CLINICAL TRIAL PROTOCOL: 201

Title:	Dose Ranging Study of Tolperisone in Acute Muscle Spasm of the Back, "STAR Study"
Substance Identifier	Tolperisone hydrochloride
IND number	069169
Protocol Number	201
Sponsor	Neurana Pharmaceuticals, Inc. 4370 La Jolla Village Drive, Suite 860 San Diego, CA 92122
Date of Protocol Amendment #	02 MAY 2019 version 2.0 1
Previous protocol	15Nov2018, version 1.0 (initial protocol)
Sponsor Representative	Tom Wessel, M.D. Chief Medical Officer Neurana Pharmaceuticals, Inc.

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation Guidelines on Good Clinical Practice (ICH E6 GCP) and regulatory requirements as applicable

1. SIGNATURES

1.1. Sponsor's Representatives – Amendment 1

I have read and understand the contents of this clinical protocol 201, the STAR Study, and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and according to Good Clinical Practice (ICH E6 GCP).

Approved by:

Tom Wessel, M.D.

Chief Medical Officer

Neurana Pharmaceuticals, Inc.

SIGNATURE

DATE
(DD/MMM/YYYY)

02 May 2019

Toni Foster

Senior Vice President, Medical Operations

Neurana Pharmaceuticals, Inc.

SIGNATURE

DATE
(DD/MMM/YYYY)

02 MAY 2019

Amy Halseth, PhD

Vice President, Medical Sciences

Neurana Pharmaceuticals, Inc.

SIGNATURE

DATE
(DD/MMM/YYYY)

02 May 2019

1.2. Principal Investigator (PI) – Amendment 1

I have read and understand the contents of this clinical protocol 201, the STAR Study, and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice and applicable regulatory requirements:

PI SIGNATURE

DATE
(DD/MMM/YYYY)

PRINTED NAME

2. PROTOCOL AMENDMENT 1: SUMMARY OF CHANGES

The purpose of this amendment is to include additional subject exclusion criteria and/or further clarify existing exclusion criteria to ensure subjects with cardiovascular risk, any potential seizure risk, and subjects that share the same household, are related, or are a family or friend of any site staff are not enrolled in this study in order to ensure that this Phase 2, dose ranging study is conducted in a generally healthy, low-risk population. Additionally, this protocol was amended to clarify a procedural detail related to supine blood pressure collection and sitting heart rate collection. The locations of changes in this amendment and rationale are detailed in the table below.

SECTION	AMENDMENT 1 Rationale
Cover page	Updated Sponsor address due to office move.
1. Signatures	Updated to include Neurana Medical Operations and Medical Science approval signatures (removed Regulatory).
2. Summary of Changes	To summarize all changes in the amended protocol from previous (initial) version.
3. Protocol Synopsis (Study Background), 7.3.2 Tolperisone Dose Levels	Clarified the typical approved dose range (generally up to 450 mg/day) and that doses of up to 900 mg/day have been used in clinical trials.
3. Protocol Synopsis (Subject Population), 9.2 Exclusion Criteria	Addition of three exclusion criteria (#26, 27, 28) to exclude subjects with any cardiovascular risk, inclusive of cardiovascular disorders, QT prolongation, and defined blood pressure/heart rate criteria. Revised previous exclusion #19 (history of seizure disorder) to also include family history of seizure or head trauma with loss of consciousness. Revised previous exclusion #25 (site staff members and family) to also include friends of site staff as well as subjects living in the same household or who are related to each other. Additions are to ensure subject safety and that this Phase 2 dose-ranging study is conducted in a generally healthy, low-risk subject population.
3. Protocol Synopsis (Safety Assessments), 11.2.1 Clinic Visit 1, 12.9 Vital Signs, 29 Schedule of Procedures (footnote “p”)	Corrected and clarified that all blood pressures collected are supine and standing; heart rate is while sitting after approximately 3 minutes at rest.
5. Abbreviations and Definitions of Terms	Updated table to include millisecond (msec).

SECTION	AMENDMENT 1 Rationale
12.12 Blood Collection for Tolperisone Plasma (PK) Concentrations (Optional)	Increased expected number of PK samples collected during the course of the study from 80 to approximately 120 due to optional sites and subjects participating more in PK collection than originally anticipated.
23. Informed Consent	Added clarifying statement regarding need to reconsent or provide new consent when ICF is revised (after IRB approval).

