic use of greater than 2 weeks, the subject should be discontinued.

Concomitant use of opioid antagonists (e.g. naloxone, naltrexone) are also prohibited during the study, unless required for urgent reversal of opioid adverse effects or opioid overdose.

Use of all other investigational drugs are prohibited during the study. A subject who initiates an investigational drug during the study should be discontinued.

If the patient is prescribed a medication(s) included on the list of those with a known risk of Torsade de Pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes), contact the Medical Monitor.

9.7.6.4 *Pre-Medications*

Nalbuphine use may be associated with nausea, vomiting, and/or constipation, particularly as the dose is escalated or upon initiation of treatment. At the Investigator's discretion, anti-emetics such as ondanestron may be administered prophylactically, prior to taking the Study Drug or, as needed, for treatment. Dietary and other prophylactic measures to avoid constipation should also be considered as clinically indicated (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes).

9.7.7 Efficacy Assessments

The below PRO instruments will be administered at the site at the site and under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual) according the Schedule of Events (see Appendix 1).

9.7.7.1 *Numerical Rating Scale (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 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).

In this study, patients will be asked to record two NRS values:

- rate itching on average over the past 24 hours
- rate worst itching over the past 24 hours

This instrument can be found in Appendix 4.

9.7.7.2 *Verbal Rating Scale (VRS)*

The VRS scale to be used in this study has three dimensions, each dimension coded with graduated adjectives (from 0 = none; to 5 = very severe) for the skin sensations of itchy, burning and stinging.

In this study, patients will be asked to record the VRS value:

- How is your skin sensation today?

This instrument can be found in the Appendix 4.

9.7.7.3 *Hospital Anxiety and Depression Scale (HADS)*

The HADS instrument includes 14 multiple-choice questions, each with 4 possible choices, scored between 0 and 3. This instrument can be found in Appendix 4.

9.7.7.4 *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, all the time=5. The instrument can be found in Appendix 4.

9.7.7.5 *Medical Outcomes Sleep Scale –Revised (MOS Sleep-R)*

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).

Additionally, a 9-item Sleep Problems Index ("Sleep Problem Index I") can be generated which assesses overall sleep problems that includes the 4 sleep disturbance and the 2 sleep adequacy items, 2 of the somnolence items, and awakening short of breath/headache; higher scores indicate greater sleep impairment, and this index is often used in clinical trials as an indication of sleep quality. The instrument can be found in Appendix 4.

9.7.7.6 *Patient Benefit Index (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". The instrument can be found in Appendix 4.

9.7.7.7 *Prurigo Activity Score (PAS)*

The PAS consists of 7 quantitative 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 percentages based on their stage (0-4). Photographs of the body are conducted with monitored lesions marked. The instrument can be found in Appendix 4. Please see the Study Reference Manual for instructions for obtaining and storing photographs collected in conjunction with the PAS.

9.7.7.8 *Exploratory Histological Endpoints (optional)*

Punch biopsy skin material for measurement of routine histology (H&E), nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) analysis was obtained during TR03 (optional procedure at select sites). Punch biopsy may be obtained (optional at select sites) at Visit 1a/1b and End of Treatment Visit of TR03ext for a comparative analysis with the results of the histological results of pre-dosing TR03 and end of study TR03 results.

9.7.7.8.1 MOR/KOR density and Nerve Fiber Density

The potential of nalbuphine HCl ER tablets to impact on the Measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken at Baseline visit and the Evaluation visit will be investigated at select sites.

In addition to skin biopsy tissue obtained prior to drug treatment for H&E and analysis by a central reading dermatopathologist, at select sites additional skin biopsy material obtained before and at the end of drug treatment will be compared to investigate, in an exploratory manner, any evidence of change in expression of MOR and KOR and nerve fiber density in relation to any noted changes in clinical study endpoints.

Bigliardi et al (2007) reports that in normal skin, keratinocytes express high amounts of MOR and it is therefore concluded that endogenous ligands are bound primarily to opioid receptors on keratinocytes and thus the endogenous opiate ligands are not binding to opioid

receptors located on nerve endings –the net result is at most a weak itch signal to the central nervous system in the normal state. In chronic pruritic skin disorders, most opioid receptors on keratinocytes are reported as internalized; therefore there are many opioid ligands available to bind to opioid receptors on sensory nerve endings. This state leads, together with the changed morphology of the epidermal nerve endings, to a strong itch signal to the CNS. The authors reported that topical administration of the opioid mu receptor antagonist naltrexone in subjects with atopic dermatitis, lichen simplex chronicus or prurigo simplex showed an antipruritic effect. In addition, there was also an upregulation of epidermal MOR expression following two weeks of treatment, but no MOR upregulation in subjects who did not experience an antipruritic response. Bigiliardi and Bigliardi-Qi (2004) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor (MOR) expression in the epidermis compared to normal skin.

Bigliardi-Qi et al (2009) reports that while it is widely accepted that KOR signaling suppresses itch, there is currently no animal, behavioral or human data relating the regulation of skin KOR expression to pruritus. Salemi et al 2007 however reported high upregulation of KOR in the skin of fibromyalgia subjects that was thought to correlate with reported complaints of pain symptoms.

With regard to peripheral sensory nerve fiber density in the skin, Bigliardi et al (2009, 2007) report that epidermal nerve endings of pruritic skin in prurigo are thinner when compared to normal skin. In addition, the nerve fibers have a different morphology which may relate to initiating the sensation of pruritus because of the altered anatomical relationship to the various cellular elements of the skin.

9.7.7.8.2 Routine histology (H&E) and immunohistochemical examination of inflammatory cells and pro-inflammatory mediators

Weigelt et al (2010) summarized the characteristic histological pattern in PN that include the presence of thick compact orthohyperkeratosis; folliculosebaceous units in nonvolar skin in conjunction with a thick and compact cornified layer; irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils.

While the skin biopsy from PN patients is reported to show a composite pattern of dermatopathologic findings, the condition is not defined internationally by a Dermpath expert board. Thus the biopsy obtained at the Baseline Visit and Evaluation Visit will be analyzed as an exploratory endpoint by a central dermatopathologist for histological review investigating possible correlation of pre-existing histopathological findings (i.e., level of inflammation, etc.) with any subsequent clinical response noted on drug

9.7.8 Safety Assessments

As summarized in Section 6.2.7 of the Investigator Brochure, the CNS has been identified as the only target organ when nalbuphine was given to animals at high doses. In addition, the most frequently reported adverse events reported in the nalbuphine HCl ER tablet dosing studies were primarily in the nervous system and gastrointestinal organ system

categories. In order to monitor any potential CNS related side effects, a brief neurological assessment will be conducted at each study visit as well as a focused neurological medical history will be obtained at screening.

Safety will be determined by evaluation of the following:

- AEs
- Vital signs including weight, BP, heart rate (HR), respiratory rate (RR), and body temperature
- Physical examination
- Clinical laboratory data (see Appendix 3 for list of analytes)
- Investigator reviewed ECG and central cardiac core laboratory read 12 Lead-ECG, cardiovascular grading, and/or cardiovascular related prohibited medications
- Subjective Opiate Withdrawal Scale (SOWS)

The SOWS is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the patient rates on a scale of 0 ("not at all") to 4 ("extremely"). The instrument can be found in Appendix 4. In this study, patients will complete SOWS daily, starting at TV14, End of Treatment Visit through to the Washout and Safety Follow-up Period Visit. The SOWS will also be completed at the Early Termination Visit. As with all subjects 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. The SOWS is a self-administered scale for grading opioid withdrawal symptoms. If the subject is experiencing any symptoms on the SOW scale to a moderate degree, the subject will be instructed to contact the site. If a subject is determined to be experiencing significant subjective withdrawal symptoms (at the Investigator's discretion), the subject will be offered treatment.

The following will be used to assess patient eligibility to continue participation if the patient experiences CHF, angina pectoris and/or other cardiovascular exclusion criteria (see Section 8.3 for the Exclusion Criteria and Appendix 5 for the grading scales)

- The Canadian Cardiovascular Society grading of angina pectoris assessment: The Canadian Cardiovascular Society grading of angina pectoris (sometimes referred to as the CCS Angina Grading Scale or the CCS Functional Classification of Angina) is commonly used for the classification of severity of angina
- The New York Heart Association (NYHA) Functional Classification: The New York Heart Association Function Classification provides a simple way of classifying the extent of heart failure by placing patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina pain.

CredibleMeds Filtered QTDrug [List: Known Risk of TdP]: Cardiovascular related prohibited medications are provided on the CredibleMeds Filtered QTDrug List. Drugs are placed into one of four risk categories based on their relative potential to

alter the electrocardiogram (QT prolongation) and/or cause life-threatening ventricular arrhythmias. See the following link to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes: https://www.crediblemeds.org/

10 STUDY DRUG

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

10.1 FORMULATION, PACKAGING AND LABELING

The Study Drug in this trial is nalbuphine HCl ER tablets. Nalbuphine HCl ER tablets are white to off white film-coated round tablet containing either 30 mg or 60 mg nalbuphine HCl.

All study medication will be supplied by the Sponsor. Following confirmation of eligibility to start the Treatment Period, the patient will receive bottles of study drug tablets containing 60 tablets each. Bottles will be labeled with at minimum: contents, storage conditions, expiration date, clinical trial statement, and the name and lot number of the study drug Sponsor (Trevi Therapeutics).

10.2 SHIPPING, STORAGE AND HANDLING

The Investigator will ensure that the Study Drug is stored and dispensed in accordance with ICH QE6(R1) (Guideline for Good Clinical Practice) and EU Clinical Trial Directive and Annex13 regulations concerning the storage and administration of investigational drugs.

Nalbuphine HCl ER tablets and placebo tablets should be stored at 20°C-25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (59° to 86°F). The storage conditions were established following ICH Q1A(R2) (Stability testing of new drug substances and drug product) and the CHMP Guideline CPMP/QWP/122/02, rev 1 corr CHMP Guideline (Stability Testing of existing active substances and related Finished products) for assessment and provision of appropriate labelling and storage conditions.

The Study Drug will be stored away from any extreme conditions of temperature, light, or humidity as an additional precaution

In the EU, the investigational medicinal products will remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfillment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps will be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

10.3 UNBLINDING

Not applicable. This is an open-label study.

10.4 DRUG ACCOUNTABILITY

The Investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all Study Drug shipped by the sponsor or the sponsor's representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all Study Drug. Current dispensing records will also be maintained including the date and amount of drug dispensed and the patient receiving the drug. All remaining drug not required by regulations to be held by the clinical facility will be destroyed on site at the end of the study.

11 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT

Patients who discontinue study drug, for reasons other than withdrawal of consent, will completed the following visits

- End of Treatment Visit (TV14)
- Washout and Safety Follow-up Period Visit
- Premature Discontinuation of Study Drug Telephone Contact Visit

11.1 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT ASSOCIATED WITH FAILURE-TO-IMPROVE CRITERIA

Patients who meet failure-to-improve criteria during the conduct of the study, will stop taking study medication. The Failure-to-Improve criteria is as follows:

> Beginning on TV 3 and at every subsequent Treatment Visit, patients with a Worst itch NRS equal to or greater than (≥) the Worst Itch NRS at Visit 1a (or at Visit 1b in the case of patient who require the Observation Visit period) will be discontinued on study drug. Subjects discontinued on 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 for final safety assessment.

See the examples below:

Examples	Visit	Worst Itch NRS	Worst Itch NRS Lower/Higher or no change from V1a/1b	Failure-to-improve met for that visit?	Next Steps
Visit 1a (or Visit 1b)		5	--	--	--
Ex #1	TV3	5	**No Change**	**Yes**	**Discontinue study drug**
Ex #2	TV3	4	**Lower**	**No**	**Maintain subject on treatment**
Ex #3	TV3	6	**Higher**	**Yes**	**Discontinue study drug**

11.2 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT FOR REASONS OTHER THAN FAILURE-TO-IMPROVE

Patients who complete Study Drug treatment according to Section 9.6 (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 prior to the maximum allowable number of Treatment Weeks based on their entry into the study at either Visit 1a or Visit 1b, will be considered to have prematurely discontinued Study Drug treatment. 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:

- Withdrawal of consent to continue Study Drug treatment
- Intercurrent Illness
- Any intolerable 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.
- ECG changes as summarized in section 17.4
- Opioid medication is introduced in anticipation for chronic use of greater than 2 weeks (see Section 9.7.8)
- Any medication prescribed for chronic anti-pruritic use of greater than 2 weeks (see Section 9.7.6.1)
- Development of substance abuse as determined by the Investigator

12 PREMATURE WITHDRAWAL OF PATIENTS FROM THE STUDY

All patients who receive study treatment should remain in the study whenever possible. Reasons for withdrawal of the patient from the study, not just discontinuation of study drug, include:

- Withdrawal of consent for study participation
- Sponsor terminates the study for any reason
- Investigator decision

  The Investigator may withdraw any patient from the study if, in the Investigator's opinion, it is not in the patient's best interest to continue on the study.
- Death of the patient

Any patient whose condition significantly changes after entering the study should be carefully evaluated by the Investigator and discussed with the Medical Monitor. Such patients should be withdrawn from the study if continuing would place them at risk or compromise the results of the study.

Patients who prematurely discontinue from the study will be asked to undergo and have completed Early Termination visit procedures and evaluations that may be necessary to ensure that the patient is free of untoward effects and to seek appropriate follow-up for any continuing problems. The date on which the patient is withdrawn from the study and the reason for discontinuation will be recorded on the CRF. Patients who withdraw from the study will not be replaced.

13 WARNINGS AND PRECAUTIONS

Please refer to the accompanying Investigator's Brochure for more details summarizing the safety data on nalbuphine HCl ER tablets. In addition, see the Warnings and Precautions sections of the parenteral nalbuphine HCl package insert for safety-related information. The package insert is contained in the Study Reference Manual.

14 EFFICACY EVALUATIONS

Efficacy measurements will be evaluated as secondary endpoints in this study. The measurements include:

- Worst itch intensity NRS
- Average itch intensity baseline.
- VRS (itchy, burning and stinging)
- ItchyQoL
- MOS Sleep-R
- HADS
- Prurigo Activity Score (PAS)
- Patient Benefit Index, pruritus version (PBI-P)
- Frequency, pattern, and reasons for dose titration
- 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 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.

14.1 EXPLORATORY

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) in skin biopsies taken during TR03 and the last week on study drug during TR03ext (optional procedures at select sites only).

15 COLLECTION, HANDLING, AND ANALYSIS OF PHARMACOKINETIC BLOOD SAMPLES

15.1 BLOOD SAMPLE COLLECTION

Blood samples will be collected for safety, pharmacokinetic and CYP analysis. At the time of sample collection and processing, study patient information will be anonymized. Only the patient's identification number, assigned by an IVR/IWR system, and a sample barcode aligned to the lab requisition form will be noted on the tube/vial.

See the study Laboratory Manual for specimen collection, handling and shipping details.

15.2 CENTRAL LABORATORY

Blood samples, including chemistry, serum pregnancy test, and hematology, and urine for urinalysis obtained for the study will be analyzed at a central laboratory.

Urine pregnancy testing will be conducted at the site.

The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment should the urine and serum pregnancy test results differ. See section 17.5.2.1 regarding how pregnancies are to be handled in this study.

15.3 PHARMACOKINETIC SAMPLES

To determine Study Drug content in plasma, blood samples will be collected at various time intervals over the duration of the study.

15.4 PREPARATION, STORAGE, AND HANDLING FOR PHARMACOKINETIC SAMPLES

Immediately after blood sample collection, the tubes will be gently inverted several times to mix the anticoagulant with the blood sample and placed on ice (4 to 8°C) until centrifuged.

The plasma fraction will be separated by centrifugation of the collection tube. It is preferable that a refrigerated (4 to 8°C) centrifuge be used. Centrifugation will be conducted in a manner to yield approximately 2 x1 mL of plasma (e.g., 10 minutes at 1,500 x g). The plasma fraction will be withdrawn by pipette and divided into 2 evenly proportioned aliquots in polypropylene freezing tubes. All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the patient identification number, the study dose, and the collection date and time.

Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be processed and placed into either a minus 70°C or minus 20°C refrigerator within 1 hour after collection. Tube labels for PK samples will be provided in the Central Laboratory kits. Each label will contain the study number, patient number, study day of sample, and time of sample. The actual date and time of blood collection will be recorded in the patient's CRF.

All plasma samples will be stored frozen (at either -70ºC or -20°C) until they are shipped for storage and analysis.

15.5 ANALYTICAL

Plasma samples will be analyzed for Study Drug using a validated liquid chromatography mass spectrometry (LC-MS/MS) method developed at Tandem Lab/s-RTP, Durham, North Carolina. The units for nalbuphine will be in ng/mL. In addition, metabolite concentrations will be assessed in these samples using an exploratory analytical LC-MS/MS method.

Analysis and reporting of results will be conducted according to the current Standard Operating Procedures for bioanalysis at Tandem labs Durham, North Carolina. Details of the sample analysis, including a bioanalytical study report, will be included with the final clinical study report.

16 TISSUE SAMPLES AND HISTOLOGY

At selected sites only, up to three 3 mm punch skin biopsy samples (optional) will be obtained at Visit 1a/1b and the End of Treatment Visit (TV14).

- A 3x3 mm punch skin biopsy is taken from an itchy region which will be fixed in formalin and then paraffin for routine histology (H&E) and immunohistochemical examination of inflammatory cells and pro-inflammatory mediators.
- For the other two 3x3 mm punch skin biopsy samples taken from an itchy region,
    - One sample will be fixed in 4% paraformaldehyde for 2 h to 5 days, and then kept in 5% sucrose overnight, buffered in 10% and 20% sucrose and after 6 h stored in liquid nitrogen. This tissue will serve for the determination of the nerve fiber density.
    - One sample will be used for RNA and protein extraction for the quantification of MOR/KOR by PCR and western blot.

Analysis will be performed at the University of Munster, Munster, Germany.

See the Study Reference Manual and the Laboratory Manual for specimen collection, handling and shipping details.

17 SAFETY EVALUATIONS

Safety evaluations will include physical examination findings, changes in vital signs and ECGs (locally and centrally read), findings from clinical laboratory studies and the incidence of AEs

17.1 PHYSICAL EXAMINATION

A complete physical examination will be performed at the Screening Visit and subsequently according to the Schedule of Events (Appendix 1). 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.

17.2 VITAL SIGN MEASUREMENTS

Blood pressure and HR will be taken while sitting or semi-recumbent/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 (BP, HR, RR, body temperature, and weight will be obtained according to the Schedule of Events (Appendix 1). The height, weight and BMI will be recorded only on Visit 1a.

17.3 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 (Appendix 1). The required clinical laboratory tests are listed in Appendix 3.

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.

17.4 ELECTROCARDIOGRAM

A standard 12-lead ECG will be obtained according to the Schedule of Events (Appendix 1); see the Study Reference Manual for ECG procedures. Electrocardiograms will be read locally by the Principal Investigator 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.

If a patient develops a QTcF >500ms associated with an increase from baseline >60ms, the ECG will be repeated at least 30min later. If these parameters are confirmed on the second ECG by the Core ECG laboratory, the subject will be discontinued from the study.

During the conduct of the trial, if a patient develops any other cardiovascular events noted as part of the exclusion criteria, the cardiovascular assessments in Appendix 5 are to be completed. See section 17.5 Adverse Events for the handling and follow-up of Adverse Events.

17.5 ADVERSE EVENTS

Adverse events 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). Adverse events that have not been directly reported to the Investigator will be promptly conveyed to the Investigator by the study staff. Investigators will additionally review any AE source documents and the patient's medical records, on a regular basis during the course of the study.

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 adverse event has stabilized.

17.5.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation patient reported on or after the first screening date. A treatment-emergent AE (TEAE) is any untoward medical occurrence in a clinical investigation patient or patient administered a pharmaceutical product on or after the initial administration of study medication. An AE does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom whether or not related to the medicinal (investigational) product, or disease temporally associated with the use of a medicinal (investigational) product.

The AE may be any of the following:

- a new illness
- worsening of a pre-existing condition
- worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- an effect of the study medication, including comparator
- a combination of 2 or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "AE."

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Adverse events fall into the categories "non-serious" and "serious."

17.5.2 Serious Adverse Events

The reporting period for serious AEs is the same as for AEs. Serious AEs must be submitted to the Sponsor within 24 hours of their discovery, even if the full information about the event is not yet available. These events should also be reported to the IRB/IEC as needed based on local requirements. Fax SAE forms to the following number:

Serious AE Fax #: 888-529-3580

Also notify the PPD Medical Monitor at (**888) 483-7729.**

17.5.2.1 ***Serious Adverse Event Definition***

An SAE is one that, at any dose, results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

A hospitalization is defined as an inpatient admission lasting 24 hours or more. Visits to urgent care centers and emergency departments that do not result in admission to a hospital for 24 hours will not be considered hospitalizations. Hospitalizations for elective procedures, defined as any procedure that was planned prior to signing of the informed consent will not, in and of themselves, be considered to fulfill criteria for an SAE. For example, for patients on the kidney transplant waiting list prior to signing the ICF who subsequently are hospitalized for a transplant, the hospitalization would be considered elective.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the SAE. It does not refer to a SAE that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. 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 development of drug dependency or drug abuse.

Female patients who become pregnant should be immediately discontinued from the study if they have not yet received Study Drug. If a patient is found to be pregnant after they have received Study Drug, she should discontinue dosing, complete all end-of-study procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications or less than a healthy, normal outcome will be recorded as an AE or SAE.

Clarification on the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

17.5.3 Non-Serious Adverse Events

A non-serious AE is any AE not meeting the SAE criteria.

17.5.4 Definition of Relationship to Study Medication

Association or relatedness to the study medication will be graded as either "probably," "possibly," or "unlikely." Determination of relatedness includes:

PROBABLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- abates upon discontinuation of the drug;
- cannot be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.

UNLIKELY – The AE:

- does not follow a reasonable temporal sequence from drug administration;
- is readily explained by the patient's clinical state or by other modes of therapy administered to the patient.

17.5.5 Definition of Severity

All AEs will be graded, if possible, by the 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]. This is also provided in the Study Reference Manual for reference purposes.

The severity of AEs that cannot be graded by the most current version of CTCAE will be categorized as follows:

- **Grade 1** – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Grade 2** – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Grade 3** – Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
- **Grade 4** – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable.
- **Grade 5** – Death.

17.5.6 Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with the current Investigator Brochure, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

17.6 DATA SAFETY MONITORING BOARD

An unblinded, independent Data Safety Monitoring Board (DSMB) will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter. The DSMB will periodically review group-unblinded study information (on a treatment group level, using random letters instead of actual treatments) during the conduct of the study. If necessary, unblinding of individual subject data and treatment groups may be done.

18 EMERGENCY PROCEDURES

In case of study-related medical questions, or if a pregnancy is confirmed in a trial patient, the Investigator should contact the designated Medical Monitor.

18.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the Investigator should contact the designated sponsor representative at the following address:

Thomas Sciascia, MD
Trevi Therapeutics, Inc.
195 Church Street, 14th Floor
New Haven, CT 06510 USA
Telephone: (203) 304-2499
Mobile: (617) 913-6808

19 CONSIDERATION, ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

19.1 GENERAL

As a companion to this protocol and in an effort to provide a more detailed explanation of the statistical methodology to be used for this study, which will consist of data summaries, a statistical analysis plan (SAP) will be developed prior to locking the data base.

No formal statistical testing is planned for this study. Data summaries will provide the basis for clinical interpretation of efficacy and safety outcomes

19.2 INTERIM ANALYSES

There is no interim analysis planned in this study.

19.3 METHODS FOR HANDLING MISSING DATA

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

19.4 PATIENT DISPOSITION

Patient disposition will be summarized, including the reasons for discontinuation. The number of patients in each analysis population will be displayed and an accounting of exclusions from each study population will be provided.

19.5 BASELINE CHARACTERISTICS

Demographics, medical history, laboratory data, and physical examination findings will be summarized.

19.6 CONCOMITANT MEDICATIONS

Concomitant medications will be tabulated by Anatomic and Therapeutic Class (ATC) of WHO drug, preferred term, and treatment group. A medication's usage will be considered concomitant if it was started or continued after administration of the study medication. If the start date is missing, it will be assumed that the medication was used concomitantly. Rescue and opioid medication usage will be tabulated separately from all other concomitant medications.

19.7 STUDY DRUG DOSING

The percentage of patients reaching various achieved doses at the end of Treatment Week 4 and through Study Week 50 will be summarized. The mean dose during the Treatment Period and the dose distribution by Treatment Period Visit will be reported. Descriptive statistics will be used to describe the mean daily dose by Visit.

19.8 EFFICACY ANALYSES

19.8.1 Efficacy Population

The Safety population, consisting of all enrolled patients who have received a single dose of study medication, 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 for the endpoint of interest, 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.

19.8.2 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 will be summarized. Patients who prematurely discontinue after having been followed in the Observation Period only will be also be summarized.

19.9 SAFETY ANALYSES

19.9.1 Safety Population

The Safety Population will consist of all patients who have received a single dose of study medication, i.e., this same population will be used both for the efficacy and safety evaluations. The Safety Population will be used in all safety analyses.

19.9.2 Adverse Events

All treatment emergent AEs will be summarized overall and for each body system and preferred term by treatment group, relationship to study medication, and severity. For tabulations by severity, only a patient's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. Adverse events will be dichotomized into "related" (probably and possibly) and "unrelated" (unlikely). "Treatment-emergent" will be defined as starting or worsening after the first dose of study medication. If the start date is missing, the event is assumed to be treatment emergent. All SAEs will be tabulated as well.

Although nalbuphine is not a controlled substance in the United States, adverse events of special interest that suggest a possible addiction or abuse potential or withdrawal will be specifically analyzed to screen for these effects. The list of MedDRA preferred terms for adverse events of special interest will be described in the Statistical Analysis Plan.

19.9.3 Vital Signs

Vital signs, including BP, HR, body temperature, and RR, and weight will be summarized by treatment group at Baseline and at each assessment time point during the post dosing period.

19.9.4 Laboratory Evaluations

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and at each scheduled visit. Summaries of safety laboratory parameters will include the first measurement of each scheduled assessment but repeat assessments done at the same study time point will not be included in summary calculations. Lab data will also be listed by treatment, patient, and visit. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values, as defined in the Statistical Analysis Plan, will additionally be generated.

19.9.5 Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening will be reported as AEs and analyzed as such. Clinically significant findings noted prior to start of Study Drug treatment will be recorded as medical history and analyzed as such.

19.9.6 Electrocardiograms

A standard 12-lead ECG will be obtained on Visit 1a/1b (pre-treatment) and subsequently, according to the Schedule of Events in Appendix 1. Electrocardiogram intervals (PR, RR, QTcF) will be summarized with descriptive statistics. All findings, including any follow-up ECGs as a result of any significant abnormal results, will be listed by treatment, patient, and visit.

19.10 Determination of 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 (i.e., up to 60 patients).

19.11 PHARMACOKINETIC AND PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The Study Drug plasma concentration data will be provided as data listings and will be summarized descriptively (mean, median, SD, minimum, and maximum) by collection time and nalbuphine dose. Additionally, these PK data may be analyzed through population, nonlinear mixed effects modeling (NONMEM), using the software package NONMEM (Version V, Level 1.1 or higher; GloboMax LLC, Hanover, MD).

20 ETHICS

20.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

Prior to initiation of the study, the Investigator will submit the study protocol, sample informed consent form (ICF), and any other documents that pertain to patient information, recruitment methods such as patient diaries, and advertisements, to the Institutional Review Board/Independent Ethics Committee (IRB/ IEC). The Investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the Study Monitor prior to initiation of this study. This letter will be forwarded to the Sponsor prior to the initiation of the study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site, as well as other AE reports received the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study.

20.2 ETHICAL CONDUCT OF THE STUDY

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice [GCP], 1 May 1996), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations.

The Investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator should maintain a list of Subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties. Should the Investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

20.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An ICF that includes information about the study will be prepared and given to the patient. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the patient and must specify who informed the patient. Where required by local law, the person who informs the patient must be a physician.

After reading the ICF, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed ICFs must be given to the patient. The original signed ICFs will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

21 STUDY ADMINISTRATION

21.1 CLINICAL MONITORING

Monitoring and auditing procedures, developed or endorsed by Trevi Therapeutics will be followed to comply with GCP guidelines. Access to the on-site study documentation and medical records will be ensured.

The study will be monitored by Trevi Therapeutics or its designee. Throughout the course of the study, the Study Monitor will make frequent contact with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents must be made available to the Study Monitor for review. The Study Monitor will also perform drug accountability checks and will request to perform a review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the Study Monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The Investigator, or appointed delegate, will meet with the Study Monitor during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of Trevi Therapeutics or the regulatory agencies.

