Official Title: A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy and Safety Study in Prurigo Nodularis (PN) With Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)

NCT Number: NCT03497975

Document Date: Protocol Version 7.0 (Amendment 6) : 21 July 2021

CLINICAL STUDY PROTOCOL

A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy, and Safety Study in Prurigo Nodularis with Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)

Protocol No.: TR11	IND No.:
113770 EudraCT No.: 2018-001219-53	
Test Product:	Nalbuphine ER Tablets (NAL ER)
Indication:	Itch associated with Prurigo Nodularis
Sponsor:	Trevi Therapeutics, Inc.
Development Phase:	2b/3
Sponsor Medical Expert/Signatory:	[redacted] MD
Sponsor Contact:	[redacted]
Date of the Protocol:	21 July 2021
Version of the Protocol:	Version 7.0 (Amendment 6)

The confidential information in this document is provided to you as an Investigator, potential Investigator or consultant for review by you, your staff and applicable Independent Ethics Committee and/or Institutional Review Board. This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation (ICH) E6, and Title 21 of the Code of Federal Regulations (CFR), Parts 50, 56, and 312 (or equivalent regulatory body regulations/guidelines, as applicable)

2 SIGNATURE PAGE

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy, and Safety Study in Prurigo Nodularis with Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)

PROTOCOL NUMBER: TR11

Trevi Therapeutics, Inc.

[redacted] MD

[redacted] Date (day/month/year)

3 GENERAL INFORMATION

A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy, and Safety Study in Prurigo Nodularis with Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)

Protocol No.:	TR11
Date and number of the Protocol:	21 July 2021 (Amendment 6, Version 7)
Date and Number of prior Protocol Versions:	08 May 2018 (Original) 09 October 2018 (Amendment 1, Version 2) 14 March 2019 (Amendment 2, Version 3.1) 22 January 2020 (Amendment 3, Version 4) 04 August 2020 (Amendment 4, Version 5) 05 March 2021 (Amendment 5, Version 6)
Sponsor:	Trevi Therapeutics, Inc. 195 Church Street, 14th FloorNew Haven, CT 06510 USA
Clinical Research Organization:	ICON Clinical Research Ltd.South County Business Park Leopardstown Dublin 18 D18 X5R3 Ireland
Sponsor Medical Expert/Signatory:	[redacted] MD 195 Church Street14th Floor New Haven, CT 06510USA Tel No.: [redacted] Fax No.: [redacted]
Sponsor Contact:	[redacted] 195 Church Street14th Floor New Haven, CT 06510USA Tel No.: [redacted] Fax No.: [redacted]

4 STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Trevi Therapeutics, Inc.</td><td>Name of Product:
Nalbuphine extended release (NAL ER) tablets</td><td>Name of Active Ingredient:
Nalbuphine hydrochloride (HCl)</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 2-Arm, Efficacy, and Safety Study in Prurigo Nodularis with Nalbuphine ER Tablets for Pruritus Relief Through Itch Scratch Modulation (PRISM Study)</td></tr>
<tr><td colspan="3">Study Center(s):
Approximately 70 centers will be initiated for this study in 5 countries.</td></tr>
<tr><td colspan="3">Publication(s):
None</td></tr>
<tr><td colspan="2">Planned Study Period Following Sample Size Re-Estimation:
May 2018 to June 2022
(Primary Week 14 endpoint Dec 2021)</td><td>Development Phase:
Phase 2b/3</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective:
• To evaluate the effect of NAL ER on itch as assessed by the percentage of Responders (‘response’ is defined as a ≥ 4-point reduction in the 7-day average Worst Itch – Numerical Rating Scale [WI-NRS])
Secondary Objectives:
Key secondary objectives are as follows:
• To evaluate the effect of NAL ER on itch-related quality of life as assessed by the ItchyQoL™ total score
• To evaluate the effect of NAL ER on Prurigo Nodularis (PN) skin lesions as assessed by the Prurigo Activity Score (PAS) Question 5a
• To evaluate the effect of NAL ER on sleep as assessed by the PROMIS Sleep Disturbance Short Form 8a
Other secondary objectives are as follows:
• To evaluate the effect of NAL ER on itch as assessed by the mean change in WI-NRS
• To evaluate the benefit to subjects of NAL ER using the Patient Benefit Index, pruritus version (PBI-P)
• To characterize the safety and tolerability of NAL ER
• To assess the pharmacokinetics (PK) of nalbuphine and its metabolites</td></tr>
<tr><td colspan="3">Methodology:
This is a randomized, double-blinded, placebo-controlled, 2-arm study, with an open-label extension period following double-blind treatment. The study will investigate the anti-pruritic efficacy and safety of NAL ER when used for the treatment of itch in PN.
Subjects will be randomized to NAL ER (2-week titration followed by 162 mg twice daily [BID] for 12 weeks) or matching placebo (14 weeks duration), with the primary endpoint evaluation at Week 14. If permanent discontinuation of investigational product occurs anytime between Day 1 and the Week 14 visit, the subject will be asked to complete the Off-Treatment Visit, the Last Visit, and the End of Study telephone call, and to return to the clinic for the Week 14 visit (unless consent is withdrawn). During the open-label extension, subjects who received NAL ER will continue on NAL ER for a total of 38 additional weeks (total treatment duration 52 weeks including titration) and subjects who received placebo will crossover to NAL ER for a total of 38 weeks (including titration). Upon discontinuation of investigational product, all subjects will complete a 2-week off-treatment safety follow-up period, regardless of when and why the subject discontinued study treatment; unless they withdraw consent. In addition, a final follow-up itch and safety assessment will be made via telephone call (‘End of Study telephone call’) 4 weeks after the last dose of investigational product. The total planned study duration from randomization through to the last telephone contact is 56 weeks.</td></tr>
</table>

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Name of Product: Nalbuphine extended release (NAL ER) tablets	Name of Active Ingredient: Nalbuphine hydrochloride (HCl)

Subjects with diagnosed PN will be randomized (1:1) to 1 of the following treatment arms:

Arm 1: Blinded active titration over 2 weeks (to achieve a final NAL ER dose of 162 mg) followed by 162 mg BID for 12 weeks with continuation into the extension titration period (blinded), and the open-label fixed-dose period, followed by a 2-week off-treatment safety follow-up period and a final telephone contact, for itch and safety assessment, 4 weeks after investigational product discontinuation.

Arm 2: Placebo "titration" over 2 weeks followed by placebo BID for 12 weeks with continuation into the extension titration period (blinded; to achieve a final NAL ER dose of 162 mg BID) and the open-label fixed-dose period (NAL ER 162 mg BID), followed by a 2-week off-treatment safety follow-up period and a final telephone contact, for itch and safety assessment, 4 weeks after investigational product discontinuation.

Number of Subjects:

Approximately 360 subjects with diagnosed PN will be randomized. This amendment increases the original sample size from 240 to 360 randomized. The increase results from the interim sample size re-estimation (SSRE) which was introduced in Amendment 2, Protocol 3.1. The results of the interim analysis provided a conditional power in the pre-specified "promising zone", therefore the study Data Safety Monitoring Board (DSMB) recommended that the sample size should be increased to 360 randomized.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects eligible for randomization to receive investigational product must meet all of the following criteria:

1. Individuals diagnosed with generalized PN, defined as the presence of ≥ 10 pruriginous nodules, involving at least 2 distinct anatomical areas: for example, either 2 limbs; or a single limb and some axial portion of the body. Individuals with only axial lesions but involving 2 distinct anatomical areas that have no peripheral nervous system overlap are also eligible: for example, lesions involving a portion of the cranium and a portion of the trunk of the body. For purposes of this study, the axial portion will be defined as any non-appendicular portion of the body.
2. If there is any history of a primary pruritic skin condition other than PN, that condition must have been inactive for at least 6 months prior to screening.
3. Subjects with a history of acute secondary dermatoses within the preceding 6 months may enroll only if the dermatosis has resolved completely as follows per medical history or patient self-report and current clinical assessment: (a) Localized contact dermatitis, environmental exposures, superficial burns, or viral exanthems must have been resolved for at least 4 weeks prior to screening. (b) Skin or environmental infestations, such as scabies, lice, or bed bugs, must have been resolved for at least 8 weeks prior to screening.
4. Any identified systemic, non-dermatologic disease that could be a potential cause of concomitant pruritus (e.g., thyroid disease, celiac disease, hepatitis C virus [HCV]) must either have resolved, been successfully treated (i.e., HCV RNA negative), or must be successfully managed with stable, optimized treatment (e.g., thyroid replacement, dietary management with resolution of symptoms, respectively) for at least 3 months prior to screening.
5. WI-NRS score, recorded daily over the 7 contiguous days prior to and including the day of the baseline visit via electronic diary, must have at least 5 measurements recorded and all individual measurements must be ≥ 6. The arithmetic mean value of the measurements must be ≥ 7 as confirmed by the Trialogics Eligibility Check report immediately prior to randomization. The last WI-NRS value used in the calculation should be recorded on the day of the baseline visit and prior to dosing.
6. Subjects using antidepressants must be on a stable dose for a minimum of 4 weeks prior to screening and must be willing to remain on their stable dose for the entire duration of the study.
7. Subjects who are human immunodeficiency virus (HIV) positive may enroll if they meet the following criteria: (a) currently on a stable (> 6 months stable use) and well tolerated highly active antiretroviral therapy regimen; (b) CD4 count > 500 cells/mL; and (c) HIV ribonucleic acid (RNA) < 50 copies/mL documented for at least 6 months prior to enrollment. If enrolled, these subjects should continue to have their CD4 and HIV RNA monitored by their HIV provider per their standard of care for the duration of

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the TR11 study, and the data should be reported and documented at the next study visit.

8. Females of childbearing potential must be using an acceptable method of birth control (if sexually active) for 14 days prior to randomization and throughout the study. All females of childbearing potential must have a negative pregnancy test at the screening and baseline visits.

   For the purpose of this study, all females are considered to be of childbearing potential unless they are postmenopausal (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).

   Sexually active female subjects of childbearing potential are required to use 1 barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to 1 other method (e.g., intrauterine device in place at least 1 month, stable hormonal contraception for at least 3 months, or Essure procedure, or spermicide).

   Female subjects 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.
9. Age 18 years and older at the time of consent, and a life expectancy of at least 18 months.
10. Willing and able to understand and provide written informed consent.
11. Willing and able to comply with study requirements and restrictions.
12. Agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.

Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Pruritus due to localized PN (only 1 body part affected, for example only 1 arm).
2. Active, uncontrolled, pruritic dermatoses in need of treatment (such as atopic dermatitis or bullous pemphigoid for example).
3. Prurigo Nodularis associated with a history of atopic dermatitis is excluded if acute eczematous lesions are present, as characterized by erythematous, active predominant lichenified plaques with oozing and crusting.
4. History of a major psychiatric disorder such as bipolar disorder or schizophrenia is excluded. Subjects with a history of isolated major depression > 3 years previously may be eligible for enrollment if they have access to appropriate psychiatric care. An 'isolated major depression' is defined as a single event of depression that includes recurrent thoughts of death, recurrent suicidal ideation with or without a specific plan, or any history of a suicide attempt. Enrollment must be approved by the Medical Monitor. Subjects with general depression who are considered stable may be enrolled.
5. Serum bilirubin > 1.5 × upper limit of normal range at screening unless explained by a clinical diagnosis of Gilbert's Syndrome.
6. Serum hepatic alanine aminotransferase or aspartate aminotransferase enzymes > 100 U/L at screening.
7. Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at screening.
8. Significant medical condition, occupational restrictions (see Section 9.3), and/or other factors that in the opinion of the Investigator may interfere with the conduct of the study.
9. Subjects who have an active malignancy (either solid tumor or hematologic) are excluded. Subjects who have a past history of malignancy and who have no evidence of active disease, but who continue on therapy to prevent disease recurrence (i.e., tamoxifen for breast cancer, testosterone blockade for prostate cancer, etc.), may be eligible if approved by the Medical Monitor.
10. History of active substance abuse within the past 3 years.
11. Known intolerance of, or hypersensitivity or allergy to nalbuphine or vehicle components.
12. Pregnant or lactating females.
13. Concurrent enrollment in an ongoing clinical trial or anticipated enrollment in a concurrent clinical trial. Potential subjects who are actively participating in the safety follow-up of an ongoing COVID-19

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vaccination trial may enroll in this study if they meet the following criteria:

a. the vaccine under study has already been approved under an Emergency Use Authorization or via an equivalent regulatory review by the Health Authority in the country where they are enrolling;
b. they have completed the full vaccination series and are participating in a safety observation period without anticipation of any further vaccine trial intervention;
c. the COVID-19 trial permits co-enrollment.

Medication-Related Exclusions:

14. Known intolerance (gastrointestinal, central nervous system symptoms) or hypersensitivity/drug allergy to opioids.
15. Potential subjects taking monoamine oxidase inhibitors are excluded, as concomitant opiate use may increase the risk for serotonin syndrome.
16. Potential subjects taking cyclosporin A are excluded unless they undergo a 6-week washout. Subjects are prohibited from using cyclosporin during the study. Please refer to Table-3 (including footnote 3) and Section 9.1.3.1.
17. Potential subjects taking non-insulin biologics (including monoclonal antibodies), which modify the immune system, are excluded unless they undergo a 3-month washout. Please refer to Table-3 (including footnote 3) and Section 9.1.3.1.
18. Prior Exclusion criterion 18 is not applicable to subjects enrolling under Protocol V6 and later.
19. Exposure to any investigational medication, including placebo requires a 4-week washout (3 months for noninsulin biologics [e.g., monoclonal antibodies]). Please refer to Table-3 and Section 9.1.3.1.
20. Potential subjects receiving UV-therapy (PUVA, UVA, UVB, Excimer) requires a 4-week washout. Subjects are prohibited from using UV-therapy for the duration of the study. Please refer to Table-3 and Section 9.1.3.1.
21. Potential subjects who are taking opiates require a 14 –day washout. Subjects are prohibited from using opioids, including naltrexone, for the duration of the study. Please refer to Table-3 and Section 9.1.3.1.
22. Potential subjects receiving gabapentin, pregabalin, calcineurin inhibitors, cannabinoid agonists, capsaicin, cryosurgery, topical doxepin, thalidomide or methotrexate, topical antihistamines, and topical corticosteroids require a 14-day washout. These medications are prohibited for the duration of the study. Use of systemic antihistamines are not permitted unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study. Please refer to Table-3 and Section 9.1.3.1.
23. Potential subjects who have received systemic corticosteroids or local steroid injections of the PN lesions require a 4-week washout. These medications are prohibited for the duration of the study. Please refer to Table-3 and Section 9.1.3.1.
24. Potential subjects are excluded if they have had any addition or discontinuation of their regularly used prescription drugs, or any changes in the doses of their regularly used prescription drugs in the 14 days prior to the screening period e-diary WI-NRS collection.
25. Potential subjects taking central nervous system suppressants, such as barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics, and clonidine are excluded. These medications are prohibited for the duration of the study (see Section 10.6.2, footnotes 1 and 2 to Table-3 for definitions of ‘short-actingbenzodiazepines’).

Cardiac-related Exclusions:

26. Subjects with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association scale. (see Appendix 9)
27. Subjects with a history of angina pectoris Grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale. (see Appendix 8)
28. History of ventricular tachycardia, Torsade de Pointes, or family history of sudden death.

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29. Myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.
30. Serum potassium below the laboratory lower limit of normal. Note: If the initial screening value is low, but not considered clinically significant in relation to cardiac risk, then potassium supplementation may be prescribed and the serum potassium level repeated once at least 2 weeks later, during the screening period. If the repeat potassium remains < LLN, then the subject must be screen-failed.
31. QTcF interval > 450 ms (mean of 3 screening ECG QTcF values) if QRS <120 ms (mean of 3 screening ECG QRS values); QTcF interval >480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS ≥ 120 ms.
32. Heart rate < 45 bpm on any screening measurement either in the clinic or on the central ECG readings.
33. Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds® website; see Appendix 10) is not permitted unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study.
34. Prior Exclusion 34 criterion is not applicable for subjects enrolling in Protocol V7 and later.

Test Product, Dose and Mode of Administration:
NAL ER tablets, 162 mg BID, orally administered

Reference Therapy, Dose and Duration of Administration:
Matching placebo, orally administered

Duration of Treatment:
Up to 52 weeks

Assessments:

Efficacy:

Primary Efficacy Endpoint

The primary efficacy endpoint is the difference between the percent "Responders" at Week 14 for the NAL ER treatment arm versus the placebo arm. A "Responder" is defined as a subject with a ≥ 4-point decrease in the 7-day average WI-NRS from baseline to Week 14.

Secondary Efficacy Endpoints

Key secondary efficacy endpoints include the following:

- The mean change in ItchyQoL from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in the percentage of prurigenous lesions with excoriations/crusts (item 5a) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- The mean change in sleep disturbance (PROMIS Sleep Disturbance Short Form 8a) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm

Other secondary efficacy endpoints include the following:

- The mean change in 7-day average WI-NRS from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in the percentage of healed lesions (item 5b) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in the percentage number of lesions (item 2) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in Investigator Global Assessment-Prurigo Nodularis (IGA-PN) as assessed by the percentage of subjects having a 1-category improvement in activity
- Change in IGA-PN as assessed by the percentage of subjects having a 1-category improvement in stage

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- The proportion of subjects having a PBI-P score of ≥ 1 at Week 14 for the NAL ER treatment arm versus the placebo arm

Safety: All on-treatment safety data will be assessed descriptively based on the number and rates of adverse events (AEs), Serious AEs (SAEs), clinical laboratory measurements, central cardiac core laboratory read 12-lead ECGs, vital signs, and physical examinations. Subjects will also complete the Subjective Opiate Withdrawal Scale (SOWS) on a daily basis for the 2 weeks following the last dose of investigational product, whenever that occurs and regardless of the reason (unless consent is withdrawn). The totality of these data addresses the secondary objective of characterizing the overall safety and tolerability of NAL ER in subjects with PN.

An independent Data Safety Monitoring Board will periodically review safety data.

Pharmacokinetics: Nalbuphine plasma concentration and its metabolites.

Statistical Methods:

Sample Size and Power

The original planned sample size of approximately 240 subjects (120 per group) was based on assumed responder percentages for placebo and NAL ER of 25% and 45%, respectively. These responder percentages represent estimates based on the Week 10 data from the TR03 study; taking into account the longer blinded treatment period in this study, and the range of placebo responses observed in the literature for studies using patient reported outcome scales in related fields such as pain and neuropsychiatric diseases. Power is set at 90% with a 2-sided significance level of 0.05.

To address the concern of the reliability of the estimates of treatment effectiveness from the TR03 study, an adaptive mid-course Sample Size Re-Estimation (SSRE) procedure was introduced in Amendment 2, Protocol v3.1, when less than 10 subjects had been randomized. The analysis was to be performed after 50% of subjects (N=120) had either completed the Week 14 primary endpoint assessment or terminated the study early. Due to COVID 19-related delays, and because the key boundary for the lower margin of the SSRE did not differ if conducted at 45% of subjects, the SSRE was performed based on the Week 14 data for 109 subjects (including pre-Week 14 discontinuations). The analysis was performed as planned by a single, external, unblinded statistician, and was presented and discussed at a closed session of the study DSMB (July 9, 2020). Based on the DSMB's recommendation, the sample size for this study is being increased to 360 subjects since the SSRE conditional power fell within the 'promising zone' as defined by Mehta and Pocock.[33]

Efficacy

The proportions of NAL ER and placebo subjects that meet the primary endpoint definition of Responder (a ≥ 4-point reduction of the 7-day average WI-NRS from baseline to Week 14) will be analyzed using a mixed-effects logistic regression model which will include the baseline WI-NRS score as a covariate. Study sites (pooled) will be treated as a random effect to account for possible correlation between subjects within a site. The analysis will be based on the modified intent-to-treat (MITT) population. The primary endpoint will also be analyzed using the per-protocol population as a sensitivity analysis to assess the impact of protocol deviations such as selected pre-specified concomitant medications that might affect the primary endpoint outcome. Subjects with missing data at Week 14 will be imputed to have non-responder status in the primary mixed-effects model. Strategies to address missing data will include multiple imputation and a completers analysis, which will be used as sensitivity analyses. Details will be described in the statistical analysis plan.

For all open-label visits, descriptive statistics will be displayed by treatment.

All secondary endpoints will be analyzed using the MITT population. The change from baseline in continuous endpoints (WI-NRS, ItchyQoL, PROMIS Sleep Disturbance Short Form 8a) up to Week 14 will be analyzed based on a mixed model for repeated measures analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, and baseline value. The main treatment comparison of interest is at Week 14. For PAS, individual items will be presented with counts and percentages for categories by treatment group and visit; for excoriations/crusts, a logistic regression analysis will be performed for data at Week 14, with responders defined as subjects who had a ≥ 1-category improvement from baseline. For IGA-PN, individual items (PN Activity and PN Stage) will be presented with counts and percentages for categories by treatment group and visit; a logistic regression analysis will be performed for PN Activity at Week 14, with responders defined as subjects who had a

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≥ 1-category improvement from baseline. For PBI-P, the count and percentage of responders (defined as those with a PBI-P score of ≥ 1 at Week 14) will be presented by treatment group. For extension period visits, descriptive statistics will be displayed by treatment for all secondary variables.

Safety

The incidence of AEs will be summarized through the presentation of proportions by Medical Dictionary for Regulatory Activities (MedDRA) body system classification and preferred term. Vital signs and laboratory data will be summarized using descriptive statistics. The extent and duration of use of prohibited or restricted medications will be similarly summarized using descriptive statistics. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

AEs of special interest that code to the most relevant abuse-related MedDRA preferred terms will be tabulated and brief descriptions will be written. Additional AEs that are considered "possibly related to abuse potential" will be tabulated separately.

Electrocardiograms will be read centrally by specially trained staff at ERT® Clinical, with real-time feedback to clinical sites regarding any findings relevant to safety. Once the database is complete, ECG data (e.g., heart rate, PR, QTcF intervals etc.) will be presented in listings by subject and collection date/time. A complete ECG assessment will be documented in a separate ECG report from ERT Clinical.

Pharmacokinetics

Investigational product plasma concentration data (nalbuphine and metabolites) will be listed by collection time, as applicable.

Two additional sets of analyses will be conducted and provided in separate reports: 1) Analysis and reporting of concentration results by Covance Laboratory; and 2) pharmacokinetic–pharmacodynamic (PK-PD) analyses to describe the exposure-response relationships between nalbuphine plasma concentrations and efficacy parameters.

Additional PK-PD analyses may be conducted to include safety and/or tolerability parameters, as appropriate.

Date of the Protocol: 21 July, 2021 (Version 7, Amendment 6)

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
BID	Twice daily
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
e-diary	Electronic diary
ER	Extended release
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial FDA Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HCl	Hydrochloride
HCV	Hepatitis C virus

HD	Hemodialysis
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFSI	International Forum for the Study of Itch
IGA-PN	Investigator Global Assessment-Prurigo Nodularis
IgA-TTG	Immunoglobulin A tissue transglutaminase
IRB	Institutional Review Board
IND	Investigational New Drug
IV	Intravenous
IWRS	Interactive Web Response System
LFT	Liver function test
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MITT	Modified intent-to-treat
NAL	Nalbuphine hydrochloride
n	number of available observations
NRS	Numerical Rating Scale
OTC	Over-the-counter
PAS	Prurigo Activity Score
PBI-P	Patient Benefit Index, pruritus version
PCC	Positive comparative control
PK	Pharmacokinetic

PK-PD	Pharmacokinetic-pharmacodynamic
PN	Prurigo Nodularis
PP	Per-protocol
PRO	Patient-reported outcome
RNA	ribonucleic acid
QD	Once daily
QoL	Quality of life
q4wk	every 4 weeks
q8wk	every 8 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SHBG	Sex hormone binding globulin
SOWS	Subjective Opiate Withdrawal Scale
SubP	Substance-P
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UP	Uremic Pruritus
US(A)	United States (of America)
UV	Ultraviolet
W	Week
WHO	World Health Organization
WI-NRS	Worst Itch Numerical Rating Scale
WOCBP	Woman of childbearing potential

7 INTRODUCTION

7.1 General Information on Prurigo Nodularis

Prurigo Nodularis (PN) is an intensely pruritic dermatologic condition with the presence of nodular pruriginous lesions with excoriations and ulcerations, together with other types of pruriginous lesions such as papules and/or plaques[1]. While triggering pathology of varying etiologies may have preceded and initiated the itch-scratch cycle that leads to PN, once the distinct pruriginous lesions evolve, there has been a neuronal sensitization process that is now self-sustaining. The clinical persistence and further evolution of PN now depends on the sustained scratch-itch cycle. Therefore, PN can and often does exist in the absence of an ongoing, separate, triggering pathology. Moreover, the initial triggering etiology may never have been identified, and often is no longer identifiable when the subject is initially diagnosed with PN[2,3,4].

With regard to the types of preceding conditions that are associated with chronic pruritus and that have been reported as part of the clinical history of subjects with PN, pruritus secondary to multi-factorial etiologies ("mixed origin") was the most common pattern identified for "trigger" events. The majority of the "mixed origin" subjects had a combination of dermatological and systemic diseases or a combination of several systemic disorders.

There is no approved agent or treatment modality which has Health Authority labeling supporting its use in PN. In the literature generated by expert clinicians in this field, a variety of treatment options and medical interventions have been discussed, generally relying on evidence from case reports and treatment experience with modest case series. A review of the therapies that included topical, systemic, and intra-lesion steroid administration; antihistamines; anxiolytics; opiate receptor antagonists; thalidomide; gabapentin; capsaicin cream; topical anesthetics; occlusive therapies; ultraviolet (UV) light was performed, and reported that they had "mild to moderate success at best"[5]. Prurigo Nodularis has been described as a debilitating condition and a therapeutic challenge, for which conventional treatments with steroids, standard anti-pruritic agents, phototherapy and immune-suppressors often fail[6].

7.2 Nalbuphine

Trevi Therapeutics, Inc. is developing an oral pharmaceutical product, nalbuphine hydrochloride (HCl) extended release (NAL ER) tablet which is currently in development for the treatment of PN. Nalbuphine is currently only available as a generic medication in an injectable form; no oral formulation of the drug is approved for any medical indication.

The commercially available approved drug product was first marketed in 1979 in the United States (US) as Nubain®, on which the presently sold generic injectable formulations are based. Approved indications in the US include: the relief of moderate to severe pain, as a supplement to balanced anesthesia, pre-operative and post-operative analgesia, and obstetrical analgesia during labor and delivery. Commercial availability in the European Union (EU) dates to 1986, with approved indications for short-term relief of moderate to severe pain and pre- and post-operative analgesia. The most recent renewal evaluation for the current generic parenteral product in the EU was in 2010 by the Medicines Evaluation Board in the Netherlands[7]. Nalbuphine remains an unscheduled

drug with respect to the US Drug Enforcement Agency[8] and as of 2008, was not considered a controlled drug in most European countries including Austria, France, Germany, and Poland[9].

The nalbuphine moiety is a derivative of 14-hydroxymorphine and is structurally related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone. The pharmacologic mechanism of action has 2 components, with competitive antagonism of the opioid μ-receptor and simultaneous agonism at the opioid κ-receptor[10,11,12]. Imbalance of activity across the μ- and κ–opioid system has been associated with severe, chronic itch conditions and there is asubstantial literature suggesting that agonism of κ–receptors may have a therapeutic benefit in these settings[13]. The κ–agonist, nalfurafine, has been approved in Japan for the treatment of itch associated with both Uremic Pruritus (UP)[14] and chronic liver diseases including primary biliary cholangitis.

7.2.1 Preclinical Animal Data

A preclinical investigation was undertaken to demonstrate the effects of nalbuphine HCl on substance-P (SubP) induced scratching behavior in the mouse, a standard animal model for itch[15]. Scratching behavior induced by peripheral stimulation with the pruritogen SubP mimics the characteristics of itch-related scratching in humans[15,16]. Significant reduction in itch ($P < 0.001$) was noted following nalbuphine subcutaneous administration with approximately 43% reduction in itch at a 10-mg/kg dose and 52% at a 30-mg/kg dose. 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 shown to be as effective as the positive comparative control (PCC), nalfurafine, at reducing SubP-induced itch, with no statistical difference between nalbuphine and PCC effect, regardless of the dose.

The oral bioavailability of nalbuphine solution was low in rats and dogs (~5%), largely due to substantial first pass metabolism. Absorption was rapid with maximum plasma concentrations (C_{max}) achieved in both species between 20 and 30 minutes after dosing. The mean half-life of nalbuphine in rats and dogs was ~1 hour.

In vitro inhibition studies demonstrated that nalbuphine does not inhibit any of the major cytochrome P450 isozymes. Thus, the potential for a metabolism-based interaction of nalbuphine on other drugs is unlikely.

Several oxidative and conjugated metabolites of nalbuphine were identified in all species tested, with no metabolites being unique to humans. The metabolites have weak to no pharmacological activity and are unlikely to contribute to the drug activity in vivo.

7.2.2 Drug Metabolism and Pharmacokinetics of Nalbuphine in Humans

Nalbuphine is well absorbed in humans following oral administration of NAL ER tablets. Following single and multiple oral doses, exposure was dose-dependent and increased with increasing dose in a near dose proportional manner. Median C_{max} occurred between 3 and 6 hours postdose, with mean half-life varying between 6.6 and 9.6 hours which supports twice daily (BID) dosing. Steady state exposure is achieved within 2 to 3 days following repeat-dosing with a stable regimen. In common with high clearance drugs in general and opioids in particular, the absolute bioavailability following administration of an oral solution was low and highly variable[17]. The low oral bioavailability is likely due to extensive first pass metabolism and is similar across all species studied (see Section 7.2.1). The inter-subject variability of nalbuphine pharmacokinetic (PK) parameters (area under the curve and C_{max}) was high, with lower intra-subject variability, which is consistent with extensive hepatic metabolism.

Nalbuphine elimination is consistently reported to be slower following oral compared to intravenous (IV) administration. The prolonged elimination half-life of nalbuphine associated with oral administration is most likely due to enterohepatic circulation.