3. SYNOPSIS

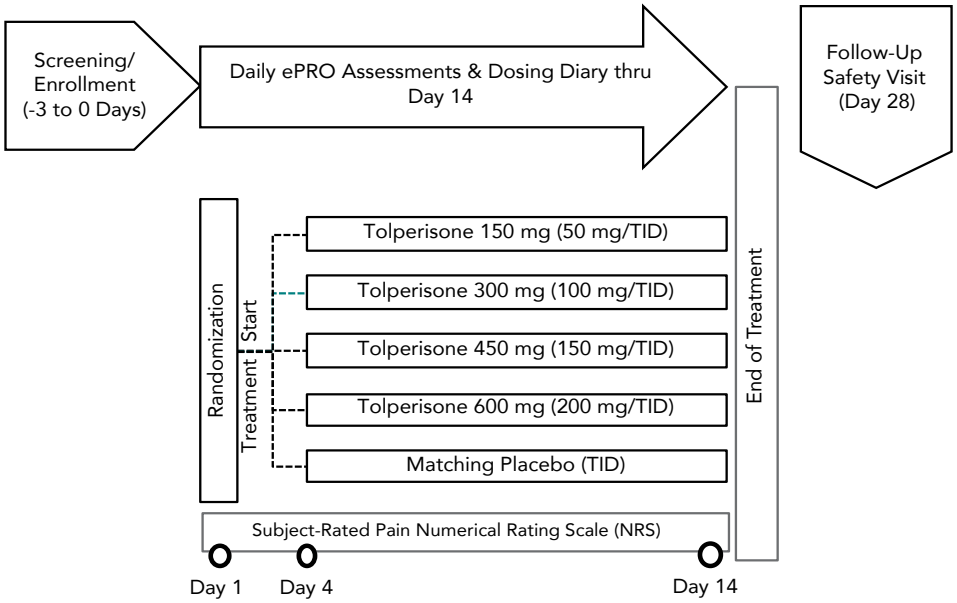
Sponsor: Neurana Pharmaceuticals, Inc.
Name of Finished Product: Tolperisone hydrochloride
Name of Active Ingredient: Tolperisone hydrochloride
Study Title: Dose Ranging Study of Tolperisone in Acute Muscle Spasm of the Back, "STAR Study"
Study Number: 201
Study Phase: Phase 2
Study Background: Tolperisone hydrochloride (tolperisone) is a centrally active muscle relaxant that is an (non-opioid) investigative drug in the US. It has been in therapeutic use elsewhere throughout the world since the 1960s. In many European countries, the highest approved dose is 450 mg/day (150 mg TID), while in some countries (e.g., Switzerland), doses of 600 mg/day are approved. Doses of up to 900 mg/day have been studied in clinical trials of adults with spasticity (see Investigator's Brochure). The Phase 2 study with tolperisone is designed as a dose-ranging study to identify the recommended Phase 3 dose to aid in supporting the proposed claim of relief of back pain due to muscle spasm of acute onset. Doses for the Phase 2 study are based on years of historical use of tolperisone for treatment of painful muscle spasms where the therapeutic dose is 300 to 450 mg per day.
Study Design: This is a double-blind, randomized, placebo-controlled, parallel group study of the efficacy and safety of tolperisone or placebo administered as multiple doses three times a day (TID) in approximately 400 male and female subjects experiencing back pain due to or associated with muscle spasm. The tolperisone groups consist of dose levels of 150, 300, 450, and 600 mg administered TID in doses of 50, 100, 150, or 200 mg for 14 days, with a visit at 28 days as follow-up. Subjects randomized to the placebo group will receive matching placebo tablets TID for 14 days with a follow-up visit at Day 28. Subject participation will be approximately 4 weeks. Subjects will be screened for eligibility for participation in the study at the Screening/Baseline Visit 1 (Day 1) after reviewing and signing the informed consent form. Subjects meeting all inclusion/exclusion criteria will then be randomized into the study (Day 1) and begin dosing this same day. If needed, screening assessments may be completed up to 3 days prior to Day 1 (first dose) as described below. It is highly recommended to complete all screening and baseline assessments on the same day the subject presents at the site due to their acute pain relief needs. However, to accommodate real world logistical issues and time constraints of either the subject or site, the site has the flexibility to allow completion of screening assessments within 3 days (-3 days) prior to Day 1

baseline assessments, deployment of study-provisioned smartphone/download of trial application on subject's smartphone, randomization, and first dose (in that order).