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

21.2 DATA QUALITY ASSURANCE

The Investigator, or designee, will enter study data required by the protocol into an electronic data capture (EDC) system. The clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review the electronic CRF (eCRF) for completeness and accuracy. Any discrepancies found between source documents and completed eCRF will be entered as a discrepancy in the EDC system by the clinical research associate. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for eCRF correction (queries) will be discussed during the study site initiation visits and will be documented in the study operations manual.

Data from eCRF and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data from eCRF and data from other external sources for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be documented, and the study site should be requested to review and resolve the queries. Only authorized personnel can make corrections to the clinical database, and all corrections should be documented in an audit trail.

Adverse events will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

21.3 RETENTION OF STUDY RECORDS

The following records must be retained by the Investigator for a minimum of 2 years after the Sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed ICFs for all patients
- Patient identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of all communications between the Investigator and Sponsor (or Contract Research Organization [CRO])
- List of Subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all patients
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient records, hospital records, laboratory records, etc.)

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

However, because of international regulatory requirements, the Sponsor may request retention for a longer period of time. The Investigator must therefore obtain approval in writing from the Sponsor prior to destruction of any records.

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

21.4 CONFIDENTIALITY

Patient names will not be supplied to the Sponsor. Only the patient number and patient initials will be recorded in CRF (unless not allowed by local regulations), and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The will be told that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

21.5 DOCUMENTATION OF STUDY RESULTS

As part of the responsibilities assumed by participating in the study, the Investigator or Subinvestigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator or Subinvestigator agrees to maintain accurate eCRF and source documentation as part of the case histories. These source documents may include laboratory reports and ECG recordings.

The Investigator or designees must enter all results collected during the clinical study into the eCRF. Guidelines for completion of the eCRF will be reviewed with study-site personnel at the site initiation visits. There is a 2-part process to review and collect the eCRF data. Study-site personnel will enter the data from each study visit. The Investigator is responsible for approval of the entered/corrected data. The eCRF responsibilities of the study team members will be documented on the site delegation log, which will be collected at the closeout visits.

The Investigator can authorize Sub-investigators to sign and approve the eCRF if they are designated on Form FDA 1572 as Sub-investigators, have been trained on the EDC system, and have their own user name and password. The Investigators or designees must review and approve the data before database lock.

In the EU, the Investigator agrees to maintain documentation of the data generated by the trial so that it complies with the requirements of Directive 2001/20/EC, as amended and Directive 2005/28/EC as amended to incorporate recommendations on ‘The Trial Master File and Archiving’.

21.6 USE OF STUDY RESULTS

All information concerning the product, as well as any matter concerning the operation of Trevi Therapeutics (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Trevi Therapeutics and are unpublished) are confidential and must remain the sole property of Trevi Therapeutics. The Investigator and participating vendors will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Trevi Therapeutics is obtained. The Sponsor has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Trevi Therapeutics. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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APPENDICES

Appendices 1 through 4 are provided on the following pages.

Appendix 1: Schedule of Events

Table 4: Schedule of Events for Visits 1a and 1b (Day 1 of Week 1 of Treatment Period)

Visit	1a[1]	1b[4]
Informed Consent[2]	X	
Confirm Eligibility	X	
Vital Signs[3]	X	X
Physical Examination	X	X
Neurological Exam	X	X
Central Clinical Labs[5] & serum PregnancyTest[6]	X	X
Urinalysis	X	X
Urine for pregnancy test[11]	X	X
Blood for PK	X	X
Perform skin biopsy (only at select sites and the procedure is optional)[9]	X	X
12-lead ECG[12]	X	X
Worst itch Numerical Rating Scale (NRS)[7]	X	X
Average itch intensity Numerical Rating Scale (NRS)[7]	X[9]	X
Verbal Rating Scale (VRS)[7]	X[9]	X
ItchyQoL[7]	X[9]	X
MOS Sleep-R[7]	X[9]	X
Hospital Anxiety and Depression Scales (HADS)[7]	X[9]	X
Patient Benefit Index Pruritus (PBI-P)[7]	X[9]	X
Prurigo Activity Score (PAS)	X[9]	X
Record AEs	X	X
Review Rescue Medications and Concomitant Medications	X[8]	X
Retrieve TR03 study drug	X	
Dispense Study Drug for TR03ext[13]	X[9]	X
Collect Rescue Medication Log for TR03	X	
First dose of Study Drug for TR03ext[10,13]	X[9]	X
Dispense Drug Dosing Instructions and Dosing Diary	X	X
Dispense TR03ext Rescue Medication Log	X	X

[1]Study TR03 Visit 6 procedures in common with Study TR03 extension Visit 1a procedures do not have to be repeated.

[2] To be completed any time before start of Visit 1a procedures

[3]BP and HR (sitting or semi-recumbent), RR, temperature, and weight

[4] Visit 1b is the first visit of the Treatment Period for patients transitioning from the Observation Period to the Treatment Period.

[5]Hematology and chemistry

[6]Females of Childbearing potential only

[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)

[8]Includes review of patient TR03 Rescue Medication Log

[9]Study procedures only conducted if patient qualifies to enter the Treatment Period based on Worst itch NRS **≥ 5**

[10]Titrate study drug according to the schedule in Table 3;

The first dose of study drug treatment will define enrollment into the study

[11] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing study drug.

[12] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review

[13]The first dose of study drug is to be taken in the evening, see Section 9.7.1 and Section 9.3

Table 5: Treatment Weeks 2-4

	TC 1[1]	TV 2[1]	TC 2[1]
Treatment Week	**2**	**3**	**4**
Dispense Study Drug[2]		X	
Titrate Study Drug[2]	X	X	
Confirm Maintenance Dose			X[2]
Vital Signs[3]		X	
Neurological Assessment		X	
Urine pregnancy test[5]		X	
Blood for PK		X	
12-lead ECG[6]		X	
Worst itch NRS[4]		X	
Average itch intensity NRS[4]		X	
VRS[4]		X	
MOS Sleep-R[4]		X	
HADS[4]		X	
ItchyQoL[4]		X	
Study Drug BID		X	
Record AEs	X	X	X
Record Concomitant Medications		X	
Reinforce Compliance[7]	X	X	X
Study Drug Accountability		X	
Dispense Dosing Diary		X	
Dispense Rescue Medication Log		X	

[1] The window for TC 1-2 and TV2 is +/-3 days
[2] Instruct the patient in the dose titration/maintenance according to the schedule in Table 3 and assess tolerability/intolerability to study drug
[3] BP and HR (sitting or semi-recumbent), RR, temperature.
[4]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[5] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.
[6] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review
[7]Includes review of Rescue Medication Log and Drug Dosing Diary for accuracy and completeness.

Table 6: Treatment Period Visits[12] During Study Weeks 5-50 and Washout/Safety Follow-up Visit or Treatment Period Early Termination Visit

	TV 3	TV 4	TV 5	TV 6	TV 7	TV 8	TV 9	TV 10	TV 11	TV 12	TV 13	End of Treatment Visit (TV14)	Washout / Safety Follow-up Period	Premature Discontinuation of Study Drug Telephone Contact[14]	ET[9]
Treatment Week[1,3]	**5**	**9**	**13**	**17**	**21**	**26**	**30**	**34**	**38**	**42**	**46**	**--[2]**	**--**	**--**	
Physical Examination						X						X			X
Brief Neurological Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Central Clinical Labs[6]						X						X	X		X
Serum pregnancy test to central lab[11]												X			X
Urinalysis to central lab						X						X			X
PAS						X						X			X
PBI-P[7]												X			X
12-lead ECG[13]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Skin biopsy (at select sites and is an optional procedure)												X[10]			X
Blood for PK	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Failure-to-Improve Evaluation[17]	X	X	X	X	X	X	X	X	X	X	X			X	
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X				
Urine pregnancy test[5]	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Worst itch NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Average itch intensity NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ItchyQoL	X	X	X	X	X	X	X	X	X	X	X	X	X		X
VRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MOS Sleep-R[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
HADS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
SOWS[7]												X			X
Dispense 14 day SOWS packet[15]												X			
Retrieve 14 day SOWS packet[15]													X		
Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reinforce Compliance	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Accountability	X	X	X	X	X	X[8]	X	X	X	X	X	X			X[8]
Study Drug BID	X	X	X	X	X	X	X	X	X	X	X				

[1]Patients who were previously in the Observation Period should start the Treatment Period at Visit 1b and continue in the study for 38-46 weeks; the total number of weeks in the combined Observation and Treatment Periods is no more than 50 weeks. The last scheduled visit on study drug for patients previously in the Observation Period should be TV 14 regardless of the study week.

[2] The number of Treatment Weeks prior to TV 14 will vary for patients who prematurely discontinue study drug for reasons other than withdrawal of consent see Section 11.

[3]Two allowable dose reductions are permitted during Treatment Weeks 5 – 50 (a patient can be reduced to 30 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study.

[4] BP and HR (sitting or semi-recumbent), RR, temperature

[5]For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.
[6] Hematology and chemistry.
[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[8] Retrieve remaining study drug at TV 14 or ET Visit
[9] ET Visit is conducted within 2 weeks of study drug termination, see Section 12
[10] Skin biopsy material for nerve fiber density, histology (H&E) and MOR/KOR density to be performed, only at select sites (optional procedure)
[11]Females of Childbearing potential only
[12] Visit windows will be +/-3 Days
[13] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review
[14]The Premature Study Drug Discontinuation Telephone Contact is to take place for all patients who prematurely discontinue study drug for reasons noted in Section 11. This telephone contact takes place 30 days (+2 weeks) from the last dose of study drug.
[15]The 14 Day SOW packet is to be completed at home by the patient. A SOWS is to be completed each day starting at TV14. The packet is to be retrieved at the Washout and Safety Follow-up Period Visit
[16]Includes review of Rescue Medication Log and Drug Dosing Diary for accuracy and completeness
[17]See Section 11.1 for the Failure-to-Improve criteria; perform End of Treatment Visit (TV14) procedures for patients that meet the Failure-to-Improve criteria

Table 7: Observation Period Visits[5]

Observation Visit	OV 2	OV 3	OV 4
Observation Study Week	4	8	12[1]
Check Worst itch NRS[2]: If ≥ 5 , patient must undergo Visit 1b	X[4]	X[4]	X[4]
Vital Signs[3]	X	X	X
Average itch intensity NRS[2]			X
VRS[2]			X
MOS Sleep-R[2]			X
HADS[2]			X
ItchyQoL[2]			X
Record AEs	X	X	X
Record concomitant medications	X	X	X

[1]Patients whose NRS is <5 at OV 4 are to be screen failed from the study
[2] Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[3]BP and HR (sitting or semi-recumbent), RR, temperature
[4]If patient's NRS is **≥ 5** proceed to Visit1b procedures and no need to record any further data under OV visit procedures
[5]Visit windows will be +/-3 Days

Table 8: Treatment Visit Schedule for Patients Entering Treatment via Visit 1b

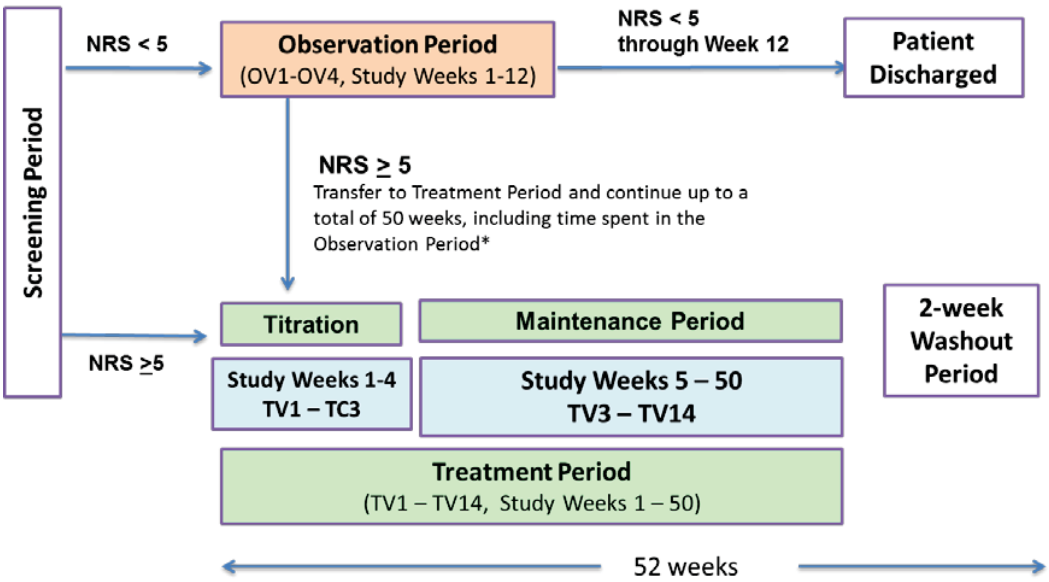
Patients with a Worst Itch NRS score of greater than or equal to 5 (≥5) at an Observation Visit are to complete Visit 1b and transition from the Observation Period to the Treatment Period.
If the above criteria are met, Visit 1b procedures are to be completed at the Observation Visit

Visit of Transition	**OV2**	**OV3**	**OV4**
Treatment Visits to Complete	Visit 1b/TV1, TV2 through TV12, and TV13	Visit 1b/TV1, TV2 through TV11, and TV12	Visit 1b/TV1, TV2 through TV10, and TV11
Last Treatment Visit	**TV13** **Dispense 1 week of study drug** Week 46 is last week of treatment for a patient who transitioned to the Treatment Period from OV2 Conduct the End of Treatment Visit (TV14) during week 47	**TV12** **Dispense 1 week of study drug** Week 42 is last week of treatment for a patient who transitioned to the Treatment Period from OV3 Conduct the End of Treatment Visit (TV14) during week 43	**TV11** **Dispense 1 week of study drug** Week 38 is last week of treatment for a patient who transitioned to the Treatment Period from OV4 Conduct the End of Treatment Visit (TV14) during week 39
Total Potential Weeks on Treatment	46	42	38

Table 9: 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	✓	---

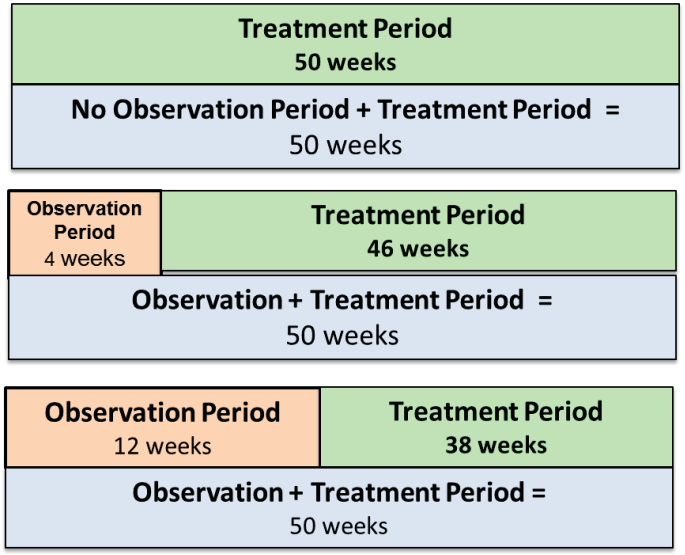
Appendix 2: Study Schematic Flow Charts

Figure 2: Overview of TR03-EXT Study Design



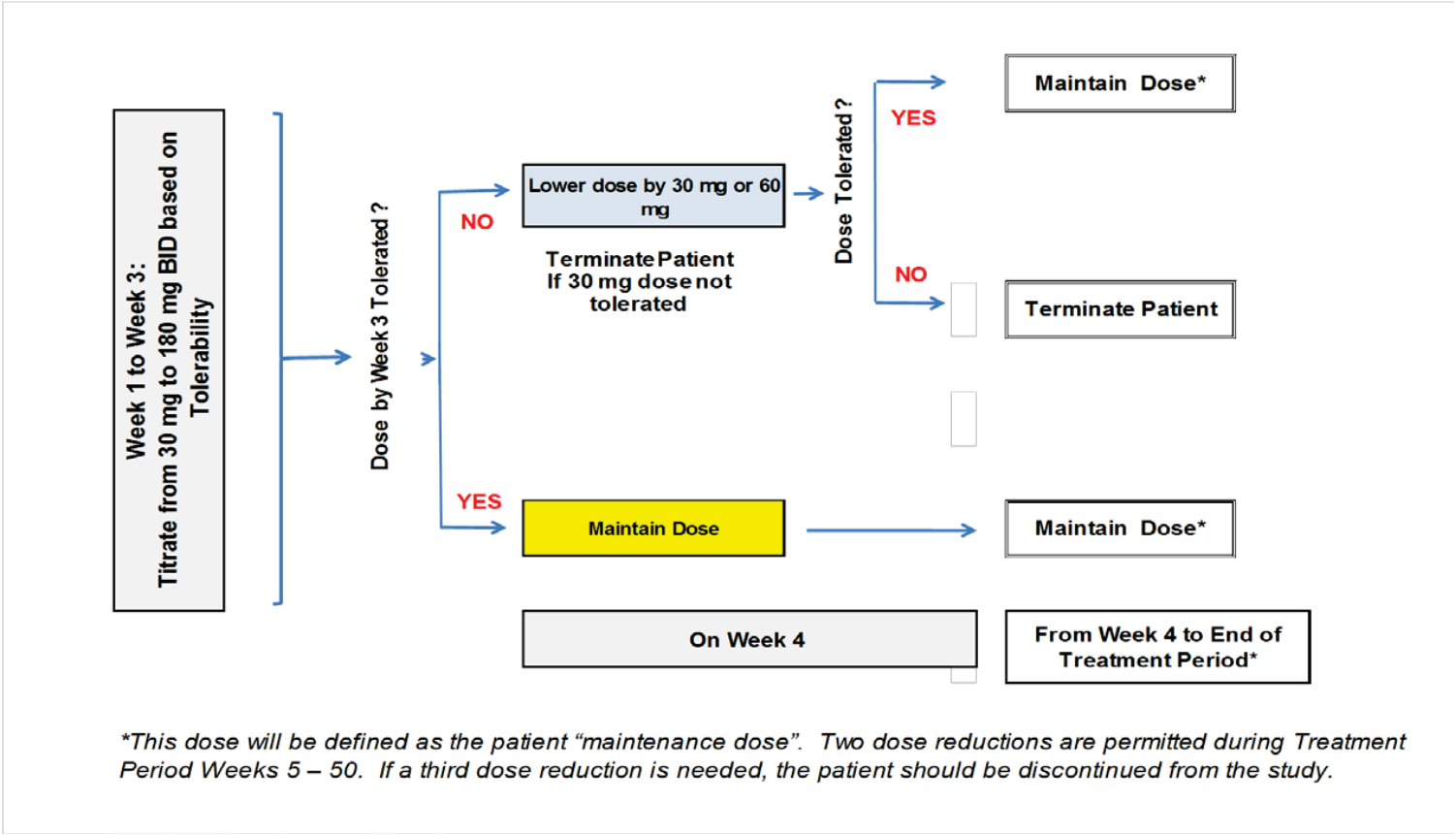
Patients transferring from the Observation Period will start with Visit 1b/TV1. Their follow-up in the Observation + Treatment Period will be 50 weeks in total.

Figure 3: Examples illustrating possible Observation and Treatment periods Scenarios in TR03-Ext



- Some patients will not be followed in the Observation Period (Top Scenario).
- For patients followed in the Observation Period, the total duration of time in the Observation and Treatment Periods will be up 50 weeks, regardless of when they transfer from the Observation Period to the Treatment Period (Middle and Bottom Scenarios)
- The first Observation Period visit at which the patient qualifies for treatment (see Table 1) will also be defined as Visit Ib/TV1.

Figure 4: Dosing Schedule in TR03ext



Appendix 3: Clinical Laboratory Tests

Hematology:

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

Urine:

Urinalysis
Pregnancy

Serum Pregnancy:

β-Human Chorionic Gonadotropin (HCG) (women of childbearing potential)

Serum Chemistry:

Potassium
Chloride
Carbon Dioxide
Blood Urea Nitrogen (BUN)
Creatinine
Calcium
Phosphorus
Total Protein
Albumin
Total Bilirubin
AST
ALT
Alkaline Phosphatase
LDH
Glucose

Appendix 4: Patient Reported Outcomes

The Patient Reported Outcomes are provided on the subsequent pages.

Medical Outcomes Sleep Scale (Revised MOS Sleep-R)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Your Sleep

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. How long did it usually take for you to <u>fall asleep</u> during the <u>past 4 weeks</u>?

0-15 minutes	16-30 minutes	31-45 minutes	46-60 minutes	More than 60 minutes
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. On the average, how many hours did you sleep <u>each night</u> during the <u>past 4 weeks</u>?

Write in number of hours per night: ☐☐

3. How often during the <u>past 4 weeks</u> did you…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	get enough sleep to feel rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	awaken short of breath or with a headache?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	have trouble falling asleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

MOS 12-Item Sleep Scale – Revised 2010
United States (English)

Medical Outcomes Sleep Scale (Revised MOS Sleep-R) (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

How often during the <u>past 4 weeks</u> did you…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
f	awaken during your sleep time and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	snore during your sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	take naps (5 minutes or longer) during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	get the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ItchyQoL™

Sample – actual assessment scale will be provided to the patient at appropriate visits

ITCHING QUALITY OF LIFE SURVEY

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My itchy skin condition bleeds.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. My skin hurts because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. My itchy skin condition burns or stings.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. I get scars from my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. I need to scratch my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. I spend a lot of money treating my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Updated 06 August 2013
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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
10. My itchy skin condition affects how well I sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. My itchy skin condition often makes it difficult to concentrate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. My itchy skin condition limits the types of clothes I can wear.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. I am frustrated by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I am embarrassed by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Updated 06 August 2013
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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

	How often during the past week do these statements apply to you?				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. My itchy skin condition drives me crazy/nuts.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. My itchy skin condition makes me angry or irritable.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. My itchy skin condition makes me feel depressed or sad.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. I worry about what other people think about me because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I worry that the itching will last forever.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. I feel self-conscious because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. My personality has changed because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Subject signature Date

Updated 06 August 2013
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Prurigo Activity Score (PAS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

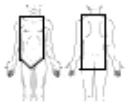
1. Type
a) Which efflorescences do you see?
□ papules
□ nodules
□ plaques
□ umbilicated ulcers
□ hypo-/hyperpigmented maculae

b) Which type of prurigo is predominant?
□ Prurigo papular type
□ Prurigo nodular type
□ Prurigo plaques type
□ Prurigo umbilicated "Kyrle" type
□ completely healed

2. Number
a) How many Prurigo lesions do you see? (do not count scars)
□ 0
□ 1 - 19
□ 20 – 100
□ > 100

3. Distribution:
□ disseminated
□ localized (only 1 or 2 areas affected)
□ neither of them

4. Please mark the affected area(s) (for definition of trunk see image).



whole body except head	□	
whole body head included	□	
or		
forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal
head	□ capillitium	□ face

5. Please choose a representative area:

forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal

Number of prurigo lesions in representative area (do not count scars):_____

6. Monitor lesions. Please mark the biggest (B) and a representative (R) prurigo lesion (remains the same in every visit).

	Highest elevation [mm]	Biggest diameter [mm]	
		longitudinal	crosswise
biggest prurigo lesion			
representative prurigo lesion			

7. Activity. Please mark the stage.

	stage 0	**stage 1**	**stage 2**	**stage 3**	**stage 4**
Prurigo lesions with excoriations/crusts compared to all prurigo lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
Healed prurigo lesions compared to all prurigo lesions	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

8. Take photos of the patient: Overview front and back, area(s) of marked monitor lesions to recognize on next visit

SST-Pr-10-2007, Amendment 9, PAS, Version 0.7; 11.09.2013

Patient Benefit Index, Pruritus Version (PBI-P)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Importance of Treatment Goals

With the help of the following questions, we'd like to know how important the goals mentioned below are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you.
If a statement does not apply to you, for example because you are not experiencing pain, please mark "*does not apply to me*".

	As a result of therapy, how important is it for you to ...	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on your skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...concentrate better	O	O	O	O	O	O
6	...be less nervous	O	O	O	O	O	O
7	...be able to wear all types of clothing	O	O	O	O	O	O
8	...be able to bathe and shower normally	O	O	O	O	O	O
9	...sleep better	O	O	O	O	O	O
10	...feel less depressed	O	O	O	O	O	O
11	...experience greater enjoyment of life	O	O	O	O	O	O
12	...have no fear that the disease will get worse	O	O	O	O	O	O
13	...lead a normal everyday life	O	O	O	O	O	O
14	...be more productive in everyday life	O	O	O	O	O	O
15	...be less of a burden to relatives and friends	O	O	O	O	O	O
16	...engage in normal leisure activities	O	O	O	O	O	O
17	...be able to lead a normal working life	O	O	O	O	O	O
18	...be able to have more contact with other people	O	O	O	O	O	O
19	...be more comfortable showing yourself in public	O	O	O	O	O	O
20	...be less burdened in your partnership	O	O	O	O	O	O
21	...be able to have a normal sex life	O	O	O	O	O	O
22	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	...need less time for daily treatment	O	O	O	O	O	O
24	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	...have fewer side effects	O	O	O	O	O	O
26	...find a clear diagnosis and therapy	O	O	O	O	O	O
27	...have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

PBI-P (Cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Treatment Benefits

When the treatment began, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent to which those treatment goals **were achieved**, indicating if the treatment has benefited you. If a statement did not apply to you, for example because you did not experience any pain, please mark "*did not apply to me*".

	The current treatment has helped me to …	not at all	somewhat	moderately	quite	very	*did not apply to me*
1	…be free of pain	O	O	O	O	O	O
2	…be free of itching	O	O	O	O	O	O
3	…no longer have burning sensations on my skin	O	O	O	O	O	O
4	…be healed of all skin defects	O	O	O	O	O	O
5	…concentrate better	O	O	O	O	O	O
6	…be less nervous	O	O	O	O	O	O
7	…be able to wear all types of clothing	O	O	O	O	O	O
8	…be able to bathe and shower normally	O	O	O	O	O	O
9	…sleep better	O	O	O	O	O	O
10	…feel less depressed	O	O	O	O	O	O
11	…experience greater enjoyment of life	O	O	O	O	O	O
12	…have no fear that the disease will get worse	O	O	O	O	O	O
13	…lead a normal everyday life	O	O	O	O	O	O
14	…be more productive in everyday life	O	O	O	O	O	O
15	…be less of a burden to relatives and friends	O	O	O	O	O	O
16	…engage in normal leisure activities	O	O	O	O	O	O
17	…be able to lead a normal working life	O	O	O	O	O	O
18	…be able to have more contact with other people	O	O	O	O	O	O
19	…be more comfortable showing myself in public	O	O	O	O	O	O
20	…be less burdened in my partnership	O	O	O	O	O	O
21	…be able to have a normal sex life	O	O	O	O	O	O
22	…be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	…need less time for daily treatment	O	O	O	O	O	O
24	…have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	…have fewer side effects	O	O	O	O	O	O
26	…find a clear diagnosis and therapy	O	O	O	O	O	O
27	…have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

Numerical Rating Scale (Worst Itch)

How would you rate your most severe itching over the past 24 hours?

Numerical Rating Scale

0	1	2	3	4	5	6	7	8	9	10

No Itch Worst Imaginable Itch

Numerical Rating Scale (Average-Itch)

How would you rate your itching on average over the past 24 hours?