Several clinical single- and multiple-dose PK studies and clinical efficacy itch studies of 2 to 12-month duration have been conducted with a range of NAL ER doses (27 to 162 mg BID). Clinical data in itch and pharmacokinetic-pharmacodynamic (PK-PD) modelling both support the decision to take the 162 mg BID dose forward into future studies in itch, given the benefit-risk profile as observed to date.

The 162 mg BID dose selection was further corroborated by the exposure-response model for itch intensity (Worst Itch – Numerical Rating Scale [WI-NRS] using the Study TR03 PN dataset) and PK-PD simulations over dosing regimens of 81 to 216 mg BID. The exposure- response modelling provided evidence that nalbuphine exposures were associated with improved itch score responses and that a dose of 162 mg BID was the most optimal for achieving maximal efficacy reductions in Numerical Rating Scale (NRS) for itch from baseline. Doses higher than 162 mg were predicted to contribute minimal additional efficacy.

The safety profile of the NAL ER 162 mg BID dose was comparable to the 81 mg BID dose, and there was no obvious indication of either a dose-associated increase in adverse events (AEs) or in discontinuations due to AEs, beyond the titration period. Consequently, given its better efficacy profile, the NAL ER 162 mg BID dose (with appropriate titration to that dose) was considered a better candidate for future study.

Based on previous clinical observations in itch and the convergence of the PK-PD simulations, the selected dose of 162 mg of NAL ER is expected to show a significant improvement in PN-associated pruritus in this study. Lower doses are not expected to provide meaningful relief from itch in a significant number of subjects.

7.2.3 NAL ER Clinical Safety Data

The most frequently reported AEs in clinical trials to date have been central nervous system (CNS) and gastrointestinal (GI) symptoms. Specifically, the following events are considered potentially drug related: nausea, only in a minority of cases associated with vomiting; dizziness; somnolence, and headaches. Distinct from the opiate class in general, constipation has not been observed as a frequent or clinically troublesome AE in PN clinical trials with NAL ER. Thus, the overall safety profile observed with NAL ER is consistent with that typically associated with the mixed agonist-antagonist opioid class drugs[10]. Most of the AEs noted in the study program have been mild to moderate in severity, and tended to occur within the first weeks of dosing. It is thought that a slow initial titration to the target therapeutic dose may help induce tolerance, thereby minimizing the frequency and severity of these CNS and GI side effects (as the nausea may in part be mediated through CNS mechanisms). Therefore, in clinical trials with NAL ER in adults with PN, dosing begins with 27 mg taken once at bedtime and progresses over a 2-week titration period to the full dose of 162 mg BID.

The above summary provides the key clinical safety observations that have been observed to date in studies of NAL ER. In the TR11 study, 2 organ systems - endocrine and cardiac - are being further evaluated. Thyroid stimulating hormone (TSH) and testosterone levels (men only), and electrocardiogram (ECG) monitoring are performed at specified intervals. The background and rationale for these 2 organ system evaluations are provided below:

- Case reports and small prospective datasets for several orally administered opiates used in chronic disease management have shown evidence for associated endocrine alterations in humans. In the US, these data have resulted in mandatory class labeling but this class warning does not appear in EU labeling at the current time. The US warning addresses: (1) the potential for serotonin syndrome when opiates are used concomitantly with certain antidepressants (this study excludes monoamine oxidase inhibitors); (2) rare cases of adrenal insufficiency; and (3) a risk for lowered sex hormone levels. For nalbuphine, standard animal toxicology studies did not show any signal for endocrine toxicity based on the gross and microscopic findings in endocrine organs. To date, no cases of serotonin syndrome have been observed, and no cases of adrenal insufficiency, or abnormal endocrine levels have been attributed to nalbuphine use in NAL ER studies.

Definitive data on NAL ER's effect on cardiac conduction is not yet available from a thorough QT study. In this setting, the ECG procedures and enrollment criteria are a standard precaution appropriate for long-term studies. In previous clinical efficacy studies conducted by the sponsor (TR02 and TR02EXT in UP, and TR03 and TR03EXT in PN), independent reviews of ECG data were performed by a blinded reviewer. These reviews found no evidence that nalbuphine meaningfully prolongs cardiac repolarization. Heart rate changes were overall small and did not suggest an effect by nalbuphine at any of the studied doses. The benign ECGobservations from these prior clinical studies are supported by the preclinical in vitro study in the human ether-à-go-go-related gene assay, in which nalbuphine exhibited an inhibitory effectat concentrations that far exceed the nalbuphine plasma C_{max} by approximately 200-fold.

In summary, there are no nonclinical or clinical data suggesting that either of these endocrine and cardiac concerns is of specific relevance to NAL ER.

7.2.4 Overview of NAL ER Efficacy

The Phase 2 Study TR02 evaluated 2 doses (54 mg and 108 mg) of NAL ER versus placebo for the treatment of moderate to severe UP in 371 subjects on chronic hemodialysis (HD). The blinded treatment duration was 8 weeks, and results demonstrated both a dose response across the 2 NAL ER groups, and a significant difference in the change from baseline in the mean NRS values for the NAL ER 108 mg BID dose group versus placebo (difference of -0.73; *P* value 0.017). For the subset of subjects with severe UP (NRS ≥ 7) at baseline, the treatment difference was larger (difference of -1.39; *P* value 0.007).

The Phase 2 Study TR03 evaluated 2 doses of NAL ER versus placebo for the treatment of moderate to severe itch in the setting of established PN. This randomized, double-blind study evaluated 2 doses of NAL ER (81 mg and 162 mg BID) versus placebo across a total of 62 treated subjects with moderate to severe itch (WI-NRS ≥ 5). The total treatment duration was 10 weeks, including an initial 2-week titration period. The primary endpoint was the proportion of subjects with a reduction in the 7-day WI-NRS from baseline to the Week 10 assessment interval of ≥ 30%. Although the primary endpoint was not met (NAL ER 162 mg: 44% responders versus placebo 36%; $P = 0.323$), a secondary analysis of the completers subset did differentiate NAL ER 162 mg versus placebo (67% versus 40% [$P = 0.063$]). Assessing "responders" as those with a 50% reduction in WI-NRS from baseline showed greater discrimination, with 33% responders for NAL ER 162 mg versus 18% for placebo ($P = 0.083$) in the modified intent-to-treat (MITT) analysis and rates of 50% for NAL ER 162 mg versus 20% for placebo ($P = 0.028$) in a completers analysis.

Subjects who completed TR03 had the option to rollover into a separate open-label study, TR03 Extension, which provided a single arm experience using NAL ER with flexible dosing based on tolerability, and a total duration that could be as long as 1 year depending on when the subject moved from the qualification period into the active treatment period. Thirty-six subjects received treatment in this rollover study; 21 and 16 subjects completed 6 months and 1 year of treatment, respectively, though not all had complete data at both time points. Results across serial Prurigo Activity Score (PAS) assessments of the prurigo lesions showed that 10/18 subjects at 6 months and 9/15 subjects at 1 year had a ≥ 1 category improvement in excoriations/crusts. Similarly, 11/18 and 7/15 subjects had a ≥ 1 category improvement in lesion healing at 6 months and 1 year, respectively.

7.3 Rationale

In summary, Trevi has selected PN as the focus of the clinical development plan for NAL ER because the neuro-pharmacology of nalbuphine appears to be particularly well suited to address the pathophysiology of PN. In this chronic disease, the itch-scratch cycle, once established, results in a self-perpetuating neurologic pattern involving not just the skin itself, but importantly the signal processing from skin to spinal cord, spinal cord to brain, and back again. Moreover, the totality of the clinical efficacy data in subjects across 2 severe itch conditions provides a strong empiric rationale to further investigate the effects of NAL ER in subjects with PN.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) guidelines on GCP.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To evaluate the effect of NAL ER on itch as assessed by the percentage of Responders ('response' is defined as a ≥ 4-point reduction in the 7-day average WI-NRS)

8.2 Secondary Objectives

Key secondary objectives are as follows:

- To evaluate the effect of NAL ER on itch-related quality of life as assessed by the ItchyQoL total score
- To evaluate the effect of NAL ER on PN skin lesions as assessed by the PAS Question 5a
- To evaluate the effect of NAL ER on sleep as assessed by the PROMIS Sleep Disturbance Short Form 8a

Other secondary objectives are as follows:

- To evaluate the effect of NAL ER on itch as assessed by the mean change in WI-NRS
- To evaluate the benefit to subjects of NAL ER using the Patient Benefit Index, pruritus version (PBI-P)
- To characterize the safety and tolerability of NAL ER
- To assess the PK of nalbuphine and its metabolites

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a randomized, double-blinded, placebo-controlled, 2-arm study, with an open-label extension period following double-blind treatment, to investigate the anti-pruritic efficacy and safety of NAL ER tablets. Eligible subjects will be randomized to NAL ER (2-week titration followed by 162 mg BID for 12 weeks) or matching placebo (14 weeks duration), with the primary endpoint evaluation at Week 14. If permanent discontinuation of investigational product occurs anytime between Day 1 and the Week 14 visit, the subject must be asked to complete the Off-Treatment visit, the Last Visit, the End of Study telephone call, and to return to the clinic for the study planned Week 14 visit (unless consent is withdrawn). During the open-label extension, subjects who received NAL ER will continue on NAL ER for a total of 38 additional weeks (total treatment duration 52 weeks including titration) and subjects who received placebo will

crossover to NAL ER for a total of 38 weeks (including titration). Upon discontinuation of investigational product, all subjects will complete the 2-week off-treatment and safety follow-up period, regardless of when and why the subject discontinued study treatment, unless they withdraw consent. In addition, a final follow-up itch and safety assessment will be made via the End of Study telephone call 4 weeks after the last dose of investigational product. The total planned study duration from randomization through to the last telephone contact is 56 weeks.

Approximately 360 subjects with diagnosed PN will be randomized (1:1) to one of the following treatment arms:

Arm 1: Blinded active titration over 2 weeks (to achieve a final NAL ER dose of 162 mg) followed by 162 mg BID for 12 weeks with continuation into the extension titration period (blinded), and the open-label fixed-dose period, followed by a 2-week off-treatment safety follow-up period and a final telephone contact, for itch and safety assessment, 4 weeks afterinvestigational product discontinuation.

Arm 2: Placebo "titration" over 2 weeks followed by placebo BID for 12 weeks with continuation into the extension titration period (blinded; to achieve a final NAL ER dose of162 mg) and the open-label fixed-dose period (NAL ER 162 mg), followed by a 2-week off-treatment safety follow-up period and a final telephone contact, for itch and safety assessment, 4 weeks after investigational product discontinuation.

At the regularly scheduled study visits for Week 28, Week 32, and Week 36, an elective dose reduction to a 108 mg NAL ER BID dose may be considered for subjects who achieve a confirmed WI-NRS ≤ 3 **and** visible lesion healing as assessed by an improvement of at least 1 category in the PAS Item 5b lesion healing activity score (e.g. if "0-24%" of PN lesions at baseline were assessed as 'healed', then a 1-category change means that "25-50%" of current Week 28 PN lesions are now healed). The decision to reduce dose is at the discretion of the Investigator and with the agreement of the subject. Dose reduction is not permitted prior to Week 28 or after Week 36 and once this dosing has started, no re-escalation will be permitted.

The study design schematic is presented in Figure-1.

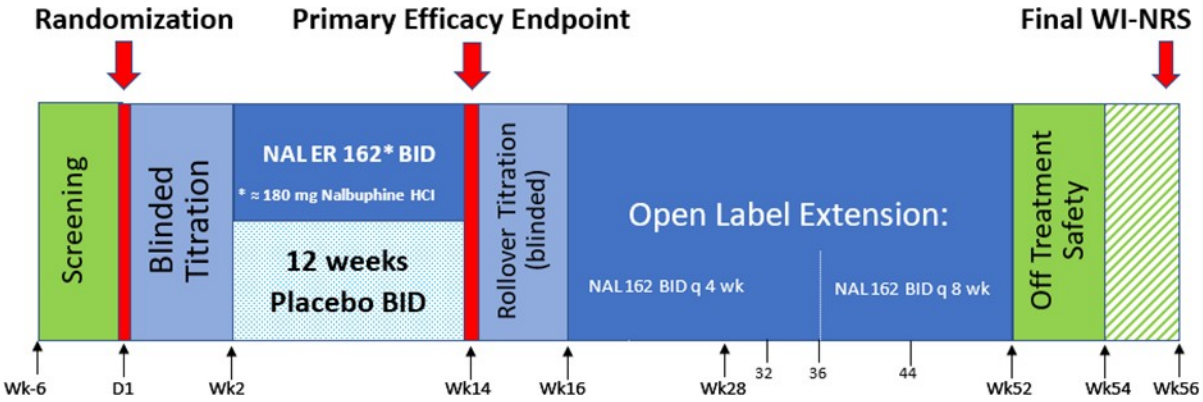

Figure-1. Study Design

BID: twice daily; D: day; NAL ER: Nalbuphine 162 mg extended release; WI-NRS: Worst Itch – NumericalRating Scale; W =week.

9.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 1 and Table 2.

Table-1. Schedule of Assessments – Double-blind, Placebo-controlled Period

Study Period →	**Screening and Washout[1,2]**	**Double-blind Titration Period[10]**				**Double-blind Fixed-dose Period[10]**					**Extension Titration Period**			**Open-label Fixed-dose Period**
						W3D1 to W14D7					**Transition to Open-label**			**W17, D1 to W52, D7**
Assessment ↓	**Screening and Washout**	**Baseline[1]**	☎	☎	**End of Titration**	☎	☎	**Repeating visit q4wk**			☎	☎	**End of Titration**	**Repeating extension visits**
Visit Week	**-6 to -1**	**1**	**1**	**1**	**2[9]**	**3**	**3**	**6**	**10**	**14**	**15**	**15**	**16[11]**	**Weeks 17 to 52**
Study Day (±2 days*;Day 14 and Day 112: -2 days ONLY)[14]	**Up to Day -1**	**1**	**3**	**7**	**14 ***	**15**	**21**	**42**	**70**	**98**	**101**	**105**	**112 ***	**Days 113 to 364**
Informed consent[13]	X													Refer to **Table-2** for schedule of open-label extension period
Medical, neurological,and Prurigo Nodularishistory	X													
Physical examination	X									X				
Brief neurological assessment	X	X			X								X	
Vital signs[3]	X	X			X			X	X	X			X	
Height, weight, and BMI[15]	X	X			X			X		X				
Central ECG[4] (triplicate)	X				X			X		X			X	
Clinical Laboratory assessments[5]	X	X			X			X		X				
Tolerability Intervention			X	X	X	X	X				X	X		
Urinalysis	X	X												
Urine pregnancy[5]	X	X			X			X	X	X			X	
Inclusion/exclusioncriteria[1]	X	X												
Randomization viaIWRS		X												
Blood for PKassessment		X			X			X	X	X			X	
Record and assess AEs/AESIs, concomitant medications, and therapies (includingrestricted and prohibited medications)[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table-1. Schedule of Assessments – Double-blind, Placebo-controlled Period														
Study Period →	**Screening and Washout[1,2]**	**Double-blind Titration Period[10]**				**Double-blind Fixed-dose Period[10]**					**Extension Titration Period**			**Open-label Fixed-dose Period**
						W3D1 to W14D7					**Transition to Open-label**			**W17, D1 to W52, D7**
Assessment ↓	**Screening and Washout**	**Baseline[1]**	☎	☎	**End of Titration**	☎	☎	**Repeating visit q4wk**			☎	☎	**End of Titration**	**Repeating extension visits**
Visit Week	**-6 to -1**	**1**	**1**	**1**	**2[9]**	**3**	**3**	**6**	**10**	**14**	**15**	**15**	**16[11]**	**Weeks 17 to 52**
Study Day (±2 days*;Day 14 and Day 112: -2 days ONLY)[14]	**Up to Day -1**	**1**	**3**	**7**	**14 ***	**15**	**21**	**42**	**70**	**98**	**101**	**105**	**112 ***	**Days 113 to 364**
e-diary[7] – Dispense and train/review use	X													
e-diary – retrieve and review use and entry compliance[7]	X	X			X			X	X	X			X	
Dispense Subject Medication Log and Subject Symptom Log[6]	X													
Retrieve/review/re-dispense Subject Medication Log and Subject Symptom Log[6]		X			X			X	X	X			X	
ItchyQoL[7]	X	X						X	X	X				
PAS and IGA-PN	X	X							X	X				
PBI-P[7]	X	X							X	X				
Sleep Scale(PROMIS)[7]	X	X						X	X	X				
WI-NRS[7]	X	X	X	X	X	X	X	X	X	X			X	
Photography[8]		X								X				
Dispense investigational product		Card **12**			B			B	B	Card			B[9]	
Dispense Instructions for Taking TR11 Study Medication[12]		X			X					X			X	
Retrieve investigational productand containers					NA[9]			B + Card	B	B			NA[11]	

Table-1. Schedule of Assessments – Double-blind, Placebo-controlled Period

Study Period →	Screening and Washout[1,2]	Double-blind Titration Period[10]				Double-blind Fixed-dose Period[10]					Extension Titration Period			Open-label Fixed-dose Period
						W3D1 to W14D7					Transition to Open-label			W17, D1 to W52, D7
Assessment ↓	Screening and Washout	Baseline[1]	☎	☎	End of Titration	☎	☎	Repeating visit q4wk			☎	☎	End of Titration	Repeating extension visits
Visit Week	-6 to -1	1	1	1	2[9]	3	3	6	10	14	15	15	16[11]	Weeks 17 to 52
Study Day (±2 days*;Day 14 and Day 112: -2 days ONLY)[14]	Up to Day -1	1	3	7	14 *	15	21	42	70	98	101	105	112 *	Days 113 to 364
Investigational product accountability					X			X	X	X			X	
Investigational product - review dosingcompliance					X			X	X	X			X	

AE: adverse event; **B**: bottle; **BMI**: body mass index; **Card**: blister card; D: Day; **ECG**: electrocardiogram; **e-diary**: electronic diary; **IGA-PN**: Investigator Global Assessment-Prurigo Nodularis; **IWRS**: Interactive Web Response System; **LFT**: liver function test; **NA**: not applicable; **PAS**: Prurigo Activity Score; **PBI-P**: Patient Benefit Index, pruritus version; **PK**: pharmacokinetic; **PRO**: patient-reported outcome; **q4wk**: every 4 weeks; **SHBG**: sex hormone binding globulin; **SOWS**: Subjective Opiate Withdrawal Scale; **TSH**: thyroid stimulating hormone; **W**: Week; **WI-NRS**: Worst Itch – Numerical Rating Scale; **WOCBP**: woman of childbearing potential; ☎: telephone call.

1. If clinically indicated, **screening procedures** may be completed over multiple visits (such as needed for washout of medications intended for anti- pruritic treatment) as long as they occur within the screening period. However, if the subject meets all inclusion/exclusion criteria, they should be randomized as soon as possible after meeting study requirements, but no later than 6 weeks after the initial screening visit. Except in cases of medication washout, the baseline (randomization) visit can take place in as little as 7 days after all screening procedures have been performed, the required testing results have been obtained, and eligibility has been verified.
2. If a **medication washout** is required, WI-NRS collection should begin following completion of the washout.
3. **Vital signs** are to be obtained after the subject has been seated for at least 5 minutes.
4. **ECGs** are to be performed in triplicate (3 serial ECGs at least 1 minute apart) after the subject has been in the supine position for at least 5 minutes. ECGs are to be transmitted to be read centrally by a core ECG laboratory. The average of the QTcF values from the triplicate ECGs wil be performedand presented in a report to be used as the final eligibility assessment for the subject,
5. **Laboratory Evaluations:** Hematology and serum chemistry, LFTs, specified endocrine tests (at screening and Week 14 only: TSH, with reflex free T4 if above Upper Limit Normal (ULN) or below Lower Limit Normal (LLN), free testosterone [the fraction not bound to SHBG or albumin] and SHBG for males), and serum pregnancy test if WOCBP (regardless of sexual status at screening and baseline); urine pregnancy test to be performed by the local laboratory and confirmed to be negative prior to dispensing investigational product. TSH values above the upper limit of normal (ULN) should be repeated at the next study visit (or approximately 1 month later; whichever occurs first). If TSH remains above ULN, a Free T4 will be performed on the existing laboratory sample.
6. **AEs** are to be continually assessed starting with the signing of the informed consent. Concomitant medications should be collected from 14 days priorto the signing of consent. During the screening visit, subjects must be instructed to record any **new AEs or concomitant medication use** on the **Subject Symptom Log and Subject Medication Log** and to bring the logs to every visit (including the telephone contacts). Site to retrieve and review these logs at each subsequent visit prior to re-dispensing them or issuing new logs to the subject. Events of special interest should trigger the collection of additional information using the **AESI worksheet** and documented under the **AESI section of the Adverse Event eCRF**. Event details and both **subject and investigator narratives** should be thoroughly documented in the AESI worksheet and completed under the AESI

Table-1. Schedule of Assessments – Double-blind, Placebo-controlled Period

Study Period →	Screening and Washout[1,2]	Double-blind Titration Period[10]				Double-blind Fixed-dose Period[10]					Extension Titration Period			Open-label Fixed-dose Period
						W3D1 to W14D7					Transition to Open-label			W17, D1 to W52, D7
Assessment ↓	Screening and Washout	Baseline[1]	☎	☎	End of Titration	☎	☎	Repeating visit q4wk			☎	☎	End of Titration	Repeating extension visits
Visit Week	-6 to -1	1	1	1	2[9]	3	3	6	10	14	15	15	16[11]	Weeks 17 to 52
Study Day (±2 days*;Day 14 and Day 112: -2 days ONLY)[14]	Up to Day -1	1	3	7	14 *	15	21	42	70	98	101	105	112 *	Days 113 to 364

section of the Adverse Event eCRF. **Refer to section 12.1.1. Definitions.**

7. During screening, the **e-diary** must be dispensed to minimally allow for **7 contiguous days of WI-NRS collection** prior to the baseline visit (collection during this period provides formal study data required for randomization). The **e-diary administers the WI-NRS, medication compliance, and SOWS** when applicable. Other PROs (Itchy QoL, PBI-P, and PROMIS sleep scale) are collected at select visits as described in Section 11.2. PROs administered during screening, but prior to Day -7, are to familiarize the subject to the instruments only, and not for the purpose of data collection. If multiple visits occur during the screening period, collection of these data (WI-NRS and PROs) should begin at the visit prior to the Week 1 baseline visit. Throughout the double-blind period, the subject is to record the WI-NRS data daily; daily WI-NRS data collection via the e-diary or in the Trialogics web portal ends at the Week 14 visit.
8. **Photography** to be performed at selected sites only. See the Canfield Quick Reference Guide and the User Reference Manual for photography procedures as applicable.
9. The **Double-blind Titration blister card** will be **reviewed, but not be retrieved at this visit**. See the Pharmacy Manual and Instructions for TakingTR11 Study Medication for additional instructions.
10. **Subjects who discontinue investigational product for any reason** (other than withdrawal of consent) prior to the Week 14 visit must be asked to complete the Off-Treatment visit, the Last Visit, and the End of Study telephone call and to return to the site for their study schedule planned Week 14 visit at study Day 98 (see **Table-2**).
11. The **Open-Label Titration blister card** will be **reviewed, but not retrieved**, at this visit. See the Pharmacy Manual and Instructions for Taking TR11 Study Medication for additional instructions.
12. Site to dispense the Instructions for Taking TR11 Study Medication as applicable to the subject's dosing period (i.e., Double-blind titration blister card or Double-blind fixed dose bottle). Note: Although both AM and PM doses are present on Day 1, only the PM dose will be taken (both Arms)
13. At the time of informed consent, **subjects identified as taking a concomitant short-acting benzodiazepine should be provided with the Benzodiazepine Patient Information Sheet**, informing them of safety information and warnings regarding the use of NAL ER in combination with this class of drug. Likewise, any subject who is subsequently prescribed short-acting benzodiazepines **during the course of the study** should also be provided with this information sheet.
14. At study Day 14 and Day 112, the **titration card** only contains 14 days of dosing. Subjects should be scheduled to come in on the target date or up to 2 days prior to ensure not to run out of investigational product.
15. **Height** and **BMI** will be obtained at the screening visit only. Weight will be obtained at the screening visit and subsequently according to the schedule.

Table-2. Schedule of Assessments – Open-label Extension Period

Study Period →			**Open-label Fixed-dose Period**						**Washout and Safety Follow-up Period**		**Last Contact for WI-NRS**
			Repeating visit q4wk or q8wk								
Assessment ↓	☎	☎	**W17 to W52**						**Off-Treatment[1]**	**Last Visit[1]**	**End of Study telephone call[1]**
Visit Week	**17**	**17**	**20**	**24**	**28[2]**	**32[2]**	**36[2]**	**44**	**52**	**54**	**56**
Study Day (±2 days)	**113**	**120**	**140**	**168**	**196**	**224**	**252**	**308**	**364**	**378**	**392**
Physical examination									X	X	
Brief neurological assessment									X	X	
Vital signs[3]			X	X	X	X	X	X	X	X	
Weight					X			X	X	X	
Central ECG[4]			X		X				X		
Clinical Laboratory assessments[5]					X			X	X	X	
Blood for PK assessment			X		X	X	X	X	X		
Urinalysis					X				X		
Urine pregnancy (WOCBP)			X	X	X	X	X[3]	X	X	X	
Record and assess AEs/AESIs[6], concomitant medications, and therapies (including restricted and prohibited medications)	X	X	X	X	X	X	X	X	X	X	X
Tolerability intervention	X	X			X		X				
e-diary[7] – retrieve and/or review entry compliance			X	X	X	X	X	X	X	X	

Table-2. Schedule of Assessments – Open-label Extension Period

Study Period →			**Open-label Fixed-dose Period**						**Washout and Safety Follow-up Period**		**Last Contact for WI-NRS**
			Repeating visit q4wk or q8wk								
Assessment ↓	☎	☎	**W17 to W52**						**Off-Treatment[1]**	**Last Visit[1]**	**End of Study telephone call[1]**
Visit Week	**17**	**17**	**20**	**24**	**28[2]**	**32[2]**	**36[2]**	**44**	**52**	**54**	**56**
Study Day (±2 days)	**113**	**120**	**140**	**168**	**196**	**224**	**252**	**308**	**364**	**378**	**392**
Retrieve/review/re- dispense Subject Medication Log and Subject Symptom Log[8]			X	X	X	X	X	X	X	X	
ItchyQoL[7]			X	X	X		X	X	X		
PAS and IGA-PN			X	X	X	X	X	X	X		
PBI-P[7]			X		X		X	X	X		
Sleep Scale (PROMIS)[7]			X	X	X		X	X	X		
WI-NRS[7]			X	X	X	X	X	X	X	X	X
Photography[8]					X				X		
Administer 14-daySOWS[9]									X		
Retrieve 14-daySOWS[9]										X	
Dispense investigational product			B	B	B	B	BB	BB			
Retrieve investigational product and containers			B + Card	B	B	B	B	BB	BB (B)[10]		
Investigational product - accountability			X	X	X	X	X	X	X		

Table-2. Schedule of Assessments – Open-label Extension Period

Study Period →			Open-label Fixed-dose Period						Washout and Safety Follow-up Period		Last Contact for WI-NRS
			Repeating visit q4wk or q8wk						Off-Treatment[1]		End of Study telephone call[1]
Assessment ↓	☎	☎	W17 to W52							Last Visit[1]	
Visit Week	**17**	**17**	**20**	**24**	**28[2]**	**32[2]**	**36[2]**	**44**	**52**	**54**	**56**
Study Day (±2 days)	**113**	**120**	**140**	**168**	**196**	**224**	**252**	**308**	**364**	**378**	**392**
Investigational product - review dosing compliance			X	X	X	X	X	X	X		

AE: adverse event; **B**: bottle; **BID**: twice daily; **Card**: blister card; **ECG**: electrocardiogram; **e-diary:** electronic diary; **IGA-PN**: Investigator Global Assessment-Prurigo Nodularis; **LFT**: liver function test; **NA**: not applicable; **PAS**: Prurigo Activity Score; PBI-P: Patient Benefit Index, pruritic versions; **PK**: pharmacokinetic; **PRO**: patient-reported outcome; q4wk: every 4 weeks; q8wk: every 8 weeks; **SHBG**: sex hormone binding globulin; **SOWS**: Subjective Opiate Withdrawal Scale; **TSH**: thyroid stimulating hormone; **W**: Week; **WI-NRS**: Worst Itch – Numerical Rating Scale; **WOCBP**: woman of childbearing potential; ☎: telephone call.