After completing all screening and baseline assessments by/on Day 1, subjects will receive all study drug and rescue medication (acetaminophen 500 mg) and will be instructed to begin taking their study drug that same day. Depending on the time of their clinic visit, they should be instructed to begin dosing with either the midday dose (12-2 pm) or the evening dose (6-8 pm). Subjects will be instructed to continue taking study drug TID through Day 14 and complete dosing dairy and daily electronic Patient-Reported Outcomes (ePRO) assessments.

Subjects will return to the clinic to complete the procedures listed in the Schedule of Procedures on Day 4 (±1 day; Visit 2) and Day 14 (+1 day, End of Treatment [EOT] visit, Visit 3). Subjects must also return to the clinic for a follow-up visit on Day 28 (+3 days, 2-week follow-up visit, Visit 4).

For all subjects, safety laboratory assessments will be performed on Day 1 (Screening/Baseline visit, -3 to 0 days) and Day 14 (Visit 3). In addition, a sample for genotyping will be collected on Day 1 (Screening/Baseline visit). For select sites with additional consenting subjects, pharmacokinetic samples will be collected on Day 4 (Visit 2).



Primary Objective:

- To assess the efficacy of tolperisone daily doses 150, 300, 450, and 600 mg for relief of pain due to acute back muscle spasm.

Secondary Objectives:

- To assess the safety and tolerability of tolperisone in subjects with pain due to acute back spasm.
- To determine the onset of action of tolperisone in treatment of pain due to acute back spasm.
- To determine the duration of pain relief of tolperisone in treatment of pain due to acute back spasm.
- To determine the need for rescue medication when treated with various doses of tolperisone for pain due to acute back spasm.

Endpoints:

Data for primary efficacy analysis will be assessed during the clinic visits by the subject on the study-provisioned tablet provided to each site for use at baseline, and at Days 4 and 14. Additional efficacy endpoints and dosing will be collected daily at specified times from the subjects via a smartphone/trial application for ePROs. At baseline, and at Days 4 and 14, efficacy endpoints will be assessed during the clinic visit on the study-provisioned tablet provided to each site. See the Schedule of Procedures for all assessments to be conducted during the study. For the endpoints below, baseline is defined as the last assessment prior to the first dose of study drug.

Primary Endpoint:

- Subject-rated pain due to acute back spasm using a Numerical Rating Scale (NRS; 0-10 scale, from no pain to worst possible pain) on Day 14 “right now”.

Secondary Endpoints:

Efficacy Endpoints

- Subject-rated pain due to acute back spasm using an NRS (0-10 scale, from no pain to worst possible pain) on Day 4 “right now”.
- Subject rating of medication helpfulness (SRMH; 1-5 scale, from poor to excellent) on Days 4 and 14.
- Subject-rated NRS (0-10 scale) of pain due to acute back spasm on Days 1 to 14; average over past 12 hours.
- Subject-rated NRS (0-10 scale) of pain due to acute back spasm on Days 1 to 14, average over the past hour.
- Subject-rated NRS (0-10 scale) of average pain due to acute back spasm on rest or movement, rated at the end of the day on Days 1 to 14.
- Time to relief of pain due to acute back spasm using subject-rated NRS (0-10 scale) on Days 1 to 14.
- Clinician’s Global Impression of Severity (CGI-S) (1–5 scale) at baseline (Day 1).
- Clinician’s Global Impression of Change (CGI-C) (1-7 scale from worse to marked improvement) on Days 4 and 14.
- Patient’s Global Impression of Severity (PGI-S) (1-5 scale) at baseline (Day 1).
- Patient’s Global Impression of Change (PGI-C) based on subject’s global assessment

(1-7 scale, from worse to marked improvement) on Days 4 and 14.

