Official Title: A Phase 1, Open-Label, Non-Randomized, Parallel-Group, Multiple-Escalating -Dose Pharmacokinetic Study of Nalbuphine Extended-Release Oral Tablets in Subjects with Impaired Hepatic Function Compared to Healthy Subjects and Exploratory Effect on Itch

NCT Number: NCT04020016

Document Date: Protocol Version 3.0 (Amendment 2) : 05 November 2019

PROTOCOL 182018
Trevi Therapeutics, Inc.
Study Number: TR10
IND Number: 113770

A Phase 1, Open-Label, Non-Randomized, Parallel-Group, Multiple-Escalating-Dose Pharmacokinetic Study of Nalbuphine Extended-Release Oral Tablets in Subjects with Impaired Hepatic Function Compared to Healthy Subjects and Exploratory Effect on Itch

Contract Research Organization:
inVentiv Health Clinical Research
Services LLC (« inVentiv »)
a Syneos Health company
1951 NW 7th Avenue, Suite 450
Miami, FL 33136
USA
Tel.: 1-305-547-5800

Sponsor:
Trevi Therapeutics, Inc.
195 Church Street
14th Floor
New Haven, CT 06510
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Tel.: 1-203-304-2499

CONFIDENTIAL

Protocol Historical File

Version Number	Brief Description/Summary of Changes	Date
Final v1.0	Version submitted to the IEC.	03-OCT-2018
Final v2.0	Amended protocol; protocol amendment 1 added single ascending dose (SAD) cohorts (Part 1 of the study) before the multiple ascending dose (MAD) cohort (Part 2 of the study). Dose escalation stopping rules were added.	14-MAY-2019
Final v3.0	Amended protocol; protocol amendment 2 revised dosing of severe hepatic subjects to a single dose of 27 mg (Part 1 of the study), clarified that Part 2 (MAD) may be terminated if in the judgement of the Safety Committee, the PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects of Part 1 (SAD), such that PK modeling can be predictive of steady state dosing levels. Administrative clarifications were added throughout.	05-NOV-2019

Signature Page

Sponsor

Trevi Therapeutics, Inc.
195 Church Street
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USA
Tel.: 1-203-304-2499

Sponsor's Representative:

[redacted]

[redacted]

Date

Investigator Signature Page

Contract Research Organization (CRO)

inVentiv Health Clinical Research Services LLC, a Syneos Health company

Principal 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]

Date [redacted]

Investigator Signature Page

Orlando Clinical Research Center, Inc.

Principal 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] MD

[redacted] Orlando Clinical Research Center

Date [redacted]

1. Facilities and Responsible Staff

1.1 Clinical Research

This study will be conducted at the following facilities:

inVentiv Health Clinical Research Services LLC « inVentiv »

1951 NW 7th Avenue, Suite 450
Miami, FL 33136, USA
Tel.: 1-305-547-5800
Principal Investigator:
[redacted], MD

Orlando Clinical Research Center, Inc.

5055 S. Orange Avenue
Orlando FL 32809
Tel.: 1-407-240-7878
Principal Investigator:
[redacted], MD

1.2 Biomedical Laboratory Facilities

Biomedical laboratory testing will be performed by the following laboratories:

Eccolab Group Co.
8370 W. Flagler Street, Suite 216
Miami, FL 33144, USA
Tel.: [redacted]

inVentiv
1951 NW 7th Avenue, Suites 180 and 450
Miami, FL 33136, USA
Tel.: 1-305-547-5800

Orlando Regional Medical Center
1414 Kuhl Avenue
Orlando, FL 32806, USA
Tel.: 1-321-841-5111

If another biomedical laboratory is used, this will be documented and annexed to the protocol.

1.3 Clinical Pharmacology and Regulatory Affairs

inVentiv
2500, rue Einstein
Québec (Québec), Canada, G1P 0A2
Tel.: 1-418-527-4000

[redacted], M.Sc.
[redacted] Clinical Pharmacology & Data Services
[redacted] Ph.D.
[redacted] Regulatory & Scientific Affairs
[redacted] M.Sc.
[redacted]

1.4 Bioanalytical Facility

Covance Labs
3301 Kinsman Blvd, Room IS 160
Madison, WI 53704
USA

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2. Synopsis of Protocol

Project No.:	182018 Trevi Therapeutics study number: TR10
Study Title:	A Phase 1, Open-Label, Non-Randomized, Parallel-Group, Multiple-Escalating-Dose Pharmacokinetic Study of Nalbuphine Extended-Release Oral Tablets in Subjects with Impaired Hepatic Function Compared to Healthy Subjects and Exploratory Effect on Itch
Objectives:	**Primary objectives:** • To evaluate the effect of hepatic impairment on nalbuphine extended release (NAL ER) pharmacokinetics (PK) as a function of dose. • To evaluate the safety and tolerability of NAL ER in hepatic impaired subjects. **Secondary objectives:** • To select doses and dosing frequency for NAL ER tablets in subjects with impaired hepatic function. • To assess potential of oral NAL ER to reduce itch in the hepatic impaired population.
Study Design:	This is a Phase 1, open-label PK and safety study of NAL ER in subjects with impaired hepatic function compared to healthy subjects. It will be performed in 2 parts: • **Part 1:** single-ascending-dose (SAD) cohorts • **Part 2:** multiple-ascending-dose (MAD) cohort **Part 1 (SAD) – Dose Cohorts 1 to 5** • **Cohort 1 (27 mg):** 6-8 subjects with mild hepatic impairment, 6-8 subjects with moderate hepatic impairment, and 4-6 subjects with severe hepatic impairment • **Cohort 2 (54 mg):** 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment • **Cohort 3 (108 mg):** 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment • **Cohort 4 (162 mg):** 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment • **Cohort 5 (highest dose tested in subjects with mild or moderate hepatic impairment):** 6-8 healthy control subjects who have been appropriately age-, body mass index (BMI)-, and gender-matched to subjects with mild and moderate hepatic impairment from Cohorts 1 to 4 In Part 1 of the study (SAD), each of the cohorts will be dosed sequentially starting with the lowest dose for subjects with mild or moderate hepatic impairment. Subjects enrolled in Cohort 1 can also be enrolled in Cohorts 2, 3, and 4. For each dose cohort, enrollment of subjects with mild or moderate hepatic impairment can be done in parallel. An evaluation of safety and tolerability of the combined mild and moderate hepatic impairment subject data will be done at each dose level before proceeding to the next dose level.

	Subjects with severe impairment will be enrolled with the 27 mg dose upon completion of SAD in subjects with mild and moderate impairment. After review of the safety and tolerability for the first 2 severe subjects dosed at 27 mg, it will be determined whether or not to complete that dose level for the remaining severe subjects. At the completion of all subjects dosed in the cohort, there will be an evaluation of safety and tolerability to determine whether to proceed to the next dose level for this group. The drug pharmacokinetics in the hepatic impairment subject population will be compared relative to the healthy subject population (Cohort 5). **Part 2 (MAD) – Dose Cohort 6** • **Cohort 6:** 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment In Part 2 of the study (MAD), subjects will receive multiple doses over 13 days according to a dose escalation scheme. Part 2 of the study may be initiated after Groups 1 and 2 (which consist of subjects with mild and moderate hepatic impairment - see Subject Distribution) complete Part 1 of the study (SAD) and following satisfactory review of the safety and tolerability data by the Safety Committee. Subjects enrolled in Part 1 can also be enrolled in Part 2. However, once the Part 1 SAD portion of the study is completed, if in the judgement of the Safety Committee the PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study.
Subjects:	Up to a maximum of 94 adult male or female subjects, ≥ 18 and ≤ 80 years of age will be enrolled in the study. Subjects with normal hepatic function and hepatic impaired subjects may be non-smokers or light smokers (no more than 5 cigarettes/day). Subjects who withdraw or are withdrawn from the study after dosing, for reasons other than safety and tolerability, may be replaced after consultation between the Investigator and Sponsor. The total number of subjects dosed (including potential replacement subjects) will remain within a maximum of 94 subjects for the whole study. An effort will be made to carefully match the healthy subjects (Cohort 5, SAD) with the subjects with mild and moderate hepatic impairment (Cohorts 1 to 4) by age (± 10 years), BMI (± 15%), and gender, to the extent possible. Matching strategy is to enroll control subjects with normal hepatic function who meet demographically matched mean criteria of the pooled subjects with mild and moderate hepatic impairment. The study will enroll up to 8 subjects in Part 2 of the study (MAD) in each of the mild and moderate Child-Pugh categories (a total of up to 16 subjects). An effort will be made to enroll subjects who self-categorize as having some itch (Worst Itch Numerical Rating Scale [WI-NRS] mean score of ≥ 3 at screening). Worst itching intensity scores will be recorded twice daily as specified in the schedule of events. WI-NRS will be used to determine the severity of itch in the hepatic-impaired subjects.
Subject Distribution:	Cohorts 1 to 4 (Part 1, SAD) will each include the following groups of hepatic-impaired subjects:

	• Group 1: Child-Pugh Group A: score 5-6 points; 6-8 subjects with mild hepatic impairment • Group 2: Child-Pugh Group B: score 7-9 points; 6-8 subjects with moderate hepatic impairment • Group 3: Child-Pugh Group C: score 10-15 points; 4-6 subjects with severe hepatic impairment Cohort 5 (Part 1, SAD) will include dosing of healthy subjects with normal hepatic function (control group) to obtain 6-8 subjects who did not vomit within 6 hours of dosing or have any episode of vomiting in order to obtain adequate PK data. The total number of subjects dosed (including potential replacement subjects) will remain within a maximum of 94 subjects for the whole study (up to 78 subjects in the SAD and up to 16 subjects in the MAD). Subjects enrolled in Cohort 1 can also be enrolled in Cohorts 2, 3, and 4. Subjects enrolled in Part 1 can also be enrolled in Part 2.
Screening Procedures:	Demographic data, medical and medication histories, complete physical examination, body measurements, 12-lead electrocardiogram (ECG), vital signs (blood pressure, heart rate, and respiratory rate), pulse oximetry, body temperature, hematology, coagulation (PT, aPTT, and INR), clinical chemistry, human immunodeficiency virus (HIV), hepatitis B and C tests, urinalysis, WI--NRS (Part 2 only), urine and serum pregnancy test (females only), and urine alcohol and drug screen. Assessment of liver function will be performed, and the degree of hepatic impairment will be categorized using Child-Pugh system at screening.
Confinement and Washout:	**Part 1 (SAD)** Subjects in Cohorts 1 to 4 will be confined from the morning of Day -1 until Day 4 (after the 72-hour post-dose blood draw). Cohort 5 subjects will be confined from the morning of Day -1 until Day 3 (after the 48-hour post-dose blood draw). Subjects will come back to the clinic on Day 4 for the final blood draw and safety procedures at the study exit visit. There will be a washout period of at least 7 days between each administration of the investigational product (IP) in Part 1 of the study and between Parts 1 and 2 of the study. **Part 2 (MAD)** Cohort 6 subjects will be confined from the morning of Day -1 until Day 16 (after the 72-hour post-last dose blood draw). Subjects will come back on Day 17 for the final blood draw (96-hour post-last dose blood draw) at the Study Exit visit.
Drug Administration:	**Part 1 (SAD)** Hepatic impairment subjects will receive single ascending oral doses and healthy subjects will receive a single oral dose, under fasting conditions, of NAL ER, at the following dose levels:

Cohort	Planned Dose of NAL ER
1	27 mg
2	54 mg
3	108 mg
4	162 mg

	5 (healthy subjects) | Up to 162 mg For Cohort 1, a minimum of 6 subjects from Group 1 (mild impairment), 6 subjects from Group 2 (moderate impairment), and 4 subjects from Group 3 (severe impairment) will receive a single dose of NAL ER. For Cohorts 2-4, a minimum of 6 subjects from Group 1 (mild impairment) and 6 subjects from Group 2 (moderate impairment) will receive a single dose of NAL ER. Cohort 5 (healthy) will also receive a single dose of NAL ER as determined by the Safety Committee review of the mild and moderate impaired data. Cohorts 1-4 will be dosed sequentially in an ascending design. Enrollment of subjects with mild impairment and moderate impairment can be done in parallel. Subjects with severe impairment will be enrolled upon completion of the highest dose level in mild and moderate impairment subjects. There will be at least 7 days between dosing of each dose level, within the same group of impairment (mild and moderate). Subjects will be observed for a period of 4 days. Safety, tolerability, and combined mild and moderate impaired subject data will be evaluated by a Safety Committee at the completion of each cohort dose level before proceeding to the next cohort dose level. Therefore, the highest dose administered may be lower than 162 mg. Depending on safety and tolerability, the dose escalation scheme may be modified such that intermediate dose levels are administered. Based on the overall safety and tolerability observed in the subjects with mild and moderate impairment, at the completion of all doses tested, it will be determined by the Safety Committee whether or not it is safe to proceed with dosing for the first 2 subjects with severe impairment starting with the 27 mg dose. After review of the safety and tolerability for the first 2 severe subjects dosed, it will be determined whether or not to complete that dose level for the remaining 2 severe subjects at the 27 mg dose. The Safety Committee will be composed of at least the Investigators and one medically qualified Sponsor representative. Some adjustments to the currently outlined doses and/or dosing regimen may be implemented by the Safety Committee, but the dose to be administered in a given dose cohort will not exceed the one currently outlined in the protocol. No food will be allowed from at least 8 hours before NAL ER dosing until at least 2 hours after. A standardized breakfast will be served at least 2 hours after NAL ER dosing. A lunch, supper, and a light snack will be served at appropriate times thereafter. Except for water given with NAL ER, no fluids will be allowed from 1 hour before dosing until 1 hour post-NAL ER dose. **Part 2 (MAD)** Drug administration in Part 2 of the study (MAD) may be initiated following satisfactory review of the safety and tolerability data from Groups 1 and 2 (mild and moderate impairment) from Part 1 of the study (SAD) by the Safety Committee. Depending on safety and tolerability, the dose escalation scheme may be modified such that intermediate dose levels are administered. The dosage regimen (once daily versus twice daily) will be confirmed following review of PK data, as available, from Part 1 of the study (SAD). Part 1 subjects may enter Part 2 of the study after a 7 day washout period. Subjects will receive a single 27 mg dose in the morning of Day 1. Doses will be subsequently escalated for each subject to twice daily, 12 hours apart, 27 mg, 54 mg, 108 mg, and 162 mg over 13 days. On the last treatment day,

<table>
<tr><td></td><td>subjects will receive a single 162 mg dose in the morning. Subjects will remain at each dose level for 2-3 days (minimum 5 consecutive doses) with dose escalation predicated on tolerability of the prior dose.
<table>
<tr><th rowspan="2">Study Day</th><th colspan="2">Dose (mg)</th></tr>
<tr><th>AM</th><th>PM</th></tr>
<tr><td>1</td><td>27</td><td>0</td></tr>
<tr><td>2</td><td>27</td><td>27</td></tr>
<tr><td>3</td><td>27</td><td>27</td></tr>
<tr><td>4</td><td>27</td><td>54</td></tr>
<tr><td>5</td><td>54</td><td>54</td></tr>
<tr><td>6</td><td>54</td><td>54</td></tr>
<tr><td>7</td><td>54</td><td>108</td></tr>
<tr><td>8</td><td>108</td><td>108</td></tr>
<tr><td>9</td><td>108</td><td>108</td></tr>
<tr><td>10</td><td>108</td><td>162</td></tr>
<tr><td>11</td><td>162</td><td>162</td></tr>
<tr><td>12</td><td>162</td><td>162</td></tr>
<tr><td>13</td><td>162</td><td>–</td></tr>
<tr><td>14</td><td>–</td><td>–</td></tr>
<tr><td>15</td><td>–</td><td>–</td></tr>
<tr><td>16</td><td>–</td><td>–</td></tr>
</table>
On Day 1 and Day 13, no food will be allowed from at least 8 hours before NAL ER dosing until at least 2 hours after. A standardized breakfast will be served at least 2 hours after NAL ER dosing. For other dosing days, no food will be allowed from at least 2 hours before each dosing until at least 2 hours after dosing.
Except for water given with NAL ER, no fluids will be allowed from 1 hour before each dosing until 1 hour post-NAL ER dose.</td></tr>
<tr><td>Study Restrictions:</td><td>Subjects will be asked to refrain from the following:
For Cohorts 1 to 4 and 6, new prescription medications from 14 days prior to the first dosing until the study exit (stable regular medication deemed to not interact with investigational product PK will be allowed)
For Cohort 5, prescription medications from 14 days prior to the first dosing until the study exit
Over-the-counter products from 7 days prior to the first dosing until study exit unless a hepatic impaired subject is taking such products for their routine care
Natural health products from 7 days pre-first dose until study exit unless a hepatic impaired subject is taking such products for their routine care
Food containing poppy seeds within 24 hours prior to admission and for the duration of the study</td></tr>
</table>

	• Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours pre-first dose until study exit • Food or beverages containing grapefruit, Seville orange, starfruit, pomegranate, pineapple, or pomelo from 14 days pre-first dose until study exit • Alcohol-based products from 24 hours prior to admission until study exit • Artificial nails or nail polish at screening and during confinement Subjects will be allowed to engage in normal activity throughout the study. Given the long confinement of the study, outings will be permitted during the confinement. Pre-scheduled and supervised outings will also be permitted for smoking subjects during confinement. Outings will be supervised at all times by the clinical staff to ensure compliance with protocol and will be limited to the grounds surrounding the clinic, as per the clinical site-specific procedures for supervised outings. **Part 1 (SAD)** Subjects will be required to avoid lying down or sleeping, unless medically necessary or procedurally required, for 4 hours after drug administration. **Part 2 (MAD)** On Days 1, 4, 7, 10, and 13, subjects will be required to avoid lying down or sleeping, unless medically necessary or procedurally required, for 4 hours after morning drug administration.
PK Sample Collection:	**Part 1 (SAD) – Cohorts 1 to 5** A total of 11 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, and 72 hours post-dose. **Part 2 (MAD) – Cohort 6** On Day 1, a total of 10 blood samples will be collected for quantitation of nalbuphine and metabolite(s) in plasma: at pre-dose and 1.5, 3, 4, 5, 6, 7, 9, 12, and 24 hours post-dose. On Days 4, 7, and 10, a total of 9 blood samples will be collected; at pre-morning dose and 1.5, 3, 4, 5, 6, 7, 9, and 12 hours post-dose (prior to the evening dose administration). On Day 13, a total of 12 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose. Trough blood samples will be collected on Days 2, 3, 5, 6, 8, 9, 11, 12, and 13 prior to the morning and evening dose administrations (if applicable). Plasma samples will be analyzed to determine nalbuphine and M1, M2, M4, and M5 metabolite concentrations using validated assay methods.
Pharmacodynamic Assessment:	WI-NRS measure will be used to determine the severity of itch experienced by subjects with hepatic impairment (for Cohort 6 only) at screening. Subjects will complete the two WI-NRS forms (the "Nighttime Itch" and the "Daytime Itch") at the same time during the screening visit, and the average will be taken to determine the baseline severity. For all Cohort 6 subjects, WI-NRS measure will also be performed on a daily basis from Day -1 to Day 16, twice a day, once within an hour (+/- 1 hour) of completing their morning and evening meals (if applicable). Subjects will fill

	in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.
Subject Safety:	**<u>Part 1 (SAD) – Cohorts 1 to 5</u>** Brief physical examination: on Day -1 and Day 4. Vital signs: on Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and Day 4. Body temperature: on Day -1 and Day 4. ECG: on Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and Day 4. Baseline continuous pulse oximetry will be measured during the nighttime of Day -1 (minimum of 8 hours prior to dose administration). Following the dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-dose and 1.5, 4.5, and 8 hours post-dose. Oxygen saturation will be monitored via continuous pulse oximetry overnight beginning at bedtime and until awaking the next morning from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am. Drug screen and urine alcohol: on Day -1. Urine and serum pregnancy test (females only): on Day -1 and Day 4. Clinical chemistry, hematology, urinalysis, and coagulation (all clinical laboratory tests following a fasting period of at least 8 hours): on Day -1 and Day 4. Medical surveillance: Beginning with informed consent, subjects will be monitored throughout the study by the study staff for adverse events. An Investigator will be on site/campus for drug administration and until 4 hours after administration and available on call for the remainder of the dosing period. **<u>Part 2 (MAD) – Cohort 6</u>** Brief physical examination: on Day -1 and Day 16. Vital signs: on Day -1, pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, approximately 2 and 6 hours post-morning dose on Days 2 to 12, and once on Days 14, 15, and 16. Body temperature: on Day -1 and Day 16. ECG: on Day -1, pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, and once on Days 14, 15, and 16.Baseline continuous pulse oximetry will be measured during the nighttime of Day -1 (minimum of 8 hours prior to first dose administration). Following the first dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-morning dose at 1.5, 4.5, and 8 hours following the morning dose, and at 2 hours following the evening dose. Oxygen saturation will be monitored via continuous pulse oximetry overnight beginning at bedtime and until awaking the next morning from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am. Drug screen and urine alcohol: on Day -1. Urine and serum pregnancy test (females only): on Day -1 and Day 16.

	Clinical chemistry and hematology (following a fasting period of at least 8 hours): on Days -1, 5, 10, and 16. Coagulation and urinalysis (following a fasting period of at least 8 hours): on Day -1 and Day 16. Medical surveillance: Beginning with informed consent, subjects will be monitored throughout the study by the study staff for adverse events. An Investigator will be on site/campus for each morning drug administration and until 4 hours after morning administration on Days 1, 4, 7, 10, and 13 and available on call for the remainder of the dosing period.
Dose Escalation Stopping Rules:	Dose escalation can be stopped if any treatment-emergent adverse event (TEAE) occurs in a subject dosed with NAL ER during the study that, in the opinion of the Investigator, raises concerns about the safety and tolerability of a higher dose. In addition, the following dose escalation rules will apply. Dose-limiting toxicity (DLT) in the hepatic impaired subject population participating in this study is defined as the dose at which a confirmed Grade 3 adverse event develops in any 2 subjects, even if in two different organ systems, that is IP related and is unlikely to be related to the disease process. Overnight oximetry that drops more than 10% from a subject's baseline lowest value for a consistent period of 5 minutes will be considered a DLT TEAE. Any subject who experiences a DLT TEAE will not receive further doses of study drug, and safety follow-up procedures will be performed. **Part 1 (SAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Mild and Moderate Hepatic Impairment (Group 1 and Group 2)** Upon completion of the dosing of subjects with mild and moderate hepatic impairment in each of Cohorts 1 to 4 in Part 1 of the study, the safety data and nalbuphine PK parameters will be reviewed by the Safety Committee to determine the continuation of the progression of Part 1 dose escalation and to evaluate the safety for that dose level to be included in Part 2 of the study (MAD). If in the judgement of the Safety Committee the Part 1 PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study. If 2 subjects develop a DLT at the same dose, then that dose will be confirmed as DLT. If 2 subjects develop a DLT at 2 different doses (eg, 108 mg and 162 mg), then the higher of the 2 doses (162 mg in this example) will not be pursued in remaining Group 1 and Group 2 subjects (if not already dosed). **Part 1 (SAD) Dosing Procedures in Cohort 5 (Healthy Volunteers)** Cohort 5 will receive the highest dose tested in subjects with mild or moderate hepatic impairment (Cohorts 1 to 4), and if any dose is confirmed to be a DLT during dosing of Cohorts 1 to 4, then that dose will not be studied in Part 1 (SAD) in Cohort 5. **Part 1 (SAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Severe Hepatic Impairment (Group 3)** Severe Hepatic Impairment (Group 3 Subjects) will receive a single dose of NAL ER 27 mg.

	If 2 subjects with severe hepatic impairment develop a DLT, then the NAL ER 27 mg will not be dosed in the remaining Group 3 subjects. **<u>Part 2 (MAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Mild and Moderate Hepatic Impairment (Group 1 and Group 2)</u>** If 2 subjects develop a DLT at the same dose, then that dose will be confirmed as DLT. If 2 subjects develop a DLT at 2 different doses (eg, 108 mg and 162 mg), then the higher of the 2 doses (162 mg in this example) will not be pursued in remaining Group 1 and Group 2 subjects (if not already dosed). The study maximum safe dose (MSD) will be determined as the dose level below the DLT dose. Subjects who are currently receiving a confirmed DLT dose will not receive further doses of study drug. Subsequent subjects in Part 2 of the study will only be dosed through the completion of the MSD per the days specified in the titration table. After last dose, subjects will immediately enter the DLT Follow-Up Period (see Section 9.11.1).
Discharge/Study Exit Procedures:	Part 1 (SAD) on Day 4: brief physical examination, vital signs, body temperature, ECG, pulse oximetry, clinical chemistry, hematology, coagulation, urinalysis, PK sample, urine and serum pregnancy test (females only), and adverse events monitoring. Part 2 (MAD) on Day 16: brief physical examination, vital signs, body temperature, ECG, pulse oximetry, clinical chemistry, hematology, coagulation, urinalysis, PK sample, urine and serum pregnancy test (females only), WI-NRS, and adverse events monitoring. On Day 17: PK sample. In the case that a subject experiences a DLT or a DLT dose is confirmed in 2 subjects during Part 2 (MAD), post last-dose study procedures will be performed as laid out in the DLT Follow-Up Period (see Section 9.11.1). Early Termination procedures are only applicable to subjects who discontinue study drug for reasons other than those related to DLT.
Analytical Method:	The Bioanalytical Division of Covance Labs will analyze nalbuphine and M1, M2, M4, and M5 metabolite concentrations (for select samples) in plasma using validated methods.
Pharmacokinetics:	Parameters calculated with plasma concentrations: **<u>Part 1 (SAD)</u>** AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $T_{½\ el}$, Residual area, Cl/F, V_d/F, and K_{el} **<u>Part 2 (MAD)</u>** Day 1: AUC_{0-12}, AUC_{0-24}, C_{max}, T_{max} Days 4, 7, and 10: $AUC_{0-12,}$ C_{max}, T_{max} Day 13: AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, C_{max}, C_{trough}, T_{max}, Residual area, $T_{½}$, K_{el}, Fl, Cl/F, and V_d/F.
Statistical Analyses:	For Part 1 for each dose level, using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed dose-normalized AUC_{0-t}, AUC_{0-inf}, and C_{tmax} at the alpha level of 0.05 for nalbuphine

	and metabolite(s). The 90% confidence intervals (CIs) (Mild/Control, Moderate/Control, and Severe/Control) will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. For these analytes, T_{max} will be analyzed non-parametrically with point estimates and 90% CIs for the median differences of T_{max} between groups (Mild-Control, Moderate-Control, and Severe-Control). For Part 2 for each day (as appropriate), using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, $C_{max,}$ and C_{trough} at the alpha level of 0.05 for nalbuphine and metabolite(s). For Part 2 of the study, a repeated measures analysis will be carried out on ln-transformed pre-morning and evening dose concentrations (when applicable) (on Days 2, 3, 5, 6, 8, 9, 11, 12, and 13) to determine attainment of steady state. Within each group, dose proportionality will be assessed by a visual assessment of the individual and mean nalbuphine PK parameters. A power model analysis may also be performed to evaluate the doses-exposure, if warranted. For the WI-NRS variables, post-dose scores will be assessed as an increment or decrement relative to the pre-dose baseline values. Each time point will be evaluated separately, relative to the baseline (pre-dose) value. Pair-wise comparisons among the groups will be made. Review of interim safety analyses will be performed between cohorts or groups. Interim PK analyses may be performed between cohorts or groups if requested or warranted. A complete description of the statistical analyses to be performed with the safety and tolerability data, as well as PK parameters will be presented in a Statistical Analysis Plan, which will be finalized prior to database lock.

3. List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
C_{trough}	Last plasma concentration
COC	Combined oral contraceptives
CONMED	Concomitant medication
CP	Child-Pugh classification
CRF	Case Report Form
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
Fl (%)	Percentage of fluctuation
GCP	Good Clinical Practice
GGT	Gamma glutamyl-transpeptidase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B
HCV	Hepatitis C
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
ICF	Informed Consent Form

IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational Product
IV	Intravenous
kg	Kilogram
L	Liter
LIMS	Laboratory Information Management System
LLN	Lower limit of normal
Ln	Natural logarithm
MAD	Multiple ascending dose
MDMA	3,4-methylenedioxymethamphetamine
mg	Milligram
min	Minute
mL	Milliliter
mmHg	Millimeters mercury
MSD	Maximum safe dose
NAL ER	Nalbuphine Extended-Release
NOAEL	No Observed Adverse Event Level
NO	Nitric oxide
PCP	Phencyclidine
PK	Pharmacokinetic
PN	Prurigo Nodularis
aPTT	Activated partial thromboplastin time
PT	Prothrombin time
QA	Quality assurance
QC	Quality control
QT	QT interval
QTcF	Fridericia's corrected QT interval
SAD	Single ascending dose
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SD	Standard deviation
SID	Subject identification
SOPs	Standard Operation Procedures
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
$T_{1/2}$	Half-life
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
UP	Uremic pruritus
WBC	White blood cell
WI-NRS	Worst Itch Numerical Rating Scale

4. Schedule of Events

4.1 Schedule of Events – Part 1 (Single Ascending Dose)

Procedure	Screening (Day -28 to Day -2)	Cohorts 1 to 5 Each Dose Level[a]			Study Exit D4 (72 h) or Early Termination
		D-1	D1	D2 (24 h) D3 (48 h)	
Informed consent	X				
Review inclusion/exclusion	X	X	X		
Demographic data	X				
Medical and medication histories	X				
Review and monitoring of AEs and concomitant medications	X	X	X	X	X
Physical examination[b]	X	X			X
Height, weight, and BMI	X				
Vital signs[c]	X	X	X	X	X
Body temperature	X	X			X
12-lead ECG[d]	X	X	X	X	X
Pulse oximetry[e]	X	X	X	X	X
Clinical chemistry[f]	X	X			X
Hematology[f]	X	X			X
Coagulation (PT, aPTT, and INR)[f]	X	X			X
HIV and hepatitis	X				
Urinalysis[f]	X	X			X
Urine alcohol and drug screen	X	X			
Urine and serum pregnancy test (as applicable)	X	X			X
Confinement[g]		X	X	X	
Drug administration			X		
PK samples[h]			X	X	X

a. Subjects in Cohorts 1 to 4, Part 1 of study, can participate in all 4 dose levels. There will be a washout period of at least 7 days between drug administration at each dose level and between each part of the study. The same procedures will be followed for all dose levels. Screening procedures are required only for naïve subjects in Cohorts 2-4 who have not previously been screened.

b. A complete physical examination will be performed at screening. A brief physical examination will be performed on Day -1 and Day 4. The complete physical examination will include at least the following components: head, eyes, ears, nose, throat (HEENT), neck, lungs, abdomen, skin, cardiovascular and musculoskeletal evaluation, and general neurological examination.

c. Blood pressure, heart rate, and respiratory rate: at screening, in the morning of Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and Day 4.

d. 12-lead ECG: at screening, in the morning of Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and on Day 4.

e. Oxygen saturation via pulse oximetry will be measured at screening. Baseline continuous pulse oximetry will be measured during the nighttime of Day -1 (minimum of 8 hours prior to first dose administration). Following the dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-dose and 1.5, 4.5, and 8 hours post-dose. Pulse oximetry measurements may be collected within 10 min before or after the specified time point. Oxygen saturation will be monitored via pulse continuous oximetry beginning at bedtime and continuing overnight until waking time from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.

f. Laboratory assessments (ie, clinical chemistry, hematology, coagulation, and urinalysis) will be done at screening, in the morning of Day -1, and Day 4 following a fasting period of at least 8 hours.

g. Subjects in Cohorts 1 to 4 will be confined from the morning of Day -1 until discharge on Day 4 (after the 72-hour post-dose blood draw). Cohort 5 subjects will be confined from the morning of Day -1 until discharge on Day 3 (after the 48-hour post- dose blood draw), and will come back for the Day 4 procedures.

h. PK blood samples: A total of 11 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, and 72 hours post-dose.