Numerical Rating Scale

0	1	2	3	4	5	6	7	8	9	10

No Itch Worst Imaginable Itch

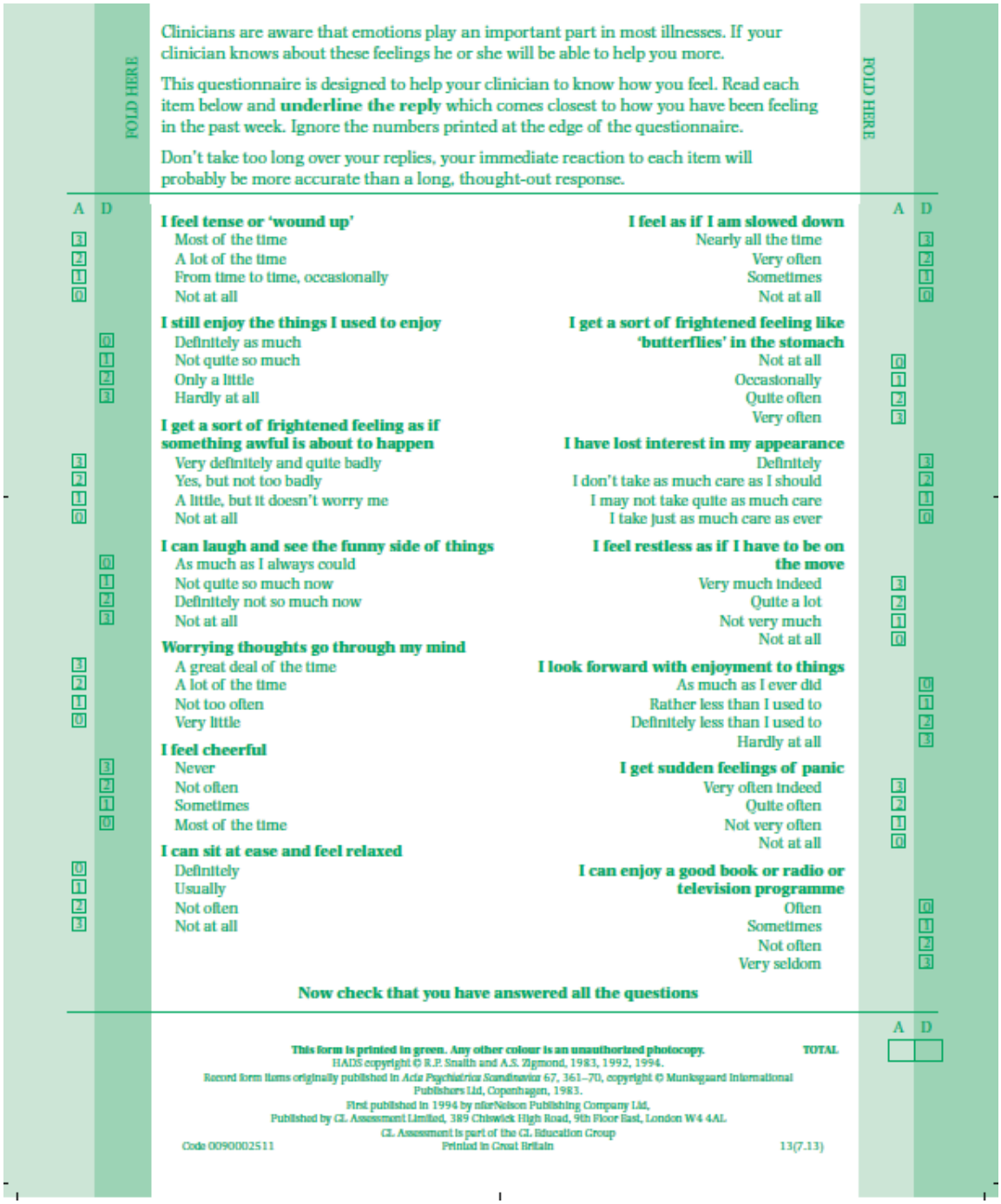
Verbal Rating Scale

How is your skin sensation today?

	0: not present	**1:** mild present	**2:** moderately present	**3:** severely present	**4:** very severely present
Itchy					
Burning					
Stinging					

Hospital Anxiety and Depression Scale (HADS)

Sample – actual assessment scale will be provided to the patient at appropriate visits



FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A D

I feel tense or 'wound up'
3 Most of the time
2 A lot of the time
1 From time to time, occasionally
0 Not at all

I still enjoy the things I used to enjoy
0 Definitely as much
1 Not quite so much
2 Only a little
3 Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
3 Very definitely and quite badly
2 Yes, but not too badly
1 A little, but it doesn't worry me
0 Not at all

I can laugh and see the funny side of things
0 As much as I always could
1 Not quite so much now
2 Definitely not so much now
3 Not at all

Worrying thoughts go through my mind
3 A great deal of the time
2 A lot of the time
1 Not too often
0 Very little

I feel cheerful
3 Never
2 Not often
1 Sometimes
0 Most of the time

I can sit at ease and feel relaxed
0 Definitely
1 Usually
2 Not often
3 Not at all

I feel as if I am slowed down
3 Nearly all the time
2 Very often
1 Sometimes
0 Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach
0 Not at all
1 Occasionally
2 Quite often
3 Very often

I have lost interest in my appearance
3 Definitely
2 I don't take as much care as I should
1 I may not take quite as much care
0 I take just as much care as ever

I feel restless as if I have to be on the move
3 Very much indeed
2 Quite a lot
1 Not very much
0 Not at all

I look forward with enjoyment to things
0 As much as I ever did
1 Rather less than I used to
2 Definitely less than I used to
3 Hardly at all

I get sudden feelings of panic
3 Very often indeed
2 Quite often
1 Not very often
0 Not at all

I can enjoy a good book or radio or television programme
0 Often
1 Sometimes
2 Not often
3 Very seldom

Now check that you have answered all the questions

A D

TOTAL

Subjective Opiate Withdrawal Scale (SOWS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	NOT AT ALL	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

APPENDIX 5: CARDIOVASCULAR RELATED PROHIBITED MEDICATIONS AND CARDIOLOGICAL ASSESSMENTS

The Cardiological Assessments are provided on the subsequent pages.

Canadian Cardiovascular Society Grading of Angina Pectoris

Sample – actual grading scale will be completed at appropriate visits

Grade	Description
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

References

Campeau Lucien. Grading of angina pectoris. Circulation 1976;54:522-3

Available on the Canadian Cardiovascular Society Website at www.ccs.ca

NYHA FUNCTIONAL CLASSIFICATION

Sample – actual grading scale will be completed at appropriate visits

The NYHA classifies heart failure into classes based on functional limitations and severity.

Class	Patient Symptoms
Class I (Normal)	**Few observable symptoms, no limitation in ordinary physical activity.**
Class II (Mild)	**Mild observable symptoms and slight limitation during ordinary activity. Comfortable at rest.**
Class III (Moderate)	**Marked limitation in physical activity due to symptoms even during less-than-ordinary activity. Comfortable only at rest.**
Class IV (Severe)	**End-stage heart failure. Severe limitations. Experience symptoms even while at rest.**

ACC/AHA CLASSIFICATION OF CHF

The ACC/AHA created four classifications from risk for developing the disease to severe disability.

Stage	**Description**
A (High risk for developing CHF)	**Hypertension, diabetes mellitus, family history, coronary artery disease**
B (Asymptomatic HF)	**Previous myocardial infarction (heart attack), valvular disorders, left ventricular dysfunction**
C (Symptomatic HF)	**Structural heart disease, fatigue, low tolerance level for physical activity**
D (Refractory end-stage HF)	**Severe limitations. Experience symptoms even while at rest.**

Source: American Heart Association

CLINICAL PROTOCOL

Protocol Number: **TR03ext**

Version Number: **3.0**

Version Date: **02 June 2016**

EudraCT No. **2013-005628-41**

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

Study Sponsor: Trevi Therapeutics, Inc.
195 Church Street, 14th Floor
New Haven, Connecticut 06510
United States
Phone: (203) 304-2499
www.trevitherapeutics.com

Investigators: Multicenter

Research Facilities: Multicenter

Institutional Review Board/ Independent Ethics Committee: Multicenter

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Sponsor's Representative

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Director, Clinical Operations
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Signature — 6 Jun 2016 — Date

Sponsor's Medical Expert:

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Thomas Sciascia MD — June 5, 2016
Signature — Date

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Howard Hait, MS
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Howard J Hait — 05 June 2016
Signature — Date

INVESTIGATOR SIGNATURE PAGE

I have read the attached protocol entitled: An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients dated 0**2 JUNE 2016** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 of the CFR, Parts 11, 50, 54, 56, and 312 and European Union Directive 2001/20/EC or equivalent regulatory body regulations/guidelines, as applicable.

I agree to ensure that Financial Disclosure Statements will be completed by:

- Myself (including, if applicable, my spouse [or legal partner], and dependent children)
- My sub-investigators (including, if applicable, their spouses [or legal partners], and dependent children)

The Financial Disclosure Statements will be completed before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Trevi Therapeutics, Inc.

Principal Investigator:

_____ _____
Name of Principal Investigator Date

_____
Institution or Clinical Practice

_____
Signature

1 STUDY SYNOPSIS

Title	An Open Label Extension Study of the Safety and Anti-Pruritic Efficacy of Nalbuphine HCl ER Tablets in Prurigo Nodularis Patients
Sponsor	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, Connecticut 06510 United States Phone: (203) 304-2499 www.trevitherapeutics.com
Protocol Number	TR03ext
Version and Date	Amendment 2: Version 3.0 dated 02 JUNE 2016 Amendment 1: Version 2.0 dated 11 MARCH 2015 Version 1.0 dated 24 JUNE 2014
Indication	Prurigo Nodularis (PN)
Investigational Product	nalbuphine hydrochloride (HCl) extended-release (ER) tablets
Active Ingredient	nalbuphine hydrochloride
Route of Administration	Oral
Duration of Study	The total study duration for any individual patient will be up to 53 weeks. Patients will receive drug treatment for up to 50 weeks.
Study Phase	Phase 2/3
Study Design	Open label
Planned Sample Size	No *a priori* planned sample size is designated for this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., approximately 60 patients)
Total Number of Centers	Up to 20 sites in North America and Europe

Primary Objective	• To evaluate the safety and tolerability of nalbuphine HCl ER tablets during a drug treatment period of up to 50 weeks.
Secondary Objectives	• To evaluate the safety of nalbuphine by achieved maintenance dose at the end of Treatment Week 4 • Assess skin lesion improvement using the metrics of the PAS • Change from Baseline in Patient-Reported Outcome measures Worst (i.e., most severe itching over the past 24 hours) itch NRS, average itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS by the final Treatment Period Visit • Change between Baseline and the final Treatment Period Visit in PBI-P • 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.
Exploratory Objectives	A single exploratory objective of the study is to evaluate: 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 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)

Selection Criteria	**Inclusion Criteria:** Patients must meet all of the following criteria to be eligible: 1. Have been adequately informed of the nature and risks of the study and have given written informed consent at the conclusion of TR03 Visit 6 and prior to Visit 1a. 2. Have completed participation in the TR03 study Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6 3. Agree to comply with the contraception requirements as below: Sexually active female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, Essure procedure, or spermicide) For the purpose of this study, all females are considered to be of childbearing potential unless they are post-menopausal (i.e., at least 1 year since last menses and age >50 years) or surgically sterile (i.e., tubal ligation, hysterectomy and/or bilateral oophorectomy) Female patients who are abstinent may participate in the study, however; they must be counseled on the requirement to use appropriate contraception should they become sexually active. This counseling should occur at each study visit and must be documented in source records 4. Ability and acceptance to provide written informed consent. 5. Willing and able to comply with study requirements and restrictions 6. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.

Selection Criteria	**Exclusion Criteria:** If a patient meets any of the following criteria, he or she is *not* eligible: 1. Patients with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association scale (scale provided in Appendix 5) 2. Patients with a history of angina pectoris grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale (scale provided in Appendix 5) 3. History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the patient. 4. Serum potassium below the laboratory lower limit of normality at TR03 Visit 5. Note: Potassium levels below the laboratory lower limit of normal at Visit 6/Visit 1a should be repeated and potassium supplementation provided as appropriate. 5. QTcF interval >450ms on screening/Visit 1a ECG. 6. Heart rate <50 BPM on any screening measurement. Patients with a resting heart rate of <50 bpm will have it repeated once after 5 minutes in the supine position, and if it remains <50 bpm during the repeat, they will be considered a screen failure. 7. Use of a medication known to be associated with risk of torsade de pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes) 8. History of substance abuse within the past year as determined by the Investigator 9. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study 10. Known hypersensitivity or allergy to nalbuphine or formulation components 11. Is a pregnant or lactating female
Study Treatment Allocation	All patients who are enrolled into the study will receive active treatment with nalbuphine HCl ER tablets.
Study Procedures	Visit 1a of the TR03ext study is temporally the same visit as TR03 Visit 6. Patients who do not consent by the end of the TR03 study visit 6 are no longer eligible for the extension study. Study TR03 Visit 6 procedures in

	common with Study TR03ext Visit 1a procedures do not have to be repeated. **For All Patients:** For all patients, TR03ext Visits (both during the Treatment Period and Observation Period) will include recording of vital signs, completion of PRO questionnaires, assessment of AEs, and recording of concomitant medications. On Visit 1a, patients will either enter directly into the drug Treatment Period or into a no-drug Observation Period based on their reported Worst itch NRS scores (defined as most severe itching over the past 24 hours) on that Visit day. **Patients with a Worst Itch NRS score greater than or equal to 5 (≥ 5) enter the Treatment Period:** Patients with Worst itch NRS ≥ 5 at Visit 1a will start in the drug Treatment Period of the study and will receive Study Drug starting with an evening 30 mg dose (to be taken at home), after the Treatment Visit 1a procedures have been completed. Receipt of the first dose of study drug will define Treatment Period Day 1. Treatment Visit 1a for these patients is also Treatment Visit 1 (TV1). Subsequent visits will be defined as TV2, TV3, etc. In addition, during the time period of dose titration, information will be obtained via telephone communication; these will be defined as TC1, and TC2. The dose will be titrated for up to 4 weeks based on tolerability, after which time the dose achieved (as of the end of Treatment Week 4) will be maintained up to an additional 46 weeks (with the exception of permitted down titrations); see Table 3 Study Drug Dosing schedule. For patients transitioning from the Observation period, the total time in the Treatment Period plus any time in the Observation Period will be a total of 50 weeks. Safety laboratory data and blood for PK, ECGs (locally and centrally read), and physical examinations including the PAS assessment will be performed periodically according to the Schedule of Events (See Appendix 1). Schematic descriptions of the study can be found in Appendix 2. All patients on drug treatment will enter a 2-week wash-out and safety follow up period following the end of the Treatment Period with procedures conducted according to the Schedule of Events (See Appendix 1). **Patients with a Worst Itch NRS score less than 5 (< 5) enter the Observation Period:** Patients with a Worst Itch NRS score < 5 at Visit 1a will enter into an extended screening period, Observation Period (no drug treatment), of the study and will be followed for

	up to 12 weeks (extended screening weeks). Visit 1a for these patients is also Observational Visit 1 (OV1). Subsequent visits will be defined as OV2, OV3 and OV4 and will occur at approximately monthly intervals for the next 3 months. During this Observation period, patients who report an increase in their Worst Itch NRS with a score of ≥ 5 at any one of their Observation Visits and meet all other eligibility criteria will be able to enroll immediately into the Treatment Period of the study and Visit1b procedures are to be performed. Patients will receive open-label Study Drug starting with an evening 30 mg dose (to be taken at home), after the Visit 1b procedures have been completed. Receipt of the first drug will indicate the start of their Treatment Period and enrollment into the study. The duration of the Treatment Period for such a patient will vary depending upon the visit at which they transition from the Observation Period to the Treatment Period. Patients in the Observation Period whose Worst Itch NRS score remains <5 over the 12 extended screening weeks will be screen failed from the study at the end of that time period. **Failure to Improve Criteria:** Beginning on TV 3, and at every subsequent Treatment Visit, patients with a Worst itch NRS equal to or greater than (≥) the Worst Itch NRS at Visit 1a (or at Visit 1b in the case of patients who require the Observation Visit period) will be discontinued from taking study drug. Patients discontinued from taking 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.
Safety Assessments	Safety will be assessed based on adverse events (AEs), clinical laboratory measurements, Investigator review and central cardiac core laboratory read-12-lead electrocardiogram (ECG), vital signs and physical examinations. An unblinded, independent Data Safety Monitoring Board (DSMB) will periodically review safety data during the time period that the blinded part of the nalbuphine HCl program remains ongoing. The frequency of data review and DSMB processes are outlined in the DSMB charter.
Efficacy Assessments	**Efficacy Measurements:** • Worst itch intensity (from NRS) • Average itch intensity (from NRS)

	• VRS (itchy, burning and stinging) • ItchyQoL • MOS Sleep-R • HADS • PAS • PBI-P • Frequency, pattern, and reasons for dose titration • Use of rescue medications for itching Optional Procedures (at select sites only): • Nerve fiber density (histology) at Baseline and the final Treatment Period Visit • MOR/KOR density (histology, Western Blot) at Baseline and the final Treatment Period Visit • Histological analysis (H&E) at Baseline and the final Treatment Period Visit
Pharmacokinetic Assessments	Blood samples for nalbuphine plasma concentration (and metabolites as needed) will be collected periodically according to the Schedule of Events (Appendix 1).
Study Endpoints	**Primary Endpoint:** • A description of the incidence and nature of Treatment Emergent Adverse Events (TEAE) during Treatment Weeks 5- 50 **Secondary Endpoints** 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. Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time. • Assess skin lesion improvement using the metrics of the PAS • Change from Baseline in Patient-Reported Outcome 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 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 criteria • Changes in the PRO measurements during the Washout Period after cessation of treatment of nalbuphine HCl ER tablets • Time to the 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 **Exploratory Endpoint** 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 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).
Statistical Methodology	**Efficacy:** All efficacy endpoints will be evaluated through the generation of 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. **Safety:** The incidence of AEs will be summarized through the presentation of proportions by MedDRA body system classification and preferred term. Vital signs and laboratory data will be summarized using continuous-based descriptive statistics (n, mean, SD, median, minimum, maximum). The extent and duration of use of rescue

	medications will be similarly summarized using descriptive statistics. Summary statistics for AEs with onset during the Observation Period will be separately summarized. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomic and Therapeutic Class
BID	Twice daily
BMI	Body Mass Index
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CNS	Central nervous system
CRF	Case report form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Extended release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&E	Hematoxylin and eosin
HADS	Hospital Anxiety and Depression Scale
HCG	Human chorionic gonadotropin
HCl	Hydrochloric acid
HD	Hemodialysis
H pylori	Helicobacter pylori
HR	Heart rate
ICF	Informed consent form
ICD-10	International Classification of Diseases, 10th revision

Abbreviation	Definition
ICH	International Conference on Harmonization
IFSI	International Forum for the Study of Itch
IRB	Institutional Review Board
IUD	Intra-uterine device
KOR	Kappa Opiate Receptor
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MOR	Mu Opiate Receptor
MOS	Medical Outcomes Study
MITT	Modified Intent-To-Treat
NONMEM	Non-linear mixed effects modeling
NRS	Numerical Rating Scale
NYHA	New York Heart Association
OV	Observation Period Visit
OTC	Over-the-counter
PAS	Prurigo Activity Score
PBI-P	Patient Benefit Index, pruritus version
PD	Pharmacodynamic(s)
PK	Pharmacokinetic
PN	Prurigo Nodularis
PRO	Patient-Reported Outcome; In this study, PRO instruments administered at the site are as follows: NRS, VRS, ItchyQoL, PBI-P, MOS Sleep-R, HADS, SOWs
PUVA	Psoralen plus Ultraviolet Light A
QoL	Quality of Life
RR	Respiratory rate
SAE	Serious adverse event
SD	Standard deviation
SOWS	Subjective Opiate Withdrawal Scale
TC	Telephone Call
TdP	Torsade de Pointes
TV	Treatment Period Visit
UP	Uremic Pruritus
VRS	Verbal Rating Scale
WHO	World Health Organization

3 INTRODUCTION

3.1 PRURIGO NODULARIS AND STUDY RATIONALE

3.1.1 General Information on Prurigo Nodularis

Prurigo Nodularis (PN) is an intensely pruritic dermatologic condition with the presence of papules as well as nodules with excoriations and ulcerations. The basis of PN is a pre-existing severe and chronic pruritus of various etiologies (see Table 1). The pruritus leads to scratching. However, the etiology or predisposing factors leading to the development of papules and nodules of PN are largely unknown (Eigelshoven et al 2009; Valdya and Schwartz 2008; Lee and Shumack 2005). Iking et al (2012) reports that in the past few years the hypothesis for the etiology of PN as being a reaction pattern due to a "vicious cycle of repeated itching and scratching" is gaining wider acceptance in the medical community.

With regard to the types of pre-existing chronic pruritus conditions that have been reported in PN patients, Table 1 summarizes data reported by Iking et al (2012) in their study of PN patients (N=108). Pruritus secondary to multi-factorial etiologies ("Mixed Origin") was the most common source attributed to the cause of the chronic pruritus. The majority of the "mixed origin" patients had a combination of dermatological and systemic diseases or a combination of several systemic disorders.

Iking et al (2012) did not attribute any cases of PN to an underlying diagnosis that was solely psychological in origin. In the subjects who were diagnosed with PN from mixed origin etiologies (summarized in Table 1), the authors attributed psychological factors related to chronic pruritus etiology to be present in 5.6% of the PN subjects categorized as having mixed (multi-factorial) origin pruritus. In a study focused on understanding psychosomatic/psychiatric dimensions related to chronic itch, Schneider et al (2006) reported on 44 PN patients. The authors stated that 34% of subjects had no accompanying psychiatric diagnosis and 46.8% were given a diagnosis of "psychological or behavioral factors associated with disorders classified elsewhere" (ICD-10 code F54) –indicating that psychological factors may play a role in the development and course of the condition. Payne et al (1985) reported psycho-social problems may have been relevant in about 33% of the studied 42 subjects that were adequately questioned.

Table 1: Etiology of Chronic Pruritus Reported in Prurigo Nodularis Patients (N=108)

Origin of Pruritus by Organ System	Number of Patients (%)	% Mixed with Organ Category Contribution to Chronic Pruritus	Most Common Disease
Mixed (pruritus of multi-factorial etiologies)	64 (59.3%)		
		Dermatological Disease (19.4%)	Atopic diathesis
		Systemic Diseases (70.9%)	Sorbitol Intolerance
			Lactose Intolerance
			Iron Deficiency
			H pylori Infection
			Diabetes Mellitus
			Renal Failure
		Neurological Disease (4.1%)	Chronic pain Syndrome
			Neuropathy
			PUVA-pain
		Psychological Factors (5.6%)	Psychological Factors (non-specific)
Origin of Pruritus by Organ System	Number of Patients (%)	Most Common Disease	
Dermatological	20 (18.5%)	Atopic diathesis/dermatitis	
Systemic	8 (7.4%)	Sorbitol Intolerance	
		Lactose Intolerance	
		Hepatitis C	
		H pylori infection	
		Iron Deficiency	
		Diabetes Mellitus	
Unknown	14 (13%)	-	
Neurological	2 (1.9%)	Brachio-radial Pruritus	
Psychological	0 (0%)	-	

Source: Iking et al (2012)

Iking et al (2012) reported that the median value of the NRS average intensity pruritus measured 8 on a rating scale with anchor points of zero (no pruritus)-10 (worst imaginable pruritus). Itch intensity scores ≥ 7 are considered severe in terms of itch intensity and itch intensity scores ≥ 3 are considered moderate in terms of itch intensity (Stander et al 2013). Accioly-Filho et al (2000) reports that once the cycle of pruritus-excoriation-pruritus begins, it is difficult to stop as PN is very resistant to therapeutic intervention strategies. Papoiu et al (2013) report a central nervous system relationship to the itch-scratch cycle. The authors showed that there is a complex interaction of sensory, motor and emotional components

based on their investigation of using real-time flare brain MRI imaging and psychophysical ratings of itch relief or pleasurability of scratching conducted in healthy volunteer experimental subjects.

Eigelshoven et al (2009) reports that patients present with excruciating pruritus that is usually anatomically symmetrical and mainly involves the extensor aspects of the extremities, the shoulders, chest and sacral regions with the appearance of typical lesions.

Payne et al (1985) reported in a study of 46 subjects that the patients came from all social classes and racial groups, almost equally divided by gender and with a mean age of 39.5 years at the time of PN onset. Iking et al (2012) reported in their study that the patients were distributed in age between 11.9 years - 95.6 years with a median age of 61.9 years and there were more females than males affected by the disease.

Weigelt et al (2010) summarized the characteristic histological findings in PN that include the presence of thick compact orthohyperkeratosis; folliculosebaceous units in nonvolar skin in conjunction with a thick and compact cornified layer; irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils.

In terms of treatment options for PN, there have been a variety of medical interventions discussed. Hogan et al (2012) recently reviewed the therapies discussed in the literature that included topical, systemic and intra-lesion steroids administration; antihistamines; anxiolytics; opiate receptor antagonists; thalidomide; gabapentin; capsaicin cream; topical anesthetics; occlusive therapies; ultraviolet light; and reports that they had “mild to moderate success at best”. The authors also comment on the potential imbalance in the mu-kappa opiate receptor system and mention the possibility of studying the kappa agonist nalfurafine (see Section 3.1.3.1, where nalfurafine was used as a positive control in Sponsor’s preclinical substance P mouse model of itch investigation). Spring et al (2014) reported on the use of methotrexate and the need for chemotherapeutic related regular medical monitoring. Liu et al (2013) and Kanavy (et al 2012) both reported on lenalidomide is case reports, but the drug led to side effect of a reversible myopathy in one of the subjects. Accioly-Filho (2000) reported the condition is “notoriously resistant to therapy”. Iking et al (2012) and Valdya and Schwartz (2008) reported a significant impact on the patient’s quality of life (2008). Spring et al (2014) report PN to be debilitating condition and a therapeutic challenge where conventional treatments with steroids, standard anti-pruritic agents, phototherapy and immune-suppressors often fail.

3.1.2 Potential Mechanism of Prurigo Nodularis Pathophysiology

3.1.2.1 *Opiate Neurobiology*

The initiating biological event in the skin is unclear but assumed to patho-physiologically result from a complex cross talk of different skin cells. The neurobiology of opioid peptides may be involved at the peripheral level as part of a reaction to the skin tissue injury. Therapeutic intervention at the peripheral level through opioid pharmacology to break the scratch-itch cycle via interrupting positive feedback loops that have developed between

elements of the peripheral nervous system, immune system and various skin cell interactive dynamics may be possible. In addition, central nervous system opiate neurobiology may be involved in a positive feedback loop between the tremendous urge to scratch and the pleasurable anti-pruritic relief gotten from scratching that could also be a level of therapeutic intervention using opioid pharmacology.

3.1.2.2 *Systems Biology Hypothesis to Prurigo Nodularis Etiology*

Diseases that arise from an abnormal interaction between integrated body system networks, and exhibit the concept of a positive feedback cycle which lead to an amplification of a biological signal; can be discussed using concepts from systems biology (Kitano 2004). The physiological phenomena of a "scratch-itch cycle" ("positive feedback loop") underlying the patient's behavior, the intense ("amplified") nature of the pruritus and the large areas of body surface involvement in the absence of an active dermatosis suggest a "generalized" process either potentially due to central nervous system circuitry pathophysiology and/or widespread derangement of the dermal-immune-nervous system component interactions. PN may be analogous to chronic regional pain syndrome – a condition where there may or may not be an initiating etiological event, the intensity of pain is severe, the sensation of pain spreads to wide areas of the body surface and the condition is regarded as a systemic disease that involves both the central and peripheral components of the nervous system along with interactions with the immune system (Schwartzman et al 2009). Complex regional pain syndrome is completely independent of any potential nociceptive initiating event. Schmelz (2005) reviewed the literature on the evidence of similar biological patterns occurring in chronic pain and chronic itch conditions. Iking et al (2012) reported that on onset, PN was localized in 68.5% of patients with only 31.5% having generalized PN. In the majority of patients (56.5%), a secondary generalization of PN was observed. In the course of PN, only 12.0% still suffered from a localized form of PN.

3.1.2.3 *Relevant Cutaneous Peripheral Neurobiology in the Skin*

The complex neurochemical/neurohumoral interactions between the cutaneous resident mast cells and epidermal keratinocytes with peripheral non-myelinated type C nerve endings responsible for initiating the behavior of scratching as an evolved protective response to exogenous invading skin irritants is well summarized by Raap et al (2011) and the current understanding of the peripheral neuroanatomy-spinal cord synaptic connections underlying itch is well summarized by Dhand et al (2014). Selected aspects of this neurobiology as they relate to the development of some specifics of the known pathology in PN will be summarized.

The cellular initiation of itch can begin with the mast cell release of histamine that binds to H1 receptors on nerve fibers (Raap et al 2011). Endorphins and other opiate peptides are known to cause histamine mast cell release (Barke et al 1993). Endorphin itch initiation biology may be more direct. Bigiliardi and Bigliardi-Qi (2004) observed that while histamine interaction with nerve fibers may be a source of itch sensation, they summarize evidence for direct opiate peptide interaction with nerve fiber endings expressing endorphin receptors as a contributor to itch sensation initiation.

With regard to the skin cells themselves, keratinocytes are known to produce different neuropeptides that include proopiomelanocortin (POMC), which is a precursor for the opiate

peptide beta-endorphin (Bigliardi et al 1998). In addition, mast cell activation can initiate the itch process via non-histamine mediated processes that that lead to substance P presence in the interstitium (Raap et al 2011). Substance P, a neuropeptide member of the tachykinin family, is thought to induce itching in humans via histamine degranulation from mast cells (Potenzieri et al 2012). Keratinocytes are known to express Substance P receptors (Peters et al 2006) and opiate receptors (Bigliardi et al 1998).

There is also a close link between endorphins and substance P in nerve fibers innervating the epidermis. Opioid receptors destined for insertion onto the distal portions of Type C cutaneous nerve fiber membrane and the neuropeptides (such as substance P) that are capable of release into the interstitium are both synthesized in the same dorsal root ganglion nerve cells and transported to the peripheral nerve processes in the skin (Stein et al 2003).