1. **Off-Treatment visit** occurs upon stopping investigational product; regardless of reason. Subjects who elect to go off-treatment prior to 52 weeks of treatment (**premature discontinuation** of investigational product) should be asked to complete the Off-Treatment visit, the 2-week SOWS evaluation, the Last Visit (occurs 14 days after off-treatment visit date), and the End of Study telephone call.
2. Assess **eligibility for down titration** based on criteria of confirmed WI-NRS ≤ 3 and 1 category improvement in PAS lesion healing. If both criteria are met, may discuss the option for a permanent dose reduction to 108 mg BID. Note: if criteria are met, this decision is at the discretion of the Investigator and with the agreement of the subject, but once dose reduction has been initiated no re-escalation is permitted.
3. **Vital signs** are to be obtained after the subject has been seated for at least 5 minutes.
4. **ECGs** are to be performed in triplicate (3 serial ECGs at least 1 minute apart) after the subject has been in the supine position for at least 5 minutes. ECGs are to be transmitted to be read centrally by a core ECG laboratory. The average of the QTcF values from the triplicate ECGs wil be performed and presented in a report to be used as the final eligibility assessment for the subject.
5. **Laboratory Evaluations:** Hematology and serum chemistry, LFTs, specified endocrine (TSH all subjects with reflex free T4 if above Upper Limit Normal (ULN) or below Lower Limit Normal (LLN), ; free testosterone [the fraction not bound to SHBG or albumin] and SHBG for males) and pregnancy if WOCBP (regardless of sexual status); urine pregnancy test to be performed by the local laboratory and confirmed to be negative prior to dispensing investigational product. TSH values above the upper limit of normal (ULN) should be repeated at the next study visit (or approximately 1 month later; whichever occurs first). If TSH remains above the ULN, a Free T4 will be performed on the existing laboratory sample).
6. **AEs** are to be continually assessed starting with the signing of the informed consent. Subjects should continue to record any new AEs or concomitant medication use on the Subject Symptom Log and Subject Medication Log. Site staff are required to remind subjects to bring the logs to each visit (including the telephone contacts). Logs should be reviewed by site staff at every visit prior to re-dispensing (or issuing new logs as needed) to subjects. Final retrieval of the logs, for filing in source records, should occur at the last clinic visit. **Events of special interest should trigger the collection of additional information using the AESI worksheet and documented under the AESI section of the Adverse Event eCRF**. Event details and both subject and investigator narratives should be thoroughly documented in the AESI worksheet and completed under the AESI section of the Adverse Event eCRF. Referto section 12.1.1. Definitions.
7. **PROs** (Patient Reported Outcomes) are to be administered by site staff or e-diary as described in the Trialogics User Manual. WI-NRS data will also be collected from the subject via the Trialogics web portal at each clinic visit (beginning at Week 20).
8. **Photography:** To be performed at certain sites only. See the Canfield Quick Reference Guide and User Reference Manual for photography procedures as applicable.
9. The 14-day **SOWS** is to be completed, on the e-diary, at home by the subject. Site staff must change the subject's status to "Off-treatment" on the Trialogics web portal to

Table-2. Schedule of Assessments – Open-label Extension Period

Study Period →			Open-label Fixed-dose Period						Washout and Safety Follow-up Period		Last Contact for WI-NRS
			Repeating visit q4wk or q8wk								
Assessment ↓	☎	☎	W17 to W52						Off-Treatment[1]	Last Visit[1]	End of Study telephone call[1]
Visit Week	17	17	20	24	28[2]	32[2]	36[2]	44	52	54	56
Study Day (±2 days)	113	120	140	168	196	224	252	308	364	378	392

trigger the launch of the SOWS. Subjects must be instructed to enter SOWS data daily for the 14 days following discontinuation of investigational product regardless of when this occurs (i.e. Week 52 visit or Premature Discontinuation). Data should be reviewed by site staff during the 14-day collection period in order to assess the need for any withdrawal intervention. The e-diary is to be retrieved at the last clinic study visit.

10. (B) Applicable if subject discontinues before Week 52.

9.1.3 Study Procedures and Assessments

In the event of recurrent COVID-19 restrictions on in-person study visits, processes are in place to provide home delivery of study drug using an external courier service, and study visits may be conducted by phone or video conference. The study will permit continued study drug dosing and study participation with up to 2 missed laboratory and ECG assessments when those are scheduled less than or equal to 8 weeks apart, and up to 1 missed laboratory or ECG assessment when they arescheduled greater than 8 weeks apart.

9.1.3.1 Medication Washout and Screening Period (Week -6 through Week -1)

Subjects are to undergo a screening visit 1 to 6 weeks prior to the planned first day of study treatment.Screening may occur over multiple visits within the 6-week screening period if clinically indicated (for example, to allow for washout of prohibited medications). However, subjects should berandomized as soon as it is determined they meet all study inclusion/exclusion criteria.

Any required medication washout should be completed prior to initiating collection of the WI-NRS in the e-Diary.

Subjects whose washout equals or exceeds the 6-week screening window should complete laboratoryand ECG screening as early as possible. This ensures that the washout period is not prolonged unnecessarily, and they can resume non-study treatment for their itch in the event that they fail laboratory or ECG criteria. Those who complete the washout and are otherwise eligible for study participation will be permitted to re-screen with written consent from the Medical Monitor.

Subjects who fail their initial screening due to the requirement for an extended medication washout may be re-screened at the discretion of the Medical Monitor and with written permission from the Sponsor. In cases of other unique circumstances that may justify re-screening, Investigators must contact the Medical Monitor to discuss the specific conditions under which subjects may qualify forre-screening.

Screening assessments are as follows:

- Obtain written informed consent (must be completed first, before any screening assessments areperformed)
- Review eligibility criteria
- Record medical, neurological, and PN history
- Physical examination
- Brief neurological assessment
- Vital signs
- Record height, weight, and body mass index (BMI)
- Central ECG (triplicate)

- Clinical laboratory assessments
- Urinalysis
- Quantitative serum pregnancy tests will ONLY be conducted at the initial screening visit, and again at baseline, to confirm non-pregnant status prior to dispensation of investigational product.Once on study, subjects will be expected to adhere to protocol required birth control requirementsand serum pregnancy testing will not be done at regularly scheduled intervals.
- Urine pregnancy test (woman of childbearing potential [WOCBP])
- Record and assess AEs, concomitant medications, and therapies (including restricted and prohibited medications)
- Dispense electronic diary (e-diary) at least 7 days prior to projected baseline visit, train on its use
- Review ability to comply with e-diary entry use in the Trialogics portal and counsel and/or retrainsubject as needed.
- Dispense and train on use of the Subject Symptom Log and Subject Medication Log
- ItchyQoL
- PAS
- Investigator Global Assessment-Prurigo Nodularis (IGA-PN)
- PBI-P
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)

9.1.3.2 Double-blind Titration Period (Weeks 1 and 2)

The subject will return for the Week 1 baseline visit, at which point it will be determined if the subjectmeets the entry criteria. If the subject meets all inclusion/exclusion criteria, the subject will be randomized and the titration period will begin. During the double-blind titration period, subjects willhave 1 study site visit (baseline visit), just prior to entering Week 1 and 2 telephone contacts, followedby 1 end of titration visit at Week 2.

Baseline Visit (Week 1, Day 1)

The following procedures will be performed during this visit:

- Confirm eligibility against inclusion/exclusion criteria (Section 9.5) and perform e-diary eligibility assessment
- Brief neurological assessment
- Vital signs and weight
- Clinical laboratory assessments
- Quantitative serum pregnancy tests will ONLY be conducted at the initial screening visit, and again at baseline, to confirm non-pregnant status prior to dispensation of investigational

product.Once on study, subjects will be expected to adhere to protocol required birth control requirementsand serum pregnancy testing will not be done at regularly scheduled intervals.

- Urinalysis
- Urine pregnancy test (WOCBP)
- Randomization via Interactive Web Response System (IWRS)
- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Review e-diary entry and retrain on use or compliance as needed
- WI-NRS (should be entered by subject via e-diary [prior to randomization] if not entered prior tothe visit; reminder that subject should enter WI-NRS score via e-diary daily through the Week 14visit)
- ItchyQoL
- PAS
- IGA-PN
- PBI-P (“Importance of Treatment Goal” questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- Photography (if applicable)
- Dispense investigational product (Blister card)
- Dispense Instructions for Taking TR11 Study Medication (Double-blind titration blister card)

Telephone Contacts 1 and 2 (Week 1, Day 3 and Week 1, Day 7)

During the telephone contact, the following will be assessed and documented:

- Tolerability intervention (See Section 10.6.3)
- Record and assess AEs, concomitant medications, and therapies
- WI-NRS (reminder that subject should enter WI-NRS score via e-diary or Trialogics web portaldaily through the Week 14 visit)

End of Titration Visit (Week 2, Day 14)

The following procedures will be performed during this visit:

- Brief neurological assessment
- Vital signs

- Central ECG (triplicate)
- Clinical laboratory assessments
- Tolerability intervention (See Section 10.6.3)
- Urine pregnancy test (WOCBP)
- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review compliance
- Dispense investigational product (bottle)
- Dispense Instructions for Taking TR11 Study Medication (Double-blind fixed dose bottle)
- Investigational product accountability
- Review investigational product compliance
- WI-NRS (reminder that subject should enter WI-NRS score via e-diary or Trialogics web portaldaily through the Week 14 visit)

9.1.3.3 Double-blind Fixed-dose Period (Weeks 3 to 14)

During the 12-week double-blind fixed-dose period, there will be 2 telephone contacts (TelephoneContacts 3 and 4) and 3 study visits.

Telephone Contacts 3 and 4 (Week 3, Day 15 and Week 3, Day 21)

During the telephone contacts, the following will be assessed and documented:

- Tolerability intervention (Week 3, Days 15 and 21 only; Day 15 is first day of 162 mg BID foractive treatment group, see Section 10.6.3)
- Record and assess AEs, concomitant medications, and therapies
- WI-NRS (reminder that subject should enter WI-NRS score via e-diary or Trialogics web portaldaily through the Week 14 visit)

Week 6 Visit

The following procedures will be performed during this visit:

- Vital signs
- Central ECG (triplicate)
- Clinical laboratory assessments
- Urine pregnancy test (WOCBP)

- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS (reminder that subject should enter WI-NRS score via e-diary or Trialogics web portaldaily through the Week 14 visit)
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

Week 10 Visit

The following procedures will be performed during this visit:

- Vital signs
- Urine pregnancy test (WOCBP)
- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P (“Treatment Benefit Assessment” questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS (reminder that subject should enter WI-NRS score via e-diary or Trialogics web portaldaily through the Week 14 visit)
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability

- Review investigational product compliance

Week 14 Visit

The following procedures will be performed during this visit:

- Physical Examination
- Vital signs
- Central ECG (triplicate)
- Clinical laboratory assessments
- Urine pregnancy test (WOCBP)
- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P ("Treatment Benefit Assessment" questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS (last daily entry) to be entered by subject via e-diary or Trialogics web portal; reminderthat all future entries will occur during visits via the Trialogics web portal or the e-diary.
- Photography (if applicable)
- Dispense investigational product (blister card)
- Dispense Instructions for Taking TR11 Study Medication (open-label titration blister card)
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

9.1.3.4 Extension Titration Period (Weeks 15 and 16)

During the 2-week extension titration period, there will be 2 telephone contacts (Telephone Contacts 5 and 6) and 1 end of titration study visit at Week 16.

Telephone Contacts 5 and 6 (Week 15, Day 101 and Week 15, Day 105)

During the telephone contacts, the following will be assessed and documented:

- Tolerability intervention (See Section 10.6.3)
- Record and assess AEs, concomitant medications, and therapies

End of Titration Visit (Week 16, Day 112)

The following procedures will be performed during this visit:

- Brief neurological assessment
- Vital signs
- Central ECG (triplicate)
- Urine pregnancy test (WOCBP)
- Blood sample for PK analysis
- Record and assess AEs, concomitant medications, and therapies
- WI-NRS to be entered by the subject via Trialogics web portal or e-diary
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs as needed)
- Retrieve e-diary data and review entry compliance
- Dispense investigational product (bottle)
- Dispense Instructions for Taking TR11 Study Medication (open-label fixed dose bottle)
- Investigational product accountability
- Review investigational product compliance

9.1.3.5 Open-label Fixed-dose Period (Weeks 17 to 52)

During the 36-week open-label fixed-dose period, there will be 2 telephone contacts (TelephoneContacts 7 and 8) and study visits will occur in the clinic every 4 or 8 weeks.

Telephone Contacts 7 and 8 (Week 17, Day 113 and Week 17, Day 120)

During the telephone contacts, the following will be assessed and documented:

- Tolerability intervention (See Section 10.6.3)
- Record and assess AEs, concomitant medications, and therapies

Week 20 Visit

The following procedures will be performed during this visit:

- Vital signs
- Central ECG (triplicate)
- Blood sample for PK analysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P ("Treatment Benefit Assessment" questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Dispense investigational product (bottle)
- Investigational product accountability
- Review investigational product compliance

Week 24 Visit

The following procedures will be performed during this visit:

- Vital signs
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Dispense investigational product (bottle)

- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

Week 28 Visit

The following procedures will be performed during this visit:

- Vital signs
- Central ECG (triplicate)
- Clinical laboratory assessments
- Blood sample for PK analysis
- Urinalysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Tolerability intervention (See Section 10.6.3)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P (“Treatment Benefit” questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Photography (if applicable)
- Assess whether subject is eligible for down titration based on criteria of confirmed WI-NRS ≤ 3 and 1 category improvement in PAS lesion healing (PAS item 5b). For example, if “0-24%” of PN lesions at baseline were assessed as ‘healed’, then a 1-category change means that “25-50%”of current Week 28 PN lesions are now healed. If both criteria are met, the option for a permanentdose reduction to 108 mg BID may be discussed. Note: if criteria are met, this decision is at the discretion of the Investigator and with the agreement of the subject, but once dose reduction has been initiated no re-escalation is permitted
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability

- Review investigational product compliance

Week 32 Visit

The following procedures will be performed during this visit:

- Vital signs
- Blood sample for PK analysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- PAS
- IGA-PN
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Assess whether subject is eligible for down titration based on criteria of confirmed WI-NRS ≤ 3 and 1 category improvement in PAS lesion healing (PAS item 5b). For example, if "0-24%" of PN lesions at baseline were assessed as 'healed', then a 1-category change means that "25-50%"of current Week 28 PN lesions are now healed. If both criteria are met, the option for a permanentdose reduction to 108 mg BID may be discussed. Note: if criteria are met, this decision is at the discretion of the Investigator and with the agreement of the subject, but once dose reduction hasbeen initiated no re-escalation is permitted
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

Week 36 Visit

The following procedures will be performed during this visit:

- Vital signs
- Blood sample for PK analysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs as needed)

- Tolerability intervention (See Section 10.6.3)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P ("Treatment Benefit Assessment" questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Assess whether subject is eligible for down titration based on criteria of confirmed WINRS ≤ 3 and 1 category improvement in PAS lesion healing (PAS item 5b). For example, if "0-24%" of PN lesions at baseline were assessed as 'healed', then a 1-category change means that "25-50%"of current Week 28 PN lesions are now healed. If both criteria are met, the option for a permanentdose reduction to 108 mg BID may be discussed. Note: if criteria are met, this decision is at the discretion of the Investigator and with the agreement of the subject, but once dose reduction has been initiated no re-escalation is permitted
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

Week 44 Visit

The following procedures will be performed during this visit:

- Vital signs
- Clinical laboratory assessments
- Blood sample for PK analysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data and review entry compliance
- ItchyQoL
- PAS
- IGA-PN
- PBI-P ("Treatment Benefit Assessment" questions only)

- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Dispense investigational product (bottle)
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

9.1.3.6 Washout and Safety Follow-up Period and Last Contact

The washout and safety follow-up period begins after the subject discontinues investigational product;regardless of when this occurs. The Off-Treatment visit procedures will occur at the Week 52 (end of treatment) visit for subjects who complete the study or upon premature, permanent discontinuationof investigational product at any time during the study, regardless of reason (other than withdrawal of consent).

The last clinic visit will occur at the end of the washout period; 14 days post discontinuation of dosing.The Last Visit should be scheduled 2 weeks after the Off-Treatment visit and the End of Study telephone call will occur 4 weeks after investigational product discontinuation.

If a subject discontinues the study early, the specific instructions in Section 9.6 Premature Discontinuation of Investigational Product Treatment take precedence.

Off-Treatment Visit (Week 52, Day 364 or at Premature Discontinuation)

The following procedures will be performed during this visit:

- Physical examination
- Brief neurological assessment
- Vital signs
- Central ECG (triplicate)
- Clinical laboratory assessments
- Blood sample for PK analysis
- Urinalysis
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- Review Subject Symptom Log and Subject Medication Log and re-dispense (or issue new logs asneeded)
- Retrieve e-diary data
- ItchyQoL

- PAS
- IGA-PN
- PBI-P ("Treatment Benefit Assessment" questions only)
- Sleep Scale (PROMIS Sleep Disturbance Short Form 8a)
- WI-NRS to be entered by subject via Trialogics web portal or e-diary
- Photography (if applicable)
- Launch Subjective Opiate Withdrawal Scale (SOWS) via the subject status update to "Off-treatment/Week 52 (Activate SOWS)" in the Trialogics portal. The SOWS will be activated andsubjects should be instructed to complete the questionnaire daily for the next 14 days. **For subjects who discontinue study drug early (including in-between study visits), the change insubject status to "Off-treatment**/Week 52 (Activate SOWS)**" in the Trialogics portal should be made immediately as the site becomes aware of discontinuation;** SOWS entries providevalid information ONLY if they are collected in the first 14 days off-treatment.
- Retrieve investigational product and containers
- Investigational product accountability
- Review investigational product compliance

Last Study Visit (Week 54, Day 378)

The following procedures will be performed during this visit:

- Physical examination
- Brief neurological assessment
- Vital signs
- Clinical laboratory assessments
- Urine pregnancy test (WOCBP)
- Record and assess AEs, concomitant medications, and therapies
- WI-NRS to be entered by subject via Trialogics web portal. Review Subject Symptom Log andSubject Medication Log and collect for filing in source records
- Retrieve e-diary
- Retrieve the 14-day SOWS, review data and assess need for withdrawal intervention

End of Study Telephone Call (Telephone Contact 9; Week 56, Day 392)

During this telephone contact, the following will be assessed and documented:

- Record and assess AEs, concomitant medications, and therapies

- Ask the subject to verbally report their current WI-NRS score and site staff must enter the reportedscore into the Trialogics web portal. The recommended question text is: “On a scale of zero to ten, with zero being ‘no itch’ and 10 being the ‘worst imaginable itch’, how would you describe your worst itch experience over the last 24 hours?”

9.2 Rationale for Study Design

The randomized, parallel, 2-arm design during the double-blind period of this study allows for comparison of the efficacy and safety of NAL ER to placebo. The open-label extension period provides all subjects an opportunity to receive active treatment and provides a long-term safety experience with NAL ER. It also provides an opportunity to document the effect of long-term NAL ER therapy on skin lesion healing, in the context of immediate versus delayed treatment groups.

During the screening and washout period, prior to investigational product administration, subjects must refrain from using any potentially confounding drug therapies (as specified by the eligibility criteria, Sections 9.5.1 and 9.5.2) that could interfere with the baseline and subsequent assessments of pruritus. If the subject is being washed out from anti-pruritic therapy during the screening and washout period, palliative treatment is permitted with cleansing lotion or nonmedicated emollients (pure emollients without active substances such as menthol, urea, topical corticosteroids, antihistamines, etc.).

The study staff, subjects, and Sponsor/Clinical Research Organization (CRO) clinical staff will all beblinded to treatment assignment to avoid potential bias. Blinding will be maintained through the completion of data lock for the primary endpoint at which time all subjects will either have completedthe study or will have rolled over onto the open-label period. To maintain study integrity, increase the likelihood of establishing tolerance to the recognized early side effects of this drug class, and based on titration experience in prior studies, subjects will be titrated in a blinded manner up to 162 mg BID during the first 2 weeks of active treatment (i.e., in both the initial double-blind titrationperiod and the extension titration period for subjects in Arm 2). Site staff will be educated that symptoms occurring during the titration period may be attributable either to a nocebo effect in susceptible subjects receiving placebo as investigational product, or to side effects of the active investigational product. Therefore, these observations should not be interpreted as a reliable sign ofassignment to treatment group. To evaluate durability of the NAL ER effect, the 162 mg BID dose will be continued for 50 weeks for Arm 1 (i.e., the double-blind fixed-dose period, extension titrationperiod, and open-label fixed-dose period), and 36 weeks for Arm 2 (i.e., the open-label fixed-dose period).

The target dose of NAL ER 162 mg is within the dose range that was well tolerated in HD subjects and healthy volunteers from study TR01 (27 mg to 216 mg BID for up to 15 days). Data from TR01suggested a decrease in itching intensity in this dose range. In addition, NAL ER has shown evidencefor an effect on itch in 2 very different subject populations: subjects on HD with UP (108 mg BID, with nalbuphine exposures higher than would occur at that dose in subjects with normal renal function), and subjects with PN (162 mg BID). With respect to safety, limited 1-year on treatment data are available from the TR03EXT population.

The most common treatment-emergent AEs (TEAEs) occurring in subjects receiving NAL ER are dizziness, nausea, headache, and fatigue. In the PN and UP patient populations, no new safety signalsspecific to that population were identified based on the clinical data obtained to date. The TEAEs associated with extended dosing of NAL ER in both the PN study TR03EXT (N = 20 and 16 for 6 months and 1 year, respectively) and UP population (N = 55 and 19 for 4 and 6 months, respectively) were similar to those observed in the shorter exposure duration (N = 66 up to 10 weeksin TR03, and N = 246 for 8 weeks in TR02) and also consistent with the previously established safetyand tolerability profile of nalbuphine[18,19]. There were no significant clinical issues related to physicaldependence based upon an evaluation of the data from these studies.

The primary endpoint, reduction in the average worst itch intensity (average assessed over 1-week periods), is measured using an itch NRS scale. The NRS is a widely used instrument recommended by the International Forum for the Study of Itch (IFSI) for quantifying itch intensity as well as a usefulinstrument for grouping subjects into categories of itch intensity described as mild, moderate, or severe[20]. The itch NRS has been investigated in subjects with chronic pruritus of a variety of originswith high reliability and concurrent validity[13]. Assessing pruritus using "worst itch" as a key target parameter and recording once daily (QD) measurements of itch intensity is a widely used methodology for studying itch[20].

The ItchyQoL was the first pruritus-specific quality of life (QoL) instrument that is reliable, valid, and responsive[21]. Investigation of QoL factors[22] related to chronic pruritus has found that itch severitysignificantly influences the ItchyQoL total score and all 3 subscores; the itch frequency significantlycorrelates with total ItchyQoL and all 3 ItchyQoL subscores indicate that symptoms, functional status,and emotional health deteriorate as chronic pruritus persists.

The IFSI recommends a measurement scale to directly evaluate subject-relevant benefits of the pruritus treatment under study[20]. The PBI-P is an instrument that measures subject-defined treatmentobjectives and benefits acquired during the course of treatment[23]. The PBI-P was recommended by IFSI[20] as a "highly valuable" measurement instrument.

The PAS is a measurement instrument that was designed to classify, monitor and grade the number and physical characteristics (with excoriations/crusts and healed) of PN lesions during therapeutic interventions[24].

The IGA-PN is an instrument that collects an Investigator Global Assessment of the status of the PNskin lesions based on a 5-category scale (scoring 0 to 4) with respect to 2 aspects: the excoriation/crusting activity on the surface of the PN lesions, and the presence and character of the lesions.

It is recognized that subjects with chronic itch may scratch in their sleep, whether or not they are aware of an itch sensation, and that in severe cases the itch itself may disrupt sleep. The degree of sleep disturbance in subjects with severe PN is not well understood, and no specific sleep assessmentscale exists that is targeted to this population. The PROMIS Sleep Disturbance Short Form 8a has been developed as a general tool for assessing sleep in the context of clinical trials.

Subjects will receive an e-diary for daily collection of WI-NRS data and will be trained on the use ofthe e-diary during the screening period. They will also receive training on the proper completion of the other patient-reported outcomes (PROs) used in this study.

9.3 Safety Monitoring

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.

Subjects will be closely monitored for safety. AEs will be continuously evaluated throughout the study. Vital signs, central cardiac core laboratory-read 12-lead ECGs, physical examinations, and clinical laboratory testing will be conducted to monitor subject safety.

Although nalbuphine is not a controlled substance in the US, AEs of special interest (AESIs) that code to the most relevant abuse-related Medical Dictionary for Regulatory Activities (MedDRA) preferred terms will be tabulated and descriptive narratives will be written. Additional AEs that are considered "possibly related to abuse potential" will be tabulated separately[25]. The list of MedDRApreferred terms for AESIs will be described in the statistical analysis plan (SAP; see Section 13.4.7)

Subjects will complete the SOWS on a daily basis for the 2 weeks following the last dose of investigational product. Any subjects who are discontinued from investigational product will also complete the SOWS daily for the 2 weeks following the last dose of investigational product (unless consent is withdrawn). The SOWS is a self-administered scale for grading opioid withdrawal symptoms and will be collected via the study issued e-diary.

If subjects experience significant withdrawal symptoms during the 2-week safety observation period,they should contact the Investigator. At the Investigator's discretion, they will be offered treatment.

The most frequently reported AEs from NAL ER Phase 1 and 2 clinical studies were primarily in thenervous system and GI organ system categories, consistent with other opiates. The specific AEs thatare considered to be expected with use of NAL ER are nausea, vomiting, somnolence, sedation, dizziness, vertigo, and constipation. These are generally mild or moderate in severity and usually resolve over the titration and early dosing period. In order to monitor any potential CNS-related sideeffects, a brief neurological assessment will be conducted according to the schedule of events (Table-1 and Table-2), as well as a focused neurological medical history which will be obtained at screening.

To mitigate opioid-related side effects, NAL ER will be initiated with a titration schedule for 2 weeks in a double-blinded manner until the target dose is reached. Titration is a clinical management strategy consistent with dosing of opioids in general[26]. The titration regimen planned in this study is similar to the regimen used in Phase 2 studies in UP and PN, in which doses in the planned range were well tolerated. In this study, the combination of a low starting dosing (27 mg NAL ER on the first day) followed by a relatively slow titration is expected to minimize treatment-limiting opioid adverse effects.

It is known from prior studies, that GI adverse effects (e.g., nausea and vomiting) and CNS adverse effects (e.g., dizziness, somnolence, and headaches) occur early and can be treatment-limiting. In anticipation of the possible occurrence of these effects, pre-medications for these symptoms will be permitted.

In anticipation of the possible occurrence of CNS AEs such as somnolence, subjects will be instructedto 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"Instructions for Taking TR11 Study Medication"). Subjects will be instructed that the investigational product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the titration period and in combination with alcohol or tranquilizers or other pharmacologic CNS depressants. Subjects will be instructed not to drive or operate machinery unless they are tolerant tothe drug and know how they will react to the medication. In discussing potential participation in thisstudy with their subjects, Investigators and site staff should ensure that they understand the lifestyle of each individual, the nature of his or her professional activities, and any medication prohibitions ortoxicology screening requirements that may be associated with his or her employment. The assessment should address the overall suitability of the subject for this study based on the safety considerations noted above.

9.4 Risk/Benefit and Ethical Assessment

The selected dose of 162 mg BID for this study in PN was chosen in the context provided by safety and efficacy observations in non-clinical animal studies, the clinical efficacy and safety observationsfrom the 4 Phase 2 studies evaluating the clinical response to itch in 2 distinct disease settings (TR02and TR02EXT in UP; and TR03 and TR03EXT in PN), and the associated PK data and PK-PD modelling assessments based on these clinical trial datasets. These data have been summarized further in the Investigator's Brochure[27].

With respect to potential benefit, the neurobiology of PN supports the concept that use of NAL ER may have therapeutic benefit in this condition, as previously discussed with respect to interruption ofthe self-perpetuating itch-scratch cycle.

Two sets of Phase 2 data support the decision to further investigate the use of NAL ER as a potentialtherapeutic intervention in PN. In study TR02, 371 subjects on chronic HD with UP were randomizedacross 3 arms to placebo, and either of 2 doses of NAL ER for a blinded treatment duration of 8 weeks. Results demonstrated a dose response across the 2 NAL ER groups, and a significant difference between the higher dose group (NAL ER 108 mg BID) and placebo for the change in the mean NRS through Week 8 (difference of -0.73; $P = 0.017$). In those with severe UP (NRS ≥ 7) at baseline, the treatment difference was larger (difference of -1.39; $P = 0.007$).

The smaller TR03 study (63 subjects across 3 arms), in moderate to severe itch due to PN, did not meet its primary endpoint based on a responder criterion. However, a distinct signal for efficacy wasobserved, with the mean reduction (baseline to last observation at Week 10) in WI-NRS of -1.11 points ($P = 0.083$), with a completers analysis showing a wider spread (reduction of -1.57 points, $P = 0.025$). Importantly, 36 subjects rolled over into the open-label, single arm extension study, in which favorable category shifts were observed in the PAS skin

exam for the activity of the prurigo lesions among those who completed 6 and 12 months of treatment. Specifically, a ≥ 1 category improvement in excoriations/crusts was documented in 10/18 and 9/15 subjects, and for healed lesions in 11/18 and 7/15 subjects, each at 26 and 50 weeks, respectively. There are no approved treatments for itch in the setting of PN, and current treatment algorithms rely on expert clinical judgment, small case series, and individual case reports. The subject's experience usually involves along sequence of attempted therapies without satisfactory resolution of the symptom or skin lesions.

Therefore, there is a strong rationale for investigating therapeutic agents that may have the potentialto address the significant unmet need in PN.

Nalbuphine has a long history of use in a parenteral formulation, generally for short-term, episodic use related to surgical interventions. The highest dose proposed in the current clinical study is 162 mgBID (324 mg daily dose), well below the highest recommended daily treatment of 144 mg IV dose (equivalent to 864-mg oral dose) for the currently available parenteral administered product. The high peak plasma concentrations that occur in the setting of parenteral use significantly exceed the peak levels observed with NAL ER oral dosing, an observation that is reassuring with respect to the potential for severe, acute toxicity. The slow titration dose escalation during the 2-week initiation oftherapy period for NAL ER provides additional safety with respect to minimizing the potential of AEs.

Opiate drug class-related concerns such as the potential for physical dependence or the evolution of endocrine abnormalities, both linked to long-term use of opiates, are acknowledged. The proposed study, TR11, will provide up to 52 weeks of dosing for those initially assigned to the NAL ER treatment arm. Therefore, limited laboratory monitoring of those endocrine parameters that can be reliably assessed in the course of usual study conduct, and a requirement for completion of a 2 week safety observation period with daily SOWs reporting have both been incorporated into the TR11 study. These procedures will facilitate rapid identification and intervention for the respective relevantrisks to subjects. With respect to other rare but serious adverse events (SAEs) which have been linkedto opiate use – including rare cases of adrenal insufficiency (usually with prolonged use) and serotoninsyndrome – (usually in combination with other suspect medications, particularly antidepressants including tricyclic antidepressants and serotonin re-uptake inhibitors, CNS stimulants, and certain herbs), Investigators and subjects will be informed of the signs and symptoms that may require evaluation and possible treatment.