4.2 Schedule of Events – Part 2 (Multiple Ascending Dose)

Procedure	Screening (Day -28 to Day -2)	Cohort 6											Dis-charge D16	Study Exit D17	Early Termination [i]
		D-1	D1	D2 D3	D4	D5 D6	D7	D8 D9	D10	D11 D12	D13	D14 D15			
Informed consent	X														
Review inclusion/ exclusion	X	X	X												
Demographic data	X														
Medical and medication histories	X														
Review and monitoring of AEs and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[a]	X	X											X		X
Height, weight, and BMI	X														
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Body temperature	X	X											X		X
12-lead ECG[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Pulse oximetry[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Clinical chemistry[e]	X	X				X			X				X		X
Hematology[e]	X	X				X			X				X		X
Coagulation (PT, aPTT, and INR)[e]	X	X											X		X
HIV and hepatitis	X														
Urinalysis[e]	X	X											X		X
WI-NRS[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine alcohol and drug screen	X	X													
Urine and serum pregnancy test (as applicable)	X	X											X		X
Confinement[g]		X	X	X	X	X	X	X	X	X	X	X			
Drug administration 27 mg qd			X												
Drug administration 27mg bid				X											
Drug administration 27 mg (morning) and 54 mg (evening)					X										
Drug administration 54 mg bid						X									

Procedure	Screening (Day -28 to Day -2)	Cohort 6											Dis-charge D16	Study Exit D17	Early Termination [i]
		D-1	D1	D2 D3	D4	D5 D6	D7	D8 D9	D10	D11 D12	D13	D14 D15			
Drug administration 54 mg (morning) and 108 mg (evening)							X								
Drug administration 108 mg bid								X							
Drug administration 108 mg (morning) and 162 mg (evening)									X						
Drug administration 162 mg bid										X					
Drug administration 162 mg qd											X				
PK samples[h]			X	X	X	X	X	X	X	X	X	X	X	X	X

a. A complete physical examination will be performed at screening. A brief physical examination will be performed on Day -1 and Day 16. The complete physical examination will include at least the following components: head, eyes, ears, nose, throat (HEENT), neck, lungs, abdomen, skin, cardiovascular and musculoskeletal evaluation, and general neurological examination.

b. Blood pressure, heart rate, and respiratory rate: at screening, in the morning of Day -1 , pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, approximately 2 and 6 hours post-morning dose on Days 2 to 12, and once on Days 14, 15, and 16.

c. 12-lead ECG: at screening, in the morning of Day -1, pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, and once on Days 14, 15, and 16.

d. Oxygen saturation via pulse oximetry will be measured at screening. Baseline continuous pulse oximetry will be measured during the nighttime of Day -1 (minimum of 8 hours prior to first dose administration). Following the first dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-morning dose, at 1.5, 4.5, and 8 hours following the morning dose, and at 2 hours following the evening dose. Pulse oximetry measurements may be collected within 10 min before or after the specified time point. Oxygen saturation will be monitored via pulse continuous oximetry beginning at bedtime and continuing overnight until waking time from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.

e. Laboratory assessments (ie, clinical chemistry, hematology, coagulation, and urinalysis) will be done at screening, in the morning of Day -1, and Day 16 following a fasting period of at least 8 hours. Clinical chemistry and hematology also on Day 5 and Day 10.

f. Cohort 6 subjects will complete both of the two WI-NRS forms (the "Nighttime Itch" and the "Daytime Itch") at the same time during the screening visit, and the average will be taken to determine the baseline severity. WI-NRS will be subsequently performed on a daily basis, from Day -1 to Day 16, to be collected twice per day: once within an hour (+/- 1 hour) of completing their morning and evening meals, if applicable. Subjects will fill in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.

g. Cohort 6 subjects will be confined from the morning of Day -1 until discharge on Day 16 (after the 72-hour post-last dose blood draw). Subjects will come back on Day 17 for the subsequent final blood draw (96-hour post-last dose blood draw) at the Study Exit visit.

h. PK blood samples:

- On Day 1: a total of 10 blood samples will be collected for quantitation of nalbuphine and metabolite(s) in plasma: at pre-dose and 1.5, 3, 4, 5, 6, 7, 9, 12, and 24 hours post-dose.
- On Days 4, 7, and 10: a total of 9 blood samples will be collected; at pre-morning dose and at 1.5, 3, 4, 5, 6, 7, 9, and 12 hours post-dose (prior to the evening dose administration).
- On Day 13: a total of 12 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose.

Procedure	Screening (Day -28 to Day -2)	Cohort 6											Dis-charge D16	Study Exit D17	Early Termination [i]
		D-1	D1	D2 D3	D4	D5 D6	D7	D8 D9	D10	D11 D12	D13	D14 D15			

- Trough blood samples will be collected on Days 2, 3, 5, 6, 8, 9, 11, 12, and 13, prior to the morning and evening dose administrations (when applicable).

i. In Part 2 of the study, Early Termination procedures are only applicable to subjects who discontinue study drug for reasons other than those related to DLT. In the case that a subject experiences a DLT or a DLT dose is confirmed in 2 subjects during Part 2, post last-dose study procedures will be performed as laid out in the DLT Follow-Up Period (see Section 4.3 schedule of events and Section 9.11.1 procedures).

4.3 Schedule of Events – Part 2 (Multiple Ascending Dose): DLT Follow-Up Period

Number of Days Post-Last Dose:	0 days	1 day	2 days	3 days	4 days
Procedure[i]	**Day of Last Dose**	**Off-Drug Follow-Up / Continued Confinement**		**Discharge**	**Study Exit**
Drug administration: last dose received	X				
Review and monitoring of AEs and concomitant medications	X	X	X	X	X
Physical examination[a]				X	
Vital signs[b]	X	X	X	X	
Body temperature				X	
12-lead ECG[c]	X	X	X	X	
Pulse oximetry[d]	X	X	X	X	
Clinical chemistry[e]				X	
Hematology[e]				X	
Coagulation (PT, aPTT, and INR)[e]				X	
Urinalysis[e]				X	
WI-NRS[f]	X	X	X	X	
Urine and serum pregnancy test (as applicable)				X	
Confinement[g]	X	X	X		
PK samples[h]	X	X	X	X	X

a. Brief physical exam will be performed prior to discharge.

b. Blood pressure, heart rate, and respiratory rate: pre-last dose and approximately 1, 2, 4, 6, 8, and 12 hours post-last dose, and once a day until end of confinement.

c. 12-lead ECG: pre-last dose and approximately 1, 2, 4, 6, 8, and 12 hours post-last dose and once a day until end of confinement.

d. Oxygen saturation via pulse oximetry will be measured: pre-last dose and at 1.5, 4.5, and 8 hours following the last dose (if morning dose), and at 2 hours following the last dose (if evening dose). Pulse oximetry measurements may be collected within 10 min before or after the specified time point. Oxygen saturation will be monitored via pulse continuous oximetry beginning at bedtime and continuing overnight until waking time through end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.

e. Laboratory assessments (ie, clinical chemistry, hematology, coagulation, and urinalysis) will be done in the morning prior to discharge following a fasting period of at least 8 hours.

f. WI-NRS will be performed on a daily basis, to be collected twice per day until end of confinement: once within an hour (+/- 1 hour) of completing their morning and evening meals, if applicable. Subjects will fill in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.

g. Subjects will be confined until after the 72-hour post-last dose blood draw and will come back for the final 96-hour post-last dose blood draw the following day at the Study Exit visit.

h. PK blood samples: a total of 12 blood samples will be collected: at pre-last dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose.

i. DLT Follow-Up Procedures are to be completed at the time points specified wherever feasible, though this may not be possible in some circumstances, including: if the last dose occurs in the evening (eg. for a subject who experiences a DLT) and time points are during the sleep period; and/or the AE leading to DLT occurs after a

procedure time point has passed (for example, if a DLT occurred 2 hours post-dose on Study Days 2-12, ECG would not have been performed 1 hour post-dose).

5. Introduction

5.1 Background Information

5.1.1 Nalbuphine

Nalbuphine is a derivative of 14-hydroxymorphine and is structurally related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone.[1] Nalbuphine is a competitive antagonist of the μ-opioid receptor while producing agonist effects at the κ-opioid receptor and is therefore classified as an opioid agonist -antagonist. Unlike morphine and other potent mu-agonists, nalbuphine produces an agonist-antagonist "ceiling effect" and does not produce a dose-dependent increase in respiratory depression as the dose is increased.[2]

Trevi Therapeutics, Inc. (Trevi) has in-licensed an oral pharmaceutical nalbuphine extended-release (ER) tablet (NAL ER) product. There is no oral formulation of the drug approved for any medical indication.

Nalbuphine hydrochloride (HCl) is currently available only as a generic medication in an injectable form. The commercially available approved drug product was first marketed in 1979 in the United States as Nubain®, on which the presently sold generic injectable formulations are based. Nubain, was withdrawn from the United States market in 2008 for commercial reasons unrelated to safety or efficacy.[3] Approved indications in the United States include the relief of moderate to severe pain, use as a supplement to balanced anesthesia, pre- and post-operative analgesia, and obstetrical analgesia during labor and delivery.[4]

Nalbuphine was originally classified as a Schedule II drug in the United States under the Controlled Substances Act (CSA) of 1970. Endo Laboratories subsequently petitioned the DEA to exclude nalbuphine from all schedules of the CSA in 1973. After receiving a medical and scientific review, the Department of Health, Education, and Welfare recommended that nalbuphine be removed from Schedule II list in 1976. Nalbuphine is not currently a controlled substance in the United States under the CSA (Nalbuphine Hydrochloride – Drug Enforcement Agency, Office of Diversion Control, Drug & Chemical Evaluation Section. August 2013).[2]

The pharmacologic mechanism of action has 2 components, with competitive antagonism of the opioid μ-receptor and simultaneous agonism at the opioid κ-receptor. Imbalance of activity across the μ- and κ-opioid system has been associated with severe chronic itch conditions and there is a substantial literature suggesting that agonism of κ-receptors may have a therapeutic benefit in these settings.[5] Specifically, the κ-agonist, nalfurafine, has been approved in Japan for the treatment of itch associated with both uremic pruritus (UP)[6] and chronic liver diseases including primary biliary cholangitis (PBC). There is a clinical literature that supports the use of mu-antagonists in the treatment of hepatic disease related itch.[7] In a standard mouse model used to assess the potential antipruritic effects of candidate therapies, nalbuphine was effective in reducing substance-P (SubP) induced scratching behavior.[7]

5.1.1.1 Nonclinical Toxicology and Clinical Safety

Subchronic and chronic dose toxicology studies showed no changes attributable to nalbuphine in the clinical chemistry, hematology, urinalysis, ophthalmologic, electrocardiographic, or gross and

microscopic pathology evaluations in usual rodent toxicologic evaluation and in dogs. The central nervous system (CNS) was identified as the only target organ when unformulated (neat) nalbuphine was given to dogs at high doses; tremors and convulsions were observed, leading to death in some cases. These events are attributed to the high systemic peak exposures (high C_{max}) achieved with this particular dosing regimen. When dogs were given high doses of nalbuphine formulated with excipients that control the rate of release of drug, thereby blunting the C_{max}, no convulsions or other signs of CNS toxicity were observed. These observations are considered unlikely to be relevant to human dosing.

A complete summary of the nonclinical and clinical investigational programs can be found in the Investigator's Brochure (IB).[1]

Clinical Safety of NAL ER

The safety and tolerability of NAL ER have been characterized across a total of 718 unique subjects (healthy volunteers and subjects) who have received at least 1 dose of NAL ER to date; this includes all clinical trials in the NAL ER development program and adjusts for duplicate participation. The data from early PK trials NAL01 through NAL 06 represent exposure to earlier, in-development ER formulations.[1]

The healthy subject studies were conducted with NAL ER (or oral solution) following single dose administration from 27 mg up to 162 mg and multiple doses ranging between 27 mg twice daily and 162 mg twice daily. The clinical trials in subjects with UP or prurigo nodularis (PN) also evaluated doses ranging from 27 mg twice daily to 162 mg twice daily and up to 216 mg BID in UP. Across the 2 studies in HD with UP, a total of 326 unique subjects received NAL ER; 55 of these subjects had drug exposure ≥ 12 weeks and 19 had ≥ 24 weeks. Across the 2 studies in PN, a total of 62 unique subjects received NAL ER. In the longer TR03 study, 16 subjects completed 50 weeks of dosing and 20 subjects completed 26 weeks.[1]

Overall, the most frequently reported adverse events (AEs) in the NAL ER clinical program to date have been primarily in the CNS and gastrointestinal (GI) organ system categories. For NAL ER in particular, during the initial titration period, nausea, dizziness, and headache can occur in approximately 15% to 30% of subjects, with complaints of fatigue and somnolence generally less frequent. Complaints of constipation in NAL ER studies to date have been infrequent and mild. In the large majority of cases, these side effects were mild to moderate in severity; they cluster markedly in the first few weeks of dosing, when symptomatic tolerance has not yet developed, and usually resolve or improve substantially after a few weeks in most subjects.[1]

These observations from NAL ER studies are consistent with the profile that has been recognized through prior experience and in the literature for drugs with opioid agonist-antagonist pharmacologic properties.[8] Multiple literature reviews address the transient interventions available to manage these early symptoms, taking into account different patient backgrounds and treatment settings.[10, 11]

To improve early tolerability, NAL ER trials initiate dosing with a gradual 2-week titration schedule starting at 27 mg once per day. Maximum efforts should be made during this titration period to support the subject and to provide short-term, appropriate medications for symptom relief

when needed (empiric prophylactic treatment for all subjects is not recommended, as only a minority will develop symptoms).

Across the NAL ER program to date, there have been a total of 8 subjects with 9 SAEs whose individual terms were assessed either by the Investigator or by the Sponsor as drug related to NAL ER. Those terms were: anxiety, constipation (2), gastritis, headache, hypotension, overdose [NOTE: the subject received single dose of NAL ER 108 mg without titration from a lower dose during a phase 1 study], and vertigo. A summary discussion of all SAEs that occurred in the NAL ER development program is summarized in the current edition of the IB. [1]

Across the PN subject population studied in TR03 and TR03EXT, a total of 3 subjects had SAEs while receiving NAL ER, and none were considered related to investigational product (1 motor vehicle accident occurring on icy roads, and 2 cases involving complications or worsening of baseline co-morbidities). As would be expected for an end-stage renal failure population receiving hemodialysis (HD), SAEs were more frequent in the UP studies, and 5 deaths occurred. An immediate cause of death related to the underlying disease or known co-morbidities was clearly identified in each case. The mortality rate across the 2 UP studies (Study TR02 and Study TR02EXT) was consistent with that reported in the literature for HD. One subject had 2 convulsions, 1 during TR02 and a second incidence in TR02EXT; this individual had a history of acquired immune deficiency syndrome (AIDS) with opportunistic infections and a prior stroke, and the seizures were not attributed to the investigational product (see current edition of the IB for a discussion of all the SAEs that occurred in the UP subject population in the NAL ER development program).[1]

In the administration of NAL ER to healthy subjects in previous phase 1 studies, the incidence of AEs in the absence of titration was dose dependent. Across the doses of 54 mg, 108 mg, and 162 mg, there is an overall dose-response relationship between dose and specific AE frequencies. Somnolence occurs in > 5% in all 3 higher dose groups (range from 6.2% to 14.8%) and vomiting occurs in > 10% (range from 12.4% to 30.4%). Other events that occur at frequencies > 15% in the 3 higher dose groups are: dizziness (range from 16.9% to 29.10%), headache (15.8% to 21.5%), nausea (17.7% to 36.7%), and somnolence (6.2% to 14.8%).[1]

Overall, the Sponsor considers that the risk to subjects in clinical trials of NAL ER is low. This assessment is based on the safety margins established in animals, the known safety profile of the nalbuphine injectable drug product that has been in clinical use for almost 40 years, and the clinical experience to date with the NAL ER and earlier extended-release tablet formulations. The potential benefit that NAL ER may offer by improving severe itch in debilitating conditions is considered to outweigh the potential risks of a clinical trial.

5.1.1.2 Pharmacokinetics

In humans, NAL ER shows a low bioavailability (BA) and a dose-related increase in nalbuphine exposure with increasing doses; the median time of maximum concentration (T_{max}) for NAL ER occurs at 3 to 6 hours post dose, with a mean half-life ($T_{1/2}$) of 6.6 to 9.6 hours across studies in subjects with normal renal function, which supports twice daily dosing. The inter-subject variability of nalbuphine pharmacokinetic (PK) parameters (area under the curve [AUC] and maximum plasma concentration [C_{max}]) is high with lower intra-subject variability. Four major metabolites of nalbuphine have been identified in humans; these are not pharmacologically active.

An overview of the PK parameter values following a single nalbuphine dose administered in the fasting state is provided Table 1.