- Functionality assessment: fingers to floor distance (FFD) is an index of mobility of the spinal cord and is measured as distance in cm when standing with the spinal cord flexed with complete extension of knee joint, on Days 4 and 14 compared to baseline (Day 1) (assessments should be conducted at the same time of day for all three time points).
- Disability assessment at baseline (Day 1), Day 4, and Day 14: Oswestry Disability Index (ODI) questionnaire (10 questions with one answer each for pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling).
- Use of rescue medications (measured daily, assessed as number of rescue tablets administered by the subject via smartphone/use of trial application). Patients are instructed not to take rescue medications on the day of clinic visits on Day 4 and 14.
- Quality of sleep rated by subjects starting at baseline (Day 1) and on Days 2 to 14.
- Visual Analogue Scale (VAS) score for subject-reported sleepiness measured in the clinic on Day 4.

Safety Endpoints

- Clinical evaluations
    - Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
    - Orthostatic effects on blood pressure
    - Physical examinations
    - 12-lead electrocardiograms (ECGs)
- Laboratory tests (blood chemistry, hematology, urinalysis, and urine pregnancy tests for women of childbearing potential)
- Adverse events (AEs)

Planned Number of Subjects and Sites:

Approximately 400 male and female subjects between the ages of 18 and 65 years, with acute and painful muscle spasms of the back at the time of informed consent will be randomized into the study.

The study will be conducted at approximately 45 clinical sites in the USA.

Subject Population:

Inclusion Criteria:

1. Ambulatory male or female, 18 to 65 years of age.
2. Current acute back pain and/or stiffness due to acute and painful muscle spasm starting within 7 days prior to study entry and more than 8 weeks after the last episode of acute back pain.
3. Subjects must have pain of 4 or more on the subject "right now" rating of pain intensity NRS scale of 0 – 10 points at baseline.
4. Must be willing to discontinue all medication used for the treatment of pain or muscle spasm on study entry at Day 1 including but not restricted to:
    a. Ibuprofen (Motrin)
    b. Diclofenac (Voltaren)
    c. Celocoxib (Celebrex)
    d. Naproxen (Aleve)
    e. Tolmetin (Tolectin)
    f. Cyclobenzaprine (Flexeril)
    g. Cyclobenzaprine (Amrix)
    h. Metaxolone (Skelaxin)
    i. Methocarbamol (Robaxin)
    j. Other nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin)
    k. Carisoprodol (Soma)
    l. Tizanidine (Zanaflex, Sirdalud)
5. Pain localized below the neck and above the inferior gluteal folds.
6. Body mass index ranging between 18 and 35 kg/m^2.
7. All subjects must be capable of understanding and complying with the protocol and have signed the informed consent document.
8. Female subjects must have a negative urine pregnancy test at screening, must be postmenopausal (amenorrhea for at least 2 years), surgically sterile, or practicing or agree to practice an effective method of birth control if they are sexually active before study entry, during the study, and 2 weeks after the end of the study by using an acceptable method of contraception. Acceptable methods of birth control must be used for at least 14 days prior to the use of study drug. Acceptable methods of birth control include oral, injectable, subdermal implant, vaginal or patch contraceptives, intrauterine device (IUD; copper or hormonal IUD), or double-barrier method (e.g., condom, diaphragm or cervical cap with spermicidal foam, cream, gel, or suppository).
9. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

1. Unwillingness to stop taking pain or antispasmodic medication other than the study medication (specifically opioid use [e.g., Vicodin], barbiturates, and cannabis).
2. Chronic back pain for the previous 3 months or longer, on more days than not.
3. Radicular pain in the lower extremity (i.e. pain radiating below the knee), sciatica pain down the leg, or pain below the knee (indicating a lumber radiculopathy); radicular pain in the upper extremity, radiating into the forearm or hand (indicating a cervical radiculopathy).
4. Concomitant severe pain in a region other than the back.
5. Spinal surgery within 1 year of study entry.
6. Back pain due to major trauma (e.g., motor vehicle accident, fracture of bone) unless resolved for more than 1 year.
7. Treatment of back pain ongoing with non-pharmacological therapy (e.g. acupuncture, chiropractic adjustment, massage, Transcutaneous Electrical Nerve Stimulation [TENS], physiotherapy).
8. Female subjects who are pregnant or lactating.
9. Subjects who are taking Baclofen (Lioresal, Liofen, Gablofen, etc.) or Botox (onabotulinumtoxin A) for pain.
10. Subjects who test positive for alcohol by breathalyzer test.
11. Known history or symptoms suspicious of:
    a. Spinal fracture within previous 3 years
    b. Osteoporosis with fracture
    c. Cancer except cutaneous cancers (e.g.,melanoma, squamous cell carcinoma)
    d. Constitutional symptoms such as recent unexplained chills or weight loss
    e. Spinal infection
    f. Intravenous drug abuse
    g. Immunosuppression
    h. Cauda equina syndrome
    i. History of chronic severe scoliosis (childhood).
12. Myasthenia gravis.
13. Recent history of severe hepatic insufficiency, i.e., aspartate aminotransferase (AST)/alanine aminotransferase (ALT) above 3 times the upper limit of normal (ULN).
14. Recent history of severe renal insufficiency, i.e., serum creatinine value above 2.5 mg/dL.
15. History or presence of a severe infection, major surgery or trauma, severe metabolic, endocrine or electrolyte disturbances.
16. A major illness, requiring hospitalization during the 3 months before commencement of the screening period.
17. Inflammatory arthritis or other diseases known to cause intermittent or chronic pain.
18. Subjects who have had a recent history (less than 2 years before entering the study) of drug or alcohol abuse, or current positive urine drug screen. Alcohol abuse is defined as current consumption of more than three alcoholic beverages per day.