3.1.2.4 *Abnormal endogenous opiates in the skin of PN patients:*

Bigiliardi and Bigliardi-Qi (2004) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor expression in the epidermis compared to normal skin. The down regulation was thought to be a biological response to abnormal tissue exposure to large amounts of endogenous opioid ligands such as endorphins. The authors comment that the epidermal skin cells such as the keratinocytes that are no longer binding the opioid ligands possibly leave the ligands available to bind to epidermal nerve endings and thus induce a nerve transmission mediated signal to the CNS resulting in a pruritus sensation.

3.1.2.5 *Abnormal substance P level in the skin of PN patients:*

Haas et al (2010) reported data showing significantly increased density of dermal substance P nerve fibers both in lesion skin samples as well as normal appearing skin samples from PN patients. The authors concluded that the hyper-innervation by substance P containing sensory nerves may have a role in the itch sensation found in these patients. Molina et al (1992) reports increased nerve fibers containing substance P in PN subjects compared to control group that could be related to the intense pruritus.

3.1.2.6 *Inflammatory Component to PN Histology:*

Neurogenic inflammation refers to the manifestation of skin diseases related to the malfunctioning of the nervous system – immune system interaction (Steinhoff et al 2003, Peters et al 2006, and Potenzieri et al 2012). Bigliardi et al (1998) conclude that the presence of receptor systems for endorphins and substance P molecules is evidence of an interaction between skin, immune and nervous system. Given the abnormal biology of substance P and endorphins in the skin of PN patients just discussed above, the hypothesis that the induction of an inflammatory component in PN is etiologically related to endorphin-substance P pathobiology is based on the following biological facts:

In addition to being a pruritogen, substance P also has pro-inflammatory and immune-stimulatory activity (Peters et al 2006). Steinhoff et al (2003), Peters et al (2006), and Potenzieri et al (2012) state that substance P may be an important mediator of cutaneous neurogenic inflammation. The immune cells that migrate under a pro-inflammatory signal from released substance P are an important source of opioid ligands. The opioid ligand containing immune cells consist of T and B lymphocytes, granulocytes, and

monocytes/macrophages (Sehgal et al 2011). As noted by Weigelt et al (2010), part of the characteristic PN histological findings is a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils (granulocytes). The opioid ligands released by immune cells interact with peripheral opioid receptors located on the cutaneous nerves (Stein et al 2003). Otherwise stated, the cutaneous nerve induced signaling from opioid ligands released by immune cells may be a source of the pruritic signal to the brain.

3.1.3 Rationale for Investigating Nalbuphine HCl ER in Prurigo Nodularis

3.1.3.1 *Pre-clinical Animal Data*

A preclinical investigation (Covance Study No. 8265903) was undertaken to demonstrate the effects of nalbuphine HCl on substance-P (SubP) induced scratching behavior in the mouse, a standard animal model (Kuraishi et al. 1995). Scratching behavior induced by peripheral stimulation by the pruritogen SubP mimics the characteristics of itch-related scratches in humans (Kuraishi et al. 1995) and Andoh et al 1998). In addition, the SubP induced scratching behavior is not inhibited by the histamine H1 receptor antagonist and elicits responses even in mast cell-deficient mice. Thus, SubP-induced scratches are likely to represent antihistamine-resistant pruritus. The model is relevant to antihistamine-resistant pruritus (Togashi et al 2002 and references cited therein).

The SubP itch mouse model was successfully established and its viability confirmed by assessing the responses using vehicle (phosphate buffered saline, PBS) only group (VEH/VEH) and nalfurafine HCl, a positive comparative control group (PCC/SubP) relative to untreated group (VEH/SubP) group. Briefly, studies were conducted in male C57BL/6 mice. Animals were acclimated to the facility at least three days prior to dosing. On the test day, mice were acclimated to the observation cages for one hour prior to dosing. Mice were then randomly assigned to treatment groups and subcutaneously (SC) dosed with vehicle (PBS), PCC (0.01 or 0.02mg/kg), or the test article nalbuphine (10 or 30mg/kg) (NAL/SubP group), and video recorded for 30 minutes to establish baseline scratching behavior. After the 30-minute baseline recording, mice received either vehicle (0.05 mL PBS) or SubP (250 nM in 0.050 mL) injected intradermally (ID) into the rostral part of the back and video recording continued immediately for an additional hour.

Itching was scored by reviewing the recording and counting the number of scratches over 30 minute periods following SubP (or vehicle) challenge. Itching was defined as scratching with the hind paw at the intradermal injection site (upper right shoulder area). Continuous scratching over one second was counted as one scratch event and paused scratches were considered separate scratching events. Scratching of other sites such as ears and face were not recorded.

Baseline scratching (pre-SubP) was similar for all treatment groups. Following SubP administration in the untreated mice, itching began within 3-5 minutes from administration of the pruritogen. The itch intensity was the highest in the first 30 minutes post-dose. By 60 minutes post-dose, the effect of the SubP injection began to wear off as scratching returned towards baseline levels.

As expected, PCC significantly ($p< 0.001$) decreased the SubP-induced scratching supporting the validity of the itch model. Subcutaneous pre-treatment with PCC resulted in a reduction of 42 and 63% reduction at the 0.01 and 0.02mg/kg dose (from 107 to 62 or 40 scratches, respectively).

Significant reduction in itch ($p< 0.001$) was noted following nalbuphine SC administration with about 43% reduction in itch at the 10 mg/kg dose (from 107 to 61 scratches) and 52% at the 30 mg/kg dose (from 107 to 52 scratches). Though there was a trend for a dose dependence on itch reduction, there was no statistical difference between the tested nalbuphine doses.

In this study, nalbuphine was as effective as PCC (nalfurafine) at reducing SubP-induced itch with no statistical difference between nalbuphine and PCC effect, regardless of the dose.

Ambulation was not suppressed in mice injected with nalbuphine dosed at 10 or 30 mg/kg indicating that attenuation of the scratching was not due to decreased locomotor activity.

3.1.3.2 *Neuropharmacologic Basis of the Rationale of Investigating Nalbuphine for the Treatment of Prurigo Nodularis*

Gutstein et al (2001) reports that nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor and simultaneously acting as an agonist at the opioid κ-receptor, and thus is a member of the "opioid agonist-antagonist" class of drugs that mechanistically work through this dual pharmacologic process. There is no published literature on the use of the moiety nalbuphine in PN. Nalbuphine was shown to be effective in reducing morphine induced pruritus, a well-known clinical pruritic condition induced by morphine administration. In several published clinical well controlled studies (which are reviewed in detail in the Investigator's Brochure Section 5.8), nalbuphine was either equally effective or superior in efficacy when compared to naltrexone or naloxone (both are pure u-antagonists) for the management of morphine induced pruritus.

Neurogenic inflammation (as discussed in Section 3.1.2.6) may induce the secondary phenomena of "central sensitization" (Woolf et al 2011). Central sensitization is a central nervous system pathologic neurobiology change in cell circuitry that results from abnormal peripheral nerve signaling and/or peripheral nerve injury. The net effect of central sensitization is that there is a lowering of neural excitation threshold to external stimulus whereby either nociceptive or low intensity pruritogen cutaneous stimuli induce a high intensity sensation of pruritus (Paus et al 2006). Schmelz (2005) reports on the evidence that there is a mu-kappa opiate gating circuitry in the spinal cord whereby kappa agonist activity would inhibit mu opiate receptor containing cell activation mediated signaling that brings to consciousness the sensation of pruritus. The analysis by Schmelz may be an example of what Pan (1998) reports as a potentially very general opioid μ-receptor antagonizing function by the opioid κ-receptor. The author reviews the literature on central neural networks where the opioid κ-receptors are located in cell groups that are distinct from the cell groups that contain the opioid μ-receptors and summarizes the evidence that agonism at the pharmacological level of the opioid κ-receptor antagonizes various opioid μ-receptor agonist mediated actions in the brain. This central gating mechanism could be important in

countering any potential pruritogenic induced sensation from a peripheral neurogenic inflammatory initiating event in PN.

As discussed in Section 3.1.2.5, there is histological evidence of abnormal substance P presence in skin samples of PN patients. In that regard, an experiment conducted by Trevi Therapeutics indicated that nalbuphine administered subcutaneously significantly ($p<0.001$) suppressed the substance P induced scratching in mice (see Section 3.1.3.1 study summary).

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%. Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. This clinical observation potentially has different anatomical locations for the mechanistic drug effect. Since Stein et al (2003) reported that inflammation increases both the number of sensory nerve terminals ("sprouting") and disrupts the perineural barrier –thus facilitating opioid access to receptors, there is the possibility that peripherally acting mu antagonist naltrexone action reduced the neural membrane excitation by blocking actions of endogenous endorphins reported by Bigiliardi and Bigliardi-Qi (2004) to be present in the epidermis. In fact, Bigiliardi and Bigliardi-Qi (2004) suggest an opiate antagonist be therapeutically investigated for this reason and also comment on the evidence that mu opiate receptors on epidermal cells may be have a role in skin healing.

However, consideration must also be given to central nervous system opioid pharmacology as a contributing antipruritic effect elicited by naltrexone. At the spinal cord level, Schmelz (2005) commented that the explanation for opiate mu antagonists being capable of reversing experimentally induced itch may be related to the neurobiology of spinal cord level neuronal kappa-mu opioid gating circuits where either a mu antagonist or kappa agonist drug may act to have a pruritus suppressing effect. Supraspinal brain level action related to interference of the circuits related to reward behavior cannot be excluded given that it is known that naltrexone, like nalbuphine, can abolish morphine induced pruritus from morphine administered intrathecally. In addition, opiate receptor neuronal systems are known to be related to the physiological psychology of human reward behaviour and mu antagonist opioid class drugs are known to block the phenomena (Le Merrer et al 2009). Nalbuphine is known to block the effects of mu agonist drugs and induce the opioid withdrawal syndrome (Nubain® label).

3.1.3.3 *Nalbuphine Clinical Data in Uremic Pruritus*

Mannenti et al (2009) summarized potential pathophysiologic mechanisms for the etiology of uremic pruritus. Included among the postulated uremia induced mechanisms to explain uremic pruritus is neurophysiologic central sensitization "wind up" phenomena related to immune-inflammatory skin pathology. Mettang and Kremer (2014) in their review of uremic pruritus comment on the recent focus given to the mechanistic hypothesis related to peripheral neuropathic changes and central nervous system pathobiology along with evidence for cutaneous micro-inflammation. The authors state that a therapeutic option may be systemic treatment with mu-opioid receptor antagonist and kappa-opioid receptor agonist. The proposed etiology of uremic pruritus pathobiology may be similar in origin to the neuroinflammatory process discussed in Section 3.1.2.6 as part of the mechanism postulated for the underlying process involved in inducing PN. In should be noted that Lee and Shumack (2005) reported prurigo nodularis occurring in patients with renal failure and Iking

et al (2012) report renal failure as a contributing source of chronic pruritus with PN that was attributed to mix origin chronic pruritic conditions (see Table 1).

In clinical study TR01, the effect of oral nalbuphine on pruritus in hemodialysis (HD) patients with uremic pruritus was explored. The results indicated that nalbuphine HCl ER tablets demonstrated ability to suppress itch in a dose response fashion (see Figure 1)

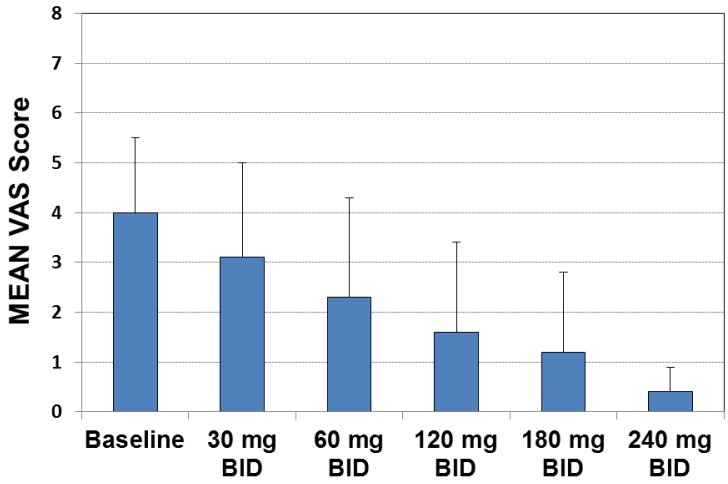

Figure 1: Mean VAS score (SD) for all patients as a function of nalbuphine HCl dose administered as nalbuphine HCl ER tablets. N= 14 except for 180 mg (N=13) and 240 mg (N=4). Source: NAL.001.TR01.PD

The TR01 study is summarized in the Investigator's Brochure Section 5.4.3.

Considering the potential similarity in the underlying postulated mechanism between uremic pruritus and PN, nalbuphine would also be expected to be therapeutic in PN patients. As such, Study TR01 in HD patients can be regarded as a proof of concept study for PN.

Based on the clinical evidence of nalbuphine to suppress itch in uremic pruritus, morphine induced pruritus, the substance P induced itch in a pre-clinical study, results and the mechanistic link between the opioid receptors and substance P with the pathophysiology of PN, a clinical investigation of efficacy of nalbuphine on itch in the PN population is justified.

3.2 NALBUPHINE

Nalbuphine HCl is currently available only as a generic medication in an injectable form. An injectable form of nalbuphine is a commercially available approved drug product in the United States since 1979 and originally marketed as Nubain®, on which the presently sold generic injectable formulations are based. It is currently approved for use in the United States for the relief of moderate to severe pain, a supplement to balanced anesthesia, for pre-operative and post-operative analgesia and obstetrical analgesia during labor and delivery. The European Union marketing experience with the injectable form of nalbuphine dates back to 1986 and this was recently reviewed (Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report 2010).

Nalbuphine is not a controlled drug in the United States. An oral dosage form of the drug is not commercially available. Nalbuphine HCl ER is an extended release oral tablet that is currently being developed for the treatment of pruritus.

Nalbuphine is a synthetic opioid with mixed μ antagonist/κ agonist opioid properties. Structurally, nalbuphine is a derivative of 14-hydroxymorphine and is related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone. Nalbuphine exerts its clinical pharmacologic action by competitively antagonizing the opioid μ-receptor while simultaneously acting as an agonist at the opioid κ-receptor (Gutstein 2001; Gharagozlou 2003 and 2006).

3.3 NALBUPHINE HCL ER TABLET CLINICAL DEVELOPMENT

3.3.1 Overall Summary

The safety, tolerability and pharmacokinetics of nalbuphine HCl ER tablets have been characterized following single and multiple ascending dose studies in healthy male and female human subjects, in a single dose study conducted in a dental pain patient population, a multi-dose study conducted in a patient population experiencing osteoarthritic related joint pain and in a multi-dose study conducted in both hemodialysis (HD) population experiencing uremic pruritus and healthy subjects. Studies were conducted with nalbuphine HCl ER tablets or oral solution following single dose administration from 30 mg up to 180 mg and multiple doses ranging between 30 mg BID and 180 mg BID in subjects with normal renal function (up to 3 weeks) and in the hemodialysis population in multiple doses ranging from 30 mg BID to 240 mg BID (up to 15 days).

In subchronic and chronic dose toxicology studies, the CNS was identified as the only target organ when unformulated (neat) nalbuphine was given to dogs at high doses. High systemic drug exposures in dogs caused CNS toxicity (tremors and convulsions) leading to deaths in some cases. It should be noted that the convulsions at high doses of nalbuphine in dogs were most likely Cmax-related. In toxicology studies in which dogs were given high doses of nalbuphine formulated with release-rate controlling excipients that blunt the Cmax, no CNS signs of toxicity were observed. Using the most conservative (lowest) margin of safety determined in all toxicity studies, a minimum 12.4-fold safety margin was calculated respectively for the mean plasma Cmax in subjects with normal renal function at the highest projected clinical dose of nalbuphine (180 mg BID) relative to the plasma Cmax at the lowest NOAEL in dogs given unformulated nalbuphine. Convulsions were not observed in any of the clinical trials conducted with nalbuphine HCl ER oral tablets in subjects with normal renal function at doses up to 180 mg BID (360 mg daily dose) or in HD patients at doses up to 240 mg BID (480 mg daily dose).

In the course of development, 355 subjects received at least one dose of oral nalbuphine HCl. The most frequently reported adverse events were primarily in the Central Nervous System (CNS) and Gastrointestinal (GI) organ system categories. All these side effects are known to occur with drugs with opioid pharmacologic properties. Most of the side effects noted in the study program were mild to moderate in severity. Initiating drug dosing in both HD patients and healthy subjects at the 30 mg BID dose resulted in good tolerability for subsequent titration related dose escalation.

No drug abuse issues were reported during any of the investigations. The incidence of opiate withdrawal effects noted at drug discontinuation in the patients was investigated in

the osteoarthritis pain treatment study when nalbuphine dosing was abruptly stopped following the end-of-study participation. There was an absence of any objective evidence of physical withdrawal symptoms in 85% of the patients and only mild evidence of physical withdrawal symptoms in the remainder of the patients.

3.3.2 Clinical Study TR01 in Hemodialysis Patients and Healthy Volunteers

Pruritus is a frequently identified sign and symptoms of uremia ("uremic pruritus") and is thus a common symptom in patients receiving hemodialysis (Pisoni et al 2006 and Narita et al 2006). Study TR01 was undertaken to assess the safety, PK, and the open label effects on pruritus intensity in hemodialysis subjects. PK and safety was compared to matched healthy control subjects.

Study TR01 was a single site, open label, non-randomized, parallel group, escalating dose study in hemodialysis patients with pruritus of at least mild intermittent intensity receiving intermittent hemodialysis three times a week compared to matched healthy control patients. All subjects were in house during the entire dosing period. Nalbuphine HCl ER tablets were administered orally for up to a 15 day period in HD subjects and 13 days in healthy subjects. Doses were sequentially escalated from 30 mg QD on Day 1 to 30mg BID then to 60 mg BID, 120 mg BID, 180 mg BID and 240 mg BID with dose escalation predicated on PK, safety, and tolerability of the preceding dose. HD subjects remained at each dose level for 2-3 days for a minimum of 4-5 consecutive doses. Healthy subjects remained at each dose level for 3-4 days for a minimum of 5 consecutive doses.

Study subjects were separated into 2 cohorts: Of the 15 HD subjects in enrolled into Cohort 1, 11 were assigned to dose escalate up to 180 mg BID and 4 were assigned to dose escalate up to 240 mg BID. 13 subjects (11 males and 2 females) completed the study. One male subject discontinued secondary to non-drug related disease progression diagnosis of pleural effusion at the 30 mg BID dose level and a female subject discontinued following a Grade 3 AE of vertigo at the 240 mg BID dose level. Cohort 2 were healthy subjects who were assigned to dose escalate up to 180 mg BID. Cohort 2 consisted of 8 healthy subjects (6 males and 2 female) who completed the study and one male subject who discontinued at the 120 mg BID dosing level with only Grade 1 intensity AEs. All study subjects were closely monitored for AEs throughout the study.

In healthy subjects, the dosing regimen resulted in mainly Grade 1 AEs and the dose escalation was tolerable in 8/9 subjects dosed. Of the nine healthy subjects enrolled, one subject withdrew from the study secondary to AE Grade 1 level gastrointestinal reflux, nausea/vomiting and vertigo symptoms at the 120 mg BD dosing level. The subject recovered from the AE following drug discontinuation. AEs that occurred in greater than two subjects were somnolence (N=2), headaches (N=2), flatulence (N=2) and constipation (N=3).

In the HD subjects, there were no deaths or drug-related serious AEs. There were no dose-limiting AEs reported as defined as two HD subjects experiencing a drug-related AE of Grade 3. A total of 72 AEs were reported in the 15 HD subjects of Cohort 1. The nervous and gastrointestinal organ systems had the highest incidence of AEs. The most frequently occurring AEs were nausea and somnolence. Of the 13 HD subjects who completed the study (10 HD patients assigned to dose up to 180 mg BID and 3 HD subjects assigned to

dose up to 240 mg BID), 12 subjects completed the trial per protocol and 1 subject completed the study but did not dose titrate beyond 120 mg BID.

With regard to the gastrointestinal organ system, of the 14 HD subjects who completed 13 days of dosing (1 subject at 120 mg BID and 13 subjects at 180 mg BID), 4/14 (29%) experienced no nausea during the study and 7/14 (50%) experienced Grade 1 intensity nausea that was self-limited and only occurred at the initiation dose of 30 mg. One subject (1/14, 7%) experienced Grade 2 nausea starting from the 60 mg BID through the 180 mg BID dose. Three subjects (3/14, 21%) only developed nausea at the 180 mg dose level.

With regard to the nervous system AEs, of the 14 HD subjects who completed the 13 days of dosing, 5/14 (36%) did not experience somnolence, 4/14 (29%) experienced somnolence that was self-limited and only occurred at the initiation dose of 30 mg. With regards to AE intensity, two subjects (2/14, 14%) experienced somnolence of Grade 2 intensity at dosing levels above 30 mg BID. Only one drug-related Grade 3 AE (vertigo) was reported in one subject at the 240 mg dose which resolved completely following drug termination. No clinically relevant findings in vital signs, blood pressure (BP), ECGs or physical examinations were noted during the study. Oxygen saturation was also monitored via pulse oximetry as a safety precaution. The oximetry readings were taken at regular intervals during the daytime and continuously monitored during the nighttime hours over the 15 days of drug dosing and up to a maximal dose of 240 mg BID.

In both the HD and healthy subjects, no clinically significant decrease in daytime readings were recorded in the oximetry readings except in the one male HD subject previously mentioned who discontinued from the study at the time of the development of a pleural effusion. There was no clinically significant decrease in the nocturnal oxygen saturation level below the pre-dosing baseline nocturnal oxygen saturation level in any HD subject.

The Investigator's Brochure and Section 5.4.4.4; Table 21 and Section 5.4.4.2.2; Table 17 summarizes the AE profile of the TR01 HD subjects and healthy subjects respectively.

During the course of TR01, the 15 HD subjects that were enrolled were on multiple concomitant medications. Common concomitant medications included heparin, vitamin D, aspirin, iron, hyperphosphatemia management with sevelamer, erythropoiesis-stimulating agent, secondary hyperparathyroidism management with cinacalcet, neuropathic pain management with gabapentin; antihypertensive medications such as amlodipine (calcium channel blocker), carvedilol (beta and alpha-1 blocker), metoprolol (beta blocker), lisinopril (ACE inhibitor); gastrointestinal medications: omeprazole, pantoprazole, ranitidine and renal vitamins and supplements. These medications seem to be commonly used by HD patients both in the US and the EU (Schmid et al 2010). There was no clinically significant difference in the adverse event profile observed based on concomitant medication use or obvious pharmacodynamic interaction over the course of the study.

Data on Itch Intensity was obtained in an unblinded fashion from the HD subjects enrolled in the open-label single arm Study TR01 using a 0 (none) to 10 cm (maximal possible intensity) itch Visual Analogue Scale (VAS) recording "worst itch" intensity. From a baseline mean daytime VAS of 4.4±2.3 cm and nighttime of 2.8±2. cm, the mean VAS decreased over a 13-day dosing period by -3.6±2.5 cm and by -1.8±2.1 cm, respectively.

Please see the Investigator's Brochure for more details on the TR01 study.

3.3.3 Additional Nalbuphine HCl ER Tablet Clinical Data

In addition to the subjects in the TR01 study, a total of 331 subjects have been exposed to nalbuphine HCl during the course of 8 previous clinical studies.

Four Phase 1 studies were early biopharmaceuticals studies conducted in healthy subjects mainly for formulation selection and as such they support the safety of the drug product. In addition, two Phase 1 studies were conducted with the current clinical formulations and each consisted of a single dose study assessing the safety, tolerability, and PK of the current tablet formulations in the 30 mg -180 mg range.

A safety and efficacy analgesic study was conducted in subjects with dental-pain following third molar extractions following a single dose (placebo or 60 mg or 120 mg). The subjects were otherwise healthy male and female subjects. The study also contained PK-PD analysis demonstrating an analgesic dose-response relationship, with clear differentiation between the nalbuphine dose groups and placebo group.

Oxygen saturation was monitored via pulse oximetry as a safety precaution during Phase 1 studies and in the single dose third molar extraction dental pain treatment study. All subjects who received the drug had oxygen saturation levels within the 90%-100% range during the studies.

A safety and efficacy analgesic study was conducted in a patient population experiencing osteoarthritic related joint pain using the current nalbuphine HCl ER 60 mg tablet. The population was demographically older with the mean age of 57 years and a range extending from age 40-70 years. Subjects were dosed continuously for up to 3 weeks starting at 60 mg BID up to a dose of 180 mg BID. Subjects who tolerated the initial dosing were titrated up in weekly increments of 60 mg BID to the maximal dose of 180 mg BID. The AEs that developed mainly had their onset at the initiation of dosing with no new type of AE developing in any statistically significant incidence during the course of dose escalation.

In both genders, the most frequently reported adverse events were primarily in the Central Nervous System and Gastrointestinal organ system categories. A higher incidence of AEs was noted in females during week one of dosing with the gender asymmetry in AE generation lessening as a function of time. This difference in AE incidence may be related to the tendency of females to have higher plasma levels than males (about 1.7 and 1.3 fold higher for Cmax and AUC, respectively). Nalbuphine total systemic clearance is reported to decrease with age leading to a higher absolute bioavailability (~ 44%) in elderly subjects (older than 65 years) relative to younger adults (11%) following oral administration (Jaillon, 1989).

In these eight clinical studies overall, the most frequently reported AEs in the single dose and multi-dose studies were CNS events, namely dizziness, headache, and somnolence. Gastrointestinal system AEs were mainly nausea and vomiting. Most of the AEs noted in the clinical study program were mild to moderate in severity.

In the case of single dose Phase 1 nalbuphine HCl ER tablet administration, there was a dose relationship to the incidence of AEs and there was minimal AEs observed at the 30 mg dose compared to initiating dosing at the higher doses. As a result, a titration to higher doses from a starting dose of 30 mg was selected for subsequent studies that also included TR01 in order to improve the tolerability of the drug.

Section 5 of the Investigator's Brochure summarizes the results of the clinical development program in detail.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To evaluate the safety and tolerability of nalbuphine HC1 ER tablets during a drug treatment period of up to 50 weeks.

4.2 SECONDARY OBJECTIVES

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

- To evaluate the safety of nalbuphine HCl ER by achieved maintenance dose at the end of Treatment Week 4
- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in Patient-Reported Outcome measures Worst (i.e., most severe itching over the past 24 hours) itch NRS, average itch intensity NRS, VRS (itchy, burning and stinging), MOS Sleep-R, ItchyQoL, HADS by the final Treatment Period Visit
- 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 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

4.3 EXPLORATORY OBJECTIVES

- The potential of nalbuphine HCl ER tablets to impact on the measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) and Histological (H&E) changes in skin biopsies taken Baseline and the final Treatment Period Visit to investigate possible correlation with any clinical response and also

compared to biopsy material assessed during study TR03 (optional procedure at select sites only).

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINT

- A description of the incidence and nature of TEAEs during Treatment Weeks 5-50

5.2 SECONDARY ENDPOINTS

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. Visit 1b will be the baseline for patients entering the Treatment Period after participating in the Observation Period for any length of time.

- Assess skin lesion improvement using the metrics of the PAS
- Change from Baseline in Patient-Reported Outcome 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 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.

5.3 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 Treatment Period Visit when compared to biopsy material assessed during study TR03 (optional procedure at select sites only).

6 NUMBER OF SITES AND PATIENTS

Up to 20 sites in the North America and Europe are planned to participate in this study. Eligible patients who have successfully completed the TR03 study and wish to participate in TR03ext may be enrolled, treated, and analyzed. The maximum number of patients will not exceed the number of patients who complete the TR03 study (i.e., approximately 60 patients).

7 ESTIMATED STUDY DURATION

The total study duration for any individual patient will be up to 53 weeks. Patients will receive drug treatment for up to 50 weeks, followed by a two week washout period.

8 SELECTION CRITERIA

8.1 STUDY POPULATION

Patients with prurigo nodularis who completed the TR03 study and have met all Inclusion and Exclusion criteria for TR03ext (see Section 8.2 and Section 8.3).

8.2 INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible:

1. Have been adequately informed of the nature and risks of the study and have given written informed consent at the conclusion of the TR03 Visit 6 and prior to Visit 1a.
2. Have completed participation in the TR03 study.

   Completion of participation in the TR03 study is defined as completion of Study Drug treatment through TR03 Visit 5 and completion of the TR03 Visit 6.

3. Agree to comply with the contraception requirements as below:

   Sexually active female patients of childbearing potential are required to use one barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to one other method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, Essure procedure, or spermicide).

   For the purpose of this study, all females are considered to be of childbearing potential unless they are post-menopausal (i.e., at least 1 year since last menses and age >50 years) or surgically sterile (i.e., tubal ligation, hysterectomy and/or bilateral oophorectomy).