Table 1 Mean (SD) Plasma Pharmacokinetics Parameters for Nalbuphine Following Single Dose Administration of Nalbuphine Extended- release Tablets, 27 to162 mg or Nalbuphine HCl Oral Solution (20 mg/mL) in Healthy Subjects (N = 8 to 22)

Formulation	Oral solution (Nubain®)	Nalbuphine ER Tablet					
Dosage strength	0 mg/mL	54 mg	54 mg	27 mg	54 mg	108 mg	162 mg
Food status	Fasted	Fasted	Fed	Fasted	Fasted	Fasted	Fasted
NAL dose (mg)	54 mg	108 mg	108 mg	27 mg	54 mg	108 mg	162 mg
Equiv. HCl	60 mg	120 mg	120 mg	30 mg	60 mg	120 mg	180 mg
$AUC_{0-\infty}$ (ng·h/mL)	85.9 (14)	161 (52)	171 (69)	58.8 (22)	113.0 (40)	209 (91)	328 (165)
AUC_{0-last} (ng·h/mL)	83.8 (24)	157 (24)	—	42.9 (20)	94.5 (40)	192 (83)	297 (155)
C_{max} (ng/mL)	18.5 (7.9)	12.5 (7.1)	18.6 (10.7)	4.13 (2.3)	7.75 (6.0)	13.3 (6.5)	21.6 (23.5)
T_{max} [a]	0.5 (0.5-1.5)	5.8 (2.0-10.0)	6.0 (1.5-6.0)	3.0 (1.5-8.0)	6.0 (3.0-12.0)	6.0 (1.0-12.0)	6.0 (2.0-6.0)
$T_{1/2}$ (h)	6.87 (1.2)	6.87 (1.8)	6.69 (2.3)	7.69 (2.3)	8.04 (1.7)	9.12 (1.9)	9.55 (2.6)
F (%) [b]	—	94	—	—	—	—	—

AUC = area under the curve; $AUC_{0-\infty}$ = area under the curve from time 0 extrapolated through infinity; AUC_{0-last} = area under the curve from time 0 to the last measurable concentration; Cmax = maximum plasma concentration; ER = extended release; F = bioavailability; NAL = nalbuphine; PK = pharmacokinetics; T1/2 = half-life; Tmax = time of maximum concentration; — = not applicable.

[a] = Median value (range).

[b] = Calculation: (AUC (tablet) × 100) / (2 × AUC (solution)).

Source: Investigator's Brochure Nalbuphine Extended-Release Tablets.

Nalbuphine exposure increased with increasing dose in a near proportional manner upon repeated dosing. In this multiple-dose study (TR01), subjects were titrated every 3 to 4 days from 27 mg once per day on day 1, to 27 mg twice daily then 54 mg twice daily, 108 mg twice daily, and finally 162 mg twice daily over a 13-day period. Steady state seemed to be reached within 2 to 3 days of dosing with a modest accumulation in exposure (accumulation factor [R] = 1.6) and no evidence of unexpected accumulation (See Table 2).

The presence of food (high-fat-high-calorie meal) did not affect the extent of absorption (AUC) or T_{max} for the current formulation of NAL ER tablets. However, the C_{max} values were about 1.5-fold higher in the fed than the fasted state.

Table 2 Summary of Mean Pharmacokinetics Parameters (N = 7 to 9) Following Multiple Escalating Oral Doses of NAL ER Tablets in Healthy Subjects (Clinical Study TR01)

Parameter	Descriptive Statistics	Healthy Subjects[a]				
		27 mg qd	27 mg bid	54 mg bid	108 mg bid	162 mg bid
		(Day 1)	(Day 4)	(Day 6)	(Day 9)	(Day 13)
$AUC_{0-\infty}$ (h·ng/mL)	n	7	—	—	—	8
	Mean	49.53	—	—	—	588.4
	SD	30.04	—	—	—	214.08
	CV%	60.7	—	—	—	36.4
AUC_{tau} (h·ng/mL)	n	9	9	9	9	8
	Mean	31.53	50.88	106.11	240.37	351.15
	SD	16.93	27.54	50.49	93.68	118.21
	CV%	53.7	54.1	47.6	39	33.7
$ARAUC_{tau}$	—	1.61	—	—	—	—
C_{max} (ng/mL)	n	9	9	9	9	8
	Mean	5.2	6.45	13.46	28	44.21
	SD	2.78	3.58	6.43	11.49	14.54
	CV%	53.5	55.5	47.8	41	32.9
T_{max} (h)	n	9	9	9	9	8
	Min	2	2	2	3	2
	Median	3	2	3	5	4
	Max	5	6	6	9	6
$T_{1/2}$ (h)	N	7	—	—	—	8
	Mean	6.81	—	—	—	8.58
	SD	2.79	—	—	—	2.05
	CV%	41	—	—	—	23.9

$ARAUC_{tau}$ = mean AUC_{tau} day 4/mean AUC_{tau} day 1; AUC = area under the curve;— $AUC_{0-\infty}$ = area under the curve from time 0 extrapolated through infinity; AUC_{tau} = AUC_{0-12h}; bid = twice daily; C_{max} = maximum plasma concentration; CV = coefficient of variation; qd = once per day; $T_{1/2}$ = half-life; T_{max} = time of maximum concentration; — = not applicable.

[a] = Subjects were dosed with multiples of 27 mg tablets.

Source: Investigator's Brochure Nalbuphine Extended-Release Tablets.

5.2 Study Rationale

In the FDA *Guidance for Industry Pharmacokinetics in Subjects with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*[12], a PK study in subjects with impaired hepatic function is recommended if hepatic metabolism and/or excretion accounts for a substantial portion (>20 percent of the absorbed drug) of the elimination of a parent drug or active metabolite. In humans, nalbuphine has high clearance and the major route of elimination is stated as fecal excretion of unchanged and conjugated nalbuphine with very little unchanged nalbuphine

excreted in the urine (Schmidt et al, 1985). In Study TR01, less than 1% of the dose was excreted as unchanged nalbuphine in urine collected from healthy subjects across the 27 mg once daily to 162 mg twice daily dose range.

A PK study in subjects with various severity of impaired hepatic function will be conducted to evaluate the effects of hepatic impairment on the PK of NAL ER following single and multiple doses. This study will allow the development of specific dosing recommendations across the spectrum of hepatic impairment and also assess potential of oral NAL ER to reduce liver itch in a dose-dependent manner.

5.2.1 Rationale for a Single- and Multiple-Escalating Dose Design

This study will include both a single-ascending-dose (SAD) portion and a multiple-ascending dose (MAD) portion. The PK, safety, and tolerability of single ascending doses (SAD) of NAL ER (4 dose levels) will be evaluated in subjects with mild and moderate hepatic impairment. Severe hepatic subjects will be evaluated at a single dose of 27 mg.

The purpose of the SAD will be to assess the safety and PK parameters of the given dose levels in hepatic impaired subjects relative to a selected healthy subject control population as part of the overall NAL ER development program. The SAD will also allow a better understanding of the safety, tolerability and expected steady state PK characteristics in mild and moderate hepatic impairment prior to undertaking safety and itch suppression efficacy studies in this patient population.

In the MAD portion of this study, PK assessment will be carried out at steady state at each respective dose level at steady state during the titration over 13 days up to the highest planned therapeutic dose of 162 mg. It is well documented, in clinical practice and the opiate literature, that gradually increasing the dose of drug with a structured titration can reduce the frequency and severity of the expected AEs associated with initiation of therapy. The NAL ER clinical program utilizes this type of structured titration strategy, starting with once per day dosing at the 27 mg dose of NAL ER, and increasing the dose in a stepwise manner over the next 13 days to the target investigational dose of 162 mg twice daily. Pharmacokinetic steady state is reached after 2 to 3 days of 162 mg twice daily.

Once the Part 1 SAD portion of the study is completed, if in the judgement of the Safety Committee the PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study.

5.2.2 Rationale for Analytes to Measure

As per the above mentioned guidance,[12] the blood sampling duration should be adequate to determine the terminal half-life of the drug and its metabolites, with the expectation that these times may be extended in the patient compared to the control population. For drugs that are highly extracted by the liver (extraction ratio > 0.7) and that are extensively bound to plasma proteins (fraction unbound < 10 percent), the FDA recommends that the unbound fraction be determined at least at trough and maximum plasma concentration.[12] Because binding of nalbuphine is not

extensive (> 50% unbound to human serum proteins), only total nalbuphine will be measured in plasma samples (and nalbuphine metabolites, at least at the 162 mg dose).

5.2.3 Rationale for the Study Population

A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m^2/day. Nalbuphine did not affect either male or female fertility in rats. Reproduction studies have been also performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day or 590 mg/m^2/day, which is approximately 6 times the MRHD, and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day or 378 mg/m^2/day, which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, or harm to the fetus.[1] However, there are no well-controlled studies in pregnant women. Therefore, males and non-pregnant, non-lactating females will be included in the study. In addition, females of childbearing potential will be included if they use appropriate methods of contraception.

5.2.4 Rationale for Monitoring of Respiratory Oxygen Saturation Levels

Oxygen saturation levels following NAL ER oral administration has been previously monitored in the in-house MAD clinical study TR01 both in healthy subjects and UP subjects, as well as in-house single dose NAL02 study conducted in third molar extraction healthy subjects who also received prior anesthetics before the surgical procedure (see the current edition of the IB).[1]

In the healthy subjects in the TR01 study, pulse oximetry readings were taken at regular intervals during waking hours (6 times over waking hours) in all subjects and continuously monitored during the nighttime hours in healthy subjects up to 13 days of dosing and up to a maximal dosing of 162 mg twice daily. No clinically significant decreases in the waking hour readings were noted in healthy subjects. There was no nocturnal oxygen saturation level that fell below the 90% lower limit that was set for monitoring nighttime oxygen levels.

In study NAL02 dental pain following third molar extraction subjects who received either a single dose of NAL ER 54 mg or NAL ER 108 mg, oxygen saturation levels were maintained within the 90% to 100% range.[1]

In the HD subjects in Study TR01, pulse oximetry readings were obtained at regular intervals during waking hours (6 times over waking hours) in all subjects and continuously monitored during the nighttime hours up to 15 days of dosing and up to a maximal dosing of 216 mg twice daily in HD subjects. No clinically significant decreases in the waking hour readings were recorded, except in 1 HD subject who discontinued secondary to pleural effusion (considered unlikely related to the investigational product by the Investigator). In the HD subjects, there was no clinically significant decrease in the nocturnal oxygen saturation level that fell below the baseline lower limit that was set following predose readings that was used for monitoring nighttime oxygen levels.[1]

The current parenteral nalbuphine HCl package insert (December 2016) has a black box warning related to respiratory depression with the recommendation that respiration be monitored, especially during the initiation or dose increase of nalbuphine. As outlined in the current IB, in previous in house Phase1 and Phase 2 studies of NAL ER, pulse oximetry recordings have shown no clinically significant oxygen desaturation effect in subjects.

Nevertheless, pulse oximetry recordings will also be undertaken in this clinical study to monitor both daytime and nighttime oxygen saturation levels. In cohorts of hepatic impaired subjects, the baseline lower limit nighttime oxygen saturation level recorded on Day -1 will be used as the basis for setting night time pulse oximetry alarm settings (as was done in the HD subject population during the conduct of clinical study TR01), since baseline oxygen saturation levels <92% are known to commonly occur in the hepatic impaired patient population (Zetterman 2013).[13]

5.2.5 Assessment of Hepatic Function

Table 3 Assignment of Study Population According to Child-Pugh Classification

Parameter	1 Point	2 Points	3 Points
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Total serum bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Prolonged prothrombin time (sec) or prothrombin time INR (ratio)	< 4 < 1.70	4 to 6 1.70 to 2.30	> 6 > 2.30
Ascites	Absent	Slight	Moderate or Subject on medication(s) to control ascites
Hepatic encephalopathy grade*	None	Grade 1 or 2	Grade 3 or 4 or Subject receiving medication(s) to prevent encephalopathy

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
Assessment as good operative risk (A or mild) if 5 or 6 points; moderate risk (B or moderate) if 7 to 9 points; and poor operative risk (C or severe) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics).[12]
Subjects with a history of stage 3 or stage 4 encephalopathy who are receiving medication such as lactulose or neomycin to prevent recurrent encephalopathy shall receive the point score for the pre-treatment degree (stage 3 or 4) of encephalopathy. The score therefore reflects the degree of encephalopathy off treatment. This will be documented in the source documents.
Subjects with a history of ascites who are receiving diuretics such as furosemide and/or spironolactone to prevent recurrence shall receive the pre-treatment point score for the degree of ascites. The score therefore reflects the degree of ascites off treatment. This will be documented in the source documents.

6. Objectives

6.1 Primary Objectives

The primary objectives of the study are as follows:

- To evaluate the effect of hepatic impairment on the PK of NAL ER as a function of dose.
- To evaluate the safety and tolerability of NAL ER in hepatic impaired subjects.

6.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To select doses and dosing frequency for NAL ER tablets in subjects with impaired hepatic function.
- To assess potential of oral NAL ER to reduce itch in the hepatic impaired population.

7. Study Design

This is a Phase 1, open-label PK and safety study of NAL ER in subjects with impaired hepatic function compared to healthy subjects. It will be performed in 2 parts:

- Part 1: SAD cohorts
- Part 2: MAD cohort

Part 1 (SAD) – Dose Cohorts 1 to 5

- Cohort 1 (27 mg): 6-8 subjects with mild hepatic impairment, 6-8 subjects with moderate hepatic impairment, and 4-6 subjects with severe hepatic impairment
- Cohort 2 (54 mg): 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment
- Cohort 3 (108 mg): 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment
- Cohort 4 (162 mg): 6-8 subjects with mild hepatic impairment and 6-8 subjects with moderate hepatic impairment
- Cohort 5 (highest dose tested in subjects with mild or moderate hepatic impairment: 6-8 healthy control subjects who have been appropriately age, body mass index (BMI)-, and gender-matched to subjects with mild and moderate hepatic impairment from Cohorts 1 to 4

In Part 1 of the study (SAD), each of the cohorts will be dosed sequentially starting with the lowest dose for mild and moderate impaired subjects. Subjects enrolled in Cohort 1 can also be enrolled in Cohorts 2, 3, and 4.

For each dose cohort, enrollment of subjects with mild (Group 1) or moderate (Group 2) hepatic impairment can be done in parallel. An evaluation of safety and tolerability of the combined mild and moderate hepatic impairment Group 1 and Group 2 subject data will be done at each dose level before proceeding to the next dose level.

Subjects with severe impairment (Group 3) will be enrolled starting with the 27 mg dose upon completion of SAD in subjects with mild and moderate and impairment. After review of the safety and tolerability for the first 2 severe subjects dosed at 27 mg, it will be determined whether or not to complete that dose level for the remaining severe subjects.

At the completion of all subjects dosed in the cohort, there will be an evaluation of safety and tolerability to determine whether to proceed to the next dose level for this group.

The drug kinetics in the hepatic impairment subject population will be compared relative to the healthy subject population (Cohort 5). Part 2 MAD – Dose Cohort 6

- Cohort 6: 6-8 subjects with mild and moderate hepatic impairment

In Part 2 of the study (MAD), subjects will receive multiple doses over 13 days according to a dose escalation scheme (see Section 9.4). Part 2 of the study may be initiated after Groups 1 and 2 (which consist of subjects with mild and moderate hepatic impairment) complete Part 1 of the study (SAD) and following satisfactory review of the safety and tolerability data by the Safety Committee.

Subjects enrolled in Part 1 can also be enrolled in Part 2. However, once the Part 1 SAD portion of the study is completed, if in the judgement of the Safety Committee the PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study.

8. Study Population

8.1 Sample Size

Up to a maximum of 94 adult male or female subjects, ≥ 18 and ≤ 80 years of age are planned to be dosed.

Subjects who withdraw or are withdrawn from the study after dosing, for reasons other than safety and tolerability, may be replaced after consultation between the Investigator and Sponsor. The total number of subjects dosed (including potential replacement subjects) will remain within a maximum of 94 subjects for the whole study (up to 78 subjects in the SAD and up to 16 subjects in the MAD).

The study will enroll up to 8 subjects in Part 2 of the study (MAD) with moderate Child-Pugh categories. An effort will be made to enroll subjects who self-categorize as having some itch (WI-NRS mean score of ≥ 3 at screening). Worst itching intensity scores will be recorded twice daily as specified in the schedule of events. WI-NRS will be used to determine the severity of itch in the hepatic subjects.