19. History of seizure disorder other than Infantile Febrile Seizures, family history of seizure, or history of head trauma with loss of consciousness.
20. Disability claim for back pain, or pending legal issue regarding back pain.
21. Subjects who have received treatment with an investigational product/device within 30 days prior to study entry.
22. Subjects who have a history of allergic reaction to tolperisone, eperisone, or other skeletal muscle relaxants, lidocaine, acetaminophen or NSAIDs, or any components of these study medications.
23. Any other condition that, in the opinion of the Investigator, would adversely affect the subject's ability to complete the study or its measures.
24. Subjects who are unwilling to stop taking moderate to potent inhibitors of cytochrome P450 (CYP) isozymes CYP2D6 and CYP2C19, which are likely to cause drug interactions with tolperisone HCl (e.g., medications such as paroxetine and fluvoxamine).
25. Subjects who are a site staff member, relative, or friend of a site staff member or subjects in same household or subjects who are related to each other.
26. Subjects with clinically significant cardiovascular disorders, such as ischemic heart disease, arrhythmias, poorly controlled hypertension, or history of acute myocardial infarction.
27. Subjects with QT interval greater than 480 milliseconds (msec) or greater than 450 msec if accompanied by a partial bundle branch block, or other clinically significant ECG abnormaility at Screening in the judgement of the Investigator.
28. Subjects with diastolic blood pressure less than 50 mmHg or greater than 105 mmHg; sitting heart rate less than 50 beats per minute (bpm) or greater than 110 bpm (after approximately 3 minutes at rest); or heart rate by ECG less than 50 or greater than 110 bpm at Screening.

Restrictions:

Subjects are to abstain from using psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations during their participation in the study.

Subjects are to abstain from using any medication or dietary supplement to promote sleep, including over the counter sleep medications, during their participation in the study.

Subject will abstain from using antihistamine or any other drugs that can cause drowsiness, and will discuss any new prescription with the Investigator.

Other medications that the subject routinely takes will be discussed and reviewed by the PI. All concomitant medication taken during the trial should be recorded with indication, daily dose, and start and stop dates of administration.

Subjects are not allowed to consume alcoholic beverages prior to the study visit on Days 1, 4, and 14. At all other times, alcohol consumption is limited to no more than 2 alcoholic drinks or equivalent (beer [24 ounces or 710 mLs], wine [12 ounces or 355 mLs], or distilled spirits [3 ounces or 89 mLs] per day.

Caffeinated beverages will be permitted to no more than 4 units per day amounts (1 unit = 120

mg caffeine, or about one eight-ounce cup of coffee).

Subjects are to refrain from vigorous physical activity, heat and ice packs, and non-pharmacological therapies (e.g., acupuncture, chiropractic adjustment, massage therapy, TENS, physiotheraphy) during Days 1 to 14.

Test Product, Dose, Mode of Administration, and Dose Regimen:

Tolperisone 50, 100, 150, and 200 mg tablets and matching placebo will be provided for the study by the Sponsor. Dosing will be three times a day, with a single tablet administered at each dose for a daily dose of 150, 300, 450, and 600 mgs per day. Subjects should be instructed to dose at 6-8 am, 12-2 pm, and 6-8 pm daily for 14 days. Subjects will be prompted via reminders on their smartphone/trial application to take their study drug at least 1 hour before and within 2 hours of the morning and evening assessments.