In addition, labeling of opiate-class drugs includes a warning that concomitant use of an opiate together with a benzodiazepine-class drug can increase the risk for respiratory depression, includinga risk for respiratory arrest. This warning is based on post-marketing real world data, assessing the experience with a wide range of drugs in these 2 classes and in varied settings including recreationalas well as therapeutic usage. In TR11, concomitant use of benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis) is prohibited. At the time of the informed consent discussion, subjects who are identified as taking a concomitant short-acting benzodiazepine should receive the Patient Information Sheet on this topic, as should anysubject for whom a concomitant short-acting benzodiazepine is subsequently prescribed.

With respect to the published literature addressing respiratory depression with nalbuphine, 1 relevant study has been identified; which evaluated the respiratory effects of serial intravenous administrationof nalbuphine in healthy volunteers. The results were interpreted by the authors as demonstrating a "ceiling" effect for respiratory depression[31]. In previous clinical trials with NAL ER, a total of 41 subjects have received concomitant benzodiazepines while receiving NAL ER, and none of these individuals experienced any event of respiratory depression.

In summary, the risk for subjects participating in the TR11 study is judged to be low based on previous experience with oral administration of NAL ER. The current study will utilize a low initiation dose of 27 mg, a gradual dose titration schedule, careful safety monitoring of subjects during the clinical study, and appropriate education of Investigators regarding symptoms of rare but significant AEs linked to the opiate class.

Finally, there is no approved therapy for PN related pruritus in the US or Europe. Should NAL ER prove effective, subjects with PN could potentially experience substantial benefit. Therefore, the overall benefit-risk assessment for the TR11 protocol is considered favorable to proceed with the study.

9.5 Selection of Study Population

9.5.1 Inclusion Criteria

Subjects eligible for randomization to receive investigational product must meet all of the following criteria:

1. Individuals diagnosed with generalized PN, defined as the presence of ≥ 10 pruriginous nodules,involving at least 2 distinct anatomical areas: for example, either 2 limbs; or a single limb and some axial portion of the body. Individuals with only axial lesions but involving 2 distinct anatomical areas that have no peripheral nervous system overlap are also eligible: for example, lesions involving a portion of the cranium and a portion of the trunk of the body. For purposes ofthis study, the axial portion will be defined as any non-appendicular portion of the body.
2. If there is any history of a primary pruritic skin condition other than PN, that condition must havebeen inactive for at least 6 months prior to screening.
3. Subjects with a history of acute secondary dermatoses within the preceding 6 months may enrollonly if the dermatosis has resolved completely as follows per medical history or patient self-report, and current clinical assessment: (a) Localized contact dermatitis, environmental exposures, superficial burns, or viral exanthems must have been resolved for at least 4 weeks priorto screening. (b) Skin or environmental infestations, such as scabies, lice, or bed bugs, must havebeen resolved for at least 8 weeks prior to screening.
4. Any identified systemic, non-dermatologic disease that could be a potential cause of concomitantpruritus (e.g., thyroid disease, celiac disease, hepatitis C virus [HCV]) must either have resolved,been successfully treated (i.e., HCV RNA negative), or must be successfully managed with stable,optimized treatment (e.g., thyroid replacement, dietary management with resolution of symptoms,respectively) for at least 3 months prior to screening.

5. WI-NRS score, recorded daily over the 7 contiguous days prior to and including the day of the baseline visit via electronic diary, must have at least 5 measurements recorded and all individualmeasurements must be ≥ 6. The arithmetic mean value of the measurements must be ≥ 7 as confirmed by the Trialogics Eligibility Check report immediately prior to randomization. The last WI-NRS value used in the calculation should be recorded on the day of the baseline visit andprior to dosing.
6. Subjects using antidepressants must be on a stable dose for a minimum of 4 weeks prior to screening and must be willing to remain on their stable dose for the entire durationof the study.
7. Subjects who are human immunodeficiency virus (HIV) positive may enroll if they meet the following criteria: (a) currently on a stable (> 6 months stable use) and well tolerated highly activeantiretroviral therapy regimen; (b) CD4 count > 500 cells/mL; and (c) HIV ribonucleic acid (RNA) < 50 copies/mL documented for at least 6 months prior to enrollment. If enrolled, these subjects should continue to have their CD4 and HIV RNA monitored by their HIV provider per their standard of care for the duration of the TR11 study, and the data should be reported and documented at the next study visit.
8. Females of childbearing potential must be using an acceptable method of birth control (if sexually active) for 14 days prior to randomization and throughout the study. All females of childbearingpotential must have a negative pregnancy test at the screening and baseline visits.

For the purpose of this study, all females are considered to be of childbearing potential unless they are postmenopausal (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).

Sexually active female subjects of childbearing potential are required to use 1 barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to 1 other method (e.g., intrauterine device in place at least 1-month, stable hormonal contraception for at least 3 months, or Essure procedure, or spermicide).

Female subjects 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.

9. Age 18 years and older at the time of consent, and a life expectancy of at least 18 months.
10. Willing and able to understand and provide written informed consent.
11. Willing and able to comply with study requirements and restrictions.
12. Agree to the confidential use and storage of all data and use of all anonymized data for publicationincluding scientific publication.

9.5.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Pruritus due to localized PN (only 1 body part affected, for example only 1 arm).

2. Active, uncontrolled, pruritic dermatoses in need of treatment (such as atopic dermatitis or bullouspemphigoid for example).
3. Prurigo Nodularis associated with a history of atopic dermatitis is excluded if acute eczematous lesions are present, as characterized by erythematous, active predominant lichenified plaques withoozing and crusting.
4. History of a major psychiatric disorder such as bipolar disorder or schizophrenia is excluded. Subjects with a history of isolated major depression > 3 years previously may be eligible for enrollment if they have access to appropriate psychiatric care. An 'isolated major depression' isdefined as a single event of depression that includes recurrent thoughts of death, recurrent suicidalideation with or without a specific plan, or any history of a suicide attempt. Enrollment must be approved by the Medical Monitor. Subjects with general depression who are considered stable may be enrolled.
5. Serum bilirubin > 1.5 × upper limit of normal range at screening unless explained by a clinical diagnosis of Gilbert's Syndrome.
6. Serum hepatic alanine aminotransferase or aspartate aminotransferase enzymes > 100 U/L at screening.
7. Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at screening.
8. Significant medical condition, occupational restrictions (see Section 9.3), and/or other factors thatin the opinion of the Investigator may interfere with the conduct of the study.
9. Subjects who have an active malignancy (either solid tumor or hematologic) are excluded. Subjects who have a past history of malignancy and who have no evidence of active disease but who continue on therapy to prevent disease recurrence (i.e., tamoxifen for breast cancer, testosterone blockade for prostate cancer, etc.), may be eligible if approved by the Medical Monitor.
10. History of active substance abuse within the past 3 years.
11. Known intolerance of, or hypersensitivity or allergy to nalbuphine or vehicle components.
12. Pregnant or lactating females.
13. Concurrent enrollment in an ongoing clinical trial or anticipated enrollment in a concurrent clinical trial. Potential subjects who are actively participating in the safety follow-up of an ongoing COVID-19 vaccination trial may enroll in this study if they meet the following criteria:
    A. the vaccine under study has already been approved under an Emergency Use Authorization or via an equivalent regulatory review by the Health Authority in the country where they are enrolling;
    B. they have completed the full vaccination series and are participating in a safety observation period without anticipation of any further vaccine trial intervention.
    C. the COVID-19 trial permits co-enrollment.

Medication-related Exclusions:

14. Known intolerance (GI, CNS symptoms) or hypersensitivity/drug allergy to opioids.

15. Potential subjects taking monoamine oxidase inhibitors are excluded, as concomitant opiate use may increase the risk for serotonin syndrome.
16. Potential subjects taking cyclosporin A are excluded unless they undergo a 6-week washout. Subjects are prohibited from using cyclosporin during the study. Please refer to Table 3, footnote 3, and Section 9.1.3.1.
17. Potential subjects taking non-insulin biologics (including monoclonal antibodies), which modifythe immune system, are excluded unless they undergo a 3-month washout. Please refer to Table 3, footnote 3, and Section 9.1.3.1.
18. Prior exclusion criterion 18 is not applicable to subjects enrolling in Protocol V6 and later.
19. Exposure to any investigational medication, including placebo requires a 4-week washout (3 months for noninsulin biologics [e.g., monoclonal antibodies]). Please refer to Table 3 and Section 9.1.3.1.
20. Potential subjects receiving UV-therapy (PUVA, UVA, UVB, Excimer) requires a 4-week washout. Subjects are prohibited from using UV-therapy for the duration of the study. Please refer to Table 3 and Section 9.1.3.1.
21. Potential subjects who are taking opiates require a 14 –day washout. Subjects are prohibited fromusing opioids, including naltrexone, for the duration of the study. Please refer to Table 3 and Section 9.1.3.1.
22. Potential subjects who have received gabapentin, pregabalin, calcineurin inhibitors, cannabinoidagonists, capsaicin, cryosurgery, topical doxepin, thalidomide or methotrexate, topical antihistamines, and topical corticosteroids require a 14-day washout. These medications are prohibited for the duration of the study. Use of systemic antihistamines are not permitted unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study. Please refer to Table 3 and Section 9.1.3.1.
23. Potential subjects receiving systemic corticosteroids or local steroid injections of the PN lesions require a 4-week washout. These medications are prohibited for the duration of the study. Pleaserefer to Table 3 and Section 9.1.3.1.
24. Potential subjects are excluded if they have had any addition or discontinuation of their regularlyused prescription drugs, or any changes in the doses of their regularly used prescription drugs in the 14 days prior to the screening period e-diary WI-NRS collection.
25. Potential subjects taking central nervous system suppressants, such as barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics,and clonidine are excluded. These medications are prohibited for the duration of the study (see Section 10.6.2, footnotes 1 and 2 to Table 3 for definitions of ‘short-acting benzodiazepines’).

Cardiac-related Exclusions:

26. Subjects with a history of congestive heart failure of Class 2 or higher as graded using the NewYork Heart Association scale (see Appendix 9).

27. Subjects with a history of angina pectoris Grade 2 or higher as graded using the CanadianCardiovascular Society grading scale (see Appendix 8).
28. History of ventricular tachycardia, Torsade de Pointes, or family history of sudden death.
29. Myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.
30. Serum potassium below the laboratory lower limit of normal. Note: If the initial screening value is low, but not considered clinically significant in relation to cardiac risk, then potassiumsupplementation may be prescribed and the serum potassium level repeated once at least 2 weekslater, during the screening period. If the repeat potassium remains < LLN, then the subject mustbe a screen-fail.
31. QTcF interval > 450 ms (mean of 3 screening ECG QTcF values) if QRS < 120 ms (mean of 3 screening ECG QRS values); QTcF interval > 480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS ≥ 120 ms.
32. Heart rate < 45 bpm on any screening measurement either in the clinic or on the central ECG readings.
33. Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds website; see Appendix 10) is not permitted unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study.
34. Prior Exclusion criterion 34 is not applicable to subjects enrolling in Protocol V7 and later.

9.6 Premature Discontinuation of Investigational Product Treatment

Subjects who complete investigational product treatment through the full study treatment course are considered to have completed treatment with the investigational product (even if some doses have been missed). Subjects who discontinue investigational product, prior to 52 weeks of treatment will be considered to have prematurely discontinued and will be asked to complete the following visits (unless consent is withdrawn):

- If the decision to discontinue treatment is made during an onsite study visit (scheduled or unscheduled), perform the procedures and assessments outlined in the Off-Treatment visit, regardless of where they are in the study visit schedule.
- If the decision to discontinue treatment is made while the subject is not at a study visit, schedulea visit as soon as logistically possible, but no later than 2 weeks later, to perform the procedures and assessments described in the Off-Treatment visit. Upon notification that the subject has permanently stopped dosing, the site should immediately update the subject's status on the Trialogics web portal, in order to launch the SOWS, and instruct the subject to begin entering their SOWS data daily via the e-diary for the next 14 days.
- Schedule the subject to return to the clinic 2 weeks after completion of the Off-Treatment visit and perform the procedures and assessments outlined in the Last Visit, regardless of where they are in the study visit schedule.

- Schedule the End of Study telephone call with the subject 4 weeks after completion of the Off- Treatment visit and perform the procedures and assessments outlined in the schedule of events for this visit, regardless of where they are in the study visit schedule.
- If discontinuation of investigational product occurs any time between Day 1 and the Week 14 visit, the subject will be asked to complete the Off-Treatment visit, the Last Visit, and the End ofStudy visit telephone call, and to return to the clinic for the study schedule planned Week 14 visit.

9.7 Premature Withdrawal of Subjects from the Study

All subjects who receive study treatment should remain in the study whenever possible. If possible and appropriate, subjects for whom withdrawal is considered for the reasons identified with an asterisk below should discontinue investigational product, but are asked to provide complete data asper Section 9.6. Reasons for withdrawal of the subject from the study, not just discontinuation of investigational product, include:

- Withdrawal of consent for study participation
- Sponsor terminates the study for any reason
- Investigator decision *
- The Investigator may withdraw any subject from the study if, in the Investigator's opinion, it is not in the subject's best interest to continue on the study *
- Develops a QTcF > 500 ms (mean of 3 ECG QTcF values) in subjects who were randomized **without** ECG findings of RBBB and/or QRS ≥ 120 ms.
- Develops QTcF > 530 ms (mean of 3 ECG QTcF values) in subjects who were randomized **with** ECG findings of RBBB and/or QRS ≥ 120 ms.
- Increase from QTcF baseline of >60 ms (mean determination from 3 ECG values).
- Death of the subject

Subjects who prematurely discontinue from the study will be asked: (1) to undergo and complete procedures and evaluations that may be necessary to ensure that the subject is free of untoward effects; and (2) to seek appropriate follow-up for any continuing problems. The date on which the subject is withdrawn from the study and the reason for discontinuation will be recorded on the electronic case report form (eCRF). Subjects who withdraw from the study will not be replaced.

10 TREATMENT OF SUBJECTS

10.1 Identity of Investigational Product

The investigational product in this trial is NAL ER tablets or matching placebo tablets. The NAL ER tablets are either round, white to off-white, film-coated tablets containing either 27 or 54 mg of nalbuphine (equivalent to approximately 30 or 60 mg nalbuphine HCl); or oval, white to off-white, film-coated tablets containing 162 mg of nalbuphine (equivalent to approximately 180 mg

nalbuphine HCl). The 27 and 54 mg NAL ER round tablets are identical in appearance. Matching placebo tablets will be used for both tablet shapes (round tablets to represent the 27 and 54 mg tablets, and oval shaped tablets to represent the 162 mg tablets).

All investigational product will be supplied by the Sponsor.

10.1.1 Administration of Study Treatments

Double-blind Treatment

Following randomization, the subject will be dispensed a 2-week blister card for the double-blind titration period. Dosing will consist of 3 tablets for the AM dose and 3 tablets for the PM dose. Arm 1 will consist of a combination of 27 mg/54 mg/placebo tablets, and Arm 2 will consist of placebo tablets only. Note: Although both AM and PM doses are present on Day 1, only the PM dose will be taken (both Arms).

At the Week 2 end of titration visit, subjects in Arm 1 will be given one 70 count bottle of NAL ER 162 mg tablets and subject in Arm 2 will be given one 70 count bottle of placebo tablets. Additional bottles will be dispensed at subsequent study visits. At each visit at which investigational product is to be dispensed, enough investigational product should be supplied to ensure that a sufficient number of tablets are available for dosing until the next visit, allowing for visit windows and/or the possibility of a late visit.

Subject dosing information for the double-blind treatment will be available in the Pharmacy Manual provided to the site. Additionally, all subjects are to be provided with the "Instructions for Taking TR11 Study Medication" which outlines dosing instructions for this treatment period.

Open-label Treatment

Subjects will be dispensed a 2-week blister card for the extension titration period. Dosing will consist of 3 tablets for the AM dose (starting on Day 2) and 3 tablets for the PM dose. (Note: There will not be any tablets to take on Day 1 AM for both Arms 1 and 2). For subjects previously assigned to Arm 2 of the double-blind treatment, the titration card will consist of combinations of either 27 mg/54 mg/placebo tablets to crossover to NAL ER. To maintain the blind, subjects previously assigned to Arm 1 will be given a card containing 3 active 54 mg NAL ER tablets for the AM dose and 3 active 54 mg NAL ER tablets for the PM dose.

At the Week 16 end of titration visit, all subjects will be given 1 x 70-count bottle for the start of the open-label fixed-dose period containing 162 mg NAL ER tablets. Additional bottles will be dispensed at subsequent study visits and subjects should again be dispensed enough investigational product to ensure that a sufficient number of tablets are available for dosing until the next visit, allowing for visit windows and/or the possibility of a late visit.

Subject dosing information for the open-label treatment will be available in the Pharmacy Manual provided to the site. Additionally, all subjects are to be provided with the "Instructions for Taking TR11 Study Medication" which outlines the dosing instructions for this treatment period.

Investigational product can be taken with or without food, as whole tablets (without crushing or chewing). Subjects will be instructed to take the AM and PM investigational product tablets at the same times of the day, 12 hours apart (± 2 hours), preferably with 240 mL (approximately 8 ounces) of water. For example, if a subject is taking the investigational product at 9:00 AM and 9:00 PM but forgets to take the 9:00 AM dose, he may take the 9:00 AM dose as late as 11:00 AM. After that time, the subject should skip the 9:00 AM dose and, instead, take the regularly scheduled next dose at 9:00 PM.

Subjects will confirm (in the e-diary) whether or not they took their dose(s) and the dosing time for both the AM and the PM dose. Any discrepancies between the dosing records in the e-diary and the number of actual versus expected tablets (based on the e-diary reporting) returned to the site, should be documented at the actual visit in which investigational product is returned. This should occur at every visit during the investigational product drug accountability and investigational product compliance assessments.

10.1.2 Down-titration

At the regularly scheduled study visits for Week 28, Week 32, and Week 36, an elective dose reduction to a 108 mg NAL ER BID dose may be considered for subjects who achieve a confirmed WI-NRS ≤ 3 **and** visible lesion healing as assessed by an improvement of at least 1 category in the PAS healing activity score, Item 5b. For example, if "0-24%" of PN lesions at baseline were assessedas 'healed', then a 1-category change means that "25-50%" of current Week 28 PN lesions are nowevaluated as 'healed'. The WI-NRS scores at and after Week 24 will be available to site staff via the Trialogics portal in order to assess eligibility for this down-titration. The decision to dose reduce is at the discretion of the Investigator and with the agreement of the subject, but once this dosing has started, no re-escalation is permitted. Dose reduction is not permitted prior to Study Week 28 or afterStudy Week 36.

10.1.3 Multiple Missed Doses

If a subject misses multiple doses of the investigational product, the procedures below should be followed. In no case should subjects take additional doses of investigational product to make up for missed doses. If investigational product is being restarted after missed doses during the titration period, the subject should be instructed not to remove the tablets from the days and/or time points on which investigational product was missed; these tablets are to remain in the blister card. The subject is to be instructed on when to resume taking investigational product.

During the Titration Periods

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

During the Fixed-dose Periods

If a subject misses 6 (or more) consecutive doses, please contact the study Medical Monitor. If authorized by the Medical Monitor, subjects who miss more than 6 consecutive doses may be allowed to continue on study. In such situations, subjects should receive the investigational

product only QD (i.e., the AM or PM dose only) for the first 3 days before returning to the full (BID) dose.

10.2 Study Treatment Packaging and Labeling

Please refer to the Pharmacy Manual for additional information on investigational product supplies, packaging, storage, dispensation, and accountability.

10.2.1 Labeling

Blister cards and bottles will be labeled with at minimum: contents, storage conditions, clinical trial statement, and the name of the Sponsor (Trevi Therapeutics).

10.2.2 Storage

NAL ER tablets and placebo tablets should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F to 86°F) or per country-specific criteria. The investigational product will be stored away from any extreme conditions of temperature, light, or humidity as an additional precaution.

10.2.3 Blinding and Randomization of Study Treatments

Randomization will be performed by IWRS. Upon confirmation of eligibility by the study site, subjects will be randomized in a 1:1 ratio to either Arm 1 or Arm 2.

10.3 Procedure for Breaking the Randomization Code

Under normal circumstances, the blind will not be broken. In the event of a medical emergency, when management of a subject's condition requires knowledge of the treatment assignment, the blind may be broken via the IWRS. Investigators contemplating unblinding a subject should make every effort to contact the Medical Monitor prior to unblinding.

Reasons for unblinding will be documented in the eCRF. The date and the identity of the person responsible for breaking the blind must be also documented.

10.4 Subject Compliance

Drug compliance is a critical data observation in all clinical trials, and is assessed through the drug accountability records. Returned blister cards and bottles will be compared to subject entries in the e-diary to assess compliance at each study visit. An accurate and current accounting of the dispensing and return of investigational product for each subject will be maintained on an ongoing basis by a member of the study site staff. The amount of investigational product dispensed and returned by the subject will be recorded on the appropriate Investigational Product Drug Accountability forms at each visit.

Compliance is defined as the amount of investigational product that should have been taken by a subject based on the dosing instructions provided during the period for which investigational product was dispensed. This is typically expressed as percent (%) compliance, and is calculated

based on the number of tablets actually taken in a particular time interval divided by the number of tablets that should have been taken or prescribed for that time interval. Compliance will be documented after each investigational product return, based on the information on the Drug Accountability forms.

Ideally, subject compliance should be 100%. Any observation of a missed or extra dose taken should trigger a discussion/re-education with the subject about the compliance expectations of this study, with the focus on ensuring maximum efficacy and minimum AEs. These discussions should be recorded at the time of the visit in source documents.

Additional eCRF questions to query the subject will be completed in situations in which there were missing tablets (e.g., fewer tablets returned than expected) to document an explanation for missing investigational product.

Any dosing and/or compliance discrepancies will be noted in source documents for the applicable subject visit.

10.5 Investigational Product Accountability

The Investigator must ensure that all investigational product supplies are kept in a secure locked area, under controlled temperature, with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all investigational product 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 investigational product.

Current dispensing records will also be maintained including the date and amount of investigational product dispensed and the subject receiving the investigational product. Additional eCRF questions to query the subject will be completed in situations in which there were missing tablets (e.g., fewer tablets returned than expected) to document an explanation for missing investigational product. All remaining investigational product 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.

10.5.1 Special Procedures for Study Drug Delivery During Periods of COVID-19 Pandemic Restrictions

A special courier service will pick up study drug at the site and deliver to the subject's home address as needed. All subject-related identifying information will be communicated by site staff to the courier without any Sponsor involvement. This courier will also safely transport drug, in the possession of the patient from a previous visit, back to the site for proper accountability.

10.6 Concomitant Medications, Prohibited Medications, Pre-Medications, Symptom Management, and Itch Intervention

10.6.1 Concomitant Medications

Subjects may receive all clinically indicated medications during the study with the exceptions noted in Section 10.6.2 and Appendix 10.

Any medication taken by a subject within the 14 days prior to the screening period, and during the course of the study, will be recorded on the eCRF along with the reason for use. During the study, each subject will be instructed to report the use of all medication, including over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements on the study specific Subject Medication Log. Sites should instruct subjects to bring the log to each study visit for review (including referring to it during telephone contacts, as applicable). Subjects will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator. After screening, if the subject begins taking prohibited or restricted medications, they are to be recorded on the corresponding Concomitant Medication eCRF (see Section 10.6.3).

10.6.2 Prohibited Medications

Prohibited medications are summarized in Table 3. Subjects receiving opiate drugs during the 14 days prior to the screening period are excluded from the study if unable to washout (see also Section 9.1.3.1).

Initiating use of opiate medications during the study should be done with caution with assessment of the subject for potential additive opiate AEs. If an enrolled subject requires daily treatment with opioid medications for greater than 7 days during the study, please contact the Medical Monitor. Use of acetaminophen, non-steroidal anti-inflammatory medications, and aspirin is permitted. If opioid medication is introduced in anticipation of chronic use, the subject is to 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.

The following classes of drugs are prohibited during participation in this study due to the risk that they may cause increased respiratory depression, which could become life threatening with excess use:

- Central nervous system suppressants, such as barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics, and clonidine.

The phrase ‘short-acting benzodiazepines’ refers specifically to the following: triazolam, temazepam, brotizolam (available in EU only), zolpidem, and zaleplon. These drugs should be prescribed at the lowest effective doses and for the shortest period of time that is clinically

indicated during the conduct of the study. Subjects receiving these agents must be provided the patient information sheet as noted in Table-1 and Table-2 and in Section 9.4.

Use of all other investigational products is prohibited during the study. A subject who initiates an investigational product during the study should be discontinued.

Subject are not to receive a medication that is classified as having a known risk for Torsade de Pointes (see Appendix 10, for cardiovascular related prohibited medications with a known risk of Torsade de Pointes, classified as "KR") unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study.

Subjects are to be washed out of any medications meeting the exclusion criteria (Section 9.5.2) for atleast the minimal time periods summarized in Table-3. This will allow the subject to be adequately washed out for any medications that could potentially confound investigational product effect[28].

Table-3. Prohibited Medications and Washout Requirements

Concomitant Medication	Study Entry (see Section 9.5)	During Study
μ-opioid receptor agonists (e.g., codeine, oxycodone, hydromorphone, oxymorphone, morphine, fentanyl, tramadol, butorphanol, pentazocine, meperidine, methadone)	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Opioid medication introduced in anticipation for chronic use is prohibited
Opioid receptor antagonists(e.g., naltrexone, naloxone)	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited except for urgent reversal of opioid adverse events or opioid overdose
Antihistamines (systemic or topical) (e.g., diphenhydramine, loratadine, cetirizine, chlorpheniramine, clemastine, fexofenadine)	Topical antihistamines: Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection Systemic antihistamines: Not permitted unless the subject has been on a stable dose for at least 4 weeks prior to the start of screening.	Topical antihistamines: Prohibited (except topicals for limited 'Itch Intervention' as in Section 10.6.4) Systemic antihistamines: There must be no plans to change the dose during the study.
Non-antihistamine class drugs that have well-established primary or secondary pharmacologic antihistaminic effects mediated via the H1 receptor (e.g., doxepin –see below for topical doxepin specifics)	Not permitted unless the subject has been on a stable dose for at least 4 weeks prior to the start of screening.	There must be no plans to change the dose during the study.

Table-3. Prohibited Medications and Washout Requirements		
Concomitant Medication	**Study Entry (see Section 9.5)**	**During Study**
Topical calcineurin inhibitors(e.g., tacrolimus)	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Topical corticosteroids	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited (except topicals for limited 'Itch Intervention' as in Section 10.6.4)
Systemic corticosteroids	Excluded within 4 weeks (e.g. 4-week washout) prior to the start of the screening e-diary WI-NRS collection.	Prohibited
Topical capsaicin	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited (except for limited 'Itch Intervention' as in Section 10.6.4)
Anti-convulsant class drugs (e.g., gabapentin or pregabalin)	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Medications with anti-itch activity as documented in published literature even if this effect is not addressed in drug labelling or chronic itch guidelines.	Consult with the Medical Monitor for assessment of washout duration	Prohibited
Cannabinoid agonists	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Topical doxepin	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited (except for limited 'Itch Intervention' as in Section 10.6.4)
Thalidomide or methotrexate	Excluded within 14 days (e.g. 14-day washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Cyclosporin A[3]	Excluded within 6-weeks (e.g.6-week washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited

Table-3. Prohibited Medications and Washout Requirements		
Concomitant Medication	**Study Entry (see Section 9.5)**	**During Study**
Non-insulin biologics (including monoclonal antibodies) that modify the immune system[3]	Excluded within 3-months (e.g. -month/12-week washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Investigational drug products	Excluded within 4 weeks (e.g. 4-week washout) prior to the start of the screening e-diary WI-NRS collection Investigational monoclonal antibodies are excluded within 3months (e.g. 3-month/12-week washout) prior to the startof the screening e-diary WI-NRS collection[3]	Prohibited
Cryosurgery	Excluded within 14 days (e.g. 14-day washout) prior tothe start of the screening e- diary WI-NRS collection	Prohibited
UV-therapy (PUVA, UVA, UVB, Excimer)	Excluded within 4 weeks (e.g.4-week washout) prior to the start of the screening e-diary WI-NRS collection	Prohibited
Medication known to be clearly associated with Torsade de Pointes (ie Credible Meds "KR- Known Risk" category (see Appendix 10)	Not permitted unless the subject has been on a stable dose for at least 4 weeks prior to the start of screening.	There must be no plans to change the dose during the study.
Central nervous system suppressants, such as barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines[2] specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics, and clonidine	Not permitted at study entry. Consult with Medical Monitor for appropriate washout period based on the specific medication.	Prohibited.

Table-3. Prohibited Medications and Washout Requirements		
Concomitant Medication	**Study Entry (see Section 9.5)**	**During Study**
[1] = Footnote no longer applicable. [2] = The phrase 'short-acting benzodiazepines' refers specifically to the following: triazolam, temazepam, brotizolam (available in EU only), zolpidem, and zaleplon. These drugs should be prescribed at the lowest effective doses and for the shortest period of time that is clinically indicatedduring the conduct of the study. Subjects receiving these agents must be provided the patient information sheet as noted in Table-1 and Table-2 and in Section 9.4. [3] = Subjects whose washout equals or exceeds the 6-week equals or exceeds the 6-week screening window should complete laboratory and electrocardiogram (ECG) screening as early as possible. This ensures that the washout period is not prolonged unnecessarily and they can resume non-study treatment for their itch in the event that they fail laboratory or ECG criteria. Those who complete the washout and are otherwise eligible for study participation will be permitted to re-screen with written consent from the Medical Monitor.		