8.2 Inclusion Criteria for Subjects with Hepatic Impairment (Cohorts 1 to 4 and 6)

Subjects enrolled in this study will be members of the community at large. Subjects must meet all of the following criteria to be included in the study:

1) Male or female with stable hepatic impairment, non-smoker and/or light smoker (up to 5 cigarettes or equivalent/day), ≥ 18 and ≤ 80 years of age, with BMI ≥ 18.0 and ≤ 40 kg/m^2 and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females.
2) Physical signs consistent with a clinical diagnosis of liver cirrhosis (eg, liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, or gynecomastia) or prior liver biopsy showing hepatic cirrhosis or prior liver imaging (eg, computed tomography, ultrasound, magnetic resonance imaging) or laboratory tests consistent with hepatic cirrhosis.
3) Have mild (Child-Pugh class A, score of 5-6 points), moderate (Child-Pugh class B, score of 7-9 points), or severe (Child-Pugh class C, score of 10-15 points) hepatic impairment at screening.
4) The absence of clinically significant unstable cardiovascular, pulmonary, gastrointestinal, hematologic, neurological or psychiatric illness as determined by the Investigator.
5) The subject must be stable for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory evaluations as determined by the study Investigator. Abnormal clinical evaluation, laboratory tests, or ECG may be repeated based on the Investigator judgement.
6) Have normal or non-clinically significant findings at physical examination clinical laboratory evaluations in the opinion of the Investigator.
7) Subjects with concurrent stable medical conditions (eg, stable diabetes or hypertension), in addition to hepatic impairment, may be enrolled if the condition will not introduce any additional risk and will not interfere in the study objectives and procedures.
8) Females of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized at least 6 months prior) must be willing to use acceptable contraceptive method throughout the study. For purposes of this study, all females are considered to be of childbearing potential unless they are postmenopausal (ie at least 1 year since last menses and age > 50 years) or surgically sterile (ie, tubal ligation, hysterectomy, and/or bilateral oophorectomy). The following are acceptable contraceptive methods while on study:
    a) Simultaneous use of intra-uterine contraceptive device without hormone release system placed at least 4 weeks prior to IP administration, and condom for the male partner;
    b) Simultaneous use of diaphragm with intravaginally applied spermicide and condom for the male partner, starting at least 14 days prior to IP administration.
9) Subjects must be able to understand the nature of the study, agree to comply with the prescribed dosage regimens, and communicate to study personnel about adverse events and concomitant medication use, as applicable.

10) Subjects must sign and date an Independent Ethics Committee-approved informed consent form prior to the conduct of any study activities.

8.3 Exclusion Criteria for Subjects with Hepatic Impairment (Cohorts 1 to 4 and 6)

1) Clinically significant unstable medical conditions or clinically significant acute exacerbation of hepatic disease within 30 days of IP administration in the opinion of the Investigator.
2) Clinically significant abnormalities of laboratory, ECG, pulse oximetry, or clinical data that would preclude participation in the study in the opinion of the Investigator. Clinical data, ECG, and laboratory results may be repeated at the discretion of the Investigator.
3) Presence of hepatocellular carcinoma or acute hepatic disease from infection or drug toxicity.
4) Presence of stage 3 or stage 4 encephalopathy.
5) History of any illness that, in the opinion of the Investigator might confound the results of the study or pose an additional risk to the subject by participation in the study. Subjects who do not qualify based on a reversible medical condition or mild inter-current illness may be re-evaluated after further testing/examination or re-screened after the condition is resolved.
6) Presence of surgically-created or transjugular intrahepatic portal systemic shunts.
7) Clinically significant illness or surgery within 4 weeks prior to dosing.
8) Positive test for HIV.
9) Estimated glomerular filtration rate (eGFR) by the MDRD4 Equation < 50 mL/min/1.73 m^2 at screening.
10) Clinically significant history or presence of any gastrointestinal pathology that will interfere with IP absorption (eg, malabsorption syndrome, chronic diarrhea, inflammatory bowel diseases).
11) Positive urine drug screen at screening or Baseline (Day -1) unless the positive drug screen is due to prescription drug use that is approved by the Investigator.
12) History of allergic reactions to nalbuphine, opioids, or other related drugs.
13) Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant reaction to any drug.
14) Use of any drugs known to be strong inducers or strong inhibitors of hepatic drug metabolism within 30 days prior to the IP administration.
15) Use of any mu-opioid agonist or mu-antagonist such as naltrexone within 14 days of screening.
16) Positive pregnancy test at screening or on Day -1 (females only).
17) Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.
18) History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.

19) Clinically significant findings on ECG as determined by the Investigator at screening, or:
    - QT interval corrected using Fridericia's formula (QTcF) >460 msec, if the QRS interval is < 110 ms,
    - [QTcF interval - QRS interval] >380 msec, if the QRS interval is > 110 ms
    - PR interval >260 msec
    - Second or third degree AV block or changes consistent with acute ischemia

20) Positive alcohol urine screen at screening or Baseline (Day -1).

21) History of significant drug abuse (by subject report) within 1 year prior to screening. Use of soft drugs (such as marijuana) within 3 months prior to the screening visit. Hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) use within 1 year prior to screening. Subjects who are positive for drug screen due to prescription drug use will be allowed if approved by the Investigator and the medical monitor.

22) Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the dosing, administration of a biological product in the context of a clinical research study within 60 days prior to the dosing, or concomitant participation in an investigational study involving no drug or device administration.

23) Use of concomitant medication with the exception of those essential for the management of hepatic impairment and the treatment of concomitant stable medical conditions for the hepatically impaired subjects as per the discretion of the Investigator.

24) Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening or menses) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the dosing.

25) Lactating subject.

26) Inability or difficulty swallowing tablets.

27) Poor venous access or inability to tolerate catheter venous access.

8.4 Inclusion Criteria for Subjects with Normal Hepatic Function (Cohort 5)

Subjects enrolled in this study will be members of the community at large. Subjects must meet all of the following criteria to be included in the study:

1) Male or female, non-smoker and/or light smoker (up to 5 cigarettes or equivalent/day), ≥ 18 and ≤ 80 years of age, with BMI ≥ 18.0 and ≤ 40 kg/m^2 and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females.

2) Healthy as defined by:
    a) Normal hepatic function (subjects with a history of self-limited Hepatitis A with complete resolution documented at least 6 months prior to entry will be allowed to participate).

b) Matched to subjects with hepatic impairment (mild and moderate) according to gender, age (± 10 years), and BMI (± 15%). A mean matching procedure will be performed.

c) The absence of clinically significant illness and surgery within 4 weeks prior to dosing. Subjects vomiting within 24 hours pre-dose will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator.

d) The absence of clinically significant history of neurological, endocrine, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic (including cholecystectomy), and metabolic disease.

e) The absence of clinically significant history of lactic acidosis and severe hepatomegaly with steatosis.

3) Females of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized at least 6 months) must be willing to use acceptable contraceptive methods throughout the study. For purposes of this study, all females are considered to be of childbearing potential unless they are postmenopausal (ie, at least 1 year since last menses and age >50 years) or surgically sterile (ie, tubal ligation, hysterectomy, and/or bilateral oophorectomy). The following are acceptable contraceptive methods while on study:

   a) Simultaneous use of intra-uterine contraceptive device without hormone release system placed at least 4 weeks prior to IP administration, and condom for the male partner;

   b) Simultaneous use of diaphragm with intravaginally applied spermicide and male condom for the male partner, starting at least 14 days prior to IP administration.

4) Subjects must be able to understand the nature of the study, agree to comply with the prescribed dosage regimens, and communicate to study personnel about adverse events and concomitant medication use, as applicable.

5) Subjects must sign and date an Independent Ethics Committee-approved informed consent form prior to the conduct of any study activities.

8.5 Exclusion Criteria for Subjects with Normal Hepatic Function (Cohort 5)

Subjects to whom any of the following applies will be excluded from the study:

1) Any clinically significant abnormality or abnormal laboratory test results found during medical screening or current diagnosis of viral hepatitis, a positive test for HBsAg, HCV, or HIV at screening; autoimmune hepatitis; primary biliary cirrhosis; non-alcoholic fatty liver disease; alcoholic liver disease or, any other liver disease.

2) History of ventricular tachycardia, torsade de pointes, family history of sudden death, myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.

3) Serum potassium below the laboratory lower limit of normality. Potassium supplementation can be prescribed and the serum potassium level repeated within the screening period.

4) Current or recent (within 3 months of IP administration) gastrointestinal disease.

5) Subjects with gastrointestinal surgery that interferes with physiological absorption and motility (ie, gastric bypass, duodenectomy) or gastric bands.
6) Positive urine alcohol or drug screen at screening or Baseline (Day -1).
7) Positive pregnancy test at screening or Baseline (Day -1) (females only).
8) Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.
9) ECG abnormalities (QTc > 450) or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate measured either by pulse or ECG tracing less than 50 bpm or over 100 bpm) at screening. Subjects with a resting heart rate of < 50 bpm or > 100 bpm will have it repeated once after 5 minutes in the supine position, and if it remains outside these parameters during the repeat, they will be considered a screen failure.
10) History of significant alcohol abuse (by subject report) within 1 year prior to screening or regular use of alcohol within six months prior to the screening visit (more than fourteen units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]) or positive urine alcohol screen at screening.
11) History of significant drug abuse (by subject report) within 1 year prior to screening. Use of soft drugs (such as marijuana) within 3 months prior to the screening visit. Hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) use within 1 year prior to screening.
12) Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the dosing, administration of a biological product in the context of a clinical research study within 60 days prior to the dosing, or concomitant participation in an investigational study involving no drug or device administration.
13) Subjects using medication other than topical products without significant systemic absorption:
    a) Prescription medication, including any mu-opioid agonist within 14 days prior to the administration of the IP;
    b) Over-the-counter products and natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to the first dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily);
    c) A depot injection or an implant of any drug within 3 months prior to the first dosing.
14) Subjects using any drugs known to induce or inhibit hepatic drug metabolism, including St. John's wort, within 30 days prior to IP administration.
15) Subject with a history of allergic reactions to nalbuphine, opioids, or other related drugs.
16) Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant reaction to any drug.

17) Donation of plasma within 7 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening or menses) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to the dosing.

18) Hemoglobin < 12.8 g/dL (males) and < 11.5 g/dL (females) and hematocrit < 36% (males) and < 32% (females) at screening.

19) Lactating subject.

20) Inability or difficulty swallowing tablets.

21) Poor venous access or inability to tolerate catheter venous access.

9. Clinical Procedures

The study will be conducted jointly at inVentiv and the Orlando Clinical Research Center.

9.1 Screening Procedures

Subject screening procedures will be performed within 28 days preceding administration of the IP. Subjects must provide written informed consent prior to initiation of any screening procedures. The study-specific ICF must be signed and dated by the subject before participation to study-specific procedures.

Screening procedures will include: demographic data, medical and medication histories, complete physical examination, body measurements, ECG, vital signs, pulse oximetry, body temperature, hematology, coagulation, clinical chemistry, HIV, HBsAG and HCV, urinalysis, WI-NRS for itching (Part 2 only), urine and serum pregnancy test, and urine alcohol and drug screen.

Assessment of liver function will be performed and the degree of hepatic impairment will be categorized using Child-Pugh system at screening.

Subjects from Cohorts 1 to 4 (mild and moderate groups) will be recruited prior to recruiting healthy control group subjects (Cohort 5) in order to facilitate subjects' matching.

For eligibility purposes, abnormal laboratory or vital signs results may be repeated if abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside the prescribed screening window, outdated screening procedures can be repeated. For inclusion, Child-Pugh categorization laboratories that are deemed inconsistent with the usual stage of hepatic impairment may be repeated.

Subjects who do not qualify based on a reversible condition or mild intercurrent illness may be re-screened after the condition is resolved.

Qualified subjects may participate in multiple cohorts (if they remain eligible) and screening procedures do not need to be repeated between cohorts. It is the responsibility of the Investigator to review and confirm that subjects continue to meet all inclusion and exclusion criteria prior to advancing subjects to the next cohort.

9.2 Confinement and Washout

In Part 1 of the study (SAD), subjects in Cohorts 1 to 4 will be confined from the morning of Day -1 until Day 4 (after the 72-hour post-dose blood draw).

Cohort 5 subjects will be confined from the morning of Day -1 until Day 3 (after the 48-hour post-dose blood draw). Subjects will come back to the clinic on Day 4 for the final blood draw and safety procedures at the Study Exit visit.

There will be a washout period of at least 7 days between each administration of the IP in Part 1 of the study and between Parts 1 and 2 of the study.

In Part 2 of the study (MAD), Cohort 6 subjects will be confined from the morning of Day -1 until Day 16 (after the 72-hour post-last dose blood draw). Subjects will come back on Day 17 for the subsequent final blood draw (96-hour post-last dose blood draw) Study Exit visit.

Participation of each subject in this study should last approximately 2½ weeks excluding the time needed for the screening visit.

9.2.1 Outings

Given the long confinement of the study, outings will be permitted during the confinement. Pre-scheduled and supervised outings will also be permitted for smoking subjects during confinements.

Outings will be supervised at all times by the clinical staff to ensure compliance with protocol and will be limited to the grounds surrounding the clinic, as per the clinical site-specific procedures for supervised outings.

9.3 Randomization and Blinding

This study will be open-label due to the objective nature of the data.

Cohorts 1 to 4 (Part 1, SAD) and 6 (Part 2, MAD) will each include the following groups of hepatic-impaired subjects:

- Group 1: Child-Pugh Group A: score 5-6 points; 6-8 subjects with mild hepatic impairment
- Group 2: Child-Pugh Group B: score 7-9 points; 6-8 subjects with moderate hepatic impairment
- Group 3 (Part 1, SAD only): Child-Pugh Group C: score 10-15 points; 4-6 subjects with severe hepatic impairment

Cohort 5 (Part 1, SAD) will include 6-8 healthy subjects with normal hepatic function (control group).

An effort will be made to carefully match the healthy subjects (Cohort 5, SAD) with the subjects with mild and moderate hepatic impairment (Cohorts 1 to 4, SAD) by age (± 10 years), BMI (± 15%), and gender, to the extent possible. Matching strategy will enroll control subjects with normal hepatic function to meet demographically matched mean criteria of the pooled subjects with mild and moderate hepatic impairment.

9.4 Investigational Product (IP)

The Investigational Product (IP) NAL ER tablets (4 strengths) will be supplied by the Sponsor. NAL ER tablets, 27 mg and 54 mg, are white to off-white film coated round tablets (7.9 mm). The NAL ER tablets 108 mg (7.6 × 15.7 mm) and 162 mg (9.3 × 15.4 mm) are white to off-white film coated oblong tablet. NAL ER tablets will be shipped to the Pharmacy packaged in 70 count HDPE bottles with an induction inner seal and child-resistant (CR) closures.

In Part 1 of the study (SAD), hepatic impaired subjects will receive single ascending oral doses and healthy subjects will receive a single oral dose, under fasting conditions, of NAL ER, at the following dose levels:

Cohort	Planned Dose of NAL ER
1	27 mg
2	54 mg
3	108 mg
4	162 mg
5 (healthy subjects)	Up to 162 mg

For Cohort 1, a minimum of 6 subjects from Group 1 (mild impairment), 6 subjects from Group 2 (moderate impairment), and 4 subjects from Group 3 (severe impairment) will receive a single dose of NAL ER.

For Cohorts 2-5, a minimum of 6 subjects from Group 1 (mild impairment) and 6 subjects from Group 2 (moderate impairment) will receive a single dose of NAL ER.

Cohorts will be dosed sequentially in an ascending design. Enrollment of subjects with mild impairment and moderate impairment can be done in parallel. Subjects with severe impairment will be enrolled upon completion of the highest dose level in mild and moderate impairment subjects. There will be at least 7 days between dosing of each dose level, within the same group of impairment (mild and moderate). Subjects will be observed for a period of 4 days.

Safety, tolerability, and combined mild and moderate impaired subject data will be evaluated by a Safety Committee at the completion of each cohort dose level before proceeding to the next cohort dose level. Therefore, the highest dose administered may be lower than 162 mg. Depending on safety and tolerability, the dose escalation scheme may be modified such that intermediate dose levels are administered.

Based on the overall safety and tolerability observed in the subjects with mild and moderate impairment, at the completion of all doses tested, it will be determined by the Safety Committee whether or not it is safe to proceed with dosing for the first 2 subjects with severe Impairment. After review of the safety and tolerability for the first 2 severe subjects dosed at 27 mg, it will be determined whether or not to complete that dose level for the remaining severe subjects.

At the completion of all subjects dosed in the cohort, there will be an evaluation of safety and tolerability to determine whether to proceed to the next dose level for this group.

The Safety Committee will be composed of at least the Investigators and one medically qualified Sponsor representative. Some adjustments to the currently outlined doses and/or dosing regimen may be implemented by the Safety Committee, but the dose to be administered in a given dose cohort will not exceed the one currently outlined in the protocol.