The subjects will be instructed to swallow the tablets whole, with approximately 4-6 ounces of water.

- Subjects in Group A (n=80) will be randomized to receive (1) 50 mg tolperisone tablet, TID for 14 days, for a total daily dose of 150 mg.
- Subjects in Group B (n=80) will be randomized to receive (1) 100 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 300 mg.
- Subjects in Group C (n=80) will be randomized to receive (1) 150 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 450 mg.
- Subjects in Group D (n=80) will be randomized to receive (1) 200 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 600 mg.
- Subjects in Group E (n=80) will be randomized to receive (1) placebo tablet administered TID for 14 days.

Duration of Treatment:

The total duration of study participation will be approximately 4 weeks, including Screening and Follow-up. Study drug treatment will be administered for 14 days.

Safety Assessments:

Adverse Events:

Adverse events will be captured from the time of first dose (Day 1) until the final clinic visit (i.e., Day 28 follow-up visit [Visit 4] or, if applicable, Early Termination (ET) Visit).

Pregnancy Test:

A urine pregnancy test will be performed at Day 1 (Visit 1, Screening/Baseline visit, -3 to 0 days) and at Days 14 (Visit 3) and 28 (Visit 4) for females of childbearing potential. A positive pregnancy test will automatically disqualify the subject from further participation in the trial.

Serum Chemistries, Hematology and Urinalysis:

Blood will be collected for serum chemistries and hematology and urine will be collected for urinalysis at the Screening/Baseline visit, (Day 1, -3 to 0 days) and at the EOT/ET visit (Visit 3, Day 14). A blood sample will be collected at baseline for DNA genotype testing for CYP450 2D6 polymorphism. Subjects will not be informed of the results of the genotype

testing since it is solely for research purposes to determine the phenotype of the enzymes responsible for metabolism of tolperisone. No other DNA testing will be performed.

Vital Signs:

Vital signs, including supine and standing blood pressure, sitting heart rate (after approximately 3 minutes at rest), respiratory rate, and body temperature will be collected at Screening/Baseline (Day 1, -3 to 0 days), and at Days 4, 14, and 28 (All Visits). Weight and height will be measured at Screening/Baseline (Visit 1, Day 1, -3 to 0 days) only.

Electrocardiogram:

Twelve-lead ECG recording will be collected at Screening/Baseline (Day 1, -3 to 0 days) and EOT/ET (Visit 3, Day 14).

Statistical Plan and Methods:

Sample Size:

The sample size for this study was determined from results of two previous studies. The first was a study in subjects with acute upper back, neck, or shoulder spasm and pain, which showed a difference of 0.4 in the average of Day 1 through Day 7 between the placebo and active groups, and standard deviations (SDs) between 1.76 and 1.93 (across placebo and active groups respectively; Collaku, 2017). A sample size of 400 subjects (80 per group) would provide at least 80% power to detect a difference of 0.9 between the placebo and treatment groups in the NRS scale, assuming a two-sample t-test at the 5% level of significance and a pooled SD of 2.0. This sample size assumes an effect size of 0.45 (0.9/2.0 = 0.45, using the formula Effect Size = Mean/SD), which is larger than that seen in the reference study but consistent with that seen in a second study.

A second previous study in subjects with acute musculoskeletal spasm associated with low back pain showed effect sizes ranging from 0.57 to 0.62 for lumbar cinelgasia, based on a treatment difference of 9.6 at Day 3, with SDs of 15.5 (treated group) and 16.7 (placebo group) (Chandanwale, 2011). This study demonstrated effect sizes ranging from 1.1 to 1.6, based on a difference of 24.2 at Day 14 with SDs of 15.1 (treated group) and 23.0 (placebo group). The effect size of the current study is expected to be similar to that in Chandanwale, though sample size estimates have been made more conservative to provide sufficient power to detect smaller differences. Though the primary comparison of interest in this study is Day 14, the study is sufficiently powered to detect a treatment difference at Day 4 based on effect sizes ranging from 0.35 to 0.45.