10.6.3 Symptom Management during the Titration Period (Tolerability Intervention)

Nalbuphine use may be associated with nausea, vomiting, headache, and dizziness upon initiation of treatment and during the titration periods. Tolerability should be assessed throughout the study (clinic visits and telephone contacts) with particular attention given to the double-blind and open-label titration periods when subjects are more likely to experience symptoms due to the initiation of active treatment or to increasing dose(s). At the Investigator's discretion, anti-emetics that are NOT classified as having a known risk for Torsade de Pointes (see Appendix 10, for cardiovascular related prohibited medications with a known risk of Torsade de Pointes classified as "KR") may be prescribed at the baseline or subsequent visits, in which case the subject should be educated on the appropriate, "as needed use" for early treatment of symptoms. Subjects may also benefit from education surrounding dosing with food and/or taking investigational product with 240 mL of water. The literature on managing opiate initiation generally recommends against prophylactic use, as only about 1 in 5 subjects will experience nausea. Headache, dizziness, nausea and vomiting can also be treated with agents that are commonly prescribed for these symptoms (e.g., acetaminophen for headache and scopolamine patch for dizziness, or ondansetron oral tablet for nausea or vomiting) during the titration period, but these symptoms are less frequent and do not warrant prophylaxis. Dietary and other prophylactic measures to avoid constipation may also be considered as clinically indicated based on subject history, but constipation has been limited with NAL ER in studies to date.

10.6.4 Itch Intervention

Baseline Through Week 14

There is no protocol-specified rescue medication for intolerable itch in this study. Once the study treatment has been initiated, every effort should be made to support the subject through the full 14-week blinded treatment period without the use of any prohibited medication for itch, including topical therapies.

During the screening and washout period, non-medicated topical emollients should be used to manage any worsening itch related to the discontinuation of a prior treatment. This may be continued throughout the study, and may be particularly important during the first 4 to 6 weeks. Observations from the TR03 study indicated that the mean WI-NRS value showed a modest decline in both placebo and NAL ER treatment groups over the initial weeks after starting investigational product, consistent with the placebo effect that is well recognized in studies of itch. The mean improvement in itch that has been associated with NAL ER in TR03 differentiated from placebo between 4 and 6 weeks, with on-going differentiation thereafter.

During these initial 4 to 6 weeks, discomfort due to ongoing itch can be addressed with continued nonmedicated topical emollients, and/or oral acetaminophen, as the latter is used broadly for pain and discomfort and may have some dulling effect on the burning and stinging component of the itch. All efforts should be made to provide emotional support to subjects through these first weeks.

If at any point during the first 10 weeks of the double-blind period, debilitating itch cannot be managed with the conservative measures recommended above, then an "itch intervention" may be considered using one of the following topical therapies on the most symptomatic area or areas: topicalcorticosteroids, topical antihistamines (including topical doxepin), or topical capsaicin. **Topical calcineurin inhibitors should not be used for this "itch intervention". The "itch intervention" should not be 1) continued for more than 10 consecutive days; 2) used more than once per subject; or 3) used after the start of Week 10. Use in any of these 3 ways constitutes use of a prohibited medication.**

Week 14 Through Week 52

Debilitating itch exacerbations that occur after Week 14 should be approached using the same sequence of management strategies recommended above. During this study period, any consideration of either extending a "itch intervention" beyond 10 days, or of repeating such an intervention should be discussed with the Medical Monitor. Use of prohibited medications or interventions (including cryotherapy and UV light therapy) other than topical corticosteroids and topical antihistamines is not permitted. If these are initiated, then the subject should be discontinued from study treatment and should complete the Off-Treatment visit, followed by the 2-week off-treatment safety follow-up period (including SOWS reporting). In addition, a final follow-up itch and safety assessment will be made via telephone call 4 weeks after last dose of investigational product.

11 EFFICACY AND PHARMACOKINETIC ASSESSMENTS

11.1 Endpoints

11.1.1 Primary Endpoint

The primary efficacy endpoint is the difference between the percent "Responders" at Week 14 for the NAL ER treatment arm versus the placebo arm. A "Responder" is defined as a subject with a ≥ 4- point decrease in the 7-day average WI-NRS from baseline to Week 14.

11.1.2 Secondary Endpoints

Key secondary efficacy endpoints include the following:

- The mean change in ItchyQoL from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in thepercentage of prurigenous lesions with excoriations/crusts (item 5a) from baseline to Week 14 forthe NAL ER treatment arm versus the placebo arm
- The mean change in sleep disturbance (PROMIS Sleep Disturbance Short Form 8a) from baselineto Week 14 for the NAL ER treatment arm versus the placebo arm

Other secondary efficacy endpoints include the following:

- The mean change in 7-day average WI-NRS from baseline to Week 14 for the NAL ER treatmentarm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in thepercentage of healed lesions (item 5b) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in PAS as assessed by the percentage of subjects having a 1-category improvement in thepercentage number of lesions (item 2) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm
- Change in IGA-PN as assessed by the percentage of subjects having a 1-category improvement in activity
- Change in IGA-PN as assessed by the percentage of subjects having a 1-category improvementin stage
- The proportion of subjects having a PBI-P score of ≥ 1 at Week 14 for the NAL ER treatment armversus the placebo arm

Secondary Safety Endpoints

The totality of the safety data will address the secondary endpoint of characterizing the overall safetyand tolerability of NAL ER in subjects with PN. Key parameters within the overall descriptive assessment of safety and tolerability are considered to be the rate of subjects having an SAE (Safety)and the rate of subjects discontinuing due to AEs (Tolerability).

Pharmacokinetics

Nalbuphine plasma concentration (and metabolites as needed).

11.2 Efficacy Assessments

11.2.1 Numerical Rating Scale for Itch

The NRS is a PRO instrument, designed to quantify the intensity of worst itching experienced duringa 24-hour period, and can be applied and validated either with reference to the average itch or to the absolute worst itch (WI-NRS) over that 24-hour period. Only the WI-NRS is being evaluated in thisstudy. The scale is a set of boxes, one for each number, from 0 (no itching) to 10 (worst possible itching). The WI-NRS is a widely used instrument recommended by the IFSI for quantifying itch intensity as well as a useful instrument for grouping subjects into categories of itch intensity describedas mild, moderate, or severe[20]. The WI-NRS has been investigated in subjects with chronic pruritusof a variety of origins and a high reliability and concurrent validity was found[13].

In this study, subjects will be asked to record the WI-NRS value daily in the e-diary during the double-blind treatment period, at approximately the same time each day usually in the late afternoon or earlyevening. If the subject cannot access the e-diary (for any reason) during the double-blind period, theTrialogics web portal may be used as a backup for entering daily study information. Daily recordingof WI-NRS score via the e-diary will end at the Week 14 visit.

In the open-label extension period, WI-NRS data will be collected from the subject via the Trialogics web portal or e-diary at the regularly scheduled clinic visits. Note: after the week 14 visit and only ifinstructed by the site and due to the necessity of a remote/phone visit, subjects may use the e-diary for recording the WI-NRS at the time of the phone visit. At the End of Study telephone call, site staffare to ask the subject to verbally report their current WI-NRS score and site staff must enter the reported score into the Trialogics web portal. The recommended question text is: “On a scale of zeroto ten, with zero being ‘no itch’ and 10 being the ‘worst imaginable itch’, how would you describe your worst itch experience over the last 24 hours?”. This instrument can be found in Appendix 5. WI-NRS information should be collected per the instructions provided in the Trialogics User Manual.

11.2.2 ItchyQoL

The ItchyQoL consists of 22 pruritus-specific items measuring how pruritus affects subjects’ 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 1. The ItchyQoL should be administered at the site or e-diary.

11.2.3 Prurigo Activity Score

The PAS consists of 5 quantitative and qualitative measurements related to the examination of the skin. The instrument can be found in Appendix 7. Type, number, distribution, quantitative number of lesions in a representative body part, and activity are documented. Prurigo lesion activity is recorded as a stage (0 to 4), based on the percentage of overall lesions with the relevant characteristic. A representative area, including the exact number of lesions present in the area, will be designated during the baseline assessment (screening visit; Question 4, Form

Version 1.0a), and will be re- evaluated during subsequent study visits; it should remain consistent throughout study visit assessments. The screening PAS Form Version 1.0a is to be used at screening only; the PAS Form Version 1.0b is to be completed for all other visits. All efforts should be made to ensure the same Investigator who performs the Baseline assessment performs the subsequent PAS assessmentsthroughout the study.

11.2.4 Investigator Global Assessment – Prurigo Nodularis

The IGA-PN collects an Investigator Global Assessment of the status of the PN skin lesions. The instrument can be found in Appendix 6. The IGA-PN uses a 5-category scale (scoring 0 to 4) to describe the status of 2 aspects of PN lesions: the excoriation/crusting activity on the surface (PN-Activity), and the presence and character of the lesions (PN Stage). All efforts should be made to ensure the same Investigator who performs the Baseline assessment performs the subsequent IGA-PN assessments throughout the study.

11.2.5 Patient Benefit Index

Before therapy, the subject fills in the PBI-P pre-therapy *Importance of Treatment Goals* questionnaire to document their personal assessment regarding the importance of each individual treatment objective specified in the questionnaire. During and after therapy, the subject completes amatched "on-treatment" *Treatment Benefits* questionnaire and rates the extent to which the treatmentobjectives have been achieved. The instrument consists of 27 multiple choice questions that can be answered "not at all", "somewhat", "moderately", "quite", "very" and "did not apply to me". The instrument can be found in Appendix 2. The PBI-P will be administered according to the schedule of events (Table-1 and Table-2), and should be administered at the site or e-diary. As the overall visual appearance of the pre- and on-treatment questionnaires is very similar, site administrators mustensure that the appropriate form is used at the appropriate visit.

11.2.6 Sleep Scale

There is no assessment scale that is targeted specifically to evaluate sleep in the PN population. The PROMIS Sleep Disturbance Short Form 8a questionnaire has been developed as a general tool for assessing sleep in the context of clinical trials. It consists of 8 open-ended statements about the subject's sleep over the past 7 days, with 5 options for completing the statement. There is 1 broad sleep quality question with options for completing with: "very poor", "poor", "fair", "good", and "very good". The remaining 7 questions can be answered with: "not at all", "a little bit", "somewhat","quite a bit", and "very much". The instrument can be found in Appendix 3. The PROMIS Sleep Disturbance Short Form 8a should be administered at the site or e-diary.

11.2.7 Photography

Only a limited number of selected sites will participate in the photographic documentation for this study. For those sites participating in the photography component of the study, chosen body areas will be monitored by photography over time. For participating subjects, 1 full truncal image (front or back), 1 full extremity image (arm or leg, front or back), and 1 reference lesion will be selected. Each of the selected areas will be followed with serial photographs over time for a total of 4 images at each selected location as specified in the Canfield Quick Reference Guide

and the User ReferenceManual. Photographs will be stored on-site and in a 21 CFR Part 11 compliant centralized study repository. Please see the Canfield User Reference Manual for instructions for selecting the chosen body areas, obtaining and storing photographs collected, and provisions for re-shooting photographsthat do not meet quality standards for evaluation. Photographs of the body are conducted with monitored lesions marked.

11.3 Pharmacokinetic Assessments

To determine the plasma concentration of nalbuphine and metabolites, PK blood samples will be collected at the site with safety labs, according to the schedule of events (Table-1 and Table-2). Further details of PK sample collection and processing will be provided to the site in the laboratory manual.

Plasma samples will be analyzed for nalbuphine and its metabolites using a validated liquid chromatography mass spectrometry method developed at Covance Laboratory, Inc., Madison, Wisconsin.

Analysis and reporting of concentration results will be conducted according to the current Standard Operating Procedures for bioanalysis at Covance Laboratory, Inc., Madison, Wisconsin. Details of the sample analysis, including a bioanalytical study report, will be included with the final clinical study report.

12 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 9.1.3. Safety will be determined by evaluation of the following:

- AEs
- Vital signs including blood pressure, heart rate, respiratory rate, and body temperature
- Physical examination
- Clinical laboratory data
- Investigator reviewed ECG and central cardiac core laboratory-read-12-Lead-ECG, cardiovascular grading, and/or cardiovascular related prohibited medications
- SOWS
- Brief neurological assessment

Post-treatment Safety:

When a subject reaches their Week 52 visit, or discontinues from investigational product (whichever occurs first), their study status should be updated to “Off-Treatment” in the Trialogics web portal. Achange in subject status to “Off-Treatment” will trigger the launch of the SOWS scale on the subject’se-diary. Any subject who completes the open-label extension period, or discontinues from investigational product at any time, is expected to complete the daily SOWS for 14 days following the last dose of investigational product (unless consent is

withdrawn). The SOWS must be administered per the instructions found in section 12.7 and in the Trialogics manual.

If subjects experience significant withdrawal symptoms during the 2-week (14 days) safety observation period, they should contact the Investigator. At the Investigator's discretion, they may be offered treatment.

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The Investigator is responsible forensuring this.

Adverse Event

An AE is defined as any untoward medical occurrence in a clinical investigation subject reported on or after the first screening date. A TEAE is any untoward medical occurrence in a clinical investigation subject or subject administered a pharmaceutical product on or after the initial administration of investigational product at baseline. 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 investigational product, including comparator
- A combination of 2 or more of these factors

No causal relationship with the investigational product 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 requiresurgery. 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.

AEs fall into the categories "non-serious" and "serious."

Serious Adverse Event

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

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

A hospitalization is defined as an in-patient 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 subjects scheduled for cholecystectomy prior to signing the informed consent form (ICF) who subsequently are hospitalized for the procedure, the hospitalization would be considered elective.

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the SAE. It does not refer to an 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 subject or may require intervention to prevent one of the other outcomes listed above, are 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.

Adverse Event of Special Interest

If a subject spontaneously reports an event, a symptom or a subjective experience that fits any of the 4 categories of AEs described below, that event should be probed with open-ended questions, such as "Can you tell me more about that?" or "Have you ever experienced that kind of feeling before?". The goal is to better understand the context and the potential clinical significance of the event or subjective experience. Importantly, this probing and additional dialogue should take place **ONLY if the subject spontaneously reports such an event or experience**. Pro-active or suggestive questioning is not recommended, since the objective is to understand what the subjects themselves identify as new and different.

Specifically, terms that relate to the following types of events should trigger the collection of additional information using the AESI worksheet and under the AESI section of the Adverse Event eCRF:

Categories of Special Interest:

- Experiences or events suggestive of euphoria, such as elation, exhilaration, feeling a sense of exaggerated well-being, or feeling intoxicated

- Experiences or events suggestive of mood changes or effects, such as reports of sedation, stimulation, or impaired attention/cognition. For example, descriptions of: somnolence, sedation, lethargy; or agitation, anxiety, restlessness; or abnormal behaviors, labile affect, and depressed mood; or poor attention, and mental or memory impairment.
- Events or descriptions that suggest dissociative or psychotic experiences, such as reports of disorientation, abnormal thoughts, hallucinations, illusions or delusions
- Observations that suggest events of drug abuse, misuse, dependence or withdrawal. These experiences or observations may be reported by the subject spontaneously (such as reports of feeling addicted, craving study drug, or complaints of withdrawal after stopping the study drug). The AE may also be based on direct observations made by the Clinician and/or study staff that suggest inappropriate use of the drug, drug tampering or drug diversion. For example, repetitive or significant single-time events of missing tablets in drug accountability assessments

The AESI worksheet and section of the AE eCRF provides for recording the following details aboutany events meeting the characteristics described above:

- A description of the AE event in the subject's own words
- The estimated time between the subject's most recent dose prior to the AE, and the onset time ofthat AE (e.g., X minutes or Y hours between preceding dose and AE onset)
- Any prior history of the same, similar or related symptoms or events, and any relevant prior diagnoses, treatments or additional details from the subject (if a subject reports dizziness, do they have a history of dizziness, vertigo or any past diagnosis of Meniere's disease?)
- Investigator full description based on subject's narrative, comments, and/or assessment

Finally, the development of a confirmed pattern of behavior that results in a new diagnosis of drug dependency or drug abuse should be reported as an SAE.

12.1.1.1 Recording of Adverse Events

AEs will be recorded starting with the signing of the informed consent. All AEs will be collected through the End of Study telephone call. 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 subject's medical records, on a regular basis during the course of the study.

Beginning at the screening visit, and continuing for the duration of the study, subjects must be instructed to record any new AEs on the Subject Symptom Log. Subjects should bring the log to every clinic visit and refer to it during telephone contacts. The Subject Symptom Log should be retrieved for review by study staff at each visit prior to re-dispensing it (or issuing a new log) to the subject.

Following the End of Study telephone call, all unresolved AEs should be followed by the Investigator for at least 30 days from the last dose of investigational product. All unresolved AEs

that were reported by the Investigator to be probably drug related should be followed until the events are resolved/stabilized, the subject is lost to follow-up, or the AE is deemed irreversible.

The reporting period for SAEs 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) as needed based on local requirements.

12.1.1.2 Definition of Relationship to Investigational Product

Association or relatedness to the investigational product will be graded as either "definitely related," "probably related," "possibly related," "unlikely related," or "not related." Determination of relatedness includes:

DEFINITELY RELATED – The AE:

- follows a reasonable temporal sequence from administration of the study intervention
- follows a known or expected response pattern to the suspected intervention, that is confirmed byimprovement on stopping
- reappearance of the event on repeated exposure that could not be reasonably explained by theknown characteristics of the subject's clinical state

PROBABLY RELATED – The AE:

- follows a reasonable temporal sequence from investigational product administration
- abates upon discontinuation of the investigational product
- cannot be reasonably explained by the known characteristics of the subject's clinical state

POSSIBLY RELATED – The AE:

- follows a reasonable temporal sequence from investigational product administration
- could have been produced by the subject's clinical state or by other modes of therapy administeredto the subject

UNLIKELY RELATED – The AE:

- does not follow a reasonable temporal sequence from investigational product administration
- is readily explained by the subject's clinical state or by other modes of therapy administered to the subject

NOT RELATED – The AE:

- clearly not related to the investigational product and another cause of the event is most plausible

- a clinically plausible temporal sequence is inconsistent with the onset of the event
- study intervention and/or causal relationship is considered biologically implausible

12.1.1.3 Definition of Severity

All AEs will be graded, if possible, by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 which can be found at the following website:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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

12.1.1.4 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 investigational product, is defined as an unexpected AE.

12.1.2 Abnormal Laboratory Values, Vital Signs, Electrocardiograms, and Physical Examinations

To confirm study eligibility and assess safety throughout the study, all laboratory and ECG results should be reviewed and assessed for clinical significance within 5 days of report availability. Laboratory abnormalities will be recorded as AEs only if they are associated with clinical symptoms/events and they worsen following the start of investigational product treatment. Clinically significant findings noted prior to the start of investigational product 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 "alanine aminotransferase increased").

Clinically significant worsening in physical examination, vital sign, and ECG findings following start of investigational treatment will be recorded as AEs. Clinically significant findings noted prior to the start of investigational product treatment will be recorded as medical history.

12.1.3 Deaths

Should a death occur within the study period or within 60 days after the last administration of investigational product an AE form and an SAE form should be completed, detailing the AE that resulted in the death (Note: death is an outcome, not an event). The SAE must be reported to the ICON Medical Monitor within 24 hours of the Investigator becoming aware of the event. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

12.1.4 Overdose

For the purpose of study monitoring and AE reporting, a study specific definition of "overdose" of blinded Investigational Product is defined here. Intake of > 1 dose taken within 4 hours, or > 2 doses taken within a day, as reported by the patient will be considered an "overdose". This should be reported as an AESI, with commentary about the details of the event. Of note, this definition of "overdose" is intended to provide a study-specific definition of the term 'overdose' based on the selected dosing regimen, but is not inherently expected to be associated with clinical 'overdose' symptoms unless dramatically exceeded.

In the event of clinical overdose, the effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Such events require urgent medical attention and sustained observation over several hours. Please see Section 6.4.7 of the Investigator's Brochure for additional information.

12.1.5 Pregnancy

Female subjects who become pregnant should be immediately discontinued from the study if they have not yet received investigational product. If a subject is found to be pregnant after they have received investigational product, 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.

12.1.6 Reporting of Serious Adverse Events

Investigators and other site personnel must inform appropriate ICON representatives of any SAE that occurs (whether or not attributable to the investigational product) in the course of the study within 24 hours of when he or she becomes aware of it.

All SAEs must be reported via the electronic data capture (EDC) system within 24 hours of Investigator's knowledge of the event. If the EDC is not available, paper reports should be used

and the EDC must be updated with the information on the paper report as soon as the EDC is available.

Paper reports must be faxed to the following number within 24 hours:

ICON DRUG SAFETY (Pharmacovigilance Department)

The preferred method of reporting on paper is via email:

E-mail: mailto: [redacted] (for Americas)

mailto: [redacted] (for Rest of World)

Fax No.: [redacted]

Tel No.: SAE hotline number [redacted] or [redacted] (within US and outside of US).

The ICON representative will work with the Investigator to compile all the necessary information and ensure that the appropriate Sponsor representative receives a report within 1 day (24 hours) for any and all SAEs.

Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON within 1 day as described above.

The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The Investigator is responsible for informing the Ethics Committee of the SAE as per local requirements. The Investigator should report to ICON, who will forward the report to the appropriate Sponsor representative.

12.2 Data Safety Monitoring Board

An unblinded, independent 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.

12.3 Laboratory Assessments

A complete series of laboratory evaluations (including hematology, serum chemistry, liver function tests [LFTs], thyroid evaluations, free testosterone and sex hormone binding globulin [SHBG for biological males only], urine/serum pregnancy, HCV antibody and reflex HCV RNA if positive, Immunoglobulin A tissue transglutaminase [IgA-TTG], and urinalysis) will be obtained during screening and subsequently according to the schedule of events (Table-1 and Table-2). A positive IgA-TTG result for this test, will require a full review of celiac-related gastrointestinal symptoms (such a diarrhea, bloating, chronic unexplained abdominal pain), and other risk factors for celiac disease should be verified. These risk factors include: a family history of celiac disease, a personal history of Dermatitis Herpetiformis; Type 1 diabetes; impaired bone mineralization; malabsorption of micronutrients such as fat-soluble vitamins, iron, and potentially B12 and folic acid. Subjects previously enrolled prior to the addition of HCV or IgA-TTG testing in Amendment 2, will be asked if they are willing to have blood drawn for these specific tests. They may choose to refuse either or both of these additional tests and will be able to continue participation in the study regardless of either their refusal of consent or the results of the tests should they consent (the results will be used to support data analyses when the study is complete).

Quantitative serum pregnancy tests will ONLY be conducted at the initial screening visit, and again at baseline, to confirm non-pregnant status prior to dispensation of investigational product. Once on study, subjects will be expected to adhere to protocol required birth control requirements and serum pregnancy testing will not be done at regularly scheduled intervals. A serum pregnancy test will be ordered/performed as follow-up to any positive and/or inconclusive urine test results (using unscheduled kit). The required clinical laboratory tests are listed in Table-4. Pregnancy test results must be confirmed as negative prior to dispensing investigational product.

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.

Specifically defined reflex testing, which will be performed for abnormal results, include:

- On-study TSH values above or below the upper or lower limit of normal (ULN or LLN), will result in reflex testing for Free T4 from the existing laboratory sample (when sample is insufficient, a re-draw is necessary).
- A positive HCV antibody will have HCV RNA processed from the existing laboratory sample, ifpossible (or on a re-draw if the original sample has insufficient material). The subject may not beenrolled if the HCV RNA result is detectable. Referral to a hepatologist or infectious disease specialist is recommended for consideration of antiviral treatment. Subject may be reconsidered,as appropriate, after treatment.

Table-4. Clinical Laboratory Assessments		
Serum Chemistry/Serology/Other	**Hematology**	**Urine**
• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Bicarbonate • Blood urea nitrogen • Calcium (screening) • Chloride • Creatinine • Direct bilirubin • Estimated glomerular filtration rate • Gamma-glutamyl transferase • Glucose (random) • Indirect bilirubin • Lactate dehydrogenase • Potassium • Phosphate • Pregnancy • Sex hormone binding globulin (for biological males) • Sodium • Free testosterone (for biological males only) • Thyroid stimulating hormone (withreflex Free T4 if > ULN or • < LLN) • Total bilirubin • Total protein • Uric acid • HCV antibody (if positive, then reflexHCV RNA; at screening only) • IgA-TTG (at screening only)	• Hematocrit • Hemoglobin • Platelet count • Red blood cell count • White blood cell count • White blood cell differential	• Urinalysis • Pregnancy
HCV = hepatitis C virus; IgA-TTG = Immunoglobulin A tissue transglutaminase.		

12.4 Electrocardiogram Assessments

A standard 12-lead ECG will be obtained in triplicate (3 serial ECGs at least 1 minute apart, after thesubject has been supine 5 minutes) according to the schedule of events (Table-1 and Table-2); see theERT Study Manual for ECG procedures. Electrocardiograms will be reviewed locally

for safety by the Investigator and/or their designee. The ECGs will be read centrally for the purpose of meeting the ECG study inclusion criteria, study withdrawal criteria and ECG intervals (PR, RR, QRS, QT, and QTcF using nomogram table), rate rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves).

During the conduct of the trial, if a subject develops any other cardiovascular events noted as part ofthe exclusion criteria, the cardiovascular assessments in Appendix 8 and Appendix 9 are to be completed.

12.5 Physical Examination

A complete physical examination will be performed at the screening visit and subsequently accordingto the schedule of events (Table-1 and Table-2). Physical examinations may be performed by physiciansor mid-level providers, such as advanced practice nurses and physician assistants, if they are appropriatelylicensed and credentialed to perform these examinations in accordance with local requirements and/or regulations.

12.6 Vital Signs

Blood pressure and heart rate will be taken while seated for at least 5 minutes. Temperature may be taken by any standard method (e.g., oral, tympanic, rectal, etc.).

Vital signs (blood pressure, heart rate, respiration rate, body temperature, and weight) will be obtained at the screening visit and subsequently according to the schedule of events. The height, weight, and BMI will be recorded only at screening. Weight will be obtained at the screening visit and subsequently according to the schedule of events (Table-1 and Table-2).

12.7 Subjective Opiate Withdrawal Scale

The SOWS is a self-administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensity the subject rates on a scale of 0 (“not at all”) to 4 (“extremely”). The instrument can be found in Appendix 4. In this study, subjects will complete SOWS daily for 14 days, starting at the Off-Treatment visit and continuing through the washout and safety follow-up period to the Last Visit on the study. **For subjects who discontinue study drug early (including in-between study visits), the change in subject status to “Off-treatment” in the Trialogics portal should be made immediately as the site becomes aware of discontinuation**; SOWS entries provide valid information ONLY if they are collected in the first 14 days off-treatment.

12.8 Brief Neurological Assessment

In order to monitor any potential CNS related side effects, a brief neurological assessment will be conducted according to the schedule of events (Table-1 and Table-2), as well as a focused neurological medical history which will be obtained at screening. Minimally, the following neurological criteria should be assessed: mental status, motor exam, sensory exam, coordination, and gait.

13 STATISTICAL EVALUATION

As a companion to this protocol and to provide a more detailed explanation of the statistical methodology to be used for this study, a SAP will be developed prior to locking the database and before unblinding the randomization.

13.1 Sample Size and Power

The original planned sample size of approximately 240 subjects (120 per group) is based on assumed responder percentages for placebo and NAL ER of 25% and 45%, respectively. These responder percentages represent estimates based on the Week 10 data from the TR03 study. The power for the sample size estimate is set at 90% with a 2-sided significance level of 0.05.

In the TR03 study, all those who achieved a 50% reduction in WI-NRS itch also achieved at least a 4-point reduction in itch from baseline, matching the responder definition for the current study. Results for all treated subjects showed a response rate for the 50% reduction criterion of 6 of 18 (33.3%) for the NAL ER 162 mg treatment group versus 4 of 22 (18.2%) for placebo (for those

who completed the 10-week study, results were 6 of 12 [50.0%] and 4 of 20 [20.0%]). Of note, the placebo response in TR03 falls on the lower end of the expected range for endpoints that reflect PRO endpoints in neurologically-mediated diseases such as pain or psychiatric disease. Studies in these areas frequently show placebo responses in the 20% to 30% range and sometimes as high as 40%[29]. The role of placebo response in dermatology has been increasingly documented and recognized in recent years[30]. Given the small size of the TR03 dataset, and the variability of placebo response in comparable disease states, the estimate of placebo response for TR11 was set at 25%.

The NAL ER 162 mg responder rate is estimated at 45% for TR11, versus the 33.3% observed in TR03, for the following reasons: firstly, the TR03 endpoint was set at Week 10, and it is expected that the additional 4 weeks of active therapy will likely increase the response rate in this treatment arm. Secondly, experience from the TR03 study indicated that with close follow-up and guidance during the titration period, subject drop-out due to early symptoms associated with opiate initiation can be decreased, although not eliminated. Given that the completer's analysis in TR03 demonstrated a response rate of 50% (again acknowledging the small size of the cohort), increasing the number of subjects completing the study is expected to result in a somewhat higher all-treated response rate in the active arm than was seen in TR03.

To address the concern of the reliability of the estimates of treatment effectiveness from the TR03 study, an adaptive mid-course Sample Size Re-Estimation (SSRE) procedure was introduced in Amendment 2, Protocol v3.1, when less than 10 subjects had been randomized. The analysis was to be performed after 50% of subjects (N=120) had either completed the Week 14 primary endpoint assessment or terminated the study early. Due to COVID 19-related delays, and because the key boundary for the lower margin of the SSRE did not differ if conducted at 45% of subjects, the SSRE was performed based on the Week 14 data for 109 subjects (including pre-Week 14 discontinuations). The analysis was performed as planned by a single, external, unblinded statistician, and was presented and discussed at a closed session of the study DSMB. Based on the DSMB recommendation, the sample size for this study is

being increased to 360 subjects based on the SSRE conditional power which fell within the 'promising zone' as defined by Mehta and Pocock. (see Section 13.4.6.4 for details).

13.2 Randomization

A randomization schedule will be computer-generated before the start of the study. After all screening procedures are performed and results of screening tests are available, eligible subjects will be activated in the IWRS, and assigned randomly on a 1:1 basis to the following treatment groups:

- Arm A: 162 mg NAL ER
- Arm B: Placebo

Randomization will be performed by the IWRS. Subjects will be stratified by site.

13.3 Statistical Analysis Sets

13.3.1 Modified Intent-to-treat Population

The MITT population will consist of all randomized subjects who have received at least a single dose of investigational product. The MITT population will be used for all efficacy analyses. In the event of a discrepancy between the randomized treatment and the actual treatment received, subjects will be analyzed for efficacy according to their randomized treatment assignment.