Drug administration in Part 2 of the study (MAD) may be initiated following satisfactory review of the safety and tolerability data from Groups 1 and 2 (mild and moderate impairment) from Part 1 of the study (SAD) by the Safety Committee. Depending on safety and tolerability as well as on available PK data, the dose escalation scheme may be modified such that intermediate dose levels are administered. The dosage regimen (once daily versus twice daily) will be confirmed following review of PK data from Part 1 of the study (SAD).

If in the judgement of the Safety Committee the Part 1 PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study

In Part 2 of the study (MAD), subjects will receive a single 27 mg dose in the morning of Day 1. Starting on Day 2, doses will be subsequently escalated for each subject to twice daily, 12 hours apart, 27 mg, 54 mg, 108 mg, and 162 mg over 13 days. On the last treatment day, (Day 13), subjects will receive a single 162 mg dose in the morning. Subjects will remain at each dose level for 2-3 days (minimum 5 consecutive doses) with dose escalation predicated on tolerability of the prior dose (See Section 9.14.4 for dose escalation stopping rules).

In Part 2 of the study (MAD), tablets will be administered as indicated in the following titration schedule:

Study Day	**Dose (mg)**	
	AM	**PM**
1	27	0
2	27	27
3	27	27
4	27	54
5	54	54
6	54	54
7	54	108
8	108	108
9	108	108
10	108	162
11	162	162

12	162	162
13	162	–
14	–	–
15	–	–
16	–	–

9.5 Drug Supplies and Accountability

It is the responsibility of the Sponsor to ensure that Investigational Product (IP) provided for this study are manufactured under Good Manufacturing Practices (GMP) and are suitable for human use. It is the responsibility of the Sponsor to ship a sufficient amount of IP to the clinical sites to conduct the study. The IP will be stored by the clinical sites per the labeled storage conditions.

Labels will be provided in appropriate languages as required by the country in which the study is conducted. The content of the labeling will be in accordance with local regulatory specifications and requirements. The IP will be stored in a locked, environmentally-controlled medication room with restricted access. Additional instructions for drug dispensing will be provided in a pharmacy manual.

All IP received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability/retention record. The Investigator must maintain accurate records of the receipt of all IP shipped by the Sponsor, or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all the IP. Upon completion of the study, all remaining IP will be returned to the depot for destruction.

9.6 Drug Administrations

In Part 1 of the study (SAD), IP will be administered in the morning to each subject with 240 mL of water; and a hand and mouth check will be performed to ensure consumption of the IP. Tablets should be swallowed whole without chewing or crushing.

In Part 2 of the study (MAD), IP will be administered in the morning on Day 1 and the morning and evening starting on Day 2, 12 hours apart (when applicable) to each subject with 240 mL of water and a hand and mouth check will be performed to ensure consumption of the IP. Tablets should be swallowed whole without chewing or crushing.

The tablets should be taken at approximately the same time each day and within 12 hours. A time window of ± 10 minutes from the scheduled dosing time will be allowed. Any deviation in IP administration that is greater than the allowed time window will be considered as protocol deviation. For every dosing day, both the planned and exact dosing times will be documented. Time of dosing will be set as the time the first tablet is administered.

9.7 Study Restrictions

9.7.1 Food and Fluids

In Part 1 of the study (SAD), no food will be allowed from at least 8 hours before NAL ER dosing until at least 2 hours after. A standardized breakfast will be served at least 2 hours after NAL ER dosing. A lunch, supper, and a light snack will be served at appropriate times thereafter. Except for water given with NAL ER, no fluids will be allowed from 1 hour before dosing until 1 hour post-NAL ER dose.

In Part 2 of the study (MAD), on Days 1 and 13, no food will be allowed from at least 8 hours before dosing until at least 2 hours after dosing. A standardized breakfast will be served at least 2 hours after NAL ER dosing. For other dosing days, no food will be allowed from at least 2 hours before each dosing until at least 2 hours after dosing. Except for water given with IP, no fluids will be allowed from 1 hour before each dosing until 1 hour post-dose. Water will be provided *ad libitum* at all other times.

In addition, subjects will be required to abstain from:

- Food containing poppy seeds within 24 hours prior to admission and for the duration of the study;
- Food or beverages containing xanthine derivatives or xanthine-related compounds (coffee, black/green tea, chocolate) or energy drinks from 48 hours prior to first dosing until study exit;
- Natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sport) from 7 days pre-first dose until study exit unless such products are deemed medically necessary for standard of care by hepatic impaired subjects;
- Food or beverages containing grapefruit, Seville orange, starfruit, pomegranate, pineapple, or pomelo from 14 days prior to first dosing until study exit.

9.7.2 Tobacco, Alcohol, and Illicit Drugs

Subjects will be required to abstain from using soft or hard drugs from screening and throughout the study, and on Day 1, 4, 7, 10, and 13, from smoking from at least 2 hours prior to dosing until 2 hours post-dose and on other dosing days from at least 1 hour prior to dosing until 1 hour post-dose. Subjects will not be allowed to smoke more than 5 cigarettes or equivalent per day.

Consumption of alcohol-based products will be prohibited from 24 hours prior to admission until the study exit.

9.7.3 Concomitant Medications

Cohorts 1 to 4 and 6: Stable medications that are not expected to interfere with the PK of NAL ER will be allowed during the study. No other concomitant drug therapy (prescription or over-the-counter medications) and/or food or beverage outside of the restrictions set out in Section 9.7.1 will be allowed during the study except one(s) required for the medical management of an adverse event, a new medical condition, or as allowed by the Safety Committee as discussed in the next

paragraph. Any concomitant medication use at the time of screening, other than the occasional use of acetaminophen, will be evaluated on a case-by-case basis by the Investigator. All concomitant medication use will be documented from screening through study exit/early termination.

In the absence of titration there is a dose response relationship between NAL ER and specific AE frequencies in healthy subjects noted in prior single dose studies, therefore the Safety Committee may determine at any time, using ongoing safety data obtained during the course of the SAD period of the study, whether prophylactic treatment (such as the use of an anti-emetic) will be allowed prior to dosing subsequent subjects.

If a subject is taking an excluded medication, the Investigator can switch the subject to an alternate medication that is allowed and subject can be screened for the study after appropriate stabilization on the new medication. This will be done after the subject signs the consent form.

Cohort 5: Prescription and over-the-counter medications will be prohibited throughout the study. No concomitant drug therapy will be allowed during the study except one(s) required for the medical management of an adverse event. Any concomitant medication use at the time of screening, other than the occasional use of acetaminophen, will be evaluated on a case-by-case basis by the Investigator. All concomitant medication use will be documented from screening through study exit/early termination.

9.7.4 Posture and Physical Activity

Subjects will be allowed to engage in normal activity throughout the study. In Part 1 of the study (SAD), subjects will be required to avoid lying down or sleeping, unless medically necessary or procedurally required, for 4 hours after drug administration. In Part 2 of the study (MAD), on Days 1, 4, 7, 10, and 13, subjects will be required to avoid lying down or sleeping, unless medically necessary or procedurally required, for 4 hours after morning drug administration.

Because excessive physical activity may increase the level of CPK above the upper normal limit value, subjects will be advised to avoid performing such activity at all times during the study duration. Vigorous activity will be prohibited at all times during the confinement.

9.7.5 Other Restrictions

Subjects will be asked not to wear artificial nails or nail polish at screening, and during confinements, at least on the fingers used for pulse oximetry monitoring, in order to avoid false readings.

9.8 PK Sample Collection and Processing

9.8.1 Plasma Samples

Part 1 (SAD) – Cohorts 1 to 5

A total of 11 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, and 72 hours post-dose (up to 3 mL for each sampling time).

For Part 1, the total volume of blood including that collected for eligibility and safety purposes should not exceed 160 mL for each dose level.

Part 2 (MAD) – Cohort 6

On Day 1: a total of 10 blood samples will be collected for quantitation of nalbuphine and metabolite(s) in plasma: pre-dose and 1.5, 3, 4, 5, 6, 7, 9, 12, and 24 hours post-dose (up to 3 mL for each sampling time).

On Days 4, 7, and 10, a total of 9 blood samples will be collected: at pre-morning dose and 1.5, 3, 4, 5, 6, 7, 9, and 12 hours post-dose (prior to the evening dose administration) (up to 3 mL for each sampling time).

On Day 13, a total of 12 blood samples will be collected: at pre-dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose (up to 3 mL for each sampling time).

Trough blood samples will be collected on Days 2, 3, 5, 6, 8, 9, 11, 12, and 13 prior to the morning and evening (if applicable) dose administrations (up to 3 mL for each sampling time). Pre-dose samples for the evaluation of steady state attainment will be collected at approximately the same time each day and within 10 minutes prior to dosing.

The 12-hour and 24-hour (when applicable) post-morning Day 1, 4, 7, 10, and Day 13 dose samples will be collected within 10 minutes of the nominal time. For timepoints up to 1 hour, a window of ± 1 minute will be allowed for blood collection. From 1.5 hour to 2 hours, a window of ± 2 minutes will be allowed. From 2.5 hours to 12 hours, the time window will be ± 5 minutes and for 16 hours to 72 hours, the time window will be ± 10 minutes. Actual post-dose sampling times will be used for PK analyses.

Unless otherwise specified or for subject safety, when blood draws and other procedures coincide, blood draws will have precedence. A saline intravenous catheter may be used for blood collection to avoid multiple skin punctures, when appropriate. Otherwise, blood samples will be collected by direct venipuncture.

For Part 2, the total volume of blood including that collected for eligibility and safety purposes should not exceed 358 mL for the whole study.

Plasma samples will be collected and processed as per the Analytical Methodology Information Sheet. Plasma samples will be analyzed to determine nalbuphine and M1, M2, M4, and M5 metabolite concentrations using validated assay methods.

9.9 Pharmacodynamic Assessment

For Part 2 only, WI-NRS measure will be used to determine the severity of itch experienced by subjects with hepatic impairment at screening. Subjects will complete the two WI-NRS forms (the "Nighttime Itch" and the "Daytime Itch") at the same time during the screening visit and the average will be taken to determine the baseline severity.

For all Cohort 6 subjects, WI-NRS measure will also be performed on a daily basis from Day -1 to Day 16, twice a day, once within an hour of completing their morning and evening meals (if applicable). Subjects will fill in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.

Please refer to Appendix 1 Section 17 for WI-NRS.

9.10 Subject Monitoring

Beginning with informed consent, subjects will be monitored throughout the study by the clinical sites' staff for adverse events.

In Part 1 of the study (SAD), an Investigator will be on site/campus for drug administration and until 4 hours after administration and available on call for the remainder of the dosing period. In Part 2 of the study (MAD), an Investigator will be on site for each morning drug administration and until 4 hours after morning administration on Days 1, 4, 7, 10, and 13. An Investigator will also be on call for the remainder of the study. If necessary, a physician, either at the clinical site/campus or in a nearby hospital will administer treatment for any adverse event(s). A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

Safety parameters, including laboratory results, vital signs, pulse oximetry, and ECG, will be assessed by the Investigator or delegate, using the clinical site's criteria for biomedical laboratory and ECG acceptance ranges as suggested guidelines in making the medical assessment.

Scheduled safety measurements will be repeated according to appropriate clinical site SOPs or upon request from a physician. Any abnormal repeated measurement will be evaluated by a physician and repeated if judged necessary. Further action may be taken upon physician's request.

Unless otherwise specified or for subject safety, when the timing of some assessments coincide with other assessments or procedures, the following priority order and sequence should be adhered to, whenever possible: ECG, vital signs, pulse oximetry, blood samples for PK, clinical laboratory samples, and physical examination.

Subjects will be advised to notify their health care professional(s) (eg, physician, dentist, and/or pharmacist) that they are participating in a clinical research study on an experimental drug called nalbuphine (NAL ER) before taking any medicines or undergoing any medical procedure.

9.10.1 Vital Signs

Blood pressure, heart rate, and respiratory rate will be measured in a sitting position after at least 5 minutes of sitting (except for safety reasons).

In Part 1 of the study (SAD), blood pressure, heart rate, and respiratory rate will be measured at screening, in the morning on Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and on Day 4. Body temperature will be measured at screening, Day -1, and Day 4.

In Part 2 of the study (MAD), blood pressure, heart rate, and respiratory rate will be measured screening, in the morning on Day -1, pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, approximately 2 and 6 hours post-morning dose on Days 2 to 12, and once on Days 14, 15, and 16. Body temperature will be measured at screening, Day -1, and Day 16.

When vital signs measurements coincide with a blood draw, they should preferably be performed before the blood collection whenever possible. A time window of 15-20 minutes for vital signs will be allowed if there are multiple procedures at the same time point.

9.10.2 Pulse Oximetry

Pulse oximetry will be performed at the screening visit. Baseline continuous pulse oximetry will be performed during the nighttime of Day -1 (minimum of 8 hours prior to first dose administration). Oxygen saturation will be monitored using a desaturation lower limit alarm of 92%. For subjects in Cohorts 1 to 4 and 6, if desaturation falls below the 92% lower limit alarm during the nighttime on Day -1, the Investigator has the discretion to lower their alarm limit on the pulse oximeter for subsequent nighttime monitoring in the study for that subject. In the event of desaturation below the lower limit alarm during the nighttime, the subject will be managed at the Investigator's discretion.

For Part 1 of the study (SAD), following the dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-dose and 1.5, 4.5, and 8 hours post-dose. Oxygen saturation will be monitored via continuous pulse oximetry overnight beginning at bedtime and until awaking the next morning from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.

For Part 2 of the study (MAD), following the first dose and throughout study conduct, oxygen saturation will be measured via pulse oximetry at pre-morning dose, at 1.5, 4.5, and 8 hours following the morning dose, and at 2 hours following the evening dose. Oxygen saturation will be monitored via continuous pulse oximetry beginning at bedtime and until awaking the next morning from Day 1 to end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.

Pulse oximetry measurements may be collected within 10 minutes before or after the specified time point.

9.10.3 12-lead ECG

For Part 1 of the study (SAD), a 12-lead ECG will be performed at screening, in the morning on Day -1, pre-dose, approximately 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, and on Day 4.

For Part 2 of the study (MAD), a 12-lead ECG will be performed at screening, in the morning on Day -1, pre-morning dose every day (Days 1 to 13), approximately 1, 2, 4, 6, 8, and 12 hours post-morning dose on Day 1 and Day 13, and once on Days 14, 15, and 16.

ECG will be performed after a resting time of at least 5 minutes in supine position. When ECG coincides with a blood draw, it should preferably be performed before the blood collection whenever possible. A time window of 15-20 minutes for ECGs will be allowed if there are multiple procedures at the same time point.

9.10.4 Physical Examination

For Parts 1 and 2 of the study, a complete physical examination will be performed at screening. The complete physical examination includes at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, and lungs, cardiovascular, abdomen, skin, musculoskeletal evaluation, and general neurological examination. Body measurements will be performed at screening and will include: body weight, height measurement, and BMI.

For Part 1, a brief physical examination will be performed on Day -1 and Day 4.

For Part 2, a brief physical examination will be performed on Day -1 and Day 16.

9.10.5 Drug and Alcohol Screen

For Parts 1 and 2 of the study, urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, PCP, MDMA, methadone) and a urine alcohol screen will be performed at screening and in the morning on Day -1.

9.10.6 Pregnancy Test

For Part 1 of the study, urine and serum pregnancy tests will be performed (females only) at screening, in the morning on Day -1, and on Day 4 or upon early termination. For Part 2 of the study, urine and serum pregnancy tests will be performed (females only) at screening, in the morning on Day -1, and on Day 16 or upon early termination.

Urine pregnancy test results will be confirmed by lab serum pregnancy test results. Pregnancy test results must be available and review documented prior to dispensation of IP (when applicable).

9.10.7 Laboratory Assessments

All scheduled clinical laboratory tests will be performed following a fasting period of at least 8 hours.

9.10.7.1 Clinical Chemistry

For Part 1 of the study, clinical chemistry will be performed at screening, in the morning on Day -1, and on Day 4. For Part 2 of the study, clinical chemistry will be performed at screening, in the morning on Day -1, and on Days 5, 10, and 16. The following will be assessed: albumin, alkaline phosphatase, AST, ALT, urea, calcium, chloride, glucose, phosphorus, potassium, creatinine, sodium, bicarbonate (CO2), total bilirubin, indirect bilirubin, CPK, direct bilirubin, and total protein.

Considering that indirect bilirubin is calculated from total and direct bilirubin values, indirect bilirubin result would not be available in case of direct bilirubin below the limit of quantification.

Estimated glomerular filtration rate (eGFR) will be calculated by the MDRD4 Equation at screening.