Statistical Plan and Methods:

Efficacy Analysis:

The primary efficacy endpoint is subject-rated pain "right now" due to acute back spasm using an NRS (0-10) scale, from no pain to worst possible pain for the clinic visit on Day 14. This analysis will be performed using a linear test of trend across doses, using a mixed effect model for repeated measures. The model will include treatment and time as fixed effects, the treatment by time interaction, and the baseline NRS rating as a covariate. Differences in linear trend for each dose level versus placebo will be presented with 95% confidence intervals and associated p-values. The analysis performed for the primary endpoint will be repeated for the NRS at Day 4. Additional analyses for secondary efficacy endpoints will be conducted using repeated measures and analysis of covariance for continuous variables, a Wilcoxon Rank Sum test for categorical variables, and Kaplan-Meier analysis for time to pain relief.

Safety Analysis:

Safety measures will be summarized using descriptive statistics and listed for each subject.

Safety analysis will be based on all subjects randomized who receive at least 1 dose of the study medication. The safety analysis will evaluate AEs and additional safety parameters. The number and percentage of subjects experiencing at least one AE will be summarized by body system, preferred term, and treatment. If appropriate, AEs will also be summarized by intensity and relationship to study drug. Serious adverse events (SAEs), if any, will be tabulated.

Additional safety parameters will be assessed from summaries of physical examinations, 12-lead ECGs and vital signs. The 12-lead ECG results will be categorized as normal, clinically significant abnormal, and not clinically significant abnormal. Hematology, chemistry and urinalysis laboratory test results will be categorized relative to the normal ranges. The changes from baseline for each of these parameters from Screening to EOT will be presented. Complete listings and summary tables for all safety information including AEs, laboratory safety data, ECG, vital signs and physical examination will be included in the study report.

4. TABLE OF CONTENTS

In-text Tables

5. ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
°C	degrees Celsius
CGI-C	Clinician's Global Impression of Change
CGI-S	Clinician's Global Impression of Severity
CI	Confidence interval
cm	Centimeter
CNS	Central nervous system
E	number of events
ECG	Electrocardiogram
eCRF	Electronic report form
ePRO	Electronic patient reported outcomes
EOT	End of Treatment
FDA	Food and Drug Administration
FFD	Fingers to floor distance
g	gram
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HCl	Hydrochloride
IATA	International Air Transport Association
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
kg	Kilogram
kg/m^2	Kilogram per meter squared

Abbreviation	Definition
LC/MS/MS	Liquid chromatography with tandem mass spectrometric detection
LOCF	Last observation carried forward
LOQ	Limit of quantification
LSMD	Least squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
msec	Millisecond
N	Number
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
pH	Potential of hydrogen
PK	Pharmacokinetic(s)
PP	Per-Protocol
PT	Prothrombin time
QA	Quality assurance
QC	Quality control
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SOPs	Standard operating procedures
TEAE	Treatment-emergent adverse event
TENS	Transcutaneous Electrical Nerve Stimulation
TID	Three times a day
TSH	Thyroid stimulating hormone
VAS	Visual Analogue Scale

6. STUDY ADMINISTRATIVE STRUCTURE

6.1. Medical Monitor

Helen Young M.D.
Precision for Medicine ("Precision")
6005 Hidden Valley Road, Suite 170
Carlsbad, CA 92011
Phone: 760.492.5698
Email: helen.young@precisionformedicine.com

6.2. Serious Adverse Event Reporting Contact Information - Sponsor

Serious adverse events (SAEs) should be reported to Precision within 24 hours via the EDC system after Investigator or Investigator's representative becomes aware of their occurrence.

6.3. Central Laboratory

The central laboratory, ACM Global Central Laboratory ("ACM'), for serum chemistry, hematology and urinalysis will be used.

The genotype laboratory, Machaon Diagnostics, (Machaon), testing for CYP450 2D6 polymorphism will be used.

7. BACKGROUND AND RATIONALE FOR THE STUDY

7.1. Introduction

Tolperisone, a centrally acting muscle relaxant, is widely used in Europe, Asia, and South America for the treatment of abnormally increased muscle tone. Tolperisone is an (non-opioid) oral formulation presented as film-coated tablets, and is being developed by Neurana Pharmaceuticals, Inc. for the treatment of symptoms associated with acute and painful back muscle spasms.