   Female patients who are abstinent may participate in the study, however; they must be counseled on the requirement to use appropriate contraception should they become sexually active. This counseling should occur at each study visit and must be documented in source records.

4. Willing and able to comply with study requirements and restrictions.
5. Agree to the confidential use and storage of all data (including photography) and use of all anonymized data for publication including scientific publication.

8.3 EXCLUSION CRITERIA

If a patient meets any of the following criteria, he or she is *not* eligible:

1. Patients with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association scale (scale provided in Appendix 5)
2. Patients with a history of angina pectoris grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale (scale provided in Appendix 5)
3. History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the patient.
4. Serum potassium below the laboratory lower limit of normality at the TR03 Visit 5. Note: Potassium levels below the laboratory lower limit of normal at Visit 6/Visit 1a should be repeated and potassium supplementation provided as appropriate.
5. QTcF interval >450ms on screening/Visit 1a ECG
6. Heart rate <50 BPM on any screening assessment. Patients with a resting heart rate of <50 bpm will have it repeated once after 5 minutes in the supine position, and if it remains <50 bpm during the repeat, they will be considered a screen failure
7. Use of a medication known to be associated with risk of torsade de pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes)
8. History of substance abuse within the past year as determined by the Investigator
9. Significant medical condition or other factors that in the opinion of the Investigator may interfere with the conduct of the study
10. Known hypersensitivity or allergy to nalbuphine or formulation components
11. Is a pregnant or lactating female.

9 STUDY PLAN

9.1 GENERAL STUDY DESIGN

This is an open label extension study for patients who have completed the TR03 study.

9.2 RATIONALE FOR STUDY DESIGN

The primary objective of this TR03ext study is to evaluate the safety of nalbuphine HCl ER tablets in patients with prurigo nodularis for up to 50 weeks on drug, followed by a two week washout period for a total of up to 53 weeks of study duration. The open label design allows all patients, who have completed the parent study TR03, an opportunity to receive active treatment for the assessment of the safety of nalbuphine HCl ER tablets over a longer term and to follow the effect of skin lesion healing in addition to reducing itch. A maximum of 50 weeks on study drug was chosen as a reasonable time frame that would add substantially to the understanding of chronic use of nalbuphine HCl ER tablets chronic use in prurigo nodularis.

Metze et al (1999) reported that 9 out of 17 patients with PN who were treated with the mu antagonist medication naltrexone reported a decrease in pruritus intensity of at least 50%. Reduced scratching as well as skin lesion healing was reported over a time period of up to 20 months on drug. Based on these clinical observations, TR03ext was designed to be of sufficient duration to observe potential anti-pruritic suppressive effects of study drug on scratching behavior and thus potentially skin lesion healing. Furthermore, the TR03ext study design anticipates potential sustained anti-pruritic effect that may outlast the actual dosing of study drug in TR03. Thus an Observation Period has been incorporated to follow patients whose Worst Itch NRS has been significantly reduced for up to 12 weeks in order to measure the durability of the anti-pruritic effect and to allow patients to receive study drug if pruritus intensity increases within the 12 week time period.

This study will also allow evaluation of a titration algorithm that mimics the manner in which opioid medications are often used in clinical practice (i.e., stepwise titration) to a tolerable dose with an improvement in worst itch intensity. To facilitate evaluation by achieved dose, the dose to which the patient has been titrated at the end of Treatment Week 4 will be maintained through Study Week 50, with the exception of two allowable down-titrations (See Table 3 for dosing schedule). Patients who require a third down-titration after Treatment Week 4 must be discontinued from the study.

Patients can enroll into TR03ext and receive drug as early as approximately 2 weeks following their last dose of study drug in the parent study TR03. Approximately one-third of patients are expected to enter the study after having received placebo in TR03. These patients are expected to have a high level of pruritus intensity. On the other hand, some patients who have received active treatment in TR03 may still have either reverted to their original pruritic conditions or may have a residual anti-pruritic effects from the drug treatment even following the 2-week wash out period. To allow for various starting levels of pruritus intensity, patients who have 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 $\geq$ **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 BID during the first 4 weeks of the Treatment Period (See Table 3 for dosing schedule). 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. While patients remain in the Observation Period, they will not be considered as enrolled into the study, but as participating in an extended screening process until they are eligible for treatment.

Patients, who fail to improve, as defined by the failure-to-improve criteria, will be taken off study drug treatment. A failure-to-improve criteria is implemented beginning on TV 3 and at every subsequent Treatment Visit, and is described in Section 11.1. The rationale for the failure-to-improve criteria is based on the following: Following a maximal titration period of up to 3-weeks, an approximate 2-week window on stable drug dose should be sufficient for the drug to start eliciting a beneficial effect. The patient's self-reporting of pruritus intensity at each visit, beginning at TV 3, will be compared to the baseline value of the

patient's pruritus intensity upon entry to TR03ext. The premise of the failure-to-improve criteria is that patients will not be allowed to continue to receive study drug for an extended period of time if there is no demonstration of diminishment in pruritus intensity. Patients discontinued from treatment are to participate in the Washout and Safety Follow-up Period, unless consent is withdrawn. These patients will also receive a Telephone Contact 30 days (+2 weeks) post the completion of study drug to collect safety information related to previous drug exposure.

In the parent study, TR03, the two target doses (90 mg and 180 mg) of nalbuphine HCl ER are both within the dose range that was well tolerated in HD subjects and healthy volunteers subjects from study TR01 (30 mg to 240 mg BID for up to 15 days). Additionally, data from TR01 suggested a decrease in itching intensity in this dose range. Further, the safety profile of nalbuphine following injection is well documented. Injectable nalbuphine has been commercially available in the United States since 1979 and there has been marketing experience within the European Union dating back to 1986 (See Nalbuphine -Medicines Evaluation Board in the Netherlands Public Assessment Report (2010) for a recent review).

In order to facilitate analysis of the clinical safety data and efficacy data, patients in the present study will begin titration at the 30 mg QD dose and titrate to only a maintenance dose ranging between 30 mg BID and 180 mg BID. The 30 mg BID and 60 mg BID doses are believed to be only marginally effective doses based on available TR01 data. However there is a two time dose reduction permitted for all patients during Treatment Weeks 5-50 (see Table 3) to the next lower allowed dose (e.g., a patient at the 90 mg BID maintenance dose will be permitted a dose reduction to 60 mg BID or subsequently to 30 mg BID and then be maintained at that dose level for the remainder of the study).

The study population being evaluated is an intended target population for oral nalbuphine HCl ER tablets: prurigo nodularis patients.

Patients will be closely monitored for safety. All patients will be seen at the Investigator site (See Schedule of Events in Appendix 1). Adverse events and vital signs will be recorded. Additionally, 12-lead ECGs (locally and centrally read), physical examinations, and clinical laboratory testing will be conducted to monitor safety on patients receiving study drug. Safety monitoring will be done to address the primary objective of evaluating the longer term safety of study drug exposure. The primary endpoint is a description of adverse events during up to 50-weeks of treatment with nalbuphine HCl ER tablets. An important secondary endpoint objective of the study is to use recorded PAS metrics to assess the study drug anti-pruritic suppression of the scratching behavior of the patient and impact on skin lesion improvement. Changes in patient-reported outcome measures will be explored to include: Worst itch NRS, Average itch intensity NRS, VRS (itchy, burning and stinging), ItchyQoL, MOS Sleep-R, HADS and PBI-P.

9.3 SAFETY MONITORING PLAN

Patients will be closely monitored for safety. Adverse events will be continuously evaluated throughout the study (and in particular AEs of special interest: nausea, vomiting, constipation, somnolence, sedation, dizziness, and vertigo) and vital signs, locally and

central cardiac core laboratory read 12-lead ECGs, physical examinations, and clinical laboratory testing will be conducted to monitor patient safety.

An independent Data Safety Monitoring Board (DSMB) will periodically review safety data during the time period that the blinded part of the nalbuphine HCl program remains ongoing. The frequency of data review and DSMB processes are outlined in the DSMB charter.

Patients with apparent failure-to-improve to a stable dose of study drug will be taken off study drug.

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. The SOWS is a self-administered scale for grading opioid withdrawal symptoms. If the patient is experiencing any symptoms on the SOW scale to a moderate degree, they will be instructed to contact the site. If a patient is determined to be experiencing significant subjective withdrawal symptoms (at the Investigator's discretion), they will be offered treatment.

As summarized in Section 6.2.7 of the Investigator's Brochure, the CNS has been identified as the only target organ when nalbuphine was given to animals at high doses. In addition, the most frequently reported adverse events reported in the nalbuphine HCl ER tablet dosing studies were primarily in the nervous system and gastrointestinal organ system categories.

To mitigate opioid-related side effects, nalbuphine will be titrated over 4 weeks based on tolerability to a dose that is between 30 mg BID to 180 mg BID (see Table 3). Titration is a clinical management strategy consistent with dosing of opioids in general (Jovey 2003). The titration regimen planned in this study is similar to the regimen used in study TR01, in which doses in the planned range were well tolerated (Section 3.3.2) except up-titration is not a forced titration. This will provide flexibility for each patient to assess tolerability. In this study, the combination of a low starting dosing (30 mg on the first day) followed by a relatively slow titration (dose escalation after a minimum of six consecutive doses over approximately 3 days) is expected to minimize treatment-limiting opioid adverse effects. See Table 3 for the drug titration scheme. The time interval between dose escalations is consistent with the "three day tolerance check" suggested by the National Opioid Use Guideline Group of Canada (2010) for outpatient clinical practice management of opioid drug titration as part of monitoring patient side effects.

Nalbuphine has μ-opioid antagonist pharmacological properties. To minimize the possibility of acute opiate withdrawal occurring at drug initiation in a physically dependent subject, patients receiving daily doses of opiates are excluded from the study. Patients who require ongoing non-daily opiates concurrently with nalbuphine should be monitored carefully for additive opiate effects. If patients develop a new need for daily opiates during the study, the Investigator is required to contact the Medical Monitor to discuss the specifics of the situation.

It is known from prior studies, that gastrointestinal opioid-like adverse effects (e.g., nausea, vomiting, and constipation) occur early and can be treatment-limiting. In anticipation of the possible occurrence of these effects, pre-medications for nausea will be permitted and Investigators will be advised to use pharmacologic or non-pharmacologic means to avoid

constipation as clinically indicated. In anticipation of the possible occurrence of central nervous system (CNS) AEs such as somnolence, patients will be instructed to be aware of possible CNS AEs that may occur. The evening doses during the Titration Period should be taken at home. The first dose of any new titration step will occur with an evening dose (see Table 3). In order to monitor any potential CNS related side effects, a brief neurological assessment will be conducted at each study visit as well as a focused neurological medical history will be obtained at enrollment.

Patients will be additionally instructed that if any significant CNS AEs occur, they are to avoid activities such as driving and operation of dangerous machinery until the effect of the Study Drug can be assessed by the Investigator. Additionally, concomitant use of daily opioids during the course of the study, other than for short-term use, can be undertaken with the approval of the Medical Monitor. Overdoses or opioid-related significant central nervous system adverse effects may be reversed with opioid antagonists if clinically indicated.

Although psychological dependence or abuse can develop to opioid drugs when chronically administered, the risk for psychological dependence or abuse in this study is judged to be low based on previous clinical studies with nalbuphine HCl ER oral tablets. To date, there have been no reported cases of psychological dependence or abuse reported following dosing for 3 weeks up to 180 mg BID and dosing for 15 days up to 240 mg BID. See the Investigator's Brochure for details. Nevertheless, the nalbuphine HCl injection package insert for the product sold in the United States states that "*individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk for the development of drug abuse and dependence"*.

9.4 RISK-BENEFITS

The selected dose range for study in TR03ext of 30 mg BID to 180 mg BID were chosen given the safety profile summarized in Section 3.3.2 and discussed further in Section 9.2 as well as detailed in the Investigator's Brochure. As summarized in, Section 3.1.3.3, open label data from the TR01 study showed that pruritus suppression in the HD patients was noted with drug administration within the dose range that is planned for the current study.

Data obtained from a previous study in osteoarthritis patients dosed up to 180 mg BID with nalbuphine HCl ER tablets showed that objective opioid withdrawal symptoms at the termination of 3 weeks of therapy were absent or mild in degree (See the Investigator's Brochure Section 5.4.4.5 for details).

It should be noted that the commercially available nalbuphine HCl for Injection product in the United States (Nalbuphine HCl package insert) has a usual recommended dose of 10 mg for a 70 kg adult, administered subcutaneously, intramuscularly, or intravenously, which may be repeated every 3 to 6 hours as necessary (i.e., up to a daily dose of 40-80 mg IV); and, in non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg. Exposure following IV administration is approximately 6-fold higher than following oral administration (estimated oral bioavailability of nalbuphine HCl = 16%). Therefore, a 10-mg, 20-mg, or 160-mg IV dose would correspond to approximately 60 mg, 120 mg, and 960 mg oral nalbuphine, respectively. The highest dose proposed in the TR03 study is 180 mg BID (360 mg daily

dose), and this oral dose is well below the highest recommended daily treatment of 160 mg IV (equivalent to 960 mg oral) for the current marketed product.

The risk for patients participating in the study is judged to be low based on previous experience with nalbuphine oral tablets. In addition, in the current study, there will be a low initiation dose of 30 mg, a slow dose titration rate, and careful safety monitoring of patients during the clinical study.

There is no approved therapy for prurigo nodularis related pruritus in the United States or Europe. Should nalbuphine prove effective, patients with prurigo nodularis could potentially see benefit.

9.5 STUDY OVERVIEW

This is an open label safety and tolerability extension study for patients who have completed study TR03. Patients will either enter directly into the drug Treatment Period (Worst Itch NRS greater than or equal to 5 (≥ 5)) or enter an extended screening period of a no-drug Observation Period (Worst Itch NRS less than 5 (<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 greater than or equal to 5 (≥ 5).

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. For 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 12 extended screening weeks, patients not eligible for the Treatment Period are screen failed from the study. The study periods are summarized below in Table 2.

Table 2: TR03ext Study Periods

Study Period	Study Weeks	Duration
Observation Period	Patients who do not meet the criteria to start Treatment are followed in Observation Period visits 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 patient 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; Table 8 calculates the Treatment Visit assignments for any patient entering the Treatment Period from the respective Observation Period visits. 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 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 patients 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

9.6 STUDY PROCEDURES

Before the initiation of study-specific procedures the patient must be given a complete explanation of the purpose of the study, evaluations to be conducted, and risks/benefits for study participation. Patients must understand the requirements of the study, provide informed consent (See Section 9.6.1 and Section 20.3), agree to the study restrictions, and agree to return for the required assessments. After review of the informed consent is documented, the patient must give written consent. For this study, patients will retain their study number from study TR03.

With the exception of Visits 1a and 1b, windows for all visits will be +/-3 Days. Please see the Schedule of Events in Appendix 1 for details of the Titration Period assessments and the Study Schematics Flow Charts in Appendix 2. See Section 9.7.1 for details of Study Drug Dosing and Section 9.7.6.4 for information on the use of pre-medications with the Study Drug. Visit 6 of TR03 will serve as TR03ext Visit 1a unless these visits do not occur on the same calendar day.

Visit 1a has procedures to be done as summarized in Section 9.6.1 regardless of the patient's pruritus intensity score. Following a set of common procedures, only patients who qualify for the Treatment Period based on meeting the pruritus intensity criteria will be eligible to receive study drug; Visit 1a corresponds to TV1. For patients who, during the final visit of TR03, did not meet the pruritus intensity criteria to enter the TR03ext Treatment Period, Visit 1a corresponds to OV1, the first visit of the Observation Period. If during a subsequent observation period visit to the site, the patient meets the pruritus intensity criteria, then that observation visit immediately transitions into Visit 1b (it also corresponds to TV1 since it is now the first Treatment Period visit) – See Section 9.6.3.3 and Section 9.6.4.

For patients who transition to the Treatment Period from the Observation Period, Table 8 provides details on the treatment visit schedule based on the study week that the patient transitioned from the Observation Period to the Treatment Period. The patient will follow the Treatment Visit schedule outlined on the Schedule of Events (Appendix 1).

For clarity,

Patients with a Worst Itch NRS greater than 5 (≥ 5) enter the Treatment Period and will receive Study Drug starting with an evening 30 mg dose (to be taken at home), after the Visit 1a (or Visit 1b) procedures have been completed.

Receipt of the first dose of study drug will define Day 1. Visit 1a or Visit 1b for these patients is also Treatment Visit 1 (TV1). Subsequent visits will be defined as TV2, TV3, etc.

Patients with a Worst Itch NRS less than 5 (<5) enter the Observation Period and will not receive study drug treatment. Visit 1a for these patients is also Observational Visit 1 (OV1). Subsequent visits will be defined as OV2, OV3, etc.

Patients in the observation period can be followed for up to 12 weeks.

If during the Observation Period, a patient's Worst Itch NRS increases to greater than or equal to 5 (≥ 5) and the patient meets all other eligibility criteria**,** Visit 1b procedures are to be performed. The patient's next visit will be Treatment Visit 2 (TV2). Do not repeat the Worst Itch NRS during Visit 1b.

If, however, at Observation Visit 12 the patient does not have a Worst Itch NRS greater than or equal to 5 (≥ 5), the patient will be screen failed without having initiated treatment with nalbuphine.

Figure 2, Figure 3 and Figure 4 visually display the relationship between TR03ext study weeks, Treatment Period weeks and Observation Period weeks.

9.6.1 Visit 1a (Day 1 of Study Week 1)

See Table 4 for summary of Visit 1a procedures. See Section 20.3 regarding the informed consent process that must take place prior to any study procedures.

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To the extent possible, the TR03 Visit 6 and Visit 1a should be performed on the same calendar day. In cases where this is not possible, the Investigator must contact the Medical Monitor prior to conducting Visit 1a to discuss which procedures are required to be repeated at the visit. All patients must complete Visit 1a within 30 days of their last dose of TR03 study drug in order to be eligible for study participation.

Study TR03 Visit 6 procedures in common with Study TR03 extension Visit 1a procedures do not have to be repeated unless the two visits do not occur on the same calendar day. The following procedures will be performed:

- obtain informed consent
- confirm eligibility
- obtain vital signs
- conduct a physical examination
- conduct a neurological exam
- collect central laboratory samples (hematology and chemistry)
- collect serum pregnancy sample in women of childbearing potential (regardless of sexual activity) and send for processing at the central laboratory*
- collect urine for central lab urinalysis
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative results prior to dispensing study drug*

  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
    - instruct the patient to immediately discontinue taking study drug
    - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See Section 17.5.2.1 regarding how pregnancies are to be handled in this study.

- obtain blood for PK
- perform skin biopsy (optional procedure at select sites only). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins; also collect the TR03 rescue medication log
- retrieve any remaining study drug from the parent study TR03
- administer the Worst itch NRS (paper version) and **review score for eligibility to either enter the Treatment Period or to continue in screening under the Observation Period**

    a) If the Worst Itch NRS score is < 5, start the Observation Period. Do NOT initiate study drug treatment at this visit

    b) If Worst Itch NRS score is ≥ 5, confirm eligibility and start the Treatment Period (see below, 'For patients qualifying for drug Treatment Period only').

  The Worst Itch NRS (paper version) must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)

For patients qualifying for the drug Treatment Period only (Visit 1a is also study visit TV1):

- complete PAS
- administer PRO measurements (paper versions):
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS
    - PBI-P

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual)
- perform skin biopsy (optional procedure at select sites only). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- dispense enough Study Drug to the patient for required dosing until their return at Treatment Visit 2, TV2
- dispense the Dosing Diary and instruct the patient on how to complete it
- dispense the TR03ext Rescue Medication Log and instruct the patient on how to complete it

- instruct patients to self-administer the first dose on the evening of Visit 1a at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- instruct the patient to take the Study Drug twice daily at approximately the same times of day. All patients should be instructed to titrate to their most tolerated dose. See Table 3 Drug Dosing Schedule for more information. Here is the recommended Week 1 titration schedule for patients who tolerate study drug:

  Day 1 (the first day that the patient receives a study drug dose): No dose in the AM and 30 mg in the PM
  Day 2: No dose in the AM and 30 mg in the PM
  Day 3: 30 mg in the AM and 30 mg in the PM
  Day 4: 30 mg in the AM and 30 mg in the PM
  Day 5: 30 mg in the AM and 60 mg in the PM
  Day 6: 60 mg in the AM and 60 mg in the PM
  Day 7: 60 mg in the AM and 60 mg in the PM
- instruct patients to bring all remaining Study Drug to the Investigator site for each study visit
- If a patient misses 3 or more consecutive doses, contact the Medical Monitor.

For patients starting the Treatment Period, the next visit will be TV2, Treatment Week 3.

For patients <u>not</u> qualifying for the drug Treatment Period only (Visit 1a is also study visit OV1), the patient will enter the Observation Period and the next visit will be OV2, Extending Screening Week 4. See Section 9.6.3, Observation Period (Extended Screening Weeks 1-12).

9.6.2 Treatment Period (Treatment Weeks 1-50)

Patients who enter the Treatment Period on Visit 1a will be in the Treatment Period for up to 50 weeks and thus are eligible to receive study drug for up to 50 weeks.

Patients entering the Treatment Period after being followed in the Observation Period will have a variable number of weeks on treatment depending on how many weeks they were in the Observation Period. The total amount of time spent in the combined two periods of the study (Observation and Treatment) cannot exceed 50 weeks. The maximum number of weeks that a patient entering the Treatment Period from the Observation Period will be on study drug (Treatment Period) is 46 weeks. Patients enter the Treatment Period from an Observation Visit (OV) when their Worst itch NRS is greater than or equal to 5 (≥ 5).

Regardless of how many treatment weeks the patient was on study drug, <u>all</u> patients who enter the Treatment Period will complete End of Treatment Visit TV14 (unless consent is withdrawn). Since all patients must titrate to their maintenance dose over the first four weeks of the Treatment Period, Visits 1a/Visits 1b (TV 1) and TV 2 over the first four weeks of the Treatment Period will be common to all patients in TR03ext regardless of when they enter into the Treatment Period. Patients who transition from the Observation

Period to the Treatment Period at a respective Observation Visit will follow the Treatment Visit schedule outlined in Table 8.

9.6.2.1 *Treatment Period Weeks 2-4 (Titration Phase of Study Drug)*

The first week in the Titration phase is initiated as part of Visit 1a/1b (Day 1 Treatment Week 1, see Section 9.6.1 and Section 9.6.4). Subsequently, the following events TC1, TV2 and TC2 will be conducted during the remainder of the titration phase. See Table 5 for the Schedule of Events during the titration phase.

9.6.2.1.1 Telephone Contact Number 1 (TC1, Treatment Week 2)

The patient is to be contacted by phone and the following are to take place:

- record AEs
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- confirm that patient has titrated drug in accordance with the dosing schedule on Table 3
- document tolerability/intolerability to study drug and decision to continue dose titration/maintenance following the dosing schedule of Table 3
- discontinue study medication in patients who do not tolerate 30 mg BID dose and complete the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.1.2 TV 2 (Treatment Week 3)

The following procedures are to take place at this visit:

- complete PAS
- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity and confirm negative status prior to dispensing additional study drug
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements (paper versions):
  - Worst itch NRS
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS.

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs (including tolerability to study drug)
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study related procedures (i.e. rescue medication log, dosing diary, etc.)
- perform Study Drug accountability, retrieve previously dispensed Study Drug
- dispense enough Study Drug to the patient for required dosing until their return at TV3 (Treatment Week 5)
- document tolerability/intolerability to study drug and titration decision based on Table 3
- discontinue study medication in patients who do not tolerate 30 mg BID dose and complete the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.1.3 Telephone Contact Number 2 (TC2, Treatment Week 4)

The patient is to be contacted by phone and the following are to take place:

- record AEs
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- instruct the patient on dose titration/maintenance based on Table 3
- patients reporting intolerable side effects at their current dose should titrate down to a tolerable preceding dose and this should be record as the patient's maintenance dose
- patients at any dose who reported intolerable AEs for the previous week (Week 3 on drug) and continue to report intolerable AEs on this visit, should be discontinued from study drug and scheduled for the End of Treatment Visit, TV14 (See Section 9.6.2.2.12 and Section 11)

9.6.2.2 *Treatment Period Weeks 5-50*

During this period of the study, the patient continues on the maintenance dose established by the end of Treatment Week 4 for the remainder of the study with the exception of two allowable dose reductions permitted during Treatment Weeks 5 – 50 (e.g., a patient at 90 mg BID can be reduced to 60 mg BID and then subsequently to 30 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study (See Table 3, Section 9.6.2.2.12 and Section 11). Patients who are on the 30 mg BID dose will be discontinued if a dose reduction is required.

See Table 6 for the Schedule of Events for Treatment Weeks 5-50.

9.6.2.2.1 TV 3 (Treatment Week 5)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve criteria, perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and record patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.2 TV 4 (Treatment Week 9)

The following procedures are to take place at this visit:

- complete PAS

- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed Study Drug
- dispense enough study drug for required dosing until the patient returns for their next Treatment Visit

9.6.2.2.3 TV 5 (Treatment Week 13)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication

- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements:
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.4 TV 6 (Treatment Week 17)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.5 TV 7 (Treatment Week 21)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version)and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs

- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)
- collect blood for PK
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- administer PRO measurements (paper versions):
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability,
- retrieve previously dispensed Study Drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.6 TV 8 (Treatment Week 26)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- perform physical examination
- perform brief neurological assessment
- complete the PAS

- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)
- collect urine for urinalysis for central lab
- collect blood for central laboratory (hematology and chemistry) and for PK
- administer PRO measurements (paper versions):
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.7 TV 9 (Treatment Week 30)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DID NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)

- collect blood for PK
- perform brief neurological assessment
- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.8 TV 10 (Treatment Week 34)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)
- collect blood for PK

- perform brief neurological assessment
- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce compliance for dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.9 TV 11 (Treatment Week 38)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug
- collect blood for PK
- perform brief neurological assessment

- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.10 TV 12 (Treatment Week 42)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual status) and confirm negative status prior to dispensing study drug
- collect blood for PK
- perform brief neurological assessment

- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.11 TV 13 (Treatment Week 46)

The following procedures are to take place at this visit:

- complete PAS
- administer the Worst Itch NRS (paper version) and evaluate against the Failure-to-Improve criteria (see Section 11.1)

For patients who MEET the Failure-to Improve criteria:

- Stop study medication
- Perform End of Treatment Visit (TV14) procedures

For patients who DO NOT meet Failure-to-Improve perform the following procedures:

- obtain vital signs
- collect urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing additional study drug)
- collect blood for PK
- perform brief neurological assessment

- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- reinforce and document patient's compliance with dosing and all other required study procedures (i.e. rescue medication log, dosing diary, etc.)
- perform study drug accountability, retrieve previously dispensed study drug
- dispense enough study drug to the patient for required dosing until their next Treatment Visit

9.6.2.2.12 TV 14 (End of Treatment Visit)

This visit applies to all patients who completed TV13; including patients who met Failure-to-Improve criteria at any Treatment Visit during the study (unless consent is withdrawn).

For patients who DID NOT meet Failure-to-Improve criteria during the conduct of the study, this visit (TV14) takes place after the patient has completed dosing with study medication.

- For patients who entered the Treatment Period at Visit 1a, TV14 will take place during week 51; four (4) weeks after TV13, as these patients should complete 50 weeks of treatment prior to TV14
- For patients who entered the Treatment Period at Visit 1b see Table 8 for information on when TV14 is to take place

The following procedures are to take place at this visit:

- complete PAS
- obtain vital signs
- perform physical examination
- perform brief neurological assessment
- complete the PAS

- perform 12-lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test (regardless of sexual activity) for central laboratory
- collect urine for urinalysis at the central laboratory
- collect blood for PK
- perform skin biopsy (optional procedure at select sites only). Obtain 3 samples (i.e., H&E, nerve fiber density (histology) and MOR/KOR density (histology, Western Blot)); see the Lab and Study Reference Manuals for details
- administer PRO measurements (paper versions):
    - Worst itch NRS
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS
    - SOWS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any previously dispensed study drug
- retrieve the Dosing Diary
- Dispense the 14 Day SOWS packet, instruct the patient on how to complete the scales and to complete the scales daily for 14 days
- Schedule the patient for the Washout and Safety Follow-up Period Visit

9.6.3 Observation Period (Extended Screening Weeks 1-12)

Only patients with Visit 1a Worst itch NRS score of less than 5 (<5) should enter the Observation Period (Visit 1a for these patients is considered OV1), which includes subsequent study visits OV 2-4 at approximately one month intervals over the next 12 extended screening weeks (See Table 7). While patients remain in the Observation Period, they will not be considered enrolled into the study, but as participating in an extended screening process until they are eligible for enrollment. Patients evaluated at OV 2-4 and who record Worst itch NRS greater than or equal to 5 (≥ 5), and are otherwise eligible, can immediately begin Visit 1b and transition into the Treatment Period.