9.10.7.2 Serology

HBsAg, HCV antibody, and HIV antigen and antibody detection will be performed at screening.

9.10.7.3 Hematology

For Part 1 of the study, hematology will be performed at screening, in the morning on Day -1, and on Day 4. For Part 2 of the study, hematology will be performed at screening, in the morning on Day -1, and on Days 5, 10, and 16. The following will be assessed: complete blood count with differential, hemoglobin, and hematocrit.

9.10.7.4 Coagulation

For Part 1 of the study, coagulation tests (PT, aPTT, and INR) will be performed at screening, in the morning on Day -1, and on Day 4. For Part 2 of the study, coagulation tests will be performed at screening, in the morning on Day -1, and on Day 16. The following will be assessed: prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT).

9.10.7.5 Urinalysis

For Part 1 of the study, urinalysis will be performed at screening, in the morning on Day -1, and on Day 4. For Part 2 of the study, urinalysis will be performed at screening, in the morning on Day -1, and on Day 16. The following will be assessed: macroscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, and leukocytes. Unless otherwise specified, microscopic examination will be performed on abnormal findings.

9.11 Discharge/Study Exit Procedures

For Part 1 of the study, the following will be performed on Day 4: brief physical examination, vital signs, body temperature, ECG, pulse oximetry, clinical chemistry, hematology, coagulation, urinalysis, PK sample, urine and serum pregnancy test (females only), and adverse events monitoring.

For Part 2 of the study, the following will be performed on Day 16: brief physical examination, vital signs, body temperature, ECG, pulse oximetry, clinical chemistry, hematology, coagulation, urinalysis, PK sample, urine and serum pregnancy test (females only), WI-NRS, and adverse events monitoring. The following will be performed on Day 17: PK sample.

If not possible, all efforts will be made to complete study exit procedures within 14 days after the last participation of the subject in the study.

In the case that a subject experiences a DLT or a DLT dose is confirmed in 2 subjects during Part 2 (MAD), post last-dose study procedures will be performed as laid out in the DLT Follow-Up Period (see Section 9.11.1). Early Termination procedures are only applicable to subjects who discontinue study drug for reasons other than those related to DLT.

9.11.1 DLT Follow-Up Period for Part 2 (MAD), Post-Last Dose

In Part 2 of the study, any subject who experiences a DLT TEAE will not receive further dose of study drug, and safety follow-up procedures, per the DLT Follow-Up Period will be performed.

If 2 subjects develop a DLT, all subjects who are currently receiving a confirmed DLT dose will not receive further dose of study drug and will immediately enter into the DLT Follow-Up Period.

The maximum safe dose (MSD) will be determined as the dose level below the DLT dose.

Subsequent subjects in Part 2 of the study will only be dosed through the completion of the MSD per the days specified in the titration table. After dosing is complete, subjects will immediately enter the DLT Follow-Up Period and the following procedures will be performed:

DLT Follow-Up Period Procedures

- Subjects will be confined until after the 72-hour post-last dose blood draw and will come back for the final 96-hour post-last dose blood draw the following day at the Study Exit visit.
- Vital signs (blood pressure, heart rate, and respiratory rate): pre-last dose and approximately 1, 2, 4, 6, 8, and 12 hours post-last dose, and once a day until end of confinement.
- 12-lead ECG: pre-last dose and approximately 1, 2, 4, 6, 8, and 12 hours post-last dose and once a day until end of confinement.
- PK blood samples: a total of 12 blood samples will be collected for the last dose: at pre-last dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose.
- Oxygen saturation via pulse oximetry will be measured: pre-last dose and at 1.5, 4.5, and 8 hours following the last dose (if morning dose), and at 2 hours following the last dose (if evening dose). Pulse oximetry measurements may be collected within 10 min before or after the specified time point. Oxygen saturation will be monitored via pulse continuous oximetry beginning at bedtime and continuing overnight until waking time through end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.
- WI-NRS will be performed on a daily basis, to be collected twice per day until end of confinement: once within an hour (+/- 1 hour) of completing their morning and evening meals, if applicable. Subjects will fill in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.
- Laboratory assessments (ie, clinical chemistry, hematology, coagulation, and urinalysis) will be done in the morning prior to discharge following a fasting period of at least 8 hours.
- Urine and serum pregnancy tests will be performed prior to discharge (as applicable).
- Brief physical exam will be performed and body temperature will be taken prior to discharge.
- Subjects will be monitored by the study staff for adverse events and concomitant medications until study exit.

DLT Follow-Up Procedures are to be completed at the time points specified wherever feasible, though this may not be possible in some circumstances, including: if the last dose occurs in the evening (eg. for a subject who experiences a DLT) and time points are during the sleep period; and/or the AE leading to DLT occurs after a procedure time point has passed (for example, if a DLT occurred 2 hours post-dose on Study Days 2-12, ECG would not have been performed 1 hour post-dose).

9.11.2 Early Termination for Part 2 (MAD)

In Part 2 of the study, Early Termination follow up procedures are only applicable to subjects who discontinue study drug for reasons other than those related to DLT (see Section 9.11.1).

Early termination follow up procedures are to be completed at the time points specified wherever feasible, though this may not be possible in some circumstances, including: if the last dose occurs in the evening and time points are during the sleep period; and/or the subject is withdrawn from the study after a procedure time point has passed.

The following procedures will be performed (unless consent is withdrawn):

- Vital signs (blood pressure, heart rate, and respiratory rate) should be collected prior to discharge.
- 12-lead ECG should be collected prior to discharge.
- PK blood samples will be collected until the time of discharge for the last dose administered at pre-last dose and 1.5, 3, 5, 7, 9, 12, 24, 36, 48, 72, and 96 hours post-last dose.
- Oxygen saturation via pulse oximetry will be measured until discharge: pre-last dose and at 1.5, 4.5, and 8 hours following the last dose (if morning dose), and at 2 hours following the last dose (if evening dose). Pulse oximetry measurements may be collected within 10 min before or after the specified time point. Oxygen saturation will be monitored via pulse continuous oximetry beginning at bedtime and continuing overnight until waking time through end of confinement with oxygen saturation measurements specifically recorded at approximately midnight and 4 am.
- WI-NRS will be collected twice per day until discharge: once within an hour (+/- 1 hour) of completing their morning and evening meals, if applicable. Subjects will fill in the "Nighttime Itch" form in the morning and the "Daytime Itch" form in the evening.
- Laboratory assessments (ie, clinical chemistry, hematology, coagulation, and urinalysis) will be done in the morning prior to discharge following a fasting period of at least 8 hours (if possible).
- Urine and serum pregnancy tests will be performed prior to discharge (as applicable).
- Brief physical exam will be performed and body temperature will be taken prior to discharge.
- Subjects will be monitored by the study staff for adverse events and concomitant medications until discharge.

9.12 Data Collection and Evaluation

All clinical raw data will be recorded promptly, accurately, legibly, and indelibly by the clinical staff on raw data sheets and/or recorded electronically using validated software and transcribed into case report forms. All raw data will be conserved in order to maintain data integrity. A physician and/or the clinical staff will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

9.13 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or a delegate may withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with SOPs of the clinical sites:

- safety reason;
- non-compliance with protocol requirements;
- significant protocol deviation;
- positive urine alcohol or drug screen, or pregnancy test.

Subjects missing one dose of scheduled IP or experiencing emesis during the study will be evaluated on a case-by-case basis for possible impact on the outcome of the study.

Hematology, clinical chemistry, urinalysis, and coagulation results will be reviewed by an Investigator prior to first dosing; subjects will be withdrawn from the study if it is deemed that the subject's safety may be at risk on the basis of these test results. For subjects with hepatic impairment and taking medications that are allowed by the Investigator, a positive result to opiate/benzodiazepine/THC screen (drug screen) may have derived from these medications and these subjects will not be automatically withdrawn from the study. Subjects who withdraw or are withdrawn from the study after dosing, for reasons other than safety and tolerability, may be replaced after consultation between the Investigator and Sponsor. The total number of subjects dosed (including potential replacement subjects) will remain within a maximum of 112 subjects for the whole study.

Subjects who withdraw or are withdrawn will be asked to remain at the clinic until the Investigator or a delegate agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped. A PK blood draw may be collected at the time of withdrawal if deemed required by the Investigator. Study exit procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

9.14 Dose Escalation Stopping Rules

Dose escalation can be stopped if any treatment-emergent adverse event (TEAE) occurs in a subject dosed with NAL ER during the study that, in the opinion of the Investigator, raises concerns about the safety and tolerability of a higher dose. In addition, the following dose escalation rules will apply.

Dose-limiting toxicity (DLT) in the hepatic-impaired subject population participating in this study is defined as the dose at which a confirmed Grade 3 adverse event develops in any 2 subjects, even if in two different organ systems, that is IP related and is unlikely to be related to the disease process. Overnight oximetry that drops more than 10% from a subject's baseline lowest value for a consistent period of 5 minutes will be considered a DLT TEAE.

Any subject who experiences a DLT TEAE will not receive further dose of study drug, and safety follow-up procedures will be performed.

9.14.1 Part 1 (SAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Mild and Moderate Hepatic Impairment (Group 1 and Group 2)

Upon completion of the dosing of subjects with mild and moderate hepatic impairment (Group 1 and Group 2) in each of Cohorts 1 to 4 in Part 1 of the study, the safety data and nalbuphine PK parameters (if available or requested) will be reviewed by the Safety Committee to determine the continuation of the progression of Part 1 dose escalation and to evaluate the safety for that dose level to be included in Part 2 of the study (MAD).

If 2 subjects develop a DLT at the same dose, then that dose will be confirmed as DLT.

If 2 subjects develop a DLT at 2 different doses (eg, 108 mg and 162 mg), then the higher of the 2 doses (162 mg in this example) will not be pursued in remaining Group 1 and Group 2 subjects (if not already dosed).

9.14.2 Part 1 (SAD) Dosing Procedures in Cohort 5 (Healthy Volunteers)

Cohort 5 will receive the highest dose tested in subjects with mild or moderate hepatic impairment (Cohorts 1 to 4), and if any dose is confirmed to be a DLT during dosing of Cohorts 1 to 4, then that dose will not be studied in Cohort 5 of Part 1 (SAD).

9.14.3 Part 1 (SAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Severe Hepatic Impairment (Group 3)

Group 3 severe hepatic impairment subjects will receive a single dose of NAL ER 27 mg. Group 3 dose stopping rules will take into account the DLT from the preceding Group 1 and Group 2 data.

If 2 subjects with mild or moderate hepatic impairment developed a DLT at the 27 mg dose, then that dose will be confirmed as DLT and will not be pursued in Group 3 subjects.

If 2 subjects with severe hepatic impairment develop a DLT, then the NAL ER 27 mg will not be dosed in the remaining Group 3 subjects (if not already dosed).

9.14.4 Part 2 (MAD) Dose Escalation Procedures and Stopping Criteria for Subjects with Mild and Moderate Hepatic Impairment (Group 1 and Group 2)

If 2 subjects develop a DLT at the same dose, then that dose will be confirmed as DLT.

If 2 subjects develop a DLT at 2 different doses (eg, 108 mg and 162 mg), then the higher of the 2 doses (162 mg in this example) will not be pursued in remaining Group 1 and Group 2 subjects (if not already dosed).

The maximum safe dose (MSD) will be determined as the dose level below the DLT dose.

Subjects who are currently receiving a confirmed DLT dose will not receive further dose of study drug. Subsequent subjects in Part 2 of the study will only be dosed through the completion of the MSD per the days specified in the titration table. After last dose, subjects will immediately enter the DLT Follow-Up Period (see Section 9.11.1).

9.14.5 PK Criteria Determination for Terminating the Study Following Part 1 (SAD) Safety Committee Review.

If in the judgement of the Safety Committee the Part 1 PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects (Group 1 and Group 2 subjects), such that PK modeling can be predictive of steady state dosing levels, a decision may be made to end the study without conducting Part 2 of the study.

9.15 Adverse Events and Serious Adverse Events

The Investigator or designee and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE. Spontaneously reported or observed AEs will be recorded throughout the study, beginning at the time the subject gives informed consent. Subjects will be monitored throughout confinement for AEs and AEs may be elicited using a nonleading question at the discretion of the clinical staff. Regardless of seriousness, intensity, or presumed relationship to IP, all AEs will be recorded in the source documentation from the time of first contact with the subject (eg, screening) until the end of the follow-up period of the study. AEs that occur after screening and prior to administration of the first dose of IP will be recorded in the source documentation as baseline medical history. All measures required for management of AEs will be recorded in the source documentation. Any SAE that occurs after screening and prior to administration of the first dose of IP will be reported to Syneos Health Safety and Pharmacovigilance by the Investigator or designee within 24 hours of learning of the event.

9.15.1 Definitions

9.15.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the investigational product(s) was given (eg, during a washout period).

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

Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

9.15.2 Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening (at the time of the event),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information set out in the Reference Safety Information section of the IB or on the label of the drug.

9.15.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (eg, from clinical chemistry, hematology, or urinalysis) and other abnormal assessments (eg, from vital signs or ECGs) judged as clinically significant by the Investigator or designee will be recorded as AEs or SAEs if they meet the definitions provided in Section 9.15.1. Furthermore, abnormal laboratory findings and other abnormal assessments present at baseline that significantly worsen following the start of the study (ie, become clinically significant) will be reported as AEs or SAEs. However, abnormal laboratory findings present at the start of the study that do not worsen will not be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

In the FDA E14 Clinical Evaluation of QT/QTc and Proarrhythmic Potential Guidance (2005), mention is made that ECG analysis is considered a fundamental component of the drug candidates safety database. As part of the safety analysis that may be undertaken in the event of an ECG related AE, source ECG strips may be reviewed and evaluated by the Sponsor and/or their delegate.

9.15.4 Evaluation of Adverse Events and Serious Adverse Events

The Investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality, and outcome of an AE.

9.15.4.1 Classification of Adverse Event Intensity

For each recorded AE or SAE, the Investigator or designee must make an assessment of intensity, if possible, based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or later (*https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*).[14] A determination of grading at the time of AE occurrence is required in order to monitor for DLTs and may be modified upon continued assessment. If there is insufficient information to determine intensity, the AE must still be reported.

The severity of an AE that cannot be termed and graded by the most current version of CTCAE will be categorized as follows (Table 4):

Table 4 Classification of Adverse Event Intensity

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) available for download at: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

9.15.4.2 Classification of Adverse Event Causality

For each recorded AE or SAE, the Investigator or designee must make an assessment of causality based on the criteria in Table 5 to determine the relationship between the AE and the Investigational Product (IP).

Table 5 Classification of Adverse Event Causality

Classification	Definition
Unrelated	The AE or SAE is judged to be *clearly and incontrovertibly due only to extraneous causes* (eg, disease, environment) and does not meet the criteria for IP relationship listed under probable, possible, or unlikely.
Unlikely	The AE or SAE is *unlikely* related to the IP, when the AE or SAE • does not follow a reasonable temporal sequence from administration of the IP • may readily have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject • does not follow a known pattern of response to the IP • does not reappear or worsen when the IP is re-administered
Possible	The AE or SAE is *possibly related* to the IP, when the connection to the IP appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE • follows a reasonable temporal sequence from administration of the IP • may have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject • follows a pattern of response to the suspected IP
Probable	The AE or SAE is *probably related* to the IP, when the connection to IP can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE • follows a reasonable temporal sequence from administration of the IP • cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject • disappears or decreases upon cessation or reduction in dose (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the IP, yet drug relatedness clearly exists, eg, bone marrow depression or tardive dyskinesias) • follows a known pattern of response to the suspected IP • reappears upon re-challenge

9.15.4.3 Classification of Adverse Event Outcome

For each recorded AE or SAE, the Investigator or designee must make an assessment of outcome at the time of last observation. The outcome of AEs or SAEs will be documented as outlined in Table 6.

Table 6 Classifications for Adverse Event Outcomes

Classification	Definition
Fatal	The subject died.
Resolved	The AE or SAE has ended.
Resolved with sequelae	The AE or SAE has ended but changes are noted from baseline.
Unresolved	The AE has not ended. An AE outcome can only be categorized as unresolved, if the AE is *ongoing* at the end of the reporting period (ie, 14 days after the final Follow-up visit) and the Investigator deems that further follow-up is not medically required *lost to follow-up* after repeated unsuccessful attempts to contact the subject *ongoing and referred* to the subject's physician or a specialist

9.15.5 Reporting Procedures

Any SAE—expected or unexpected, irrespective of relationship to study treatments, including death due to any cause—experienced by a study subject will be reported to Syneos Health Safety and Pharmacovigilance by the Investigator or designee within 24 hours of learning of the event.