The mechanism of action of tolperisone is not fully characterized. The most prominent effect of tolperisone is its inhibitory action on pathways of spinal reflexes. It suppresses the mono and polysynaptic reflex transmission by both pre-synaptic and post-synaptic mechanisms. Tolperisone has sodium (Na^+) and, to a lesser extent, calcium (Ca^{2+}) channel blocking activity. It inhibits, in a relatively selective manner, voltage-gated Na^+ channels. However, even with high tolperisone concentrations, channel blockade remains incomplete and reversible. Although it demonstrated significant binding to a variety of receptors *in vitro*, including the sigma σ1 receptor, the functional effects of tolperisone at these targets is not known. In general, tolperisone causes a frequency-dependent decrease in action potential amplitude of axonal membranes. Excitability is then decreased, especially in cases of pathologically increased reflex activity. It has been proposed that tolperisone may exert a stronger inhibitory effect on sensory axons than motor axons, as indicated by inhibition of nociception-induced reflex muscle contraction and withdrawal in animal models. Vasodilatory properties of tolperisone have been repeatedly described in clinical studies. The mechanism of the blood flow-enhancing effect of

tolperisone has not been investigated systematically; however, $Ca2^{+}$-channel antagonism, or the drug's modest anti-alpha-adrenergic effects may be involved.

Animal toxicity has been extensively profiled and in repeat dosing study in rats with daily doses of 100 mg/kg for 28 days being well-tolerated, and the no observed adverse effect level (NOAEL) considered to be 300 mg/kg/day. No target organs of toxicity were identified. In a three-part, 28-day toxicology study in dogs, the NOAEL was established as 20 mg/kg/day. Chronic oral toxicity studies in the rat (6-month) and dog (9-month) have been reported and have shown NOAELs of 50 and 5 mg/kg/day, respectively.

Tolperisone was nonmutagenic in the Ames test and in two *in vivo* mouse bone marrow micronucleus tests. Tolperisone was, however, clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vitro* mouse lymphoma TK assay. The *in vitro* genotoxic activity was attributed to 4-MMPPO, a degradation product of tolperisone. The ICH guidelines for genotoxic impurities require that levels remain below 10 ppm, equivalent to a daily maximum exposure of 1.5 ug. Based on daily dosing of 450 mg tolperisone, the calculated limit of 4-MMPPO is 3.3 ppm/tablet (corresponding to 1.5 µg per total daily dose). Carcinogenicity studies in rats and mice have shown no risk of carcinogenic potential. Tolperisone had no effect on fertility or in pre- and postnatal reproductive toxicity studies in rats and was non-teratogenic in rats and rabbits.

Pharmacokinetic, toxicokinetic, and absorption, distribution, metabolism, and excretion (ADME) studies with tolperisone show the drug is highly absorbed (> 80%), widely distributed to major organs including the CNS, and excreted primarily by the kidneys. *In vitro* studies have demonstrated that tolperisone is rapidly converted into as many as 25 metabolites by liver microsomes from rat, dog, and human species. *In vivo*, both major human metabolites M4 and M5 are present at high levels in dogs. M4 is also present at high levels in the rat, but M5 is not.

Tolperisone has been evaluated in five clinical studies conducted in healthy volunteers: two pharmacokinetic (PK) studies (Study 01-316-02 and Study 01-286-02); a safety and PK study (AV650-012), a drug-drug interaction study (AV650-019); and a study to assess sedative effects (Study 115). A total of 148 subjects were exposed to tolperisone in these studies. One double-blind, placebo-controlled safety and efficacy study was conducted in patients, Study AV650-018 (IND 74864) in patients with spasticity associated with multiple sclerosis (108 tolperisone during double-blind, 146 tolperisone during open-label).

The pharmacokinetic studies conducted with tolperisone in male and female healthy volunteers have demonstrated a roughly linear relationship between dose and exposure that is more than dose-proportional across the investigated dose range (between 150 to 450 mg administered orally in single doses). Additionally, gender has no apparent influence on tolperisone's pharmacokinetic behavior in human subjects. In contrast, the plasma exposure in rats was approximately twice as high in females as in males for a given dose. Food appears to increase the drug's plasma exposure slightly in humans.

Tolperisone is extensively metabolized *in vivo*, mainly by the liver enzymes CYP2D6 and CYP2C19. Moderate to potent inhibitors of CYP2D6 and CYP2C19 are thus likely to cause drug interactions with tolperisone