13.3.2 Per-protocol Population

The per-protocol (PP) population will include all subjects in the MITT population without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variable. The deviations can include, but are not limited to:

- Key inclusion/exclusion criteria not satisfied
- Use of prohibited concomitant medications (this category includes those with anti-itch activity, see Section 10.6.4)
- Inadequate investigational product compliance, which will be determined before breaking the blind

The subjects to be excluded from the PP population will be identified in a blinded fashion and documented in a memo prior to the database lock and unblinding.

13.3.3 Safety Population

The safety population will consist of all randomized subjects who have received at least a single dose of investigational product. The safety population will be used in all safety analyses. In the event of a discrepancy between the randomized treatment and the actual treatment received, subjects will be analyzed according to the treatment they actually received.

13.4 Statistical Methods

13.4.1 General Principles

Summary statistics will be presented by treatment group. For continuous variables, unless otherwisestated, the number of available observations (n), mean, standard deviation, median, and range will beprovided. For categorical variables, the number and percentage in each category will be displayed.

For the open-label extension period, summary statistics will be presented by treatment group (as per the double-blind period) and overall as a single group. Only descriptive statistics will be displayed for open-label extension period.

Assessments of change from baseline to post-baseline will include only those subjects with both baseline and post-baseline measurements. Baseline for WI-NRS is derived as the average of the responses on the 7 days prior to the first dose of investigational product. For other variables, the last value of a variable taken before the first dose of investigational product will be used as the baseline value.

A more detailed description of study analyses will be presented in the SAP.

13.4.2 Missing Data

Unless otherwise specified, missing or dropout data will not be imputed for the purpose of data analysis. For the primary and secondary endpoint analyses, multiple imputation will be utilized to estimate missing data; details are discussed in Section 13.4.6 and will be elaborated upon in the SAP.

13.4.3 Demographic and Baseline Characteristics

Demographics and baseline disease characteristics, medical history, laboratory data, and physical examination findings will be summarized descriptively by treatment group.

13.4.4 Subject Disposition

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

13.4.5 Concomitant Medications

Concomitant medications will be tabulated by Anatomic and Therapeutic Class of World Health Organization (WHO) drug, preferred term, and treatment group. For the purposes of data collection, a medication's usage will be considered concomitant if it was started within 14 days prior to Informed Consent and continued after administration of the investigational product. If the start date is missing, it will be assumed that the medication was used concomitantly.

Concomitant medications should be collected from 14 days prior to the signing of consent. Beginning at the screening visit, and continuing for the duration of the study, subjects must be instructed to record any new concomitant medication use on the Subject Medication Log. Subjects should bring the log to every clinic visit and refer to it during telephone contacts. The Subject Medication Log should be retrieved for review by study staff at each visit prior to re-dispensing it (or issuing a new log) to the subject.

13.4.6 Efficacy Analyses

13.4.6.1 Analysis of Primary Endpoint

The proportions of NAL ER and placebo subjects who meet the primary endpoint definition of response (a ≥ 4-point reduction of the 7-day average WI-NRS from baseline to Week 14) will be compared using a logistic regression model, with baseline WI-NRS as a covariate and the pooled site as a random effect. Subjects with missing Week 14 WI-NRS data and/or who withdraw prematurely prior to Week 14 will be imputed to have non-responder status in the primary mixed-effects model. The baseline covariate was selected because it is a clinically meaningful factor related to response to treatment. Study sites, pooled where appropriate, will be treated as a random effect to account for possible correlation between subjects within a site. Sites will be evaluated to ensure that both treatment groups are reasonably represented prior to inclusion in the analysis. Smaller sites will be combined regionally for Europe and the USA, with conditions for pooling described in the SAP.

To assess the impact of the above "treatment failure" rule, the missing data strategy will employ the multiple imputation (MI) procedure, as well as the completers case (i.e., omitting subjects with missing outcomes) analysis. Multiple imputation was chosen because single imputation cannot reflect the sampling variability under one model or the uncertainty for the correct model. For sensitivity analyses, the above logistic regression model will be re-analyzed using MI to impute missing data, followed by the completers case analysis.

The analysis will be based on the MITT population. Details will be described in the SAP. For all open-label visits, descriptive statistics will be displayed by treatment.

In addition, the primary endpoint will be analyzed using the PP population.

13.4.6.2 Analysis of Secondary Endpoints

All secondary endpoints will be analyzed using the MITT population. The change from baseline in continuous endpoints (WI-NRS, ItchyQoL, PROMIS Sleep Disturbance Short Form 8a) up to Week 14 will be analyzed based on a mixed model for repeated measures analysis that includes the fixed effects of treatment, visit, treatment by visit interaction, and baseline value. The main treatment comparison of interest is at Week 14. For PAS, individual items will be presented with counts and percentages for categories by treatment group and visit; for excoriations/crusts, a logistic regression analysis will be performed for data at Week 14, with responders defined as subjects who had a ≥ 1- category improvement from baseline. For IGA-PN, individual items (PN Activity and PN Stage) will be presented with counts and percentages for categories by treatment group and visit; a logistic regression analysis will be performed for PN Activity at Week 14, with

responders defined as subjects who had a ≥ 1-category improvement from baseline. For PBI-P, the count and percentage of responders (defined as those with a PBI-score of ≥ 1 at Week 14) will be presented by treatment group. For open-label extension period visits, descriptive statistics will be displayed by treatment for all secondary variables.

13.4.6.3 Multiplicity Considerations

To control for Type I error, a fixed sequence testing procedure will be used on the primary endpoint and 3 key secondary endpoints. All endpoints will be tested at the 0.05 level of significance, following a pre-specified order. As soon as one endpoint assessment is found to be non-significant, subsequent endpoints will not be assessed; in other words, a given endpoint can only achieve significance if the prior endpoint is significant. The order of testing is as follows: (1) responders based on a ≥ 4-point decrease in the average WI-NRS from baseline to Week 14 (i.e., the primary endpoint), (2) the mean change in ItchyQoL from baseline to Week 14, (3) responders based on a 1- category improvement in the percentage of prurigenous lesions with excoriations/crusts (PAS item 5a) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm; and (4) the mean change in sleep disturbance (PROMIS Sleep Disturbance Short Form 8a) from baseline to Week 14 for the NAL ER treatment arm versus the placebo arm.

13.4.6.4 Interim Analysis (Adaptive Sample Size Re-estimation)

As described below, an adaptive mid-course Sample Size Re-Estimation (SSRE) procedure was introduced in Amendment 2, Protocol v3.1, when less than 10 subjects had been randomized. The analysis was to be performed after 50% of subjects (N=120) had either completed the Week 14 primary endpoint assessment or terminated the study early. Due to COVID 19-related delays, and because the key boundary for the lower margin of the SSRE did not differ if conducted at 45% of subjects, the SSRE was performed based on the Week 14 data for 109 subjects (including pre-Week 14 discontinuations). The analysis was performed as planned by a single, external, unblinded statistician, and was presented and discussed at a closed session of the study DSMB (July 9, 2020). Based on the DSMB's recommendation, the sample size for this study is being increased to 360 subjects since the SSRE conditional power fell within the 'promising zone' as defined by Mehta and Pocock.[33]

Description of Pre-specified SSRE Procedures: The sample size re-estimation will be performed by one unblinded study statistician, who does not have a decision-making role in the trial; no one else, including Sponsor or clinical team members, had access or saw the unblinded data in the Data Monitoring Committee (DMC). The communication plan from the DMC is to report one of the following statements based on the conditional power results: 1) "carry on"; 2) "increase sample size to XXX"; or 3) "stop the study due to unfavorable safety and/or efficacy concern." Details about the DMC and the data monitoring procedures are specified in the DMC charter. When 50% of the subjects have provided the Week 14 primary endpoint data or have terminated the study and the data are considered "lockable" by data management, the data file will be provided with limited access to the unblinded statistician in the DMC; the proportion of responders will be estimated; and the conditional power (CP) will be calculated. Given that the interim analysis is to be performed at 50% of the initial sample size (120 subjects), the targeted power is 90%, and the maximum allowable sample size is set at 1.5 times the initial sample size

(360 subjects), the conditional power cut-off value (CPmin) is 41%[34]. If the CP is between 41% and 90%, the number of subjects per treatment arm will be increased, up to the maximum allowable sample size for this study (120 × 1.5 = 180 eachgroup), to recover the targeted power of 90%.

Since sample size re-estimation occurs only when the interim conditional power falls in the pre-specified "promising" range. The study will not stop for efficacy regardless of the conditional power; the overall alpha will be protected; and the final analysis will be carried out using conventional tests, without the need for weighing the stage 1 and 2 results or adjusting the alpha value.

13.4.7 Safety Analyses

All on-treatment safety data will be assessed descriptively for AEs, SAEs, clinical laboratory measurements, vital signs, physical examinations and SOWS. ECG data will be analyzed in a separate report by ERT Clinical. The totality of these data addresses the secondary objective of characterizing the overall safety and tolerability of NAL ER in subjects with PN. Key parameters within the overall descriptive assessment of safety and tolerability are considered to be the rate of subjects having an SAE (Safety) and the rate of subjects discontinuing due to AEs (Tolerability).

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

13.4.7.1 Adverse Events

All TEAEs will be summarized overall and for each body system and preferred term by treatment group, relationship to investigational product, and severity. For tabulations by severity, only a subject's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. AEs will be dichotomized into "related" (definitely, probably, and possibly) and "unrelated" (unlikely and not related). "Treatment-emergent" will be defined as starting or worsening after the first dose of investigational product. 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 US, AESIs that code to the most relevant abuse related MedDRA preferred terms, will be tabulated and descriptive narratives will be written. Additional AEs that are considered "possibly related to abuse potential" will be tabulated separately[25]. The list of MedDRA preferred terms for AESIs will be described in the SAP.

13.4.7.2 Vital Signs

Vital signs, including blood pressure, heart rate, body temperature, respiration rate, and weight will be summarized by treatment group at baseline and at each scheduled visit.

13.4.7.3 Clinical Laboratory Assessments

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and at subsequent scheduled visits. 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. Laboratory data will also be listed by treatment, subject, and visit. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values, as defined in the SAP, will additionally be generated.

13.4.7.4 Physical Examinations

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

13.4.7.5 Electrocardiograms

Electrocardiogram data (e.g., heart rate, PR, QTcF intervals) will be presented in listings by subject and collection date/time. A complete ECG assessment will be analyzed and reported in a separate ECG report from ERT Clinical.

13.4.8 Pharmacokinetic Analyses

Investigational product plasma concentration data (nalbuphine and metabolites) will be listed by collection time, as applicable.

Two additional sets of analyses will be conducted and provided in separate reports: 1) Analysis and reporting of concentration results by Covance Laboratory; and 2) PK-PD analyses to describe the exposure-response relationships between nalbuphine plasma concentrations and efficacy parameters. Additional PK-PD analyses may be conducted to include safety and/or tolerability parameters, as appropriate.

14 DIRECT ACCESS TO SOURCE DATA/NOTES

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the Sponsor may request access to all source documents, eCRFs, 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 subject names are obliterated on the copies to ensure confidentiality.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Conduct of the Study

Trevi/ICON shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICHE6 Guideline for GCP, 01 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.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject nonevaluable.

15.2 Study Monitoring

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

The study will be monitored by the Sponsor 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 eCRF will be reviewed for completeness and adherence to the protocol. As part of the data monitoring, source documents must be made available to the Study Monitor for review. The Study Monitor will also perform investigational product accountability and subject compliance 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 and safety oversight.

Due to unforeseen circumstances such as a pandemic which restrict monitors from performing an on- site visit, remote monitoring visits are allowed.

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 the Sponsor or the regulatory agencies.

During the course of the study, certain sites may be chosen and scheduled for a routine audit by the Sponsor or its designee as part of the Sponsor's normal processes.

16 ETHICS

16.1 Independent Ethics Committee/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 subject information, recruitment methods such as subject diaries, and advertisements, to the 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.

16.2 Written Informed Consent

Potential subjects 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 subject. 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 subject and must specify who informed the potential subject. Where required by local law, the person who informs the potential subject must be a physician.

After reading the ICF, the potential subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject 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 subject. 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.

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Report Forms/Source Data Handling

The Investigator, or designee, will enter study data required by the protocol into an EDC system. Clinical research associates will visit each study site, at a frequency documented in the monitoring plan, to review the 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.

AEs will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the WHO Drug Dictionary.

17.2 Retention of Essential Documents

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

- Signed ICFs for all subjects
- Subject identification code list, screening log (if applicable), enrollment log, and any otherrelevant administrative log (e.g., training logs, site visit logs)
- 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 CRO)
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties (Delegation of Authority log), together with their roles in the study and their signatures
- Copies of eCRFs and of documentation of corrections for all subjects
- Drug accountability records including individual dispensing logs, overall site dispensing logs, room temperature logs, and drug transit logs

- Record of any body fluids or tissue samples retained
- All other source documents (subject 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, due to 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 in writing and kept in the Investigator study file.

18 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate agreement.

19 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete the Sponsor shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

20 SIGNATURE OF COORDINATING INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

[redacted] DR. [redacted]

[redacted]

Date (day/month/year)

[redacted],
University of Münster

21 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signed	Date (day/month/year)
Print name	
Job Title	

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23 APPENDICES

Appendices 1 – 5 provide the Patient Reported Outcomes (PRO) questionnaires and scales that areused in this study.

Patient Reported Outcomes:

Appendix 1 ItchyQoL™ – Itching Quality of Life Survey

Appendix 2 Patient Benefit Index, Pruritus Version

Appendix 3 PROMIS Sleep Disturbance Short Form 8a

Appendix 4 Subjective Opiate Withdrawal Scale

Appendix 5 Worst Itch – Numerical Rating Scale

Appendices 6 and 7 provide the Investigator Assessment tools that are used in this study.

Investigator Assessments:

Appendix 6 Investigator Global Assessment – Prurigo Nodularis

Appendix 7 Prurigo Activity Score Questionnaire

Appendices 8 and 9 provide Grading or Classification Criteria to be used during the Screening Periodin the assessment of Subject eligibility for this study.

Appendix 10 provides the link to the CredibleMeds website to be used for assessing whether subject concomitant medications include any with a known risk for Torsade des Pointes.

Cardiac Classification Criteria:

Appendix 8 Canadian Cardiovascular Society Grading of Angina Pectoris

Appendix 9 Classification Criteria for Congestive Heart Failure

Appendix 10 List of Drugs That Prolong QT and/or Cause Torsades de Pointes

Appendix 11 Not applicable

Appendix 12 Summary of Changes

APPENDIX 1 ITCHYQOL™ – ITCHING QUALITY OF LIFE SURVEY

Site number: _____ Subject initials: _____ Subject number: _____ Visit date (dd/mmm/yyyy): _____

ItchyQoL™

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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The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How <u>often</u> during the <u>past week</u> 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

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	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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APPENDIX 2 PATIENT BENEFIT INDEX, PRURITUS VERSION

PBI-P – Patient Benefit Index, pruritus version

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 – Patient Benefit Index, pruritus version

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

APPENDIX 3 PROMIS SLEEP DISTURBANCE SHORT FORM 8A

PROMIS Item Bank v1.0 – Sleep Disturbance – Short Form 8a

Sleep Disturbance – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep72	I tried hard to get to sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep67	I worried about not being able to fall asleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

2 June 2016
 Page 1 of 1

APPENDIX 4 SUBJECTIVE OPIATE WITHDRAWAL SCALE

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

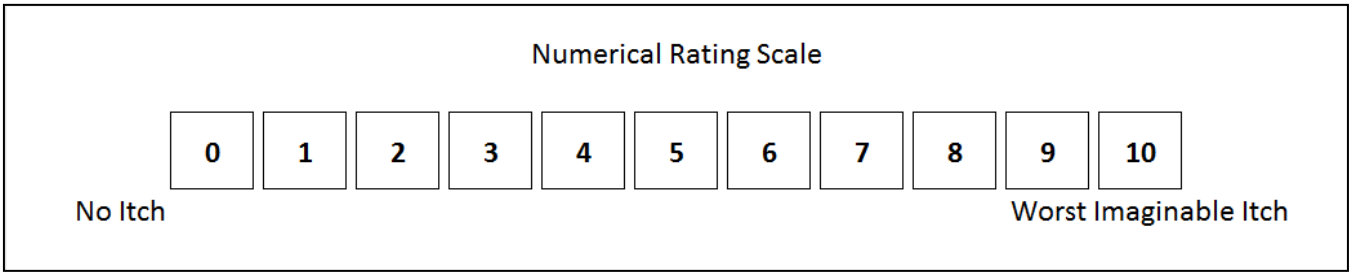
Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

APPENDIX 5 WORST ITCH NUMERICAL RATING SCALE

Numerical Rating Scale (Worst Itch)

Sample – actual assessment scale will be on e-diary

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



APPENDIX 6 INVESTIGATOR GLOBAL ASSESSMENT – PRURIGO NODULARIS

Investigator's Global Assessment - Prurigo Nodularis

IGA I: PN Activity. Considers excoriations and crusts onthe top of PN lesions (first sign of pruritus improvement)

Score	Category	Description: Activity
0	**Clear**	No nodules have excoriations or crusts
1	**Almost Clear**	Small number of nodules have excoriations or crusts
2	**Mild**	Minority of nodules have excoriations or crusts
3	**Moderate**	Most nodules have excoriations or crusts
4	**Severe**	Vast majority of nodules have excoriations or crusts

IGA II: PN Stage. Considers the nodules themselves (long-term sign of improvement)

Score	Category	Description: Presence
0	**Clear**	No nodules (0 nodules)
1	**Almost Clear**	Rare, flattened lesions, with no more than single dome-shaped palpable nodules (1-5 nodules)
2	**Mild**	Few, mostly flattened lesions, with small number of dome-shaped palpable nodules (6-19 nodules)
3	**Moderate**	Many lesions, partially flattened and dome-shaped palpablenodules (20-100 nodules)
4	**Severe**	Abundant lesions, majority are dome-shaped palpablenodules (over 100 nodules)

APPENDIX 7 PRURIGO ACTIVITY SCORE QUESTIONNAIRE

PAS, Version 1.0a (Baseline) 18.08.2017

Prurigo Activity Score (PAS)

Name:_____ Date:_____
(DD/MM/YYYY)

1a. Type of Prurigo: Which efflorescences do you see? (Multiple answers possible)

☐ Hypo-/Hyperpigmented maculae
☐ Papules
☐ Nodules
☐ Plaques
☐ Ulcers

1b. Type of Prurigo: Which type of prurigo is predominant? (Single answer only)

☐ Completely healed (except scars)
☐ Prurigo papular type
☐ Prurigo nodular type
☐ Prurigo plaques type
☐ Prurigo ulcerated type

2. Number: How many prurigo lesions do you see? (Single answer only)

☐ 0
☐ 1 - 19
☐ 20 – 100
☐ > 100

Please note
Estimate; do not count!
Do not consider scars.

3. Distribution: Please mark the affected area(s) (Multiple selection possible)

Area	Affected (Please mark as appropriate)	Code for Item 4
Left forearm	( )	(1)
Right forearm	( )	(2)
Upper left arm	( )	(3)
Upper right arm	( )	(4)
Lower left leg	( )	(5)
Lower right leg	( )	(6)
Upper left leg	( )	(7)
Upper right leg	( )	(8)
Ventral trunk (see Fig. 1)	( )	(9)
Dorsal trunk (see Fig. 1)	( )	(10)
Capillitium	( )	(11)
Face	( )	(12)

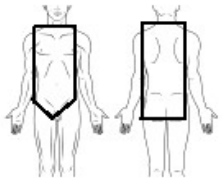


Fig. 1

4. Representative Area:
Please choose a representative area which will be re-examined during each visit. During the study the area must be always the same, please count in that area!

Representative area (see Code from item 3): _____
Exact number of pruriginous lesions in representative area (excluding scars): _____

5. Activity: Please mark the respective percentage in comparison to all pruriginous lesions.
(Single answer only)

a) Pruriginous lesions with excoriations/crusts:	0 %	1 - 25 %	26 - 50 %	51 - 75 %	76 - 100 %
b) Healed prurigo lesions:	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

PAS, Version 1.0b (Follow-Up) 18.08.2017

Prurigo Activity Score (PAS)

Name:_____ Date:_____
(DD/MM/YYYY)

1a. Type of Prurigo: Which efflorescences do you see? (Multiple answers possible)

☐Hypo-/Hyperpigmented maculae
☐ Papules
☐ Nodules
☐ Plaques
☐ Ulcers

1b. Type of Prurigo: Which type of prurigo is predominant? (Single answer only)

☐ Completely healed (except scars)
☐ Prurigo papular type
☐ Prurigo nodular type
☐ Prurigo plaques type
☐ Prurigo ulcerated type

2. Number: How many prurigo lesions do you see? (Single answer only)

☐ 0
☐ 1 - 19
☐ 20 – 100
☐ > 100

Please note
Estimate; do not count!
Do not consider scars.

3. Distribution: Please mark the affected area(s) (Multiple selection possible)

Area	Affected (Please mark as appropriate)	Code for Item 4
Left forearm	( )	(1)
Right forearm	( )	(2)
Upper left arm	( )	(3)
Upper right arm	( )	(4)
Lower left leg	( )	(5)
Lower right leg	( )	(6)
Upper left leg	( )	(7)
Upper right leg	( )	(8)
Ventral trunk (see Fig. 1)	( )	(9)
Dorsal trunk (see Fig. 1)	( )	(10)
Capillitium	( )	(11)
Face	( )	(12)

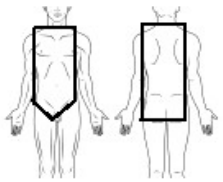


Fig. 1

4. Representative Area:
Please look for the representative area defined at baseline. During the study, the area must remain the same, please count in that area!
Representative area (see Code from item 3): _____
Exact number of pruriginous lesions in representative area (excluding scars): _____

5. Activity: Please mark the respective percentage in comparison to all pruriginous lesions.
(Single answer only)

a) Pruriginous lesions with excoriations/crusts:	0 %	1 - 25 %	26 - 50 %	51 - 75 %	76 - 100 %
b) Healed prurigo lesions:	100 %	75-99 %	50 - 74 %	25 - 49 %	0 - 24 %

APPENDIX 8 CANADIAN CARDIOVASCULAR SOCIETY GRADING OF ANGINA PECTORIS

Canadian Cardiovascular Society Grading of Angina Pectoris

Grade	Description
Grade 1	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
Reference	Campeau Lucien. Grading of angina pectoris. Circulation 1976;54:522-3

APPENDIX 9 CLASSIFICATION CRITERIA FOR CONGESTIVE HEART FAILURE

NYHA FUNCTIONAL CLASSIFICATION OF HEART FAILURE

Classification is based on functional limitations and severity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue,palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results infatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causesfatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

[1] *Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heartand great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.*

APPENDIX 10 LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES

A list of drugs that prolong QT and/or cause Torsades de Pointes is available at *www.crediblemeds.org*. All concomitant medications taken by a subject should be verified on the Credible Meds website to confirm they DO NOT have a Known Risk (i.e. KR category) for Torsadede Pointes.

APPENDIX 11 NOT APPLICABLE

Appendix 11 is not applicable effective with protocol V7.

APPENDIX 12 SUMMARY OF CHANGES: AMENDMENTS 1, 2, 3, 4, 5, 6

Amendment 6:

Clinical Research Protocol TR11 V7.0 (21 July 2021) was produced for the following purposes:

- To update the inclusion criteria 6 to remove "non-sedating" so that it is consistent with the change allowing sedating antidepressants. Duration at stable dose also changes to coincide with allowed changes for sedating antidepressants.
- To update the exclusion criteria to eliminate systemic antihistamines as excluded and add that the subject must be on a stable dose.
- To update the exclusion criteria to eliminate sedating antidepressants as excluded.
- To update Table 3 to revise exclusion information for systemic antihistamines, sedating antidepressants, and for medicines with a known risk for Torsade de Pointes.
- To provide clarification on the QTcF values to prevent exclusion of subjects who present with Right Bundle Branch block
- To allow drugs previously not allowed due to known risk for Torsade de Pointes as long as the subject has been on a stable dose for at least 4 weeks prior to screening. Elimination of exclusion criteria #34 as it is no longer required.

Change	Location of Text that Changes	Rationale
Study Modifications:		
Subjects using ~~non-sedating~~ antidepressants must be on a stable dose for a minimum of ~~8~~ 4 weeks prior to ~~signing consent~~ screening and must be willing to remain on their stable dose for the entire duration of the study	Synopsis Inclusion Criteria #6 and Section 9.5.2 Inclusion Criteria #6	To update the inclusion criteria 6 to remove non-sedating so that it is consistent with the change allowing sedating antidepressants. Duration at stable dose also changes to coincide with allowed changes for sedating antidepressants.
Potential subjects who have received gabapentin, pregabalin, calcineurin inhibitors, cannabinoid agonists, capsaicin, cryosurgery, topical doxepin, thalidomide or methotrexate, topical antihistamines ~~(systemic or topical)~~, ~~or drugs of other classes (such as oral doxepin) which have significant anti-histaminic activity~~ and topical corticosteroids require a 14-day washout. These medications are prohibited for the duration of the study. Use of systemic antihistamines are not permitted unless the subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose during the study. Please refer to Table 3 and Section 9.1.3.1.	Synopsis Exclusion Criteria #22) and Section 9.5.2 (Exclusion Criteria #22)	Elimination of the exclusion of antihistamines (systemic and topical) based on the evolving recognition that long term use of antihistamines does not meaningfully address the itch of prurigo nodularis (PN). Use of stable dose antihistamines in patients that present with severe pruritus will not interfere with the efficacy assessments of this protocol.

Change	Location of Text that Changes	Rationale
Potential subjects taking central nervous system suppressants, such as ~~sedative antidepressants,~~ barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics, and clonidine are excluded. These medications are prohibited for the duration of the study. These medications are prohibited for the duration of the study (see Section 10.6.2, footnotes 1 and 2 to Table 3 for definitions of ~~'sedative antidepressants' and~~ 'short-acting benzodiazepines').	Synopsis Exclusion Criteria #25 and Section 9.5.2 (Exclusion Criteria #25)	**Lower and delayed C_{max} Following Oral ER Nalbuphine:** • The oral BA of a nalbuphine solution was low (approximately 5%) in both rats and dogs (Studies NAL78 and NAL79) suggesting ~ 20-fold lower C_{max} after oral Nalbuphine ER administration (Ref: IB). In humans, the mean nalbuphine plasma concentration five minutes after 10 mg intravenously was 53 ng/mL (Lo et al, 1987). As the doses for injectable nalbuphine range from 10 mg to 20 mg, the maximal concentrations will range from 53 to 106 ng/mL Following a single oral 162-mg nalbuphine ER dose, the mean C_{max} was 21.6 ng/mL (Ref: IB). As expected of an ER formulation, peak concentrations were blunted and rate of absorption delayed. Thus, C_{max} after administration of 162 mg oral nalbuphine ER formulation are ~2.5-5 fold lower than the intravenous formulation. **No Drug-Drug interaction Potential of Oral Nalbuphine ER and tricyclic antidepressants, SSRI, SNRI:** • In vitro inhibition studies demonstrated that nalbuphine does not inhibit any of the major CYP isozymes. Thus, the potential for a metabolism-based interaction of nalbuphine on other drugs is unlikely. Most of the tricyclic anti-depressants are metabolized by CYPs 3A4, 2D6, 1A2, 2C9 and 2B6 (Saraghi et al, 2018). As nalbupine does not inhibit these enzyme systems at the suggested concentrations, there is negligible likelihood of a drug-drug interactions between nalbuphine and tricyclic antidepressants. Also, having a lower and blunted C_{max} will reduce the potential for any drug -drug interaction. • SSRI and SNRI may inhibit CYP 2D6 (Saraghi et al, 2018).