The contact information for the Syneos Health Safety and Pharmacovigilance is as follows:

Name	Drug Safety and Pharmacovigilance
Email	[redacted]
Fax	[redacted]

Any SAEs occurring during the trial that meet regulatory reporting criteria (ie, SUSARs) will be reported in an expedited manner to the regulatory authorities as required. Syneos Health assumes responsibility for appropriate reporting of SAEs to the sponsor in a prompt fashion. Information regarding the SAE, and all follow-up evaluations, will be transmitted to Trevi Therapeutics, Inc. by email (hard copy of documents to be scanned and attached to the email).

Contact information for the Medical Monitor in this study is as follows:

[redacted] MD
Medical Monitor
195 Church Street
14th Floor
New Haven, CT
06510 USA
Tel.: [redacted]
Fax: [redacted]
Email: [redacted]

Trevi Therapeutics, Inc. is responsible to report SUSARs to Regulatory authorities (eg, FDA) and Investigator. The Investigator must report these events to their local Independent Ethics Committee (IEC) that approved the protocol per the IEC's documented requirements.

All additional follow-up evaluations for SAEs will be reported to Syneos Health Safety and Pharmacovigilance.

9.15.6 Suspected, Unexpected, Serious Adverse Drug Reactions

The Sponsor is responsible for notifying the FDA of suspected, unexpected, serious adverse drug reactions (SUSARs) observed during conduct of studies in which the Investigational Product is administered.

FDA notification of fatal or life-threatening suspected, unexpected, serious adverse drug reaction must be made as soon as possible, but no later than 7 calendar days after becoming aware of the information. FDA notification of all other suspected, unexpected, serious adverse drug reactions that are neither fatal nor life-threatening must be made as soon as possible, but no later than 15 calendar days after becoming aware of the information.

The Sponsor is responsible to comply with any other applicable regulatory requirement(s) related to the reporting of SAE to other regulatory authority(ies).

9.15.6.1 Serious Adverse Event Reporting to the Independent Ethics Committee

It is the responsibility of the sites to report as soon as possible, but no later than 7 calendar days after first knowledge by the Investigator, fatal or life-threatening suspected, unexpected, serious adverse drug reactions to the IEC responsible for the study.

It is the responsibility of the sites to report to the IEC all other suspected, unexpected, serious adverse drug reactions that are neither fatal nor life-threatening, as soon as possible, but no later than 14 calendar days after first knowledge by the Investigator.

9.16 Pregnancy

If a subject participating in the study becomes pregnant during the study, the Investigator should report the pregnancy to the Sponsor within 24 hours of being notified.

A subject becoming pregnant while on the IP will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.17 Reportable Disease

In the case a subject has or manifested any clinical signs characteristic of a reportable disease or condition (eg, HIV, tuberculosis, SARS), it is the responsibility of the Medical Director to notify the public health department of the State of Florida within 72 hours after becoming aware of the information.

10. Study Termination

The study may be terminated by the Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Investigator will immediately inform the active study subjects and the IEC responsible for this trial, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is the Sponsor's responsibility to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

11. Analytical Methodology

When applicable, samples will be transported to the bioanalytical facility in at least two separate shipments, with each set of aliquots in separate shipments. Once the bioanalytical laboratory confirms receipt of the first shipment, the second set of aliquots may be sent. The samples should be packed on sufficient dry ice to keep them frozen for at least 72 hours.

The Bioanalytical Division of Covance labs will analyze nalbuphine and its metabolite(s) (for select samples) in plasma using validated methods.

Analyst and Watson LIMS (Laboratory Information Management System) will be used at different steps of the analysis.

Samples from subjects included in the pharmacokinetic population (see Section 12.2.2) and from subjects who were withdrawn from the study due to adverse events, or vomiting episodes will be analyzed.

12. Pharmacokinetic and Statistical Analyses

Pharmacokinetic analysis will be performed using Noncompartmental Analysis. Inferential statistical analyses will be performed according to FDA guidelines.

12.1 Pharmacokinetics

The following pharmacokinetic parameters will be calculated by standard non-compartmental methods for nalbuphine and metabolites (if required).

Part 1 (SAD):

1) AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
2) AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated)
3) C_{max}: maximum observed concentration
4) T_{max}: time of observed C_{max}
5) $T_{½\ el}$: elimination half-life
6) Residual area: calculated as $100*(1- AUC_{0-t} / AUC_{0-inf})$
7) K_{el}: elimination rate constant
8) Cl/F: apparent total body clearance of the drug from plasma
9) V_d/F: apparent volume of distribution, calculated as $Dose/(K_{el} \times AUC_{0-inf})$

Part 2 (MAD), Day 1:

1) AUC_{0-12}: area under the concentration-time curve from time zero to the 12-hour period
2) AUC_{0-24}: area under the concentration-time curve from time zero to the 24-hour period
3) C_{max}: maximum observed concentration
4) $T_{max:}$ time of observed C_{max}

Part 2 (MAD), Days 4, 7, and 10:

1) AUC_{0-12}: area under the concentration-time curve from time zero to the end of the dosing period
2) C_{max}: maximum observed concentration
3) T_{max}: time of observed C_{max}

Part 2 (MAD), Day 13:

1) AUC_{0-12}: area under the concentration-time curve from time zero to the 12-hour period
2) AUC_{0-24}: area under the concentration-time curve from time zero to the 24-hour period
3) AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
4) AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated)
5) C_{max}: maximum observed concentration
6) C_{trough}: last observed concentration
7) $T_{max:}$ time of observed C_{max}

8) Fl(%): percentage of fluctuation
9) Residual area: calculated as 100*(1- AUC_{0-t} / AUC_{0-inf})
10) $T_{½\ el}$: elimination half-life
11) K_{el}: elimination rate constant
12) Cl/F: apparent total body clearance of the drug from plasma
13) V_d/F: apparent volume of distribution, calculated as Dose/(K_{el} x AUC_{0-inf})

Additional PK analysis may be performed. Upon the Sponsor's request, PK repeats might be performed. If re-assays are requested for PK reasons, final results will include re-assay values, while results with original values will be presented in an appendix of the report as supportive data.

12.2 Analysis Populations

12.2.1 Safety Population

The safety population is defined as all subjects who received the Investigational Product (IP).

12.2.2 Pharmacokinetic Population

The PK population will include all subjects completing one dose level of the study and for whom the PK profile can be adequately characterized. This Analysis will be conducted if warranted and reported separately.

12.3 Statistical Analyses

A Statistical Analysis Plan (SAP) will be prepared after completion of the final protocol and finalized prior to database lock.

Demographic parameters will be summarized descriptively. Treatment-emergent adverse events will be summarized descriptively by treatment for all subjects who were dosed (safety population). No inferential statistical analysis of safety data is planned.

Individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of variation [CV (%)], minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented as well for the PK parameters according to the hepatic function groups included in the study (Control, Mild, Moderate, and Severe hepatic impairment). A graphical description of the relationship between measures of hepatic function and PK parameters will be presented. This may include the Child-Pugh classification scores (group and individual scores) or its individual components such as S-albumin, S-bilirubin, and prothrombin time expressed as INR.

For Part 1, for plasma nalbuphine and metabolite(s), for each dose level, using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed dose-normalized , AUC_{0-t} , $AUC_{0-inf,}$ and C_{max} at the alpha level of 0.05 to compare groups (Control, Mild, Moderate, and Severe). Factor incorporated in the model will include group as a fixed effect. The 90% CIs (Mild/Control, Moderate/Control, and Severe/Control) will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. For these analytes, T_{max} will be analyzed non-parametrically with point

estimates and 90% CIs for the median differences of T_{max} between groups (Mild-Control, Moderate-Control, and Severe-Control).

Within each group, dose proportionality will be assessed by a visual assessment of the individual and mean nalbuphine and metabolites PK parameters.

For Part 2, for each day (as appropriate), using GLM procedures in SAS, ANOVA will be performed on untransformed K_{el} and $T_{½\ el}$ and on ln-transformed AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, C_{max}, and C_{trough} at the alpha level of 0.05 for nalbuphine and metabolite(s).

Also, for Part 2 of the study, a repeated measures analysis of variance (RMA) will be carried out on ln-transformed pre-morning and evening dose (when applicable) concentrations (Days 2, 3, 5, 6, 8, 9, 11, 12, and 13) to determine attainment of steady state.

Within each group, dose proportionality will be assessed by a visual assessment of the individual and mean nalbuphine PK parameters. A power model analysis may also be performed to evaluate the doses-exposure, if warranted.

In the event that hepatic impairment has a clinically relevant effect on nalbuphine and metabolite(s) PK, the relationship between measures of hepatic function and appropriate PK parameters (eg CL/F, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, AUC_{0-t}, C_{trough}, and C_{max}) will be determined by a linear or non-linear regression.

Study results including the graphical description and the relationships between hepatic function and relevant PK parameters will be used to elaborate specific dosing recommendations if deemed clinically relevant.

For the WI-NRS variables, post-dose scores will be assessed as an increase or decrease relative to the pre-dose values. Each time point will be evaluated separately, relative to the baseline (pre-dose). Pair-wise comparisons among the group will be made if applicable.

Review of interim safety analyses will be performed between cohorts or groups. Interim PK analyses could be performed between cohorts or groups if requested or warranted.

A complete description of the statistical analyses to be performed with the safety and tolerability data, as well as PK parameters will be presented in the SAP, which will be finalized prior to database lock. Additional statistical analysis may be performed and will be described in the SAP.

13. Informed Consent

Potential subjects must provide written consent to participate after the nature, scope, and possible consequences of 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.

14. Regulatory Considerations and Quality Assurance

14.1 Independent Ethics Committee Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favourable written approvals for the above-mentioned study documents.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Principal Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

14.2 Compliance

This study will be conducted in compliance with the protocol, GCP, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), and any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

14.3 Audits, Inspections, and Monitoring

In accordance with the principles of GCP, the study may be inspected by regulatory authorities, the Sponsor and clinical sites. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

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 be ensured. The study will be monitored by the Sponsor or its designee. Throughout the course of the study, the Study Monitor will make regular scheduled contact with the Investigator including

telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness and adherence to the protocol. As part of the data monitoring, source documents must be made available to the Study Monitor for review. The Study Monitor will also perform IP 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. 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.

15. Confidentiality and Retention of Essential Documentation

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

Clinical sites will maintain adequate study records for 2 years after the marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the drug, until 2 years after the study is discontinued. The Sponsor will be notified prior to the destruction of study records.

16. References

1 Investigator Brochure for Nalbuphine Hydrochloride Extended-Release Tablets. Trevi Therapeutics, Inc.

2 U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, Nalbuphine Hydrochloride (Trade Name: Nubain®). Aug-2013. Access on 12-Dec-2015. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/nalbuphine.pdf.

3 Nubain® Withdrawal. Federal Register. 73(No. 226):70653. November 2008

4 Nubain®, Prescribing Information. Version revised on December 2016. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018024s041lbl.pdf

5 Phan NQ, Lotts T, Antal A, Bernhard JD, Stander S. Systemic kappa opioid receptor agonists in the treatment of chronic pruritus: A literature review. Acta Derm Venereal. 2012;92:555-560.

6 Kumagai H, Saruta T, Matsukawa S, Utsumi J. Prospects for a novel kappa-opioid receptor agonist, TRK-820, in uremic pruritus. In: Yosipovitch G, Greaves MW, Fleischer Jr AB, McGlone F, ed. Itch, Basic Mechanisms and Therapy. New York, NY: Marcel Dekker Inc; 2004, pp 279-286.

7 Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ; American Association for Study of Liver Diseases. Primary biliary cirrhosis. Hepatology. 2009 Jul;50(1):291-308

8 Hawi A, Hunter R, Morford L, Sciascia T. Nalbuphine attenuates itch in the Substance-P induced mouse model. Acta Derm Venereol. 2013; 93:S634.

9 Yaksh TL, Wallace MS. Opioids, analgesia and pain management. In: Goodman & Gilman's The Pharmacologic Basis of Therapeutics. 12th ed. New York, NY: McGraw Hill; 2011; Chapter 18: pp 481-525.

10 Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. Ann Palliat Med. 2012;1(2):121-129.

11 Swegh JM, Logeman C. Management of Common Opioid-Induced Adverse Effects. Am Fam Physician. 2006;74(8):1347-1354.

12 CDER - Pharmacokinetics in Subjects with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling – May 2003.

13 Zetterman RK. Pulmonary Complications of Cirrhosis. Medscape. January 16, 2013.https://www.medscape.com/viewarticle/777530_4

14 Source: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) available for download at: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

17. Appendices

17.1 Appendix 1: Worst Itch Numerical Rating Scale (WI-NRS)

The WI-NRS is comprised of one item and represents the numbers 0 (“no itch”) to 10 (“worst imaginable itch”). Subjects are asked to rate the intensity of their itch using this scale.

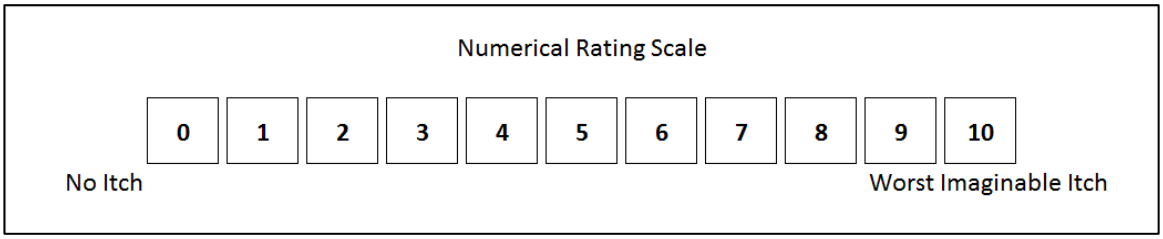
The time needed for WI-NRS completion is about 1 minute.

Subjects will fill 2 separate forms: One in the morning (“Nighttime Itch“) and the second in the evening ("Daytime Itch"). During the screening visit only, the subject will complete both forms at the same time.

A. To Be Completed by the Subject Each Morning:

NIGHTTIME ITCH: Worst itch experienced from bedtime last night to awakening this morning (ie, worst itch last NIGHT).

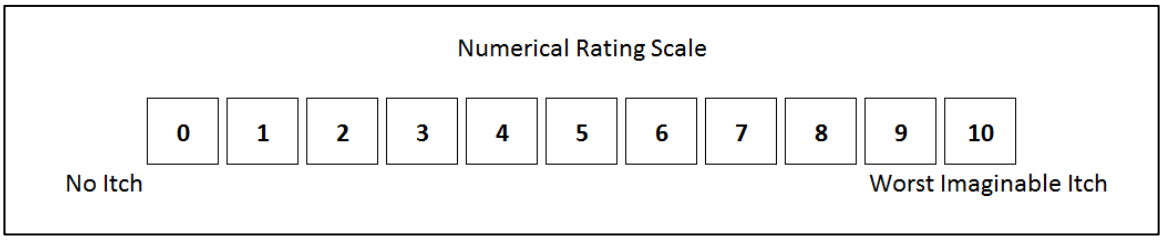
Please indicate the severity of the **WORST ITCHING** you experienced by marking the number that best describes it.



B: To Be Completed by the Subject Each Evening:

DAYTIME ITCH: Worst itch experienced from awakening this morning to now (ie, during the DAYTIME).

Please indicate the severity of the **WORST ITCHING** you experienced by marking the number that best describes it.



17.2 Appendix 2: Summary of Changes (Protocol Amendments 1 & 2)

Amendment 1 Rationale:

Clinical research Protocol TR10 (14 May 2019) was produced for the following purposes:

- To address recommendation from lead Investigator to add a single-ascending-dose portion of the study before the multiple-ascending-dose portion.
- To incorporate suggestions from Investigators based on their experiences with practical implementation of the protocol.
- To clarify study procedures and ambiguities in the previous version.

Amendment 2 Rationale:

Clinical research Protocol TR10 (05 Nov 2019) was produced for the following purposes:

- To clarify that severe hepatic subjects will receive a single 27 mg dose in Part 1 of the study (SAD).
- To incorporate provisions for terminating Part 2 of the study (MAD) PK data demonstrates dose linearity across the dose range in both the mild and moderate hepatic impairment subjects of Part 1 (SAD), such that PK modelling can be predictive of steady state dosing levels.
- To clarify study procedures and ambiguities in the previous version.