For these patients, the sum of time in the Observation Period and Treatment Period will not exceed 50 weeks. As a result, both the Observation Period and Treatment Period will differ in length for different patients. To ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug up to the

assessment of TV 2 during Treatment Week 3, and that the final Treatment Period visit is always TV14, see Table 8 for visit details. As such, visits during this period are not equivalent to Treatment Weeks. During the Observation Period, patients are participating in Extended Screening Weeks.

9.6.3.1 *Observation Visit 2 at Extended Screening Week 4 and Observation Visit 3 at Extended Screening Week 8*

The following procedures are to take place at this visit:

- administer the Worst itch NRS (paper version)
    - If the Worst Itch NRS is less than 5 (<5), perform the following Observation Visit procedures at any time during the visit
        - obtain vital signs
        - record AEs
        - record concomitant medications
    - If the Worst Itch NRS is greater than or equal to 5 (≥5), transition the patient to the Treatment Period and conduct Visit 1b procedures (described in Section 9.6.4) on the same day as this visit. See Table 8 for a summary related to future Treatment Period Visits.

9.6.3.2 *Observation Visit 4 at Extended Screening Week 12*

The following procedures are to take place at this visit:

- administer the Worst itch NRS (paper version)
    - If Worst Itch NRS is less than 5 (<5), perform the following Observation Visit procedures at any time during the visit
        - obtain vital signs
        - administer the PRO measurements (paper versions):
            - Average itch intensity NRS
            - VRS
            - ItchyQoL
            - MOS Sleep-R
            - HADS
        - record AEs
        - record concomitant medications
    - If the Worst Itch NRS is greater than or equal to 5 (≥5), transition the patient to the Treatment Period and conduct Visit 1b procedures (described in Section 9.6.4) on the same day as this visit. See Table 8 for a summary related to future Treatment Period Visits.

Patients whose Worst Itch NRS is less than 5 (<5) at the OV4 should be screen failed from the study. No Washout/Safety follow-up visit is to take place.

9.6.3.3 *Transitioning from the Observation Period to the Treatment Period*

- For patients who have a Worst NRS score that is greater than or equal to 5 (≥5) at Observation Visit 2, 3, or 4, complete Visit 1b procedures (see Section 9.6.4).
- These patients will receive up to 46 weeks of study medication treatment.
- See Table 8 for the Treatment Period Visits to be completed post Visit 1b, as well as the number of weeks of study drug to dispense at each Treatment Visit and when to schedule the End of Treatment Visit 14 (TV14) to take place.
- See Section 9.6.2 and the Schedule of Events (Appendix 1) for procedures to be performed at each applicable Treatment Visit.

9.6.4 Transition to Treatment Period (Visit 1b)

Confirm each patient's eligibility (see Sections 8.2 and 8.3) prior to performing any Visit 1b procedures. If the patient does not meet eligibility requirements, do not perform any Visit 1b procedures; the patient is to be screen failed.

See Table 4 for summary of Visit 1b procedures.

Patients evaluated at OV 2-4 who record a Worst itch NRS greater than or equal to 5 (≥ 5) and, are otherwise eligible, can immediately begin Visit 1b and transition into the Treatment Period. The following procedures are to take place at this visit:

- obtain vital signs
- conduct a physical examination
- collect central laboratory samples (hematology and chemistry)
- collect serum pregnancy test sample in women of childbearing potential (regardless of sexual activity) and send for processing at the central laboratory*
- collect urine for central lab urinalysis
- urine for pregnancy test (regardless of sexual activity) and confirm negative status prior to dispensing study drug*

  * If the urine pregnancy test result is negative and the serum pregnancy test result is positive, the patient is to be contacted and the following actions are to take place:
    - instruct the patient to immediately discontinue taking study drug
    - schedule the patient for an unscheduled visit to collect another serum pregnancy test

  The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment. See Section 17.5.2.1 regarding how pregnancies are to be handled in this study.
- obtain blood for PK
- Perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- administer PRO measurements (paper versions):
  - Average itch intensity NRS

- VRS
- ItchyQoL
- MOS Sleep-R
- HADS
- PBI-P

The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).

- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- complete the PAS
- dispense enough Study Drug to the patient for required dosing until their return at Treatment Visit 2 (TV2)
- instruct patients to self-administer the first dose on the evening of Visit 1b at home
- instruct patients to notify the Investigator if any significant CNS AEs occur, and not to drive or operate dangerous machinery until the effect of the Study Drug can be assessed by the Investigator, see Section 9.3
- all patients should be instructed to titrate to their most tolerated dose. See Table 3 Drug Dosing Schedule for more information. Here is the recommended Week 1 titration schedule for patients who tolerate study drug:

  Day 1(the first day that study drug is dispensed to a patient on treatment): No dose in the AM and 30 mg in the PM
  Day 2: No dose in the AM and 30 mg in the PM
  Day 3: 30 mg in the AM and 30 mg in the PM
  Day 4: 30 mg in the AM and 30 mg in the PM
  Day 5: 30 mg in the AM and 60 mg in the PM
  Day 6: 60 mg in the AM and 60 mg in the PM
  Day 7: 60 mg in the AM and 60 mg in the PM

- Instruct patients to bring all remaining Study Drug to the dialysis unit for each subsequent treatment period study visits.
- If a patient misses 3 or more consecutive doses, contact the Medical Monitor.

The next study visit will be Treatment Visit 2 (TV2). However, to ensure that the total number of study weeks does not exceed 50 weeks, that all patients complete proper titration of study drug, and that the End of Treatment Visit is always TV14, see Table 8 for more information.

The next visit will be Treatment Visit 2 (Section 9.6.2.1.2). See Appendix 1, Schedule of Event and Table 8 for the Treatment Visit Schedule for Patients Entering Treatment via Visit 1b.

9.6.5 Washout and Safety Follow-Up Period

All patients who received Treatment, but did not withdraw consent, will have a 2-week Washout and Safety Follow-Up Period following TV14. During this visit, the PRO questionnaires (paper versions) must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual). Please see the Schedule of Events in Appendix 1 for details of the Washout and Safety Follow-Up Period assessments. Additional information for this visit is provided below.

For patients who entered the Treatment Period at Visit 1a, the Washout and Safety Follow-Up Period Visit would take place during week 53, post TV14. However, for a patient who enters the Treatment Period at Visit 1b, the Washout and Safety Follow-up Period Visit will take place 14 days (plus the visit window) post TV14.

For patients who met Failure-to-Improve criteria or who discontinue treatment for other reasons (see Section 11.1), this visit is to take place 14 days (+ 7 days) after TV14.

The following procedures are to take place at this visit:

- obtain vital signs
- perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- perform brief neurological assessment
- collect blood for central laboratory measurements and PK
- administer PRO measurements (paper versions):
    - Worst itch NRS
    - Average itch intensity NRS
    - VRS
    - ItchyQoL
    - MOS Sleep-R
    - HADS

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- AEs and concomitant medications (including rescue medications) will be recorded
- collect the Rescue Medication Log from the patient at this visit
- retrieve any remaining study drug not previously returned by the patient
- retrieve the 14 day SOWS packet

For patients who prematurely discontinued study medication for reasons other than withdrawal of consent, schedule the Premature Discontinuation of Study Drug Follow-up Telephone Contact visit.

9.6.6 Premature Discontinuation of Study Drug Follow-up Telephone Contact Visit

Patients who prematurely discontinued study drug during the study, for reasons other than withdrawal of consent, will have completed TV14 and the Washout and Follow-up Safety

Period Visit. These patients are to be contacted by telephone 30 days (+ 2 weeks) after the visit that the patient met the Failure-to-Improve criteria and stopped study drug.

During this Telephone Contact, record AEs and changes in concomitant medications since the completion of the Washout and Follow-up Safety Period Visit.

Document any additional efforts that take place to reach a patient who is non-responsive to telephone contact.

9.6.7 Early Termination Visit for Patients who Withdraw Consent

Patients may withdraw consent from the study at any time. However, if feasible, the patient should return for an Early Termination Visit. The Early Termination Visit will be conducted as soon as practical after the Study Drug treatment is discontinued but no later than 2 weeks following the last dose of study drug. The following procedures should take place as part of an Early Termination Visit:

- obtain vital signs
- perform physical examination
- complete the PAS
- perform brief neurological assessment
- collect blood for central laboratory (hematology and chemistry) and serum pregnancy test at the central laboratory
- collect blood for PK
- Perform 12-Lead ECG after at least 5 minutes in a supine position (See the Study Reference Manual for ECG procedures, Section 17.4 Electrocardiograms for the handling of Cardiovascular adverse events)
- collect urine for urinalysis at central lab
- administer PRO measurements (paper versions):
  - Worst itch NRS
  - Average itch intensity NRS
  - VRS
  - ItchyQoL
  - MOS Sleep-R
  - HADS
  - SOWS
  - PBI-P

  The PRO questionnaires must be administered at the study site under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual).
- record AEs
- review of concomitant medications, including over-the-counter medications, nutritional supplements, and vitamins
- perform study drug accountability, final retrieval of any dispensed study drug

9.6.8 Unscheduled Visits

If a patient needs to be evaluated in relation to the study on a day other than one of the study visit days, that day will be considered an Unscheduled Visit. The reason for each unscheduled visit will be recorded and the following procedures will be performed: vital signs (BP, HR, RR, temperature), assessment for AEs, review of concomitant medications (including rescue medications), and Study Drug accountability. Additional procedures such as central or local laboratory sample collection may also take place, if clinically indicated. See Section 17.5.2.1 in regards to the handling of positive pregnancy test results. All unscheduled visits will be recorded on the Unscheduled Visit CRF.

9.6.9 Schedule of Events

The Schedule of Events is shown in Appendix 1 and is described in Section 9.6.

9.7 Study Drug Treatment and Drug Accountability

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

9.7.1 Study Drug Dosing

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

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 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, he 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 Weeks 1 - 4, according to the schedule in Table 3 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). Patients should only ever be dispensed a single strength of the study drug (e.g. 30mg bottle(s) or 60mg 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.

For example, a patient starting at 30 mg BID during **Week 1**, and titrating to 60 mg BID, would dose as follows:

Day 1 30 mg (evening dose only)
Day 2 30 mg (evening dose only)
Day 3 30 mg BID
Day 4 30 mg BID
Day 5 30 mg in AM and 60 mg in PM
Day 6 60 mg BID
Day 7 60 mg BID

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 TC1 assessment), an additional up-titration may be attempted during **Week 2.** An example of a possible titration schedule would be as follows:

Day 1 60 mg BID (Perform TC1 to assess tolerability)
Day 2 60 mg in AM and 90 mg in PM
Day 3 90 mg BID
Day 4 90 mg BID
Day 5 90 mg in AM and 120 mg in PM
Day 6 120 mg BID
Day 7 120 mg BID

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.** An example of a possible titration would be as follows:

Day 1 120 mg BID (Perform TC2 to assess tolerability)
Day 2 120 mg in AM and 180 mg in PM
Day 3 120 mg in AM and 180 mg in PM
Day 4 180 mg BID
Day 5 180 mg BID
Day 6 180 mg BID
Day 7 180 mg BID

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 dose by 60 mg BID if 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 are 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.

Table 3: Dosing Schedule for TR03ext

Week of Treatment Period[1] (TV or TC)	Day	Drug Tolerance		Discontinuation
		Acceptable	Unacceptable[3]	
Week 1 (TV1/Visit1a /1b)	1	30 mg (PM dose)	--	
	2	0 mg (AM dose) 30 mg (PM dose)	--	
	3-4	30 mg BID		
	5-7	Titrate patients to tolerability with dose increases of 30 mg BID Maintain dose for at least 3 to 4 days up to next dose level	Reduce dose incrementally by 30 mg BID	NA
The highest possible titration dose by the end of Treatment Week 1 is 60 mg BID				
Week 2[2] TC#1	1-7	Continue incremental increase in dose and maintaining at each dosed level for 3 to 4 days	Reduce dose incrementally by 30 mg BID	If 30 mg BID is not tolerated within one week, discontinue patient
The highest possible titration dose by the end of Treatment Week 2 is 120 mg BID				
Week 3[2]	1-7	Continue dose increase	Reduce dose by 30 mg BID and maintain	If 30 mg BID is not tolerated within one week, discontinue patient
The highest possible titration dose by the end of Treatment Week 3 is 180 mg BID				
Week 4[2] (TC#2)	1-7	Maintain dose at highest dose level reached on Week 3 Day 7	Reduce dose reached on Week 3 Day 7 so that subject is now in maintenance dosing at one of the following: 30 mg BID, 60 mg BID, 90 mg BID, 120 mg BID or 180 mg BID	NA
Treatment Week 5[4] up to Treatment Week 50 (TV3-TV 14)	1-7	Maintain dose from Week 4 through TV14[5,6]	*Patient may down titrate twice over remaining duration of study*	Patient discontinued if a 3rd time down-titration is needed.

[1]The decision to enter the patient into the Titration Period is based on Worst Itch NRS score NRS ≥ 5 obtained from the patient on Visit 1a or 1b

[2]The titration decision will be made based on tolerance to study drug

[3]Tolerance level is unacceptable to either the patient and/or investigator

[4] The number of Treatment Weeks prior to TV 14 will vary for patients previously in the Observation Period depending upon the number of weeks spent in the Observation Period. See Table 8

[5]The achieved dose attained 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". Two dose reductions to the next lower allowed dose are permitted during Treatment Weeks 5 – 50 (e.g., a patient at 90 mg BID can be reduced to 60 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study.

[6]Beginning on TV 3 and at every subsequent Treatment Visit, patients with a Worst itch NRS ≥ the Worst itch NRS at Visit 1a (or at Visit 1b in the case of patient who require the OV period) will be discontinued from study drug, complete the End of Treatment Visit 14, the Washout and Safety Follow-up Period and Visit, and a Telephone Contact Visit 30 days after the last dose of study drug (unless consent is withdrawn).

9.7.2 Down-Titration

Down-titration is not permitted except as discussed in Section 9.7.1.

9.7.3 Multiple Missed Doses

If a patient misses multiple doses of the Study Drug, please follow the procedures below. In no case should patients take additional doses of Study Drug to make up for missed doses. If Study Drug is re-started after missed doses, the patient should be instructed to take Study Drug from the tablets designated for the visit during which Study Drug is being re-started rather than from the visits during which Study Drug doses were missed.

- **During the Titration Period**

If a patient misses 3 (or more) consecutive doses, please contact the study Medical Monitor.

- **During the Stable Dose Period**

If a patient misses 6 (or more) consecutive doses, please contact the study Medical Monitor. If authorized by the Medical Monitor, patients who miss more than 6 consecutive doses may be allowed to continue on study. In such situations, patients should receive the Study Drug only once daily (i.e., the AM or PM dose only) for the first 3 days before returning to the full (BID) target dose.

9.7.4 Overdose

The effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Please see Guidance to the Investigator section of the Investigator's Brochure for additional information.

9.7.5 Treatment Compliance

Returned study drug tablets will be used to assess compliance at each visit. Medication compliance will be recorded on the CRF for each designated visit (See Appendix 1). Patient compliance with the study dosing schedule will be assessed as part of the planned study analyses.

9.7.6 Rescue Medications, Concomitant Medications, Prohibited Medications, and Pre-Medications

9.7.6.1 *Rescue Medications*

A secondary objective of the study is to quantitate the number of days of rescue medication used for itching during the course of nalbuphine HCl ER treatment. 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 (See Table 9). For the purposes of this study, any 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 (see Section 11.2).

9.7.6.2 *Concomitant Medications*

Any medication taken by a patient following the signing of informed consent during the course of the study, and the reason for use of the medication, will be recorded on the case report form (CRF). Each patient will be instructed to report the use of all medication to the Investigator, including over-the-counter [OTC] medications, herbal medications, vitamins, and nutritional supplements. Patients will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator.

9.7.6.3 *Prohibited Medications*

Initiating use of opiate medications during the study should be done with caution with assessment of the patient for potential additive opiate AEs. If an enrolled patient requires daily treatment with opioid medications during the study (e.g., for post-surgical pain), please contact the Medical Monitor. Use of acetaminophen, non-steroidal anti-inflammatory medications, and aspirin is permitted. If an opioid medication is introduced in anticipation for chronic use of greater than 2 weeks, the patient should be discontinued.

Concomitant use of opioid antagonists (e.g. naloxone, naltrexone) is also prohibited during the study, unless required for urgent reversal of opioid adverse effects or opioid overdose.

Use of all other investigational drugs is prohibited during the study. A patient who initiates an investigational drug during the study should be discontinued.

If the patient is prescribed a medication(s) included on the list of those with a known risk of Torsade de Pointes (see Section 9.7.8, Safety Assessments, for hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes), contact the Medical Monitor.

9.7.6.4 *Pre-Medications*

Nalbuphine use may be associated with nausea, vomiting, and/or constipation, particularly as the dose is escalated or upon initiation of treatment. At the Investigator's discretion, anti-emetics may be administered prophylactically, prior to taking the Study Drug or, as needed, for treatment. Dietary and other prophylactic measures to avoid constipation should also be considered as clinically indicated Please see Section 9.7.8, Safety Assessments, for the hyperlink to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes.

9.7.7 Efficacy Assessments

The below PRO instruments (paper versions) will be administered at the site and under the supervision of and by trained study staff, strictly adhering to PRO Administration Instructions (see Study Reference Manual) according the Schedule of Events (see Appendix 1).

9.7.7.1 *Numerical Rating Scale (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 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).

In this study, patients will be asked to record two NRS values:

- rate itching on average over the past 24 hours
- rate worst itching over the past 24 hours

This instrument can be found in Appendix 4.

9.7.7.2 *Verbal Rating Scale (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.

In this study, patients will be asked to record the VRS value:

- How is your skin sensation today?

This instrument can be found in the Appendix 4.

9.7.7.3 *Hospital Anxiety and Depression Scale (HADS)*

The HADS instrument includes 14 multiple-choice questions, each with 4 possible choices, scored between 0 and 3. This instrument can be found in Appendix 4.

9.7.7.4 *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 patient scores each question never =1, rarely=2, sometimes=3, often=4, all the time=5. The instrument can be found in Appendix 4.

9.7.7.5 *Medical Outcomes Sleep Scale –Revised (MOS Sleep-R)*

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).

Additionally, a 9-item Sleep Problems Index ("Sleep Problem Index I") can be generated which assesses overall sleep problems that includes the 4 sleep disturbance and the 2 sleep adequacy items, 2 of the somnolence items, and awakening short of breath/headache; higher scores indicate greater sleep impairment, and this index is often used in clinical trials as an indication of sleep quality. The instrument can be found in Appendix 4.

9.7.7.6 *Patient Benefit Index (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". The instrument can be found in Appendix 4.

9.7.7.7 *Prurigo Activity Score (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 percentages based on their stage (0-4).

Photographs of the body are obtained with monitored lesions marked. For consistency, the same lesion(s) documented at Visit 1a are to be documented for the duration of the study. Photographs should be obtained in the same manner at all visits regardless of healing status (i.e. if the previously affected area has healed continue to photograph this area for study purposes).

The PAS instrument can be found in Appendix 4. Please see the Study Reference Manual for instructions for obtaining and storing photographs collected in conjunction with the PAS.

9.7.7.8 *Exploratory Histological Endpoints (optional)*

Punch biopsy skin material for measurement of routine histology (H&E), nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) analysis was obtained during TR03 (optional procedure at select sites only). Punch biopsy may be obtained (optional at select sites) at Visit 1a/1b and End of Treatment Visit of TR03ext for a comparative analysis with the results of the histological results of pre-dosing TR03 and end of study TR03 results.

9.7.7.8.1 MOR/KOR density and Nerve Fiber Density

The potential of nalbuphine HCl ER tablets to impact the Measurement of nerve fiber density (histology) and MOR/KOR density (histology, Western Blot) in skin biopsies taken at Baseline visit and the Evaluation visit will be investigated at select sites.

In addition to skin biopsy tissue obtained prior to drug treatment for H&E and analysis by a central reading dermatopathologist, at select sites, additional skin biopsy material may be

obtained before and at the end of drug treatment. These biopsies will be compared to investigate, in an exploratory manner, any evidence of change in expression of MOR and KOR and nerve fiber density in relation to any noted changes in clinical study endpoints.

Bigliardi et al (2007) reports that in normal skin, keratinocytes express high amounts of MOR and it is therefore concluded that endogenous ligands are bound primarily to opioid receptors on keratinocytes and thus the endogenous opiate ligands are not binding to opioid receptors located on nerve endings –the net result is at most a weak itch signal to the central nervous system in the normal state. In chronic pruritic skin disorders, most opioid receptors on keratinocytes are reported as internalized; therefore there are many opioid ligands available to bind to opioid receptors on sensory nerve endings. This state leads, together with the changed morphology of the epidermal nerve endings, to a strong itch signal to the CNS. The authors reported that topical administration of the opioid mu receptor antagonist naltrexone in subjects with atopic dermatitis, lichen simplex chronicus or prurigo simplex showed an antipruritic effect. In addition, there was also an upregulation of epidermal MOR expression following two weeks of treatment, but no MOR upregulation in subjects who did not experience an antipruritic response. Bigiliardi and Bigliardi-Qi (2004`) reported that in PN human skin tissue samples there was a down regulation of the mu-opiate receptor (MOR) expression in the epidermis compared to normal skin.

Bigliardi-Qi et al (2009) reports that while it is widely accepted that KOR signaling suppresses itch, there is currently no animal, behavioral or human data relating the regulation of skin KOR expression to pruritus. Salemi et al 2007 however reported high upregulation of KOR in the skin of fibromyalgia subjects that was thought to correlate with reported complaints of pain symptoms.

With regard to peripheral sensory nerve fiber density in the skin, Bigliardi et al (2009, 2007) report that epidermal nerve endings of pruritic skin in prurigo are thinner when compared to normal skin. In addition, the nerve fibers have a different morphology which may relate to initiating the sensation of pruritus because of the altered anatomical relationship to the various cellular elements of the skin.

9.7.7.8.2 Routine histology (H&E) and immunohistochemical examination of inflammatory cells and pro-inflammatory mediators

Weigelt et al (2010) summarized the characteristic histological pattern in PN that include the presence of thick compact orthohyperkeratosis; folliculosebaceous units in nonvolar skin in conjunction with a thick and compact cornified layer; irregular epidermal hyperplasia or pseudoepitheliomatous hyperplasia; focal parakeratosis; hypergranulosis; fibrosis of the papillary dermis with vertically arranged collagen fibers; increased number of fibroblasts and capillaries; a superficial, perivascular and/or interstitial inflammatory infiltrate of lymphocytes, macrophages and, to a lesser extent, eosinophils and neutrophils.

While the skin biopsy from PN patients is reported to show a composite pattern of dermatopathologic findings, the condition is not defined internationally by a Dermpath expert board. Thus the biopsy obtained at the Baseline Visit and Evaluation Visit will be analyzed as an exploratory endpoint by a central dermatopathologist for histological review investigating possible correlation of pre-existing histopathological findings (i.e., level of

inflammation, etc.) with any subsequent clinical response noted on drug

9.7.8 Safety Assessments

As summarized in Section 6.2.7 of the Investigator's Brochure, the CNS has been identified as the only target organ when nalbuphine was given to animals at high doses. In addition, the most frequently reported adverse events reported in the nalbuphine HCl ER tablet dosing studies were primarily in the nervous system and gastrointestinal organ system categories. In order to monitor any potential CNS related side effects, a brief neurological assessment will be conducted at each study visit as well as a focused neurological medical history will be obtained at screening.

Safety will be determined by evaluation of the following:

- AEs
- Vital signs including weight, BP, heart rate (HR), respiratory rate (RR), and body temperature
- Physical examination
- Clinical laboratory data (see Appendix 3 for list of analytes)
- Investigator reviewed ECG and central cardiac core laboratory read 12 Lead-ECG, cardiovascular grading, and/or cardiovascular related prohibited medications
- Subjective Opiate Withdrawal Scale (SOWS)

The SOWS is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the patient rates on a scale of 0 ("not at all") to 4 ("extremely"). The instrument can be found in Appendix 4. In this study, patients will complete SOWS daily, starting at 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). The SOWS is a self-administered scale for grading opioid withdrawal symptoms. If the patient is experiencing any symptoms on the SOW scale to a moderate degree, they will be instructed to contact the site. If a patient is determined to be experiencing significant subjective withdrawal symptoms (at the Investigator's discretion), they will be offered treatment.

The following will be used to assess patient eligibility to continue participation if the patient experiences CHF, angina pectoris and/or other cardiovascular exclusion criteria (see Section 8.3 for the Exclusion Criteria and Appendix 5 for the grading scales)

- The Canadian Cardiovascular Society grading of angina pectoris assessment: The Canadian Cardiovascular Society grading of angina pectoris (sometimes referred to as the CCS Angina Grading Scale or the CCS Functional Classification of Angina) is commonly used for the classification of severity of angina
- The New York Heart Association (NYHA) Functional Classification: The New York Heart Association Function Classification provides a simple way of

classifying the extent of heart failure by placing patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina pain.

CredibleMeds Filtered QTDrug [List: Known Risk of TdP]: Cardiovascular related prohibited medications are provided on the CredibleMeds Filtered QTDrug List. Drugs are placed into one of four risk categories based on their relative potential to alter the electrocardiogram (QT prolongation) and/or cause life-threatening ventricular arrhythmias. See the following link to the CredibleMeds Filtered QTDrug List for cardiovascular related prohibited medications with a known associated risk of Torsade de Pointes: https://www.crediblemeds.org/ Users of the CredibleMeds website will be required to complete a short (one-time) registration process in order to access the QTDrug listing.

10 STUDY DRUG

Please see the Study Reference Manual for additional information on Study Drug supplies, packaging, storage, dispensation, and accountability.

10.1 FORMULATION, PACKAGING AND LABELING

The Study Drug in this trial is nalbuphine HCl ER tablets. Nalbuphine HCl ER tablets are white to off white film-coated round tablet containing either 30 mg or 60 mg nalbuphine HCl.

All study medication will be supplied by the Sponsor. Following confirmation of eligibility to start the Treatment Period, the patient will receive bottles of study drug tablets containing 60 tablets each. Bottles will be labeled with at minimum: contents, storage conditions, expiration date, clinical trial statement, and the name and lot number of the study drug Sponsor (Trevi Therapeutics).

10.2 SHIPPING, STORAGE AND HANDLING

The Investigator will ensure that the Study Drug is stored and dispensed in accordance with ICH QE6(R1) (Guideline for Good Clinical Practice) and EU Clinical Trial Directive and Annex13 regulations concerning the storage and administration of investigational drugs.

Nalbuphine HCl ER tablets and placebo tablets should be stored at 20°C-25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (59° to 86°F). The storage conditions were established following ICH Q1A(R2) (Stability testing of new drug substances and drug product) and the CHMP Guideline CPMP/QWP/122/02, rev 1 corr CHMP Guideline (Stability Testing of existing active substances and related Finished products) for assessment and provision of appropriate labelling and storage conditions.

The Study Drug will be stored away from any extreme conditions of temperature, light, or humidity as an additional precaution

In the EU, the investigational medicinal products will remain under the control of the Sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the Sponsor for use in a clinical trial following fulfillment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps will be recorded and retained in the relevant trial files held by or on behalf of the Sponsor.

10.3 UNBLINDING

Not applicable. This is an open-label study.

10.4 DRUG ACCOUNTABILITY

The Investigator must ensure that all drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all Study Drug shipped by the Sponsor or the Sponsor's representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all Study Drug. Current dispensing records will also be maintained including the date and amount of drug dispensed and the patient receiving the drug. All remaining drug not required by regulations to be held by the clinical facility will be returned to the depot for destruction at the end of the study.

11 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT

Patients who complete Study Drug treatment through the End of Treatment Visit (TV14) are considered to have completed Study Drug treatment (even if some doses have been missed). Patients who discontinue Study Drug treatment, **for reasons other than withdrawal of consent**, prior to the End of Treatment visit (TV14) will be considered to have prematurely discontinued Study Drug treatment and will be asked to complete the following visits:

- End of Treatment Visit (TV14) *regardless of where they are in the study visit schedule
- Washout and Safety Follow-up Period Visit
- Premature Discontinuation of Study Drug Telephone Contact Visit

11.1 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT ASSOCIATED WITH FAILURE-TO-IMPROVE CRITERIA

Patients, who meet failure-to-improve criteria during the conduct of the study, will stop taking study medication. The Failure-to-Improve criteria are as follows:

> Beginning on TV 3, and at every subsequent Treatment Visit, patients with a Worst itch NRS equal to or greater than (≥) the Worst Itch NRS at Visit 1a (or at Visit 1b in the case of patients who require the Observation Visit 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.