Change	Location of Text that Changes	Rationale
		Nalbuphine is metabolized by a number of cytochrome P450 isozymes (CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and is potentially conjugated by UGT2B7 (Ref: IB). Thus, inhibition of one of the CYPs alone will not impact the concentration of Nalbuphine. Hence, the potential for DDI of nalbuphine with SSRIs and SNRIs is also low. **No Pharmacodynamic Drug-Drug interaction Potential** • Even though package insert of injectable nalbuphine suggests that that the concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as SSRIs, SNRIs, TCAs, drugs has resulted in serotonin syndrome and if concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment; it should be noted that the risk of this effect is for those opioids demonstrate their effects not only via the three major opioid receptors – μ , ∂, κ but also have actions on other targets, for example blocking serotonin and noradrenaline reuptake and N-methyl-aspartate (NMDA) receptors. The contraindication of coadministration of injectable nalbuphine and sedating antidepressants is based on general contra-indication of opioids and not based on specific data for nalbuphine. • Thus, opioids such as morphine, codeine, buprenorphine, oxymorphone, hydromorphone, oxycodone have low risk for serotonin effect; fentanyl, tapentadol, methadone have medium risk; and tramadol, pethidine and dextromethorphan have high risk for serotonin syndrome. • Even in the case of occasional case reports of serotonin toxicity with low-risk opioid and antidepressant

Change	Location of Text that Changes	Rationale
		combinations, such as oxycodone and buprenorphine/naloxone (Suboxone) with other serotonergic medicines can usually be explained by very obvious alternative medical explanations for all the signs of the alleged severe serotonin toxicity. • Furthermore, based on the abuse liability screen for nalbuphine and its metabolites that included 44 targets (receptors, transporters, on gated-channel systems) related to the dopamine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, N methyl-D-aspartate (NMDA) cannabinoid, and opioid neurotransmitter systems, nalbuphine, M1, M3, M4, and M5 have no affinity to any of the non-opioid CNS receptors and nalbuphine showed significant binding to only μ -, κ -opioid receptors (95% to 100% inhibition). • Hence nalbuphine does appear to have a potential risk for serotonin syndrome when co administered with sedating antidepressants. **Different Risk/Benefit for Formulation/Indication: Anesthesia for injectable Nalbuphine vs. PN for Oral-ER nalbuphine with dose titration:** • In Study TR 11, up to 162 mg of Nalbuphine as an extended-release oral formulation is administered for potential use in PN population. In contrast intravenous nalbupine is used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia and thus concomitant use with sedating anti-depressants could be of clinical consequence (Ref: Nubain Package Insert). However, in the case of oral nalbupine ER that is dose

Change	Location of Text that Changes	Rationale
		titrated for use in PN the risk of using sedating anti-depressants may be lower. ***Thus, as nalbuphine oral extended release (ER) formulation/tablet is dose titrated and has lower, delayed and blunted maximal exposure (C_{max}) as compared to intravenous nalbuphine, with no potential for either pharmacokinetic and/or pharmacodynamic based drug-drug interaction with sedating antidepressants, the concomitant use of sedating anti-depressants in a non-anesthetic setting such as PN is acceptable.***
QTcF interval > 450 ms (mean of 3 screening ECG QTcF values) if QRS <120 ms (mean of 3 screening ECG QRS values); QTcF interval >480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS ≥ 120 ms ~~on any screening ECG tracing (triplicate)~~.	Synopsis: Exclusion Criteria (#31) and Section 9.5.2 (Exclusion Criteria # 31)	To more accurately capture the electrophysiological criteria that can be identified by ECG that will be the basis for excluding subjects who would be at potential risk for developing a clinically significant cardiac arrhythmia. In the presence of RBBB measured on ECG, the QRS is at least 30 ms wider than would otherwise be recorded in subjects with normal QRS duration. The QT interval will therefore be at least 30 ms longer in duration. In the absence of RBBB, prolonged QRS complexes are commonly noted in pulmonary disease patients, so the increase in QT due to a wide QRS may be observed in patients who do not have typical RBBB, but instead have a nonspecific intraventricular conduction defect (IVCD).
Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds website; see Appendix 10) is not permitted unless the	Synopsis: Exclusion Criteria # 33 and Section 9.5.2 (Exclusion Criteria	Based ICH Guidance E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (R3) Guidance for Industry, 2017 states that "Concentration-response analysis,

Change	Location of Text that Changes	Rationale
subject has been on a stable dose for at least 4 weeks prior to screening and there are no plans to change the dose ~~at entry or~~ during the ~~study (See Appendix 10)~~. Prior exclusion criterion 34 is not applicable to subjects enrolling in Protocol V7 and later. ~~Medications associated with a potential risk of QT prolongation, but not clearly associated with Torsade de Pointes (i.e. CredibleMeds categories of Possible Risk [PR] or Conditional Risk [KR] presuming the concomitant risk 'conditions' referenced are not present at baseline), are permitted at study entry if the following criteria are met:~~ ~~- subject has been given medication at stable doses for a full 4 weeks prior to screening~~ ~~- medication dose will not be increased after screening, or during the study, and it is anticipated that they will receive the medication for the entirety of the study~~ ~~- QTcF at screening is £ 450 ms on centrally read screening ECGs.~~	33) Synopsis: Exclusion Criteria # 34 and Section 9.5.2 (Exclusion Criteria 34)	in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-timepoint analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug." Concentration-QT (QTCF) analysis conducted to -date provides reasonable information that there is no potential QTc prolongation risk akin to what may have been provided by a TQT study and hence it is reasonable to make the revisions to exclusion criteria 33 and 34 to reflect that subjects are allowed this medication if they are on a stable dose for at least one month at the time of screening. Please note that the concentration and ECG/QT monitoring will still be part of the Protocol It was decided that exclusion criteria 34 information was covered in exclusion criteria 33 and therefore no longer required.

Change	Location of Text that Changes	Rationale
~~If the subject develops a QTcF > 500 ms or a confirmed increase from baseline of > 60 ms based on the average QTcF of the 3 ECGs obtained at the indicated on-treatment visit, versus the average at baseline.~~ Develops a QTcF > 500 ms (mean of 3 ECG QTcF values) in subjects who were randomized **without** ECG findings of RBBB and/or QRS ≥ 120 ms. Develops QTcF > 530 ms (mean of 3 ECG QTcF values) in subjects who were randomized **with** ECG findings of RBBB and/or QRS ≥ 120 ms. Increase from QTcF baseline of > 60 ms (mean determination from 3 ECG values)	Section 9.7: Premature Withdrawal of Subjects from the Study	To accurately reflect an electrophysiologically meaningful change on ECG parameters that would indicate a potential cardiac arrhythmia risk to a subject if they continued in the study.
To update Table 3 to revise exclusion information for systemic antihistamines and drugs of other classes (such as oral doxepin) that have significant antihistaminic activity, sedating antidepressants, and for medicines with a known risk for Torsade de Pointes.	Section 10.6.2, Table 3	To be consistent with the changes to Exclusion criteria 22, 25, 33 and 34.

Change	Location of Text that Changes	Rationale
Headache, ~~and~~ dizziness, nausea and vomiting can also be treated with agents that are commonly prescribed for these symptoms (e.g., acetaminophen for headache and scopolamine for dizziness and ondansetron for nausea and vomiting) during the titration period, but these symptoms are less frequent and do not warrant prophylaxis.	Section 10.6.3	Addition of another drug considered for symptom management during the titration period.
Electrocardiograms will be reviewed locally for safety by the Investigator and/or their designee. The ECGs will be read centrally for the purpose of meeting the ECG study inclusion criteria, study withdrawal criteria and ECG intervals (PR, RR, QRS, QT, and QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves) ~~Electrocardiograms will be read centrally for clinical significance and 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. In cases of Left or Right Bundle Branch Block (LBBB and RBBB, respectively) together with a QRS duration > 110 ms, a QTcF adjusted for the widened~~	Section 12.4 Electrocardiogram Assessments	To clarify Local ECG read is for safety purposes and central ECG read is related to subject inclusion/withdrawal.

Change	Location of Text that Changes	Rationale
~~QRS duration can be used to assess if a patient meets criteria for protocol exclusion, drug hold, or discontinuation using the below formula (See Appendix 10):~~ ~~"Adjusted QTcF" = measured QTcF - [measured QRS - 90 ms].~~ ~~If a subject develops a QTcF > 500 ms or presents with an increase from baseline > 60 ms, the ECG will be repeated at least 30 minutes later and the subject should be discontinued from the study.~~		

Amendment 5 Rationale:

Clinical research Protocol TR11 V6.0 (5 March 2021) was produced for the following purposes:

- To delete exclusion criterion #18 to permit enrollment of subjects who have had prior exposure to dupilumab or nemolizumab. As per Exclusion Criterion #17, eligibility still requires a minimal period of 3 months with no exposure to either dupilumab or nemolizumab immediately prior to enrollment in TR11.
- To enable co-enrollment in TR11 for potential subjects who may also be participating in the long-term safety follow-up period of a COVID-19 vaccine study so long as: 1) they have completed the full vaccine series; 2) that specific vaccine has been approved via an Emergency Use Authorization or comparable relevant Health Authority assessment in the country where enrollment takes place; and 3) the concomitant vaccine safety follow-up study permits co-enrollment.
- The additional text updates are all considered to be Operational clarifications in response to key questions from site staff and are described in the table below.
- To correct a typographic error in the body of the protocol for inclusion criterion #5. In theV5 version of the protocol the Synopsis text was updated correctly, but that update was accidentally omitted in Section 9.5.1 in the body of the protocol. The current change provides internal consistency between the Synopsis and Section 9.5.1.
- Addition of clarifications regarding the eligibility check prior to randomization, and the specific instruction that the final WINRS score entry for confirming eligibility should be performed on the day of the baseline visit and prior to dosing.
- To clarify the specific ‘lesion healing’ criterion to be used for assessing whether a subject is eligible to consider dose reduction at Weeks 28, 32 and 36 by specifically referencing the Prurigo Activity Score Item 5b.

Change	Location of Text that Changes	Rationale
Study Modifications:		
Removal of Exclusion Criterion 18 Note: In order to maintain proper trackingacross protocol versions, this deletion willnot translate to a change in numbering of the subsequent Exclusion Criteria.	Synopsis Section 9.5.2 (ExclusionCriteria)	On-going study experience shows that sites are requesting enrollment consideration for real numbers of potential patients who have now had off-label prior treatment with dupilumab or nemolizumab but who experience on-going active PN with severe itch. In response to this observation and in consultation with the Coordinating Investigator, [redacted] Dr. [redacted], it has been agreed that this exclusion criterionmay be removed. Broadening this enrollment criterionwill help to bring enrollment to closure and will more appropriately reflect the evolving clinical practice environment with respect to PN management. Note: any potential subjects who are eligible under this modification must still comply with Exclusion Criterion 17 which requires a 3-month washout for any immunologically-mediated biologic.

Change	Location of Text that Changes	Rationale
Modification of Exclusion Criterion 13 to enable co-enrollment in TR11 for potential subjects who may also be participating in the long-term safety follow-up period of a COVID-19 vaccine study so long as: 1) theyhave completed the full vaccine series; 2) that specific vaccine has been approved via an Emergency Use Authorization or comparable relevant Health Authority assessment in the country where enrollment takes place; and 3) the concomitant vaccinesafety follow-up study permits co- enrollment.	Synopsis Section 9.5.2 (Exclusion Criteria)	As the protocol permits on-study vaccination with either of the 2 currently approved COVID-19 vaccines in the course of routine medical care, it wasinconsistent to prohibit new enrollment of those whohad received the same vaccines in a prior study environment so long as their continued participation in any vaccine safety follow-up study is not jeopardized. The text is written to accommodate future potential COVID-19 vaccine approvals.
Trialogics Eligibility Check report immediately prior to randomization. ~~If necessary, t~~The last WI-NRS value used in thecalculation ~~may~~ *should* be recorded on the dayof the baseline visit *and* prior to dosing.”		

Change	Location of Text that Changes	Rationale
Operational clarification text was added toInclusion Criterion 3 as follows: "Subjects with a history of acute secondary dermatoses within the preceding 6 months may enroll only if the dermatosis has resolvedcompletely as follows per medical history *or patient self-report and current clinical assessment*	Synopsis Section 9.5.1 (Inclusion Criteria)	This text confirms that the 'medical history' requirement was not intended to be restricted to medical record documentation when not available. Therefore, references to 'patient self-report' and theInvestigator's 'current clinical assessment' were added.
Operational clarification text was added to specify the intended meaning of the 2nd criterion for down-titration eligibility at theWeek 28, Week 32, and Week 36 visits. "(as assessed by an improvement of at least 1category in the PAS healing activity score, *Item 5b). For example, if "0-24%" of PN lesions at baseline were assessed as 'healed', then a 1-category change means that "25-50%" of current Week 28 PN lesions are now evaluated as 'healed'."*	Section 9.1.3.5 – see Weeks 28, 32, and 36	The original text referenced the PAS skin healing assessment and was thought to be self-evident as thePAS only includes one reference to 'healed prurigo lesions.' However, it became clear that in practice a more specific reference and case example would be helpful to site staff.

Amendment 4 Rationale:

Clinical research Protocol TR11 v5.0 (4 August, 2020) was produced for the following purposes:

- To update the target enrolment of study subjects from 240 to 360, based on the DSMB recommendations after reviewing results from the pre-specified Sample Size Re-Estimation (SSRE). In that analysis, the Conditional Power fell within the 'promising zone' as defined in the reference Mehta and Pocock[33] publication; the increase required in the 'promising zone' waspre-specified as 360.
- To refine the exclusion criteria related to the ECG assessments of the QTcF based on advicefrom the consultant Cardiologist who is a recognized arrythmia expert.
- To clarify text that washout during screening should be completed prior to the start of the WI- NRS collection. This has been the requirement throughout prior study conduct but the specificlanguage has been confusing to sites. This confusion was primarily introduced by textual changes that inadvertently dropped the phrase 'WI-NRS collection' from the longer 'screeningperiod WI-NRS collection" in earlier protocol revisions.
- To clarify study procedures, and ambiguities noted across previous protocol versions, includingambiguity regarding the specifications for medication washout periods in relationship to the screening period and or the screening WI-NRS collection.
- To formalize and integrate into the Study Protocol document the actual changes in the Operational implementation of the study that occurred due to the initial imposition of COVID-19 Pandemic-related limitations on in-person study visits. These were previously documented and submitted to Health Authorities in real time as "COVID-19 Administrative Memorandum"numbers 1 and 2, dated April 1, 2020 and April 23, 2020, respectively.

Change	Location of Text that Changes	Rationale
Study Modifications:		
Incorporation of the increased Sample Size of 360 subjects (versus initial plan for 240) based on the protocol-specified Sample Size Re-Estimation (SSRE) procedure that was introduced in Amendment 2, Protocol Version 3.1.	Synopsis (subsections 'Number of Subjects'; 'Statistical Methods') Sections 9.1.1, 13.1, 13.4.6.4	The SSRE procedure showed that the interim Conditional Power of the study fell in the 'Promising Zone' as defined by in the paper by Pocock and Mehta[33]. This resulted in a DSMB recommendation to continue the study and to increase the sample size (ie number randomized) to 360.
"QTcF interval > 450 ms on any single screening electrocardiogram ECG, based on the central reading." was changed to "QTcF interval > 450 ms based on the central ERT calculation of the mean value from the 3 sequential screening ECGs"	Synopsis (Exclusion 31) Section 9.5.2	The consulting cardiologist expert in drug-associated Torsade de Pointes, proposed this change based on the standard approach he recommends in the pre-market screening of investigational drugs for their potential to extend the QTcF interval. This criterion will be built into the formal core ECG lab reports for both screening eligibility and on-study monitoring of the QTcF change from baseline. (Note: the historical use of the injectable nalbuphine formulation has not suggested that this drug poses a QT risk but may not be applicable to the oral formulation, for which a formal TQT study has not yet been conducted).
New text added: "In cases of Left or Right Bundle Branch Block (LBBB and RBBB, respectively) together with a QRS duration > 110 ms, a QTcF adjusted for the widened QRS duration can be used as follows: measured QTcF - [measured QRS - 90 ms]"	Section 12.4 Electrocardiogram Assessments Appendix 11	The consulting cardiologist expert in drug-associated Torsade de Pointes, proposed this change based on the fact that extension of the QRS period of depolarization does not affect the duration of repolarization, which is the key concern for the induction of Torsade de Pointes.

Operational/Executional Modifications and Clarifications:		
Change	**Location of Text that Changes**	**Rationale**
Multiple statements in the study eligibility criteria that relate to medication-specific washout periods required additional clarification. These changes now provide unambiguous guidance that is aligned with the original design principle articulated in Protocol V1 (18 May, 2018): 'the washout is required prior to the collection of the screening WI-NRS, irrespective of when it (*sic 'washout'*) occurs within or prior to the screening period.'	Synopsis: Subsection titled 'Diagnosis and Main Criteria for Inclusion' Section 9.5.2: Exclusion Criteria (subsection with the header: 'Medication-related 'Exclusions') Section 10.6.2 Prohibited Medications (see also Table 3: Prohibited medications and Washout requirements)	These changes represent logical Operational modifications that clarify executional details and result from 1) the extension of the study screening period (Amendment 3) and 2) inadvertent text deletions made in prior Amendments that resulted in references to washout "prior to screening" rather than "prior to the screening WI-NRS collection. Operational execution has been based on 'prior to screening WI-NRS'.
Added instructions for site to consult with Medical Monitor regarding concomitant use of medications with anti-itch activity as documented in published literature, even if this effect is not addressed in drug labelling or chronic itch guidelines.	Section 10.6.2, Table 3 - Prohibited Medications	The intention of the study is to exclude concomitant medications with anti-itch activity; despite the exclusion of multiple medications, sites have raised appropriate questions about a broader range of medications than was anticipated. Therefore, the need for a more general statement regarding any agent with perceived anti-itch activity is needed, and guidance from the medical monitor should be obtained on a case by case basis.

Change	Location of Text that Changes	Rationale
In the event that pandemic COVID-19 conditions recur in in the geographies where TR11 study sites are located, Operational procedures provide for the possibility of phone or videoconference visits with subjects according to the protocol-specified schedule. These provide for a review and documentation of the patient's general health status, any adverse events experienced, and any study-related concerns or questions.	Section 9.1.3, 'Study Procedures and Assessments'	In light of the uncertainty as to whether COVID-related limitations on travel and in-person attendance at clinic-based study visits will recur, the protocol now includes text regarding the potential use of modified processes and procedures should they again become necessary during the remainder of the study execution. These reflect the Changes that were implemented via the Administrative Memorandum of 23 April, 2020 (the second COVID-19 Related Administrative memo titled "COVID-19 Related Follow-on Actions in Response to Evolving Country/Site-Specific Conditions") Phone or videoconference visits are only permitted in the setting of COVID-19 restrictions or with specific approval of the study Medical Monitor and are not to be used under routine conditions.

Change	Location of Text that Changes	Rationale
In the event that pandemic COVID-19 conditions recur in the geographies where TR11 study sites are located, Operational procedures enabling direct delivery of study drug supplies to patients at their home remain available if needed. A special courier service that will pick up study drug at the site and deliver to the subject's home address. All subject-related identifying information will be communicated by site staff to the courier without any Sponsor involvement. This courier will also safely transport drug, in the possession of the patient from a previous visit, back to the site for proper accountability.	Section 10.5.1: Special Procedures for Study Drug Delivery During Periods of COVID-19 Pandemic Restrictions	In light of the uncertainty as to whether COVID-related limitations on travel and in-person attendance at clinic-based study visits will recur, the protocol now includes text regarding the potential use of modified processes and procedures should they again become necessary during the remainder of the study execution. This reflects the Changes that were implemented via the Administrative Memorandum of 23 April, 2020. This was the second COVID-19 Related Administrative memo titled COVID-19 Related Follow-on Actions in Response to Evolving Country/Site-Specific Conditions".
Revision of the TSH reflex testing requirements to accurately reflect revised testing practices which have been implemented in the interval since the prior version of the protocol document: "On-study TSH values above or below the upper or lower limit of normal (ULN or LLN), will result in reflex testing for Free T4 from the existing laboratory sample."	Section 12.3 Laboratory Assessments	The process described in the prior protocol versions required re-testing at the next visit to confirm an abnormal TSH and resulted in delayed access to real-time information regarding the full status of the subject's thyroid function.

Change	Location of Text that Changes	Rationale
Revision of text regarding the reflex testing for HCV RNA if the HCV antibody result is positive. The text now clarifies that the HCV RNA test will provide a quantitative value rather than a qualitative statement of 'detectable' or 'not detected'.	Section 12.3 Laboratory Assessments	This provides more useful information for the patient and patient's physician and is medically appropriate in the setting of a positive HCV antibody when that reflects active infection rather than resolved or successfully treated infection.
Analytic Clarifications/Revisions: No changes have been made with respect to analytic clarifications or revisions (Section 13: Statistical Evaluation" and its subsections) except as noted above that the sample size was increased in accordance with results of the Sample Size Re-Estimation Procedure specified in Amendment 2 to the protocol.		

Amendment 3 Rationale:

Clinical research Protocol TR11 v4 (22 January 2020) was produced for the following purposes:

- To incorporate Administrative Clarification Memo dated 16 July, 2019
- To incorporate Administrative Clarification Memo dated 7 November, 2019
- To clarify the intention and/or execution of various study procedures.
- To clarify procedural ambiguities in the previous version.

Change	Location of Text thatChanged	Rationale
Incorporation of Interval Administrative Memos from 16 July, 2019 and 7 November, 2019		
Exclusion Criterion #30: "Serum potassium belowthe laboratory lower limit of normal." to add to: "Note: If the initial screening value is low, but notconsidered clinically significant in relation to cardiac risk, then potassium supplementation maybe prescribed and the serum potassium level repeated once at least 2 weeks later, during the screening period. If the repeat potassium remains < LLN, then the subject must be screen-failed."	Study Synopsis Protocol Section 9.5.2	To bring the current protocol text into alignment with Administrative Clarification of 16 July, 2019.
Inclusion Criterion #5: Correction of an inadvertenttypographical error in Protocol Section 9.5.1. Inclusion Criterion # 5 was accurately represented in the Synopsis but when repeated in Section 9.5.1,the "≥" sign was inadvertently replaced by the ">" sign.	Protocol Section 9.5.1	To bring the current protocol text into alignment with Administrative Clarification of 7 November, 2019.
To clarify the intention and/or execution of various study requirements and/or procedures		
Study Centers: Increased centers fromapproximately 40 to 65.	Study Synopsis StudyCenter(s):	To align the current number of participating centers
Planned Study Period: updated to extend studyperiod to January 2022	Study Synopsis PlannedStudy Period	To align the planned study period with the updated study timeline

Change	Location of Text thatChanged	Rationale
Inclusion Criterion #8: modified the previous text to add the following italicized phrase: "Females ofchildbearing potential must be using an acceptable method of birth control (if sexually active) *for 14 days prior to randomization and throughout the study.* As a consequence, the previous sentence stating "For female subjects using a barrier methodplus spermicide, that method must be used for at least 14 days prior to screening." was also deleted.	Study Synopsis Protocol Section 9.5.1	Clarification to the requirement for use of appropriate birth control for the 14 days prior to randomization, regardless of the method of use andensures that consent has been obtained prior to the start of a study-specific requirement.
Exclusion Criterion #4: modified to clarify the meaning of the phrase "major depression" to add "An 'isolated major depression' is defined as a single event of depression that includes recurrent thoughts of death, recurrent suicidal ideation withor without a specific plan, or any history of a suicide attempt.". Clarification language of "Subjects with general depression who are considered stable may be enrolled.".	Study Synopsis Protocol Section 9.5.2	Modified to provide a definition of "major depression" (based on DSM 5, consistent with the original design intention) in response to multiple queries from site Investigators/staff requesting guidance on assessing for 'major' depression.
Exclusion Criterion #22: added "or drugs of other classes (such as oral doxepin) which have significant anti-histaminic activity".	Study Synopsis Protocol Section 9.5.2	To include clarifying language for excluding other drugs with significant antihistaminic activity.
Exclusion Criteria #31: procedural clarification to add "on any single" and "based on the central reading.".	Study Synopsis Protocol Section 9.5.2	Procedural clarification in order that the QTcF interval assessment must be based on the value reported in the formal EGC report from the Central ECG reader and (i.e. not based on a site staff reading of the paper ECG print-out which is for record documentation only) to ensure that the appropriate expert judgment is used to establish the ECG exclusionary findings; this ensures subject safety.

Change	Location of Text thatChanged	Rationale
Exclusion Criteria #34: procedural clarification toadd "on centrally read screening electrocardiograms (ECGs).".	Study Synopsis Protocol Section 9.5.2	Procedural clarification to ensure that the appropriate expert judgement is used to establishexclusionary findings.
Medication Washout and Screening Period: changed the screening period from 4 to 6 weeks. Updated "Subjects meeting certain criteria" to "Subjects who fail their initial screening due to the requirement for an extended medication washout". Added "In cases of other unique circumstances thatmay justify rescreening".	Section 9.1.3.1	Screening period modification to allow time for completion of treatment washout and/or completionand reporting of any needed reflex testing .
Open-label Fixed-dose Period (Weeks 17 to 52): updated "at the discretion of the Investigator and subject" to "at the discretion of the Investigator andwith the agreement of the subject".	Protocol Section 9.1.3.5 Protocol Section 10.1.2	Clarification to the text describing the optional dosereduction at Weeks 28, 32 or 36 for subjects meeting specified criteria to more appropriately reflect the decision making roles of the Investigatorand the subject.
Washout and Safety Follow-up Period and Last Contact: added "If a subject discontinues the studyearly, the specific instructions in Section 9.6 Premature Discontinuation of Investigational Product Treatment take precedence."	Protocol Section 9.1.3.6	Clarification on prioritization of assessments for subjects who discontinue early

Change	Location of Text thatChanged	Rationale
Off Treatment Visit: added to SOWS assessment "via the subject status update to "Off-treatment" in the Trialogics portal. The SOWs will be activated and subjects should be instructed to complete the questionnaire" and "**For subjects who discontinuestudy drug early (including in-between study visits), the change in subject status to "Off- treatment" in the Trialogics portal should be made immediately as the site becomes aware of discontinuation;** SOWS entries provide valid information ONLY if they are collected in the first 14 days off-treatment.".	Protocol Section 9.1.3.6	Clarification to SOWS assessment instruction in theTrialogics portal and for subjects who discontinue early.
End of Study Telephone Call: updated "Obtain WI-NRS score" to "Ask the subject to verbally report their current WI-NRS score and site staff must enter the reported score into the Trialogics web portal. The recommended question text is: "On a scale of zero to ten, with zero being 'no itch' and 10 being the 'worst imaginable itch', how would you describe your worst itch experience over the last 24 hours?".	Protocol Section 9.1.3.6	Clarification to the WI-NRS assessment instructionfor the End of Study Telephone Call
Down Titration: added "The WI-NRS scores at andafter Week 24 will be available to site staff via the Trialogics portal in order to assess eligibility for this down-titration.".	Protocol Section 10.1.2	Clarification to the WI-NRS score availability afterWeek 24 to assess eligibility for down-titration.
Table 3. Prohibited Medications: updated and added "Non-antihistamine class drugs" and updatedconcomitant medications. Updated washout requirements	Protocol Section 10.6.2	Clarification to prohibited medications and washoutrequirements.

Change	Location of Text thatChanged	Rationale
Numerical Rating Scale for Itch: added "At the End of Study telephone call, site staff are to ask thesubject to verbally report their current WI-NRS score and site staff must enter the reported score into the Trialogics web portal. The recommended question text is: "On a scale of zero to ten, with zero being 'no itch' and 10 being the 'worst imaginable itch', how would you describe your worst itch experience over the last 24 hours?". Thisinstrument can be found in Appendix 5. WI-NRS information should be collected per the instructionsprovided in the Trialogics User Manual." and removed "This instrument can be found in Appendix 5. WI-NRS information should be collected per the instructions provided in the StudyReference Manual.".	Protocol Section 11.2.1	Clarification to the WI-NRS assessment instructionfor the End of Study Telephone Call
Adverse Events of Special Interest: added "usingthe AESI worksheet and"	Protocol Section 12.1.1	Modification to include AESI worksheet
Adverse Events of Special Interest: added "full description based on subject's narrative,"	Protocol Section 12.1.1	Modification to include investigator instruction onAESI collection
Definition of Severity: updated "4.03 or later." With "5.0 which can be found at the following website: https://ctep.cancer.gov/protocoldevelopment/electr onic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf	Protocol Section 12.1.1.3	Modification to the latest CTCAE version.

Change	Location of Text thatChanged	Rationale
Abnormal Laboratory Values, Vital Sign, Electrocardiograms, and Physical Examination: added “To confirm study eligibility and assess safety throughout the study, all laboratory and ECGresults should be reviewed and assessed for clinicalsignificance within 5 days of report availability.”	Protocol Section 12.1.4	Modification to include definition and site requirements.
Overdose: added “For the purpose of study monitoring and AE reporting, a study specific definition of “overdose” of blinded InvestigationalProduct is defined here. Intake of >1 dose taken within 4 hours, or >2 doses taken within a day, as reported by the patient will be considered an “overdose”. This should be reported as an AESI, with commentary about the details of the event. Ofnote, this definition of “overdose” is intended to provide a study-specific definition of the term ‘overdose’ based on the selected dosing regimen, but is not inherently expected to be associated with clinical ‘overdose’ symptoms unless dramatically exceeded.”, “In the event of clinical overdose, the”, and “Such events require urgent medical attention and sustained observation over several hours.”. Removed “Guidance to the Investigator”	Protocol Section 12.1.4	Modification to include definition and site requirements.

Change	Location of Text thatChanged	Rationale
Laboratory Assessments: added “A positive IgA- TTG result for this test, will require a full review ofceliac-related gastrointestinal symptoms (such as diarrhea, bloating, chronic unexplained abdominal pain), and other risk factors for celiac disease should be verified. These risk factors include: a family history of celiac disease, a personal history of Dermatitis Herpetiformis; Type 1 diabetes; impaired bone mineralization; malabsorption of micronutrients such as fat-soluble vitamins, iron, and potentially B12 and folic acid.”, “A positive HCV antibody will have a HCV RNA processed from the existing laboratory sample, if possible (or an a re-draw if the original sample has insufficient material). The subject may not be enrolled if the HCV RNA result is detectable. Referral to a hepatologist or infectious disease specialist is recommended for consideration of antiviral treatment. Subject may be reconsidered, as appropriate, after treatment.”, and removed visit timepoints listed in table 4.	Protocol Section 12.3	Clarification to IgA-TTG and HCV RNA test assessment requirements during screening.

Change	Location of Text thatChanged	Rationale
Laboratory Assessments: added "Subjects previously enrolled prior to the addition of HCV or IgA-TTG testing in Amendment 2, will be asked if they are willing to have blood drawn for these specific tests. They may choose to refuse either or both of these additional tests and will be able to continue participation in the study regardless of either their refusal of consent or the results of the tests should they consent (the results will be used tosupport data analyses when the study is complete)."	Protocol Section 12.3	Modification to include HCV and IgA-TTG test assessment option for subjects previously enrolled prior to the addition of HCV or IgA-TTG testing inAmendment 2.
Operational/Administrative Clarifications:		
Removed IVRS (Interactive Voice Response System)	List of Abbreviations Schedule of AssessmentsProtocol Section 9.1.3 Protocol Section 10.2.3 Protocol Section 10.3 13.2	IVRS function is not used in the study.
Added LLN (Lower Limit of Normal)	Study Synopsis List of Abbreviations Protocol Section 9.5.2	Inclusion of LLN added to Exclusion Criteria #30
Added "Eligible" to	Protocol Section 9.1.1	Clarification that only eligible subjects will be randomized to NAL ER or matching placebo.
Added "Day 14 and Day 112: -2 days ONLY" toStudy Day window	Schedule of Assessments	Clarification that Days 14 and 112 will only allow a -2 day window due to investigational product supplyquantity provided during the titration periods.