Below are examples of the assessment of Failure to Improve Criteria:

Examples	Visit	Worst Itch NRS	Worst Itch NRS Lower/Higher or no change from V1a/1b	Failure-to-improve met for that visit?	Next Steps
Visit 1a (or Visit 1b)		5	--	--	--
Ex #1	TV3	5	**No Change**	**Yes**	**Discontinue study drug**
Ex #2	TV3	4	**Lower**	**No**	**Maintain patient on treatment**
Ex #3	TV3	6	**Higher**	**Yes**	**Discontinue study drug**

11.2 PREMATURE DISCONTINUATION OF STUDY DRUG TREATMENT FOR REASONS OTHER THAN FAILURE-TO-IMPROVE

Patients who complete Study Drug treatment (as defined in Section 11) are considered to have completed Study Drug treatment including those that were followed in the Observation Period prior to receiving 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 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 AE that cannot be ameliorated or safely managed with medical intervention or one that poses undue risk to the patient if Study Drug treatment were continued in the opinion of the Medical Monitor or Investigator.
- ECG changes as summarized in Section 17.4
- Opioid medication is introduced in anticipation for chronic use of greater than 2 weeks (see Section 9.7.8)
- Any medication prescribed for chronic anti-pruritic use of greater than 2 weeks (see Section 9.7.6.1)
- Development of substance abuse as determined by the Investigator

12 PREMATURE WITHDRAWAL OF PATIENTS FROM THE STUDY

All patients who receive study treatment should remain in the study whenever possible. Reasons for withdrawal of the patient from the study, not just discontinuation of study drug, include:

- Withdrawal of consent for study participation

- Sponsor terminates the study for any reason
- Investigator decision

  The Investigator may withdraw any patient from the study if, in the Investigator's opinion, it is not in the patient's best interest to continue on the study.
- Death of the patient

Any patient whose condition significantly changes after entering the study should be carefully evaluated by the Investigator and discussed with the Medical Monitor. Such patients should be withdrawn from the study if continuing would place them at risk or compromise the results of the study.

Patients who prematurely discontinue from the study will be asked to undergo and have completed Early Termination visit procedures and evaluations that may be necessary to ensure that the patient is free of untoward effects and to seek appropriate follow-up for any continuing problems. The date on which the patient is withdrawn from the study and the reason for discontinuation will be recorded on the CRF. Patients who withdraw from the study will not be replaced.

13 WARNINGS AND PRECAUTIONS

Please refer to the accompanying Investigator's Brochure for more details summarizing the safety data on nalbuphine HCl ER tablets. In addition, see the Warnings and Precautions sections of the parenteral nalbuphine HCl package insert for safety-related information. The package insert is contained in the Study Reference Manual.

14 EFFICACY EVALUATIONS

Efficacy measurements will be evaluated as secondary endpoints in this study. The measurements include:

- Worst itch intensity NRS
- Average itch intensity baseline.
- VRS (itchy, burning and stinging)
- ItchyQoL
- MOS Sleep-R
- HADS
- Prurigo Activity Score (PAS)
- Patient Benefit Index, pruritus version (PBI-P)
- Frequency, pattern, and reasons for dose titration
- 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 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.

14.1 EXPLORATORY

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) in skin biopsies taken during TR03 and the last week on study drug during TR03ext (optional procedures at select sites only).

15 COLLECTION, HANDLING, AND ANALYSIS OF PHARMACOKINETIC BLOOD SAMPLES

15.1 BLOOD SAMPLE COLLECTION

Blood samples will be collected for safety, pharmacokinetic and CYP analysis. At the time of sample collection and processing, study patient information will be anonymized. Only the patient's identification number, assigned by an IVR/IWR system, and a sample barcode aligned to the lab requisition form will be noted on the tube/vial.

See the PPD Laboratory Manual for specimen collection, handling and shipping details.

15.2 CENTRAL LABORATORY

Blood samples, including chemistry, serum pregnancy test, hematology, and urine for urinalysis will be obtained for the study and analyzed at a central laboratory.

Urine pregnancy testing will be conducted at the site.

The serum pregnancy test result will be used to determine the patient's eligibility to continue receiving study treatment should the urine and serum pregnancy test results differ. See Section 17.5.2.1 regarding how pregnancies are to be handled in this study.

15.3 PHARMACOKINETIC SAMPLES

To determine Study Drug content in plasma, blood samples will be collected at various time intervals over the duration of the study.

15.4 PREPARATION, STORAGE, AND HANDLING FOR PHARMACOKINETIC SAMPLES

Immediately after blood sample collection, the tubes will be gently inverted several times to mix the anticoagulant with the blood sample and placed on ice (4 to 8°C) until centrifuged.

The plasma fraction will be separated by centrifugation of the collection tube. It is preferable that a refrigerated (4 to 8°C) centrifuge be used. Centrifugation will be conducted in a manner to yield approximately 2 x1 mL of plasma (e.g., 10 minutes at 1,500 x g). The plasma fraction will be withdrawn by pipette and divided into 2 evenly

proportioned aliquots in polypropylene freezing tubes. All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the patient identification number, the study dose, and the collection date and time.

Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be processed and placed into either a minus 70°C or minus 20°C refrigerator within 1 hour after collection. Tube labels for PK samples will be provided in the central laboratory kits. Each label will contain the study number, patient number, study day of sample, and time of sample. The actual date and time of blood collection, as well as the processing time will be recorded in the patient's source records and/or the CRF.

All plasma samples will be stored frozen (at either -70ºC or -20°C) until they are shipped for storage and analysis.

15.5 ANALYTICAL

Plasma samples will be analyzed for Study Drug using a validated liquid chromatography mass spectrometry (LC-MS/MS) method developed at Tandem Lab/s-RTP, Durham, North Carolina. The units for nalbuphine will be in ng/mL. In addition, metabolite concentrations will be assessed in these samples using an exploratory analytical LC-MS/MS method.

Analysis and reporting of results will be conducted according to the current Standard Operating Procedures for bioanalysis at Tandem labs Durham, North Carolina. Details of the sample analysis, including a bioanalytical study report, will be included with the final clinical study report.

16 TISSUE SAMPLES AND HISTOLOGY

At selected sites only, up to three 3 mm punch skin biopsy samples (optional) will be obtained at Visit 1a/1b and the End of Treatment Visit (TV14).

- A 3x3 mm punch skin biopsy is taken from an itchy region which will be fixed in formalin and then paraffin for routine histology (H&E) and immunohistochemical examination of inflammatory cells and pro-inflammatory mediators.
- For the other two 3x3 mm punch skin biopsy samples taken from an itchy region,
    - One sample will be fixed in 4% paraformaldehyde for 2 h to 5 days, and then kept in 5% sucrose overnight, buffered in 10% and 20% sucrose and after 6 h stored in liquid nitrogen. This tissue will serve for the determination of the nerve fiber density.
    - One sample will be used for RNA and protein extraction for the quantification of MOR/KOR by PCR and western blot.

Analysis will be performed at the University of Munster, Munster, Germany.

See the Study Reference Manual and the Laboratory Manual for specimen collection, handling and shipping details.

17 SAFETY EVALUATIONS

Safety evaluations will include physical examination findings, changes in vital signs and ECGs (locally and centrally read), findings from central laboratory studies and the incidence of AEs

17.1 PHYSICAL EXAMINATION

A complete physical examination will be performed at the Screening Visit and subsequently according to the Schedule of Events (Appendix 1). Physical examinations may be performed by physicians or mid-level providers, such as advanced practice nurses and physician assistants, if they are appropriately licensed and credentialed to perform these examinations in accordance with local requirements and/or regulations. 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.

17.2 VITAL SIGN MEASUREMENTS

Blood pressure and HR will be taken while sitting or semi-recumbent/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 (BP, HR, RR, body temperature, and weight will be obtained according to the Schedule of Events (Appendix 1). The height, weight and BMI will be recorded only on Visit 1a.

17.3 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 (Appendix 1). The required clinical laboratory tests are listed in Appendix 3.

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.

17.4 ELECTROCARDIOGRAM

A standard 12-lead ECG will be obtained according to the Schedule of Events (Appendix 1); see the Study Reference Manual for ECG procedures. Electrocardiograms will be read locally by the Principal Investigator 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.

If a patient develops a QTcF >500ms, associated with an increase from baseline of >60ms, the ECG will be repeated at least 30min later. If these parameters are confirmed on the second ECG by the Core ECG laboratory, the patient will be discontinued from the study.

During the conduct of the trial, if a patient develops any other cardiovascular events noted as part of the exclusion criteria, the cardiovascular assessments in Appendix 5 are to be completed. See Section 17.5 Adverse Events for the handling and follow-up of Adverse Events.

17.5 ADVERSE EVENTS

Adverse events 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). Adverse events that have not been directly reported to the Investigator will be promptly conveyed to the Investigator by the study staff. Investigators will additionally review any AE source documents and the patient's medical records, on a regular basis during the course of the study; including all study visits.

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 adverse event has stabilized.

17.5.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical investigation patient reported on or after the first screening date. A treatment-emergent AE (TEAE) is any untoward medical occurrence in a clinical investigation patient or patient administered a pharmaceutical product on or after the initial administration of study medication. An AE does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom whether or not related to the medicinal (investigational) product, or disease temporally associated with the use of a medicinal (investigational) product.

The AE may be any of the following:

- a new illness
- worsening of a pre-existing condition
- worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- an effect of the study medication, including comparator
- a combination of 2 or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "AE."

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Adverse events fall into the categories "non-serious" and "serious."

17.5.2 Serious Adverse Events

The reporting period for serious AEs is the same as for AEs. Serious AEs must be submitted to the Sponsor within 24 hours of their discovery, even if the full information about the event is not yet available. These events should also be reported to the IRB/IEC as needed based on local requirements. Fax SAE forms to the following number:

Serious AE Fax #: 888-529-3580

Also notify the PPD Medical Monitor at **(888) 483-7729.**

17.5.2.1 *Serious Adverse Event Definition*

An SAE is one that, at any dose, results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.

A hospitalization is defined as an inpatient admission lasting 24 hours or more. Visits to urgent care centers and emergency departments that do not result in admission to a hospital for 24 hours will not be considered hospitalizations. Hospitalizations for elective procedures, defined as any procedure that was planned prior to signing of the informed consent will not, in and of themselves, be considered to fulfill criteria for an SAE. For example, for patients on the kidney transplant waiting list prior to signing the ICF who subsequently are hospitalized for a transplant, the hospitalization would be considered elective.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the SAE. It does not refer to a SAE that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. 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 development of drug dependency or drug abuse.

Female patients who become pregnant should be immediately discontinued from the study if they have not yet received Study Drug. If a patient is found to be pregnant after they have received Study Drug, she should discontinue dosing, complete all end-of-study

procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications or less than a healthy, normal outcome will be recorded as an AE or SAE.

Clarification on the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

17.5.3 Non-Serious Adverse Events

A non-serious AE is any AE not meeting the SAE criteria.

17.5.4 Definition of Relationship to Study Medication

Association or relatedness to the study medication will be graded as either "probably," "possibly," or "unlikely." Determination of relatedness includes:

PROBABLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- abates upon discontinuation of the drug;
- cannot be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLY – The AE:

- follows a reasonable temporal sequence from drug administration;
- could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.

UNLIKELY – The AE:

- does not follow a reasonable temporal sequence from drug administration;
- is readily explained by the patient's clinical state or by other modes of therapy administered to the patient.

17.5.5 Definition of Severity

All AEs will be graded, if possible, by the 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]. This is also provided in the Study Reference Manual for reference purposes.

The severity of AEs that cannot be graded by the most current version of CTCAE will be categorized as follows:

- **Grade 1** – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

- **Grade 2** – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- **Grade 3** – Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.
- **Grade 4** – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable.
- **Grade 5** – Death.

17.5.6 Definition of Unexpected Adverse Event

Any AE, the specificity or severity of which is not consistent with the current Investigator's Brochure, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

17.6 DATA SAFETY MONITORING BOARD

An unblinded, independent Data Safety Monitoring Board (DSMB) will periodically review safety data during the time period that the blinded nalbuphine HCl program remains ongoing. The frequency of data review and DSMB processes are outlined in the DSMB charter. The DSMB will periodically review group-unblinded study information (on a treatment group level, using random letters instead of actual treatments) during the conduct of the study. If necessary, un-blinding of individual subject data and treatment groups may be done.

18 EMERGENCY PROCEDURES

In case of study-related medical questions, or if a pregnancy is confirmed in a trial patient, the Investigator should contact the designated Medical Monitor.

18.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the Investigator should contact the designated Sponsor representative at the following address:

Thomas Sciascia, MD
Trevi Therapeutics, Inc.
195 Church Street, 14th Floor
New Haven, CT 06510 USA
Telephone: (203) 304-2499
Mobile: (617) 913-6808

19 CONSIDERATION, ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

19.1 GENERAL

As a companion to this protocol and in an effort to provide a more detailed explanation of the statistical methodology to be used for this study, which will consist of data summaries, a statistical analysis plan (SAP) will be developed prior to locking the data base.

No formal statistical testing is planned for this study. Data summaries will provide the basis for clinical interpretation of efficacy and safety outcomes

19.2 INTERIM ANALYSES

There is no interim analysis planned in this study.

19.3 METHODS FOR HANDLING MISSING DATA

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

19.4 PATIENT DISPOSITION

Patient disposition will be summarized, including the reasons for discontinuation. The number of patients in each analysis population will be displayed and an accounting of exclusions from each study population will be provided.

19.5 BASELINE CHARACTERISTICS

Demographics, medical history, laboratory data, and physical examination findings will be summarized.

19.6 CONCOMITANT MEDICATIONS

Concomitant medications will be tabulated by Anatomic and Therapeutic Class (ATC) of WHO drug, preferred term, and treatment group. 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. If the start date is missing, it will be assumed that the medication was used concomitantly. Rescue and opioid medication usage will be tabulated separately from all other concomitant medications.

19.7 STUDY DRUG DOSING

The percentage of patients reaching various achieved doses at the end of Treatment Week 4 and through Study Week 50 will be summarized. The mean dose during the Treatment Period and the dose distribution by Treatment Period Visit will be reported. Descriptive statistics will be used to describe the mean daily dose by Visit.

19.8 EFFICACY ANALYSES

19.8.1 Efficacy Population

The Safety population, consisting of all enrolled patients who have received a single dose of study medication, 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 for the endpoint of interest, 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.

19.8.2 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 will be summarized. Patients who prematurely discontinue after having been followed in the Observation Period only will be also be summarized.

19.9 SAFETY ANALYSES

19.9.1 Safety Population

The Safety Population will consist of all patients who have received a single dose of study medication, i.e., this same population will be used both for the efficacy and safety evaluations. The Safety Population will be used in all safety analyses.

19.9.2 Adverse Events

All treatment emergent AEs (TEAE) will be summarized overall and for each body system and preferred term by treatment group, relationship to study medication, and severity. For tabulations by severity, only a patient's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. Adverse events will be dichotomized into "related" (probably and possibly) and "unrelated" (unlikely). "Treatment-emergent" will be defined as starting or worsening after the first dose of study drug. If the start date is missing, the event is assumed to be treatment emergent. All SAEs will be tabulated as well.

Although nalbuphine is not a controlled substance in the United States, adverse events of special interest that suggest a possible addiction or abuse potential or withdrawal will be specifically analyzed to screen for these effects. The list of MedDRA preferred terms for adverse events of special interest will be described in the Statistical Analysis Plan.

19.9.3 Vital Signs

Vital signs, including BP, HR, body temperature, and RR, and weight will be summarized by treatment group at Baseline and at each assessment time point during the post dosing period.

19.9.4 Laboratory Evaluations

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and at each scheduled visit. Summaries of safety laboratory parameters will include the first measurement of each scheduled assessment but repeat assessments done at the same study time point will not be included in summary calculations. Lab data will also be listed by treatment, patient, and visit. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values, as defined in the Statistical Analysis Plan, will additionally be generated.

19.9.5 Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening will be reported as AEs and analyzed as such. Clinically significant findings noted prior to start of Study Drug treatment will be recorded as medical history and analyzed as such.

19.9.6 Electrocardiograms

A standard 12-lead ECG will be obtained on Visit 1a/1b (pre-treatment) and subsequently, according to the Schedule of Events in Appendix 1. Electrocardiogram intervals (PR, RR, and QTcF) will be summarized with descriptive statistics. All findings, including any follow-up ECGs as a result of any significant abnormal results, will be listed by treatment, patient, and visit.

ECG procedures should be automatically repeated if the following results are obtained: artifact, excessive noise, reversed leads, or baseline wander. Repeating ECG procedures for any other reason will require prior written approval from the Sponsor.

19.10 Determination of 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 (i.e., approximately 60 patients).

19.11 PHARMACOKINETIC AND PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The Study Drug plasma concentration data will be provided as data listings and will be summarized descriptively (mean, median, SD, minimum, and maximum) by collection time and nalbuphine dose. Additionally, these PK data may be analyzed through population, nonlinear mixed effects modeling (NONMEM), using the software package NONMEM (Version V, Level 1.1 or higher; GloboMax LLC, Hanover, MD).

20 ETHICS

20.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the study, the Investigator will submit the study protocol, sample informed consent form (ICF), and any other documents that pertain to patient information, recruitment methods such as patient diaries, and advertisements, to the Institutional Review Board/Independent Ethics Committee (IRB/ IEC). The Investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study, and will keep on file; records of approval of all documents pertaining to this study. A letter confirming the approval must be forwarded to the Study Monitor prior to initiation of this study. This letter will be forwarded to the Sponsor prior to the initiation of the study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site, as well as other AE reports received the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study.

20.2 ETHICAL CONDUCT OF THE STUDY

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice [GCP], 1 May 1996), in agreement with the latest revision of the Declaration of Helsinki and in keeping with local regulations.

The Investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties. Should the Investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

20.3 PATIENT INFORMATION AND INFORMED CONSENT

Patients must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An ICF that includes information about the study will be prepared and given to the patient. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the patient and must specify who informed the patient. Where required by local law, the person who informs the patient must be a physician.

After reading the ICF, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed ICFs must be given to the patient. The original signed ICFs will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

21 STUDY ADMINISTRATION

21.1 CLINICAL MONITORING

Monitoring and auditing procedures, developed or endorsed by Trevi Therapeutics will be followed to comply with GCP guidelines. Access to the on-site study documentation and medical records will be ensured.

The study will be monitored by Trevi Therapeutics or its designee. Throughout the course of the study, the Study Monitor will make frequent contact with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and adherence to the protocol. As part of the data audit, all source documents in the Investigators' possession must be made available to the Study Monitor for review. The Study Monitor will also perform drug accountability checks and will request to perform a review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the Study Monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The Investigator, or appointed delegate, will meet with the Study Monitor during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of Trevi Therapeutics or the regulatory agencies.

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

21.2 DATA QUALITY ASSURANCE

The Investigator, or designee, will enter study data required by the protocol into an electronic data capture (EDC) system. The Study Monitor will visit each study site, at a frequency documented in the monitoring plan, to review the electronic CRF (eCRF) for completeness and accuracy. Any discrepancies found between source documents and completed eCRF will be entered as a discrepancy in the EDC system by the Study Monitor. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for eCRF correction (queries) will be discussed during the study site initiation visits and will be documented in the study operations manual.

Data from eCRF and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data from eCRF and data from other external sources for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be documented, and the study site should be requested to review and resolve the queries. Only authorized personnel can make corrections to the clinical database, and all corrections should be documented in an audit trail.

Adverse events will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

21.3 RETENTION OF STUDY RECORDS

The following records must be retained by the Investigator for a minimum of 2 years after the Sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed ICFs for all patients
- Patient identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement

- Record of all communications between the Investigator and Sponsor (or Contract Research Organization [CRO])
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all patients
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

However, because of international regulatory requirements, the Sponsor may request retention for a longer period of time. The Investigator must therefore obtain approval in writing from the Sponsor prior to destruction of any records.

Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

21.4 CONFIDENTIALITY

Patient names will not be supplied to the Sponsor. Only the patient number and patient initials will be recorded in CRF (unless not allowed by local regulations), and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The will be told that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

21.5 DOCUMENTATION OF STUDY RESULTS

As part of the responsibilities assumed by participating in the study, the Investigator or Sub-investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator or Sub-investigator agrees to maintain accurate eCRF and source documentation as part of the case histories. These source documents may include laboratory reports and ECG recordings.

The Investigator or designees must enter all results collected during the clinical study into the eCRF. Guidelines for completion of the eCRF will be reviewed with study-site personnel at the site initiation visits. There is a 2-part process to review and collect the eCRF data. Study-site personnel will enter the data from each study visit. The Investigator is responsible for approval of the entered/corrected data. The eCRF responsibilities of the

study team members will be documented on the site delegation log, which will be collected at the closeout visits.

Under special circumstances, and with prior written Sponsor approval, the Investigator can authorize Sub-investigators to sign and approve the eCRF if they are designated on Form FDA 1572 as Sub-investigators, have been trained on the EDC system, and have their own user name and password. The Investigators or designees must review and approve the data before database lock.

In the EU, the Investigator agrees to maintain documentation of the data generated by the trial so that it complies with the requirements of Directive 2001/20/EC, as amended and Directive 2005/28/EC as amended to incorporate recommendations on 'The Trial Master File and Archiving'.

21.6 USE OF STUDY RESULTS

All information concerning the product, as well as any matter concerning the operation of Trevi Therapeutics (such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by Trevi Therapeutics and are unpublished) are confidential and must remain the sole property of Trevi Therapeutics. The Investigator and participating vendors will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Trevi Therapeutics is obtained. The Sponsor has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Trevi Therapeutics. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

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APPENDICES

Appendices 1 through 4 are provided on the following pages.

Appendix 1: Schedule of Events

Table 4: Schedule of Events for Visits 1a and 1b (Day 1 of Week 1 of Treatment Period)

Visit	1a[1]	1b[4]
Informed Consent[2]	X	
Confirm Eligibility	X	
Vital Signs[3]	X	X
Physical Examination	X	X
Neurological Exam	X	X
Central Clinical Labs[5] & serum PregnancyTest[6]	X	X
Urinalysis	X	X
Urine for pregnancy test[11]	X	X
Blood for PK	X	X
Perform skin biopsy (only at select sites and the procedure is optional)[9]	X	X
12-lead ECG[12]	X	X
Worst itch Numerical Rating Scale (NRS)[7]	X	X
Average itch intensity Numerical Rating Scale (NRS)[7]	X[9]	X
Verbal Rating Scale (VRS)[7]	X[9]	X
ItchyQoL[7]	X[9]	X
MOS Sleep-R[7]	X[9]	X
Hospital Anxiety and Depression Scales (HADS)[7]	X[9]	X
Patient Benefit Index Pruritus (PBI-P)[7]	X[9]	X
Prurigo Activity Score (PAS)	X[9]	X
Record AEs	X	X
Review Rescue Medications and Concomitant Medications	X[8]	X
Retrieve TR03 study drug	X	
Dispense Study Drug for TR03ext[13]	X[9]	X
Collect Rescue Medication Log for TR03	X	
First dose of Study Drug for TR03ext[10,13]	X[9]	X
Dispense Drug Dosing Instructions and Dosing Diary	X	X
Dispense TR03ext Rescue Medication Log	X	X

[1]Visit 6/1a procedures in common do not have to be repeated if visits are performed on the same day.

[2] To be completed any time before start of Visit 1a procedures

[3]BP and HR (sitting or semi-recumbent), RR, temperature. Height, weight, and BMI at Visit 1a only.

[4] Visit 1b is the first visit of the Treatment Period for patients transitioning from the Observation Period to the Treatment Period.

[5]Hematology and chemistry

[6]Females of Childbearing potential only

[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)

[8]Includes review of patient TR03 Rescue Medication Log

[9]Study procedures only conducted if patient qualifies to enter the Treatment Period based on Worst itch NRS **≥ 5**

[10]Titrate study drug according to the schedule in Table 3;

The first dose of study drug treatment will define enrollment into the study

[11] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing study drug.

[12] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review

[13]The first dose of study drug is to be taken in the evening, see Section 9.7.1 and Section 9.3

Table 5: Treatment Weeks 2-4

	TC 1[1]	TV 2[1]	TC 2[1]
Treatment Week	**2**	**3**	**4**
Dispense Study Drug[2]		X	
Titrate Study Drug[2]	X	X	
Confirm Maintenance Dose			X[2]
Vital Signs[3]		X	
Neurological Assessment		X	
Urine pregnancy test[5]		X	
Blood for PK		X	
12-lead ECG[6]		X	
Worst itch NRS[4]		X	
Average itch intensity NRS[4]		X	
VRS[4]		X	
MOS Sleep-R[4]		X	
HADS[4]		X	
ItchyQoL[4]		X	
Study Drug BID	X		
Record AEs	X	X	X
Record Concomitant Medications		X	
Reinforce Compliance[7]	X	X	X
Study Drug Accountability		X	
Dispense Dosing Diary		X	
Dispense Rescue Medication Log		X	

[1] The window for TC 1-2 and TV2 is +/-3 days
[2] Instruct the patient in the dose titration/maintenance according to the schedule in Table 3 and assess tolerability/intolerability to study drug
[3] BP and HR (sitting or semi-recumbent), RR, temperature.
[4]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[5] For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.
[6] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review
[7]Includes review of Rescue Medication Log and Drug Dosing Diary for accuracy and completeness.

Table 6: Treatment Period Visits[12] During Study Weeks 5-50 and Washout/Safety Follow-up Visit or Treatment Period Early Termination Visit

	TV 3	TV 4	TV 5	TV 6	TV 7	TV 8	TV 9	TV 10	TV 11	TV 12	TV 13	End of Treatment Visit (TV14)	Washout / Safety Follow-up Period	Premature Discontinuation of Study Drug Telephone Contact[14]	ET[9]
Treatment Week[1,3]	**5**	**9**	**13**	**17**	**21**	**26**	**30**	**34**	**38**	**42**	**46**	**--[2]**	**--**	**--**	
Physical Examination						X						X			X
Brief Neurological Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Central Clinical Labs[6]						X						X	X		X
Serum pregnancy test to central lab[11]												X			X
Urinalysis to central lab						X						X			X
PAS	X	X	X	X	X	X	X	X	X	X	X	X		X	X
PBI-P[7]												X			X
12-lead ECG[13]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Skin biopsy (at select sites and is an optional procedure)												X[10]			X
Blood for PK	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Failure-to-Improve Evaluation[17]	X	X	X	X	X	X	X	X	X	X	X			X	
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X				
Urine pregnancy test[5]	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Worst itch NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Average itch intensity NRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ItchyQoL	X	X	X	X	X	X	X	X	X	X	X	X	X		X
VRS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
MOS Sleep-R[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
HADS[7]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
SOWS[7]												X			X
Dispense 14 day SOWS packet[15]												X			
Retrieve 14 day SOWS packet[15]													X		
Record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reinforce Compliance	X	X	X	X	X	X	X	X	X	X	X				
Study Drug Accountability	X	X	X	X	X	X[8]	X	X	X	X	X	X			X[8]
Study Drug BID	X	X	X	X	X	X	X	X	X	X	X				

[1]Patients who were previously in the Observation Period should start the Treatment Period at Visit 1b and continue in the study for 38-46 weeks; the total number of weeks in the combined Observation and Treatment Periods is no more than 50 weeks. The last scheduled visit on study drug for patients previously in the Observation Period should be TV 14 regardless of the study week.

[2] The number of Treatment Weeks prior to TV 14 will vary for patients who prematurely discontinue study drug for reasons other than withdrawal of consent see Section 11.

[3]Two allowable dose reductions are permitted during Treatment Weeks 5 – 50 (a patient can be reduced to 30 mg BID). If a third dose reduction is needed, the patient should be discontinued from the study.

[4] BP and HR (sitting or semi-recumbent), RR, temperature

[5]For female patients of child-bearing potential, a urine pregnancy test must be negative prior to dispensing additional study drug.
[6] Hematology and chemistry.
[7]Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[8] Retrieve remaining study drug at TV 14 or ET Visit
[9] ET Visit is conducted within 2 weeks of study drug termination, see Section 12
[10] Skin biopsy material for nerve fiber density, histology (H&E) and MOR/KOR density to be performed, only at select sites (optional procedure)
[11]Females of Childbearing potential only
[12] Visit windows will be +/-3 Days
[13] ECGs are to be performed after the patient has been in the supine position for at least 5 minutes. ECGs will be read by the Investigators for clinical significance and centrally by a core ECG laboratory for analytical and DSMB safety review
[14]The Premature Study Drug Discontinuation Telephone Contact is to take place for all patients who prematurely discontinue study drug for reasons noted in Section 11. This telephone contact takes place 30 days (+2 weeks) from the last dose of study drug.
[15]The 14 Day SOW packet is to be completed at home by the patient. A SOWS is to be completed each day starting at TV14. The packet is to be retrieved at the Washout and Safety Follow-up Period Visit
[16]Includes review of Rescue Medication Log and Drug Dosing Diary for accuracy and completeness
[17]See Section 11.1 for the Failure-to-Improve criteria; perform End of Treatment Visit (TV14) procedures for patients that meet the Failure-to-Improve criteria

Table 7: Observation Period Visits[5]

Observation Visit	OV 2	OV 3	OV 4
Observation Study Week	4	8	12[1]
Check Worst itch NRS[2]: If ≥ 5 , patient must undergo Visit 1b	X[4]	X[4]	X[4]
Vital Signs[3]	X	X	X
Average itch intensity NRS[2]			X
VRS[2]			X
MOS Sleep-R[2]			X
HADS[2]			X
ItchyQoL[2]			X
Record AEs	X	X	X
Record concomitant medications	X	X	X

[1]Patients whose NRS is <5 at OV 4 are to be screen failed from the study
[2] Questionnaires must be administered strictly adhering to instructions (see Study Reference Manual)
[3]BP and HR (sitting or semi-recumbent), RR, temperature
[4]If patient's NRS is **≥ 5** proceed to Visit1b procedures and no need to record any further data under OV visit procedures
[5]Visit windows will be +/-3 Days

Table 8: Treatment Visit Schedule for Patients Entering Treatment via Visit 1b

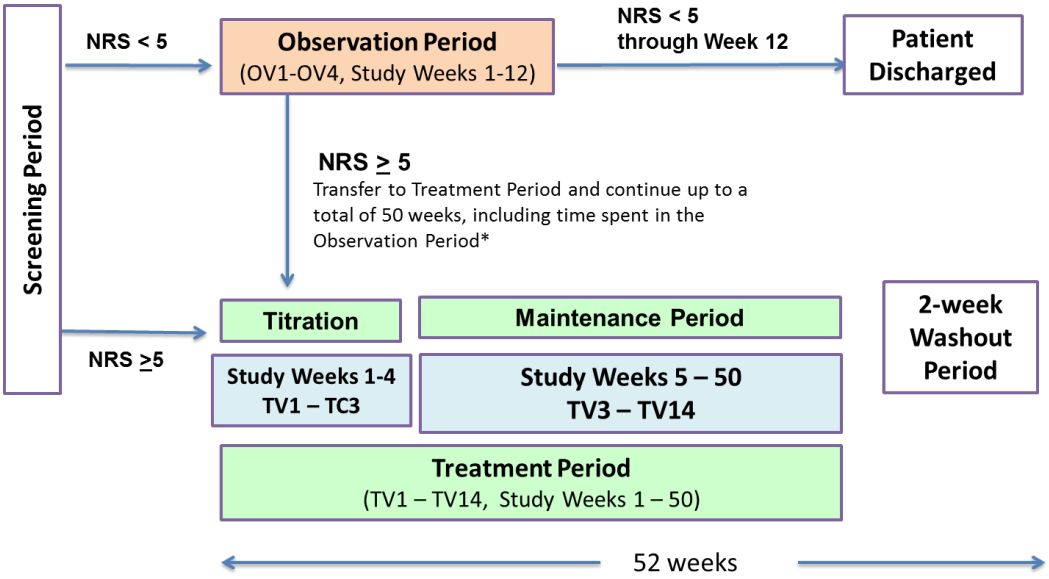
Patients with a Worst Itch NRS score of greater than or equal to 5 (≥5) at an Observation Visit are to complete Visit 1b and transition from the Observation Period to the Treatment Period. If the above criteria are met, Visit 1b procedures are to be completed at the Observation Visit

Visit of Transition	**OV2**	**OV3**	**OV4**
Treatment Visits to Complete	Visit 1b/TV1, TV2 through TV12, and TV13	Visit 1b/TV1, TV2 through TV11, and TV12	Visit 1b/TV1, TV2 through TV10, and TV11
Last Treatment Visit	**TV13** **Dispense 1 week of study drug** Week 46 is last week of treatment for a patient who transitioned to the Treatment Period from OV2 Conduct the End of Treatment Visit (TV14) during week 47	**TV12** **Dispense 1 week of study drug** Week 42 is last week of treatment for a patient who transitioned to the Treatment Period from OV3 Conduct the End of Treatment Visit (TV14) during week 43	**TV11** **Dispense 1 week of study drug** Week 38 is last week of treatment for a patient who transitioned to the Treatment Period from OV4 Conduct the End of Treatment Visit (TV14) during week 39
Total Potential Weeks on Treatment	46	42	38

Table 9: 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	✓	---

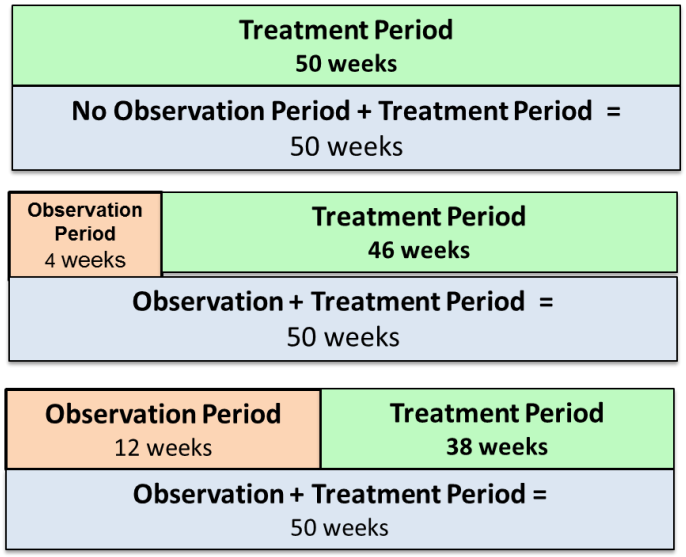
Appendix 2: Study Schematic Flow Charts

Figure 2: Overview of TR03-EXT Study Design



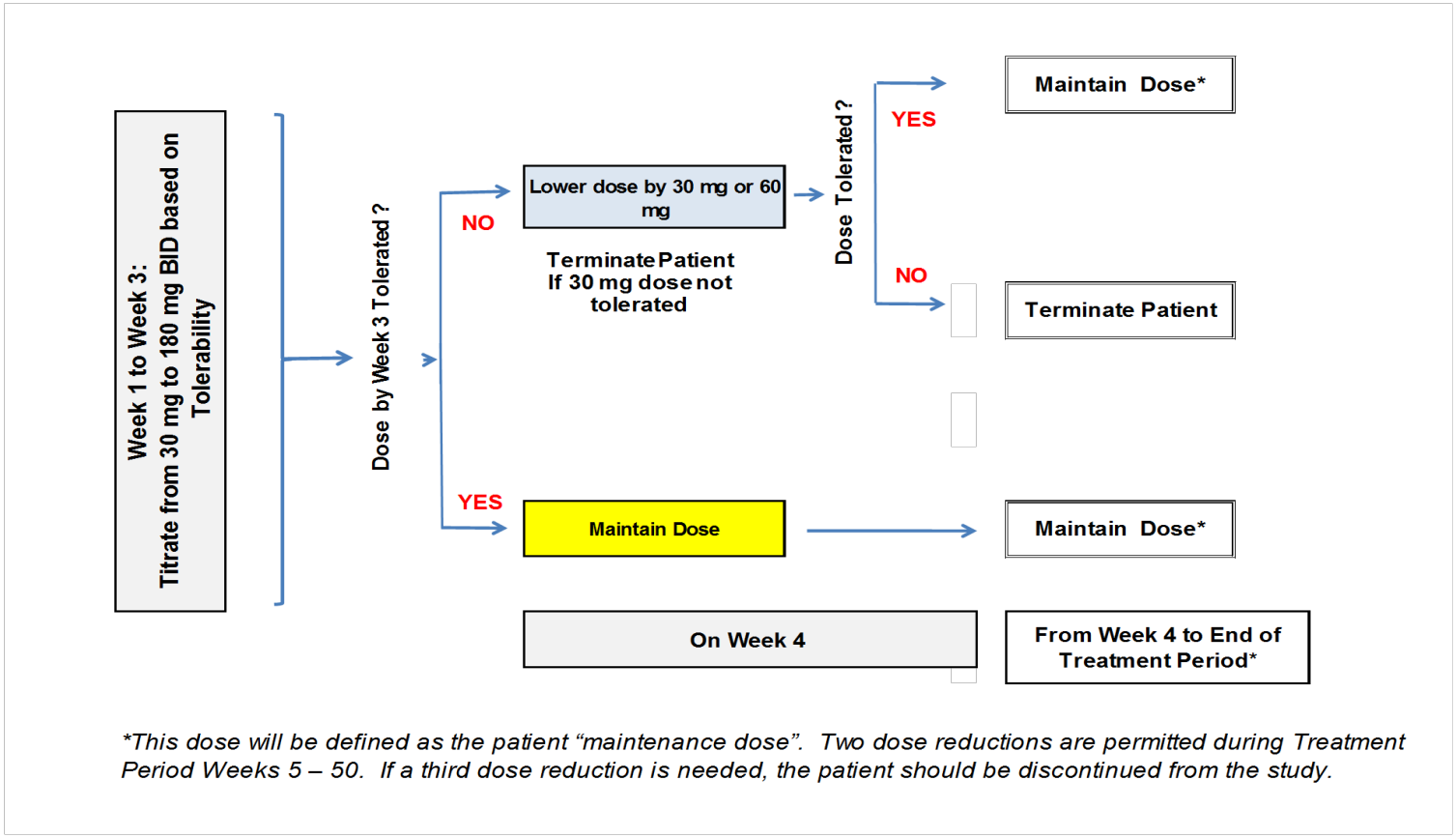
Patients transferring from the Observation Period will start with Visit 1b/TV1. Their follow-up in the Observation + Treatment Period will be 50 weeks in total.

Figure 3: Examples illustrating possible Observation and Treatment periods Scenarios in TR03-Ext



- Some patients will not be followed in the Observation Period (Top Scenario).
- For patients followed in the Observation Period, the total duration of time in the Observation and Treatment Periods will be up 50 weeks, regardless of when they transfer from the Observation Period to the Treatment Period (Middle and Bottom Scenarios)
- The first Observation Period visit at which the patient qualifies for treatment (see Table 1) will also be defined as Visit Ib/TV1.

Figure 4: Dosing Schedule in TR03ext



**This dose will be defined as the patient "maintenance dose". Two dose reductions are permitted during Treatment Period Weeks 5 – 50. If a third dose reduction is needed, the patient should be discontinued from the study.*

Appendix 3: Clinical Laboratory Tests

Hematology:	***Serum Chemistry:***
Hemoglobin	ALT
Hematocrit	Albumin
Red Blood Cell Count	Alkaline Phosphatase
White Blood Cell Count	AST
Platelet Count	Bicarbonate
White Blood Cell Differential	Blood Urea Nitrogen (BUN)
	Carbon Dioxide
	Calcium
Urine:	Chloride
Urinalysis	Creatinine
Pregnancy	Gamma-glutamyl transferase
	Glucose
	LDH
	Phosphorus
22.1.1.1.1.1 Serum Pregnancy:	Potassium
β-Human Chorionic Gonadotropin (HCG) (women of childbearing potential regardless of sexual activity	Sodium
	Total Bilirubin
	Total Protein
	Uric acid

Appendix 4: Patient Reported Outcomes

The Patient Reported Outcomes are provided on the subsequent pages.

Medical Outcomes Sleep Scale (Revised MOS Sleep-R)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Your Sleep

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. How long did it usually take for you to <u>fall asleep</u> during the <u>past 4 weeks</u>?

0-15 minutes	16-30 minutes	31-45 minutes	46-60 minutes	More than 60 minutes
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. On the average, how many hours did you sleep <u>each night</u> during the <u>past 4 weeks</u>?

Write in number of hours per night: ☐☐

3. How often during the <u>past 4 weeks</u> did you…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	get enough sleep to feel rested upon waking in the morning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	awaken short of breath or with a headache?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	have trouble falling asleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

MOS 12-Item Sleep Scale – Revised 2010
United States (English)

Medical Outcomes Sleep Scale (Revised MOS Sleep-R) (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

How often during the <u>past 4 weeks</u> did you…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
f	awaken during your sleep time and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	snore during your sleep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	take naps (5 minutes or longer) during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	get the amount of sleep you needed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ItchyQoL™

Sample – actual assessment scale will be provided to the patient at appropriate visits

ITCHING QUALITY OF LIFE SURVEY

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My itchy skin condition bleeds.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. My skin hurts because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. My itchy skin condition burns or stings.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. I get scars from my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. I need to scratch my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. I spend a lot of money treating my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
10. My itchy skin condition affects how well I sleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. My itchy skin condition often makes it difficult to concentrate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. My itchy skin condition limits the types of clothes I can wear.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. I am frustrated by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I am embarrassed by my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Updated 06 August 2013
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ItchyQoL™ (cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

	How often during the past week do these statements apply to you?				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. My itchy skin condition drives me crazy/nuts.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. My itchy skin condition makes me angry or irritable.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. My itchy skin condition makes me feel depressed or sad.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. I worry about what other people think about me because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. I worry that the itching will last forever.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. I feel self-conscious because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. My personality has changed because of my itchy skin condition.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Subject signature Date

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Prurigo Activity Score (PAS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

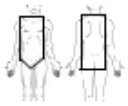
1. Type
a) Which efflorescences do you see?
□ papules
□ nodules
□ plaques
□ umbilicated ulcers
□ hypo-/hyperpigmented maculae

b) Which type of prurigo is predominant?
□ Prurigo papular type
□ Prurigo nodular type
□ Prurigo plaques type
□ Prurigo umbilicated "Kyrle" type
□ completely healed

2. Number
a) How many Prurigo lesions do you see? (do not count scars)
□ 0
□ 1 - 19
□ 20 – 100
□ > 100

3. Distribution:
□ disseminated
□ localized (only 1 or 2 areas affected)
□ neither of them

4. Please mark the affected area(s) (for definition of trunk see image).



whole body except head	□	
whole body head included	□	
or		
forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal
head	□ capillitium	□ face

5. Please choose a representative area:

forearm:	□ left	□ right
upper arm:	□ left	□ right
lower leg:	□ left	□ right
upper leg:	□ left	□ right
trunk	□ ventral	□ dorsal

Number of prurigo lesions in representative area (do not count scars):_____

6. Monitor lesions. Please mark the biggest (B) and a representative (R) prurigo lesion (remains the same in every visit).

	Highest elevation [mm]	Biggest diameter [mm]	
		longitudinal	crosswise
biggest prurigo lesion			
representative prurigo lesion			

7. Activity. Please mark the stage.

	stage 0	**stage 1**	**stage 2**	**stage 3**	**stage 4**
Prurigo lesions with excoriations/crusts compared to all prurigo lesions	0 %	1- 25 %	26 - 50 %	51 - 75 %	76 - 100 %
Healed prurigo lesions compared to all prurigo lesions	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

8. Take photos of the patient: Overview front and back, area(s) of marked monitor lesions to recognize on next visit

SST-Pr-10-2007, Amendment 9, PAS, Version 0.7; 11.09.2013

Patient Benefit Index, Pruritus Version (PBI-P)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Importance of Treatment Goals

With the help of the following questions, we'd like to know how important the goals mentioned below are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you.
If a statement does not apply to you, for example because you are not experiencing pain, please mark "*does not apply to me*".

	As a result of therapy, how important is it for you to ...	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*does not apply to me*
1	...be free of pain	O	O	O	O	O	O
2	...be free of itching	O	O	O	O	O	O
3	...no longer have burning sensations on your skin	O	O	O	O	O	O
4	...be healed of all skin defects	O	O	O	O	O	O
5	...concentrate better	O	O	O	O	O	O
6	...be less nervous	O	O	O	O	O	O
7	...be able to wear all types of clothing	O	O	O	O	O	O
8	...be able to bathe and shower normally	O	O	O	O	O	O
9	...sleep better	O	O	O	O	O	O
10	...feel less depressed	O	O	O	O	O	O
11	...experience greater enjoyment of life	O	O	O	O	O	O
12	...have no fear that the disease will get worse	O	O	O	O	O	O
13	...lead a normal everyday life	O	O	O	O	O	O
14	...be more productive in everyday life	O	O	O	O	O	O
15	...be less of a burden to relatives and friends	O	O	O	O	O	O
16	...engage in normal leisure activities	O	O	O	O	O	O
17	...be able to lead a normal working life	O	O	O	O	O	O
18	...be able to have more contact with other people	O	O	O	O	O	O
19	...be more comfortable showing yourself in public	O	O	O	O	O	O
20	...be less burdened in your partnership	O	O	O	O	O	O
21	...be able to have a normal sex life	O	O	O	O	O	O
22	...be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	...need less time for daily treatment	O	O	O	O	O	O
24	...have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	...have fewer side effects	O	O	O	O	O	O
26	...find a clear diagnosis and therapy	O	O	O	O	O	O
27	...have confidence in the therapy	O	O	O	O	O	O

Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

PBI-P (Cont'd)

Sample – actual assessment scale will be provided to the patient at appropriate visits

Treatment Benefits

When the treatment began, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent to which those treatment goals **were achieved**, indicating if the treatment has benefited you. If a statement did not apply to you, for example because you did not experience any pain, please mark "*did not apply to me*".

	The current treatment has helped me to …	**not at all**	**somewhat**	**moderately**	**quite**	**very**	*did not apply to me*
1	…be free of pain	O	O	O	O	O	O
2	…be free of itching	O	O	O	O	O	O
3	…no longer have burning sensations on my skin	O	O	O	O	O	O
4	…be healed of all skin defects	O	O	O	O	O	O
5	…concentrate better	O	O	O	O	O	O
6	…be less nervous	O	O	O	O	O	O
7	…be able to wear all types of clothing	O	O	O	O	O	O
8	…be able to bathe and shower normally	O	O	O	O	O	O
9	…sleep better	O	O	O	O	O	O
10	…feel less depressed	O	O	O	O	O	O
11	…experience greater enjoyment of life	O	O	O	O	O	O
12	…have no fear that the disease will get worse	O	O	O	O	O	O
13	…lead a normal everyday life	O	O	O	O	O	O
14	…be more productive in everyday life	O	O	O	O	O	O
15	…be less of a burden to relatives and friends	O	O	O	O	O	O
16	…engage in normal leisure activities	O	O	O	O	O	O
17	…be able to lead a normal working life	O	O	O	O	O	O
18	…be able to have more contact with other people	O	O	O	O	O	O
19	…be more comfortable showing myself in public	O	O	O	O	O	O
20	…be less burdened in my partnership	O	O	O	O	O	O
21	…be able to have a normal sex life	O	O	O	O	O	O
22	…be less dependent on doctor and clinic visits	O	O	O	O	O	O
23	…need less time for daily treatment	O	O	O	O	O	O
24	…have fewer out-of-pocket treatment expenses	O	O	O	O	O	O
25	…have fewer side effects	O	O	O	O	O	O
26	…find a clear diagnosis and therapy	O	O	O	O	O	O
27	…have confidence in the therapy	O	O	O	O	O	O

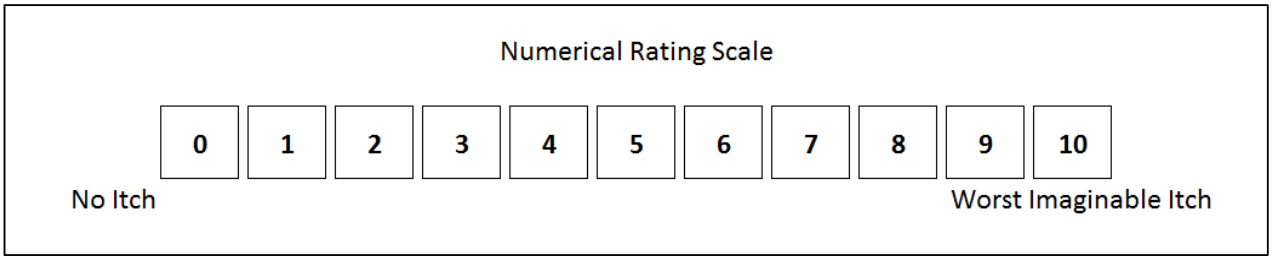
Please recheck your answers to make sure your have clearly marked each statement with an "x".

Thank you very much for your cooperation!

PBI-Patient Benefit Index (index of benefits and needs in therapy), Augustin 2006

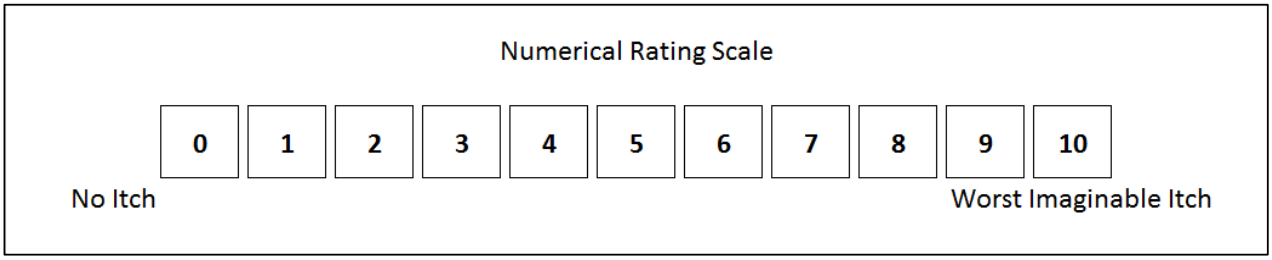
Numerical Rating Scale (Worst Itch)

How would you rate your most severe itching over the past 24 hours?



Numerical Rating Scale (Average-Itch)

How would you rate your itching on average over the past 24 hours?



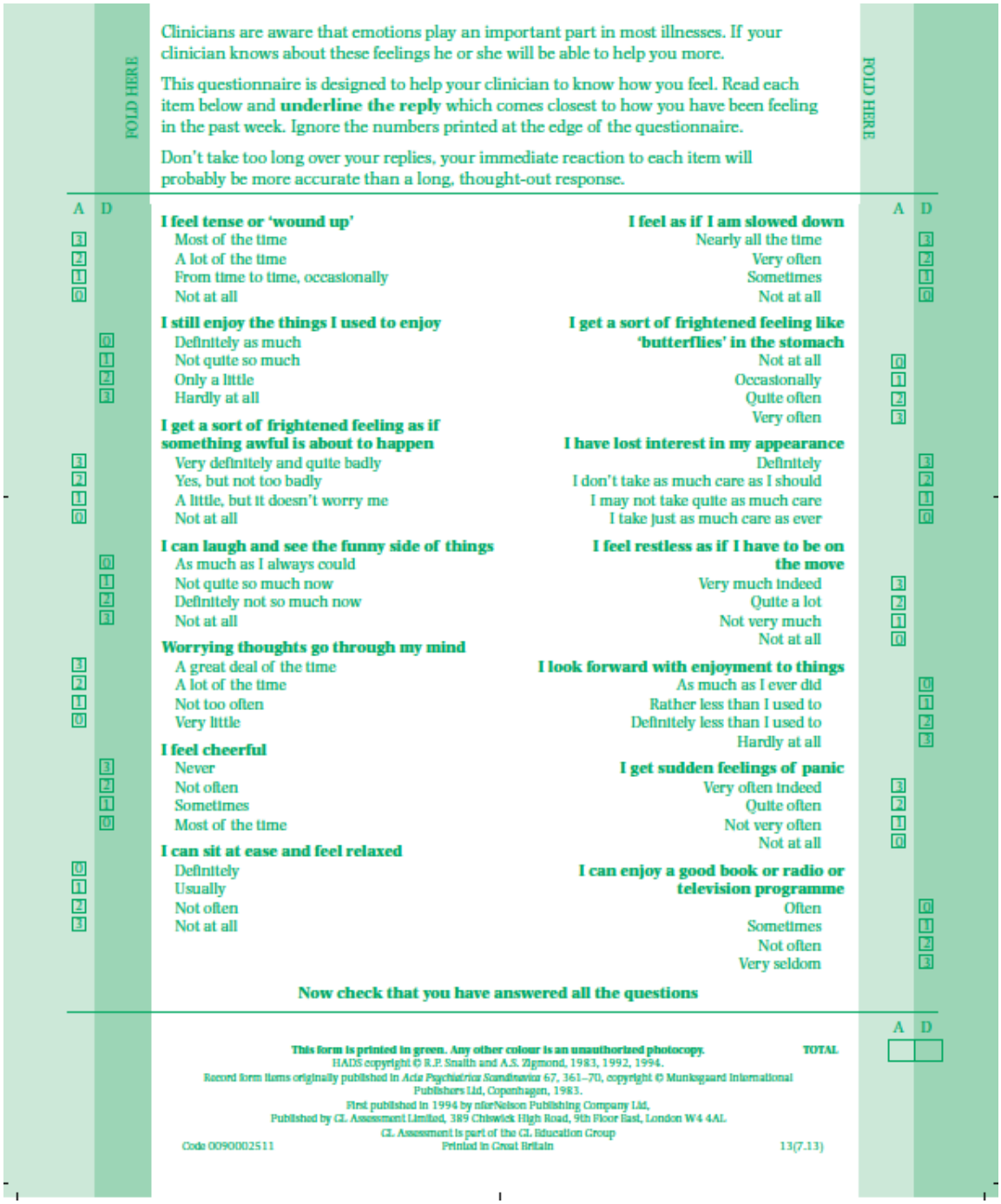
Verbal Rating Scale

How is your skin sensation today?

	0: not present	**1:** mild present	**2:** moderately present	**3:** severely present	**4:** very severely present
Itchy					
Burning					
Stinging					

Hospital Anxiety and Depression Scale (HADS)

Sample – actual assessment scale will be provided to the patient at appropriate visits



FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A D

I feel tense or 'wound up'
3 Most of the time
2 A lot of the time
1 From time to time, occasionally
0 Not at all

I still enjoy the things I used to enjoy
0 Definitely as much
1 Not quite so much
2 Only a little
3 Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
3 Very definitely and quite badly
2 Yes, but not too badly
1 A little, but it doesn't worry me
0 Not at all

I can laugh and see the funny side of things
0 As much as I always could
1 Not quite so much now
2 Definitely not so much now
3 Not at all

Worrying thoughts go through my mind
3 A great deal of the time
2 A lot of the time
1 Not too often
0 Very little

I feel cheerful
3 Never
2 Not often
1 Sometimes
0 Most of the time

I can sit at ease and feel relaxed
0 Definitely
1 Usually
2 Not often
3 Not at all

I feel as if I am slowed down
Nearly all the time 3
Very often 2
Sometimes 1
Not at all 0

I get a sort of frightened feeling like 'butterflies' in the stomach
Not at all 0
Occasionally 1
Quite often 2
Very often 3

I have lost interest in my appearance
Definitely 3
I don't take as much care as I should 2
I may not take quite as much care 1
I take just as much care as ever 0

I feel restless as if I have to be on the move
Very much indeed 3
Quite a lot 2
Not very much 1
Not at all 0

I look forward with enjoyment to things
As much as I ever did 0
Rather less than I used to 1
Definitely less than I used to 2
Hardly at all 3

I get sudden feelings of panic
Very often indeed 3
Quite often 2
Not very often 1
Not at all 0

I can enjoy a good book or radio or television programme
Often 0
Sometimes 1
Not often 2
Very seldom 3

Now check that you have answered all the questions

A D

TOTAL

Subjective Opiate Withdrawal Scale (SOWS)

Sample – actual assessment scale will be provided to the patient at appropriate visits

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

APPENDIX 5: CARDIOVASCULAR RELATED PROHIBITED MEDICATIONS AND CARDIOLOGICAL ASSESSMENTS

The Cardiological Assessments are provided on the subsequent pages.

Canadian Cardiovascular Society Grading of Angina Pectoris

Sample – actual grading scale will be completed at appropriate visits

Grade	Description
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

References

Campeau Lucien. Grading of angina pectoris. Circulation 1976;54:522-3

Available on the Canadian Cardiovascular Society Website at www.ccs.ca

NYHA FUNCTIONAL CLASSIFICATION

Sample – actual grading scale will be completed at appropriate visits

The NYHA classifies heart failure into classes based on functional limitations and severity.

Class	Patient Symptoms
Class I (Normal)	**Few observable symptoms, no limitation in ordinary physical activity.**
Class II (Mild)	**Mild observable symptoms and slight limitation during ordinary activity. Comfortable at rest.**
Class III (Moderate)	**Marked limitation in physical activity due to symptoms even during less-than-ordinary activity. Comfortable only at rest.**
Class IV (Severe)	**End-stage heart failure. Severe limitations. Experience symptoms even while at rest.**

ACC/AHA CLASSIFICATION OF CHF

The ACC/AHA created four classifications from risk for developing the disease to severe disability.

Stage	**Description**
A (High risk for developing CHF)	**Hypertension, diabetes mellitus, family history, coronary artery disease**
B (Asymptomatic HF)	**Previous myocardial infarction (heart attack), valvular disorders, left ventricular dysfunction**
C (Symptomatic HF)	**Structural heart disease, fatigue, low tolerance level for physical activity**
D (Refractory end-stage HF)	**Severe limitations. Experience symptoms even while at rest.**

Source: American Heart Association