Change	Location of Text thatChanged	Rationale
Weight assessment added beyond the screeningvisit. Added “Weight will be obtained at the screening visit and subsequently according to the schedule ofevents (Table 1 and Table 2).”.	Schedule of AssessmentsProtocol Section 9.1.3 Protocol Section 12.6Protocol Section	Modification to align weight with lab visits to ensure the current weight is applied for estimatedglomerular filtration rate calculation.
Added “and perform e-diary eligibility assessment”.	Protocol Section 9.1.3	Clarification to site instruction on the e-diary eligibility assessment
Added “or Trialogics web portal” and “to be entered by the subject via Trialogics web portal”	Protocol Section 9.1.3	Clarification to site instruction on assessment completion in the Trialogics web portal
Updated “last study visit will” to “Last Visit should” and added “scheduled 2 weeks after” and“Off-Treatment Visit and”	Protocol Section 9.1.3.6	Clarification to the visit weeks from the Off-Treatment to the Last Visit and the End of Studytelephone call.
Double-blind Treatment: Added “Although both AM and PM doses are present on”	Protocol Section 10.1.1	Clarification to sites that subjects should skip theAM dose on Day 1
Study Treatment Packaging and Labeling: updated“see” to “refer to” and “Study Reference” to “Pharmacy”	Protocol Section 10.2	Modification that treatment packaging and labelinginformation is located in the Pharmacy Manual
ItchyQoL: updated “Study Reference Manual” to“Investigator Site File”.	Protocol Section 11.2.2	Modification that the questionnaire instructions arelocated in the Investigator Site File.
Prurigo Activity Score: added “All efforts shouldbe made to ensure the same Investigator who performs the Baseline assessment performs the subsequent PAS assessments throughout the study.”.	Protocol Section 11.2.3	Clarification to that effort should be made to use thesame investigator throughout the study.

Change	Location of Text thatChanged	Rationale
Investigator Global Assessment-Prurigo Nodularis:added “All efforts should be made to ensure the same Investigator who performs the Baseline assessment performs the subsequent IGA-PN assessments throughout the study.”.	Protocol Section 11.2.4	Clarification to that effort should be made to use thesame investigator throughout the study.
Patient Benefit Index: added “pre-therapy *Importance of Treatment Goals*”, “*Treatment Benefits*”, “did not apply to me”, and “As the overall visual appearance of the pre- and on-treatment questionnaires is very similar, site administrators must ensure that the appropriate form is used at the appropriate visit.”. Removed “per the instructions found in the Study ReferenceManual.”	Protocol Section 11.2.5	Clarification to the questionnaires that should beused for the pre-therapy and on-treatment visits.
Pharmacokinetic Assessments: added “PK”, “at thesite with safety labs” and “Further details of PK sample collection and processing will be provided to the site in the laboratory manual.”	Protocol Section 11.3	Clarification to PK sample collection and referenceto the laboratory manual for further details on collection and processing.

Change	Location of Text thatChanged	Rationale
Post-treatment Safety: moved "The SOWS is a self- administered scale for grading opioid withdrawal symptoms. It contains 16 symptoms whose intensitythe subject rates on a scale of 0 ("not at all") to 4 ("extremely"). The instrument can be found in Appendix 4. In this study, subjects will complete SOWS daily for 14 days, starting at the Off- Treatment visit and continuing through the washout and safety follow-up period to the Last Visit on the study. **For subjects who discontinue study drug early (including in-between study visits), the change in subject status to "Off-treatment" in theTrialogics portal should be made immediately as the site becomes aware of discontinuation;** SOWSentries provide valid information ONLY if they are collected in the first 14 days off-treatment." to new section 12.7 Subjective Opiate Withdrawal Scale.	Protocol Section 12 Protocol Section 12.7	Modification to include SOWS description and instruction as a distinct sub-section, as for other study instruments.
Electrocaridogram Assessments: added "in triplicate (3 serial ECGs at least 1 minute apart, after the subject has been supine 5 minutes)" andremoved "Reference" from "Study Reference Manual"	Protocol Section 12.4	Clarification to ECG collection and update on themanual of ECG procedures
Appendix 6 Investigator Global Assessment–Prurigo Nodularis (IGA-PN): master questionnaireincluded with footer.	Protocol Section 23	Updated to include full version of the questionnairewith the version date of 02Sep2018 in the footer
Appendix 7 Prurigo Activity Score Questionnaire(PAS)	Protocol Section 23	Added the original source date to the title area thatwas inadvertently dropped in Amendment 1 for 1aand 1b. Content of the PAS remains stable.

Change	Location of Text thatChanged	Rationale
Appendix 9: American College of Cardiology/American Heart Association Classification of Heart Failure removed	Protocol Section 23	Removed American College of Cardiology/American Heart Association Classification of Heart Failure as it is not required tosupport study execution (see protocol exclusion criterion 26 which uses NYHA criteria).
Appendix 10: List of Drugs That Prolong QT and/or Cause Torsades de Pointes: added “All concomitant medications taken by a subject should be verified on the Credible Meds website to confirm they DO NOT have a Known Risk (i.e. KRcategory) for Torsade de Pointes.”	Protocol Section 23	Clarification to sites to verify all concomitant medications on the provided website.

Amendment 2 Rationale:

Clinical research Protocol TR11 v3.1 (14 March 2019) was produced for the following purposes:

- To address comments by Ethics Committees in Austria and Germany which proposed modification to the concomitant medication guidance for the study.
- To incorporate suggestions from Investigators based on their experiences with practical implementation of the protocol.
- To clarify study procedures.
- To clarify ambiguities in the previous version.
- To incorporate revised statistical methodology for consistency with statistical analysis plan indevelopment based on additional statistical consultation.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Secondary study objectives were divided into "key secondary objectives" and "othersecondary objectives" to align with specification of "key secondary endpoints"and "other secondary endpoints."	Synopsis Section 8.2	Secondary objectives were organized into categories of "key" and "other" to align with specification of "key secondary endpoints" and "other efficacy endpoints." The order was adjusted in recognition ofrecent Health Authority comments.
Inclusion Criterion 1: Combined first two inclusion criteria into one and changed definition of generalized PN from "presenceof ≥ 20 pruriginous nodules" to "presence of ≥ 10 pruriginous nodules."	Synopsis Section 9.5.1	Discussion with Investigators indicated that combining criteria provides greater clarity for patientselection; change in number of pruriginous nodules from 20 to 10 is a response to feasibility considerations and was approved by key PN experts.
Inclusion Criterion 2: Added clarificationthat any history of a primary pruritic skincondition other than PN must have been inactive for at least 6 months prior to screening.	Synopsis Section 9.5.1	Additional text clarifies inclusion requirement forsubjects with a history of a primary pruritic skin condition other than PN and addresses Health Authority comments.
Inclusion Criterion 3: Added criterion to allow subjects with a history of acute secondary dermatoses if the dermatosis hasresolved completely as specified.	Synopsis Section 9.5.1	Addition of this inclusion criterion clarifies conditions under which subjects with a history ofacute secondary dermatoses may be enrolled.
Inclusion Criterion 4: Added criterion tospecify that any identified systemic, non-dermatologic disease that could be a potential cause of concomitant pruritus musteither have resolved, been successfully treated, or must be successfully managed with stable, optimized treatment for at least 3 months prior to screening.	Synopsis Section 9.5.1	Addition of this inclusion criterion ensures that thestudy enrolls subjects in whom PN is the cause of their ongoing itch and addresses Health Authority comments.

Change	Location of Text that Changes	Rationale
Inclusion Criterion 5: Corrected criterion that the arithmetic mean of the 7-day dailyWI-NRS scores prior to the baseline visit must be ≥ 7.	Section 9.5.1	Criterion in Section 9.5.1 incorrectly used the > symbol instead of the ≥ symbol; the criterion listedin the Synopsis was correctly stated. Correction to the criterion in Section 9.5.1 to align with the inclusion criterion in the Synopsis.
Inclusion Criterion 6: Clarified that subjectsusing non-sedating antidepressants must be on a stable dose for a minimum of 8 weeks prior to signing consent; deleted allowance for subjects on neuroleptic medications.	Synopsis Section 9.5.1	Sedative antidepressants and neuroleptic medicationsare not permitted at study entry or through the duration of the study, per Exclusion Criterion 25.
Inclusion Criterion 8: Clarified that contraceptive requirement applies only towomen of childbearing potential.	Synopsis Section 9.5.1	Current text was ambiguous in that it could have beeninterpreted to mean that males, non-fecund females, and females of childbearing potential must have beenusing an acceptable method of birth control. New text clarifies that the contraceptive requirement applies only to females of childbearing potential.
Exclusion Criterion 4: Clarified types of psychiatric disorders that are excluded (major disorders such as bipolar disorder and schizophrenia) and removed condition of "in the opinion of the Investigator." Specified that subjects with a history of isolated major depression for longer than 3years may be eligible for enrollment if theyhave access to appropriate psychiatric care.	Synopsis Section 9.5.2	This exclusion criterion was refined to offer a more standardized method for excluding major psychiatric disorders and specifies the restricted conditions underwhich cases of isolated major depression may be enrolled.

Change	Location of Text that Changes	Rationale
Exclusion Criterion 5: Changed exclusion criterion on entry serum bilirubin level from > 2.5 ×ULN to > 1.5 ×ULN unless explained by a clinical diagnosis of Gilbert's Syndrome.	Synopsis Section 9.5.2	A more conservative approach was taken with respectto entry hepatic laboratory values given that data from a full hepatic impairment study are not available.
Exclusion Criterion 8: Added occupational restrictions (with a cross-reference to Section 9.3) as an eligibility consideration. Added text to Section 9.3 Safety Monitoringto highlight responsibility of the Investigator to understand the lifestyle of each individual, the nature of his or her professional activities, and any medication prohibitions or toxicology screening requirements that may be associated with his or her employment as safety considerations when assessing the overall suitability of the subject for the study.	Synopsis Section 9.3 Section 9.5.2	In response to an Ethics Committee question regarding the enrollment of professional groups with occupational requirements related to driving or operating heavy machinery, and given the risk for impaired attention/alertness for drugs with CNS activity and in the opiate class, occupational restrictions were added as an eligibility consideration.Text was added to reinforce the importance of the Investigator's evaluation of safety considerations when assessing the overall suitability of subjects for the study.
Exclusion Criterion 10: Clarified that a history of active substance abuse within thepast 3 years was excluded and removed condition of "in the opinion of the Investigator."	Synopsis Section 9.5.2	This exclusion criterion was refined to offer a morestandardized method for excluding substance abuse.
Exclusion Criteria 17 and 19: Clarified thatrestrictions on concomitant biologics applyto non-insulin biologics (e.g., monoclonal antibodies).	Synopsis Section 9.5.2	Clarification on biologics restriction; insulin allowed.

Change	Location of Text that Changes	Rationale
Exclusion Criterion 25: Added prohibitionof central nervous system suppressants, such as sedative antidepressants, barbiturates, benzodiazepines (with the exception of short-acting benzodiazepines specifically used on an intermittent and as needed basis), anxiolytics other than benzodiazepines, neuroleptics, and clonidine at screening and throughout participation in the study. Included definitions of sedative antidepressants and short-acting benzodiazepines.	Synopsis Section 9.4 Section 9.5.2 Section 10.6.2 Table 1 Schedule of Assessments Table 3 Prohibited Medications	In response to an Ethics Committee comment on the risk of respiratory depression with concomitant use ofsedative medications together with drugs in the opiateclass, a more conservative approach was adopted in prohibiting certain nervous system suppressants during participation in the study. Short-acting benzodiazepines specifically used on an intermittent and as needed basis are allowed.
Operational/Administrative Clarifications:		
Changed abbreviation for Worst Itch Numerical Rating Scale from WINRS toWI-NRS.	Throughout	Correction to standard abbreviation for assessmenttool.
Added WI-NRS to Schedule of Assessments. Clarified that recording of WI-NRS score is done daily throughout thedouble-blind period via e-diary (ending at the Week 14 visit) and via Trialogics web portal at subsequent study visits thereafter.	Table 1 Schedule of Assessments Table 2 Schedule of Assessments Section 9.1.3.2 Section 9.1.3.3 Section 9.1.3.4 Section 9.1.3.5 Section 9.1.3.6 Section 11.2.1	Clarification on frequency of WI-NRS data collection.

Change	Location of Text that Changes	Rationale
Added clarification that, except in cases ofmedication washout, the baseline (randomization) visit can take place approximately 8 days after screening as long as all screening procedures have beenperformed and required test results have been obtained by the site.	Table 1 Schedule of Assessments	Clarification on timing of baseline visit relative toscreening visit.
Added clarification that randomization can take place even if screening laboratory results for non-thyroid endocrine parametersare not yet available at the baseline visit.	Table 1 Schedule of Assessments	Clarification that site staff do not need to wait for results from screening non-thyroid endocrine laboratory tests before randomizing subjects as thereare no inclusion/exclusion criteria related to these results.
Added clarification regarding which part ofPBI-P (“Treatment Benefit Assessment” questions only) should be administered at Week 10.	Section 9.1.3.2	Clarification on PBI-P administration at Week 10.
Corrected unit on TSH from microIU/mL tomilliIU/mL in criterion for reflex testing; that is, TSH < 0.05 milliIU/mL will have a Free T4 processed from the existing laboratory sample, if possible.	Table 1 Schedule of Assessments Table 2 Schedule of Assessments Section 12.3	Correction.
Specified that the time frame of 3 months atscreening for prohibited investigational products applies to non-insulin biologics.	Table 3 Prohibited Medications	Correction/clarification.

Change	Location of Text that Changes	Rationale
Changed QTcF reason for withdrawal, from QTcF > 500 ms *associated with* a confirmedincrease from baseline of > 60 ms, to QTcF > 500 ms *or* a confirmed increase frombaseline of > 60 ms.	Section 9.7	Either QTcF > 500 ms or an increase from baselineof > 60 ms is a reason for withdrawal of the subjectfrom the study, as stated in Section 12.4; the statement was corrected.
Added text that the Trialogics web portal can be used for data entry if subjects cannotaccess the e-diary.	Section 11.2.1	Provision of another option for data entry if e-diarycannot be accessed.
Specified that the screening PAS Form Version 1.0a is to be used at screening onlyand the PAS Form Version 1.0b is to be completed for all other visits. Emphasized that the representative area chosen at screening should not be changed at subsequent visits.	Section 11.2.3	Clarification on PAS Forms and procedures.
Added screening laboratory assessments forHCV antibody (if positive, then reflex HCVRNA) and IgA-TTG.	Section 12.3 Table 4 Clinical LaboratoryAssessments	Screening laboratory tests (HCV antibody andIgA-TTG) were added to identify systemic, non-dermatologic disease that could be a potentialcause of concomitant pruritus (i.e., HCV, celiac disease) and align with Inclusion Criterion 4.
In list of References, deleted version number on reference for Investigator Brochure for Nalbuphine and added twonew references for updated statistical methodology information.	Section 22	Updates to list of references.
Analytic Clarifications/Revisions:		
Moved the mean change in 7-day average WI-NRS from baseline to	Synopsis Section 11.1.2	Alignment of the “key secondary efficacy endpoints”with the “key secondary study

Change	Location of Text that Changes	Rationale
Week 14 from a key secondary efficacy endpoint to another secondary efficacy endpoint; moved the mean change in sleep disturbance (PROMISSleep Disturbance Short Form 8a) from baseline to Week 14 from another secondary efficacy endpoint to a key secondary efficacy endpoint; and adjusted the description of the fixed sequence testingprocedure for the primary efficacy endpointand 3 key secondary efficacy endpoints accordingly.	Section 13.4.6.3	objectives" and the "other secondary efficacy endpoints" with the "othersecondary study objectives" to address Health Authority comments.
Added an interim analysis for adaptive sample size re-estimation when 50% of the subjects have either completed the Week 14primary endpoint assessment or terminated the study early.	Synopsis Section 13.1 Section 13.4.6.4	An adaptive mid-course sample size re-estimation procedure was added to address the concern of the reliability of the estimates of treatment effectivenessfrom the TR03 study.
Specified that multiple imputations will beused to deal with missing data.	Synopsis Section 13.4.2 Section 13.4.6.1	Clarification of imputation method for handling missing data; refinement of pre-specified statistical methodology information and alignment of protocol with statistical analysis plan in development.
Specified that a mixed-effects logistic regression model will be used for analysis of the primary efficacy endpoint instead ofthe Cochran-Mantel-Haenszel test.	Synopsis Section 13.4.6.1	Clarification of method for analysis of primary efficacy endpoint; refinement of pre-specified statistical methodology information and alignment ofprotocol with statistical analysis plan in development.

Change	Location of Text that Changes	Rationale
Clarified and adjusted statistical methodology for analysis of secondaryefficacy endpoints.	Synopsis Section 13.4.6.2	Clarification of method for analysis of secondary efficacy endpoints; refinement of pre-specified statistical methodology information in response to Health Authority feedback, and alignment of protocol with statistical analysis plan in development.
Modified PBI-P endpoint and analysismethodology.	Synopsis Section 11.1.2 Section 13.4.6.2	Modified PBI-P endpoint to be consistent with the analytic approach developed by the originator of the PBI-P instrument.
Modified language related to use of thelogistic regression model.	Synopsis Section 13.4.6.1 Section 13.4.6.2	Prior text was internally inconsistent regarding the approach to sensitivity analysis testing for the primary endpoint.

Amendment 1 Rationale:

Clinical research Protocol TR11 v2.0 (09 October 2018) was produced for the following purposes:

- To address comments by Health Authority reviewers which identified items requiring furtherclarification or precision.
- To incorporate suggestions from Investigators based on their experiences with practical implementation of the protocol.
- To clarify study procedures.
- To clarify ambiguities in the previous version.
- To address ambiguities regarding safety procedures and safety assessments by clarifying therelevant safety definitions and assessments.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Inclusion Criterion 1: Remove requirement to get written or verbal confirmation that pruriginous nodules "have been actively present and documented for at least 6 weeks prior to signing consent."	Synopsis Table 1 Schedule of Assessments Section 9.5.1	Discussion with PN experts and Study Investigators confirmed that if a potential subject has ≥ 20 pruriginous nodules (part 1 of Inclusion Criterion 1), then 100% will inherently have a history of PN lasting ≥ 6 weeks (i.e., this requirement is redundant).
Exclusion Criterion 16: Clarify the relevant "biologics" which require washout.	Synopsis Section 9.5.2	The current text was not sufficiently clear in referencing 'biologics' (i.e., long-acting insulin technically meets the broad definition of a 'biologic'). The new text clarifies the original intention and medical concern around biologics that affect the immune system and may have prolonged biological effects.
Exclusion Criteria 22 and 23: addition of appropriate restriction around prior thalidomide and systemic corticosteroid use.	Synopsis Section 9.5.2	Investigators indicated that prior/on-going thalidomide use may occur in potential subjects and requested washout clarification. Text regarding systemic corticosteroid use was inadvertently omitted. Because the exclusion period for systemic steroids exceeds that for items in Criterion 22, a separate Criterion was added.
Clarification of End of Study Definition: provide consistent language throughout the protocol with respect to the definition of the "End of the Study." This was always considered by the Sponsor to be the "End of Study Phone Call" which is scheduled to occur at Week 56 (2 weeks after the last subject visit to the study site) since this is the last study contact with the subject.	Synopsis Sections 9.1.1 and 9.1.2 Section 9.1.3.6 Section 9.6 Section 12.1.1 Section 13.4.7	The purpose of this change is to provide consistent language recognizing the final study telephone call as the "end of the Study."

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Clarification of Follow-Up for Early Discontinuations: If permanent discontinuation of investigational product occurs anytime between Day 1 and the Week 14 visit, the subject will be asked to complete the off-treatment visit, the last visit, and the end of study telephone call, and to return to the clinic for the Week 14 visit (unless consent is withdrawn).	Synopsis Section 9.1.2 and Table 1 Section 9.6	The original protocol text specified that subjects who discontinue study prematurely but who do not withdraw consent should return for all subsequent study assessments as per the study schedule of visits with the objective to avoid missing data on these subjects. However, given the TR11 standard off-treatment procedures, if a subject discontinues during the double-blind period and were to attempt to complete both off-treatment visits and the as-intended on-treatment visit schedule, there arisesan irrational overlap of visits. Therefore, this simplified set of visits was specified in order to maximize subject participation in the desired follow-up.
Clarification of Intention regarding Safety Assessment Objective and Endpoint: For consistency with the original protocol intention, the Study Objective with respect to safety has been changed to "*characterize* the safety and tolerability of NAL ER" rather than to "analyze …", which implies a more formal comparison across the 2 treatment arms. In line with this objective, text has been added in Section 11.1.2 that describes key descriptive safety parameters.	Synopsis – Objectives Section 8.2 Section 11.1.2 Section 13.4.7	A question was raised regarding the consistency between the study Objectives and the study Endpoints with respect to Safety. This was appreciated and appropriate changes made to reflectthe original design intentions.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Modification: On treatment ECG observations: change the original ECG parameters that trigger study drug discontinuation (both a QTcF > 500 ms together with an increase from baseline of > 60 ms) to the more conservative approach that either of these conditions should result in discontinuation of study drug.	Section 12.4	Change was suggested by a Health Authority reviewer and accepted by the Sponsor.
Modification: Safety Procedures: The Week 40 home urine pregnancy testing and associated telephone call check-in from site staff were removed.	Table 2 Section 9.1.2 Section 9.1.3.5	Upon clinical and operational review, this testing was assessed as being of minimal value and placing undue procedural burden on subjects.
Analytic Clarifications:		
Clarification - Inclusion Criterion 3: Re-written text clarifies the precise collection criteria, numeric requirements, and the basic calculation method (arithmetic mean) for the qualifying Worst Itch Numeric Rating Scale (WI-NRS) value (i.e., baseline value)	Synopsis Section 9.5.1	Investigators communicated that they were uncertain about whether a WI-NRS value on the Day of the randomization visit could contribute to the eligibility evaluation (collection criteria) so this was clarified. Also, although the Investigator does not calculate the baseline average score for eligibility (this calculation is pre-programmed into the e-diary site-based functions), it was considered important to clarify that this is an arithmetic mean.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
The safety relatedness scale was expanded from 3 to 5 items with the new categories "definitely related" (symptoms follow a known, expected response pattern, disappear after stop of study medication and reappear after reintroduction) and "not related" (plausible other cause, no clinically plausible temporal sequence leading to onset of AE, biologically implausible causal relationship).	Section 12.1.1.2	Increase precision of clinical assessment of possiblecausal relationship.
Clarification of the time-window for dose reduction now specifies that this can occur only at Visits at Weeks 28, 32 and 36.	Sections 9.1.1 and 10.1.2	Original wording was ambiguous as to a time limitafter Week 28 when dose reduction could be implemented.
AEs will be dichotomized into "related" (definitely, probably and possibly) and "unrelated" (unlikely and not related) in descriptive safety tables.	Section 13.4.7.1	Text added for analytic clarification
Clarification of analysis groups (safety as treated, modified intention-to treat as randomized, per-protocol as identified before unblinding).	Sections 13.3.1 to 13.3.3	Analytic Clarifications
Safety analysis: All on-treatment safety data will be assessed descriptively based on the number and rates of adverse events (AEs), serious AEs (SAEs), clinical laboratory measurements, central cardiac core laboratory read-12-lead ECG, vital signs, and physical examinations.	Synopsis Section 13.4.7	Alignment of text in synopsis and statistical Section 13.4.7.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
To clarify that the safety objective for this study is a descriptive rather than a statistical comparison, and that the totality of the safety data will address this secondary objective regarding the overall safety and tolerability of NAL ER in subjects with PN. Key parameters are considered to be the rate of subjects with SAEs (Safety) and the rate of subjects discontinuing due to AEs (Tolerability).	Sections 11.1.2 and 13.4.7	Specification of safety endpoints was requested by aHealth Authority Reviewer.
Operational/Executional Clarifications:		
Corrected the references to the vendor who will perform the analysis of the ECG data and who will generate a separate ECG report for inclusion as an appendix to the TR11 CSR. (The previous TR03 protocol used iCardiac for these vendor activities; that company has since been acquired by ERT Clinical.)	Synopsis – Safety Section 13.4.7.5 Safety Analyses – Electrocardiograms	Changed iCardiac to ERT Clinical since ERT holds the contract for TR11 (note that in the interval since the prior Trevi PN study TR03, iCardiac was acquiredby and integrated into ERT)
Multiple clarifications to the use of e-diary, Subject Symptom Log and Subject Medication Log (concomitant medication) were added. This concerns especially the e-diary to assess WI-NRS, medication compliance and SOWS and other PROs.	Table 1 Table 2 Section 9.1.3.1 Section 9.1.3.2 Section 9.1.3.3 Section 9.1.3.5 Section 10.6.1 Section 10.6.3 Sections 11.2.1 to 11.2.6 Section 13.4.5	The importance of the use of the e-diary in the assessment of PROs as well as Subject Symptom Log and Subject Medication Log makes it necessary to make instructions as clear as possible.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Updated Prohibited/Rescue medication: changed the word *'biologics'* to the phrase *"biologics (including monoclonal antibodies) that modify the immune system"*.	Section 10.6.2	Alignment with updates of Exclusion Criteria 22 and 23.
Clarifications regarding the use of Trialogics web portal to assess SOW and other PROs.	Table 2 Section 9.3 Section 9.6,	Operational/Executional Clarification
Clarification for the selection of areas tobe photographed as well as involved procedures according to the Canfield Quick Reference Guide and the User Reference Manual were added.	Table 1 Table 2 Section 11.2.3 Section 11.2.7	The technical aspects of photography require clear instructions.
Specification of procedures to retest abnormal TSH values.	Table 1 Table 2 Section 12.3	Clinical relevance of TSH abnormal values requiresclarifications of follow-up procedures to ensure safety.
Clarification of the use Titration Blister card for consistency with the Pharmacy Manual and Instructions for Taking TR11 Study Medication; additional instructions regarding confirmation of dose administration in the e-diary. Added text clarifies that the assessment of compliance will be based on comparison of returned blister cards and e-diary entries.	Table 1 Section 9.1.3.2 Section 10.1.1 Section 10.4	Operational/Executional Clarifications
Introduction of re-screening option: Subjects may be re-screened at the discretion of the Medical Monitor after discussion with Investigator and with written permission from the Sponsor.	Section 9.1.3.1	Operational clarity.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Various clarifications to provide aligned wording regarding study procedures in Table 1 and later Sections describing visit-by-visit procedures.	Table 1 Section 9.1.3.2 Section 9.1.3.4	Operational clarity.
Clarification that dose reduction may only occur only at the Week 28, 32, or 36 visits.	Table 2 Section 9.1.3.2	Operational clarification of the specific visits at which dose reduction may be implemented during the Open-Label Period.
Risk/benefit assessment was expanded by adding a discussion of the opiate class warning regarding combined usage with a concomitant benzodiazepine and the increased the risk for respiratory depression in this setting. Added text references the need to ensure subjects receive the Patient Information Sheet on this topic if they are taking or prescribed a new benzodiazepine during the study.	Table 1 Section 9.4 Section 22	Operational clarification to ensure safety, to augment the existing safety information, and to ensure that subjects for whom this risk is relevant receive the relevant Safety Information Sheet to complement the information in the ICF.
Clarification that tolerability assessment should be especially vigilant during the two dose titration periods.	Section 10.6.3	Operational/Executional Clarifications and to ensure safety.
Clarification of adverse events of special interest regarding the use of nalbuphine (as opioid). These are now explicitly stated (signs of Euphoria, Mood Changes, Dissociative or Psychotic experience, drug abuse, misuse, dependence or withdrawal).	Section 12.1.1	Operational/Executional Clarifications and to ensure safety.
Website for CTCAE version 4.03 addedfor site access and investigator reference during assessment of adverse events.	Section 12.1.1.3	Operational/Executional Clarifications and to ensure safety.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
Clarifications that physical examinations are only to be performed by appropriately licensed and credentialed health professional.	Section 12.5	Operational/Executional Clarifications and to ensure safety.
Specification of brief neurological assessment to include mental status, motor exam, sensory exam, coordination, and gait.	Section 12.7	Operational/Executional Clarifications and to ensure safety.
Changes to ensure Consistency of Terminology:		
General replacement of Numerical rating scale (NRS) by Worst Itch Numerical Rating Scale (WI-NRS) in Exclusion Criteria 16, 17, 19 and 20, as well as in the description of Study Design.	Synopsis: Exclusion Criteria 16, 17, 19 and 20 Section 9.5.1 Figure 1 Table 2 Section 9.1.3 Section 9.2 Table 4 Section 10.6.2 Section 11.2.1	The prior protocol document used the 2 acronyms - “WI-NRS” (Worst Itch Numerical Rating Scale) and “NRS” (Numerical Rating Scale”) – interchangeably. However, the only Numerical Rating Scale to be used in the protocol is the Worst Itch Numerical Rating Scale (with 24 hour recall). It was recognized that the use of 2 acronyms for a single patient reported outcome could be confusing.Therefore the acronym for the more specific terminology of “Worst Itch Numerical Rating Scale” or “WI-NRS” was applied throughout the protocol except in instances where historical studiesand associated NRS measurements are referenced.
Text Clarifications:		
Renaming end of Screening and Washout Period from Week 0 to Week 1 and Day 0 to Day 1, respectively. Accordingly randomization should not take place later than 4 weeks after initial screening.	Section 9.1.1 Table 1	Study start should be named Day 1 in Week 1.

Change	Location of Text that Changes	Rationale
Design Clarifications/Modifications:		
A section of text was removed whose original intention was to ensure the safety of subjects whose medical condition (unrelated to the Prurigo Nodularis) worsened during the course of the study. It was recognized that this language couldbe misinterpreted to support the inappropriate early discontinuation of subjects, and that it therefore presented a risk to the integrity of study data.	Section 9.7	A Health Authority reviewer noted the potential for the unintended interpretation. The Sponsor reviewed the pros and cons of a revision versus a deletion and concluded that standard safety monitoring practices are well established and sufficient to protect subject safety with respect to on-study worsening of the subject's medical condition unrelated to Prurigo Nodularis. Therefore a full deletion rather than a textual modification was implemented
Itch intervention replaces rescue intervention.	Section 10.6.2 Section 10.6.4 Section 13.3.2	More appropriate term, and for alignment with Section 10.6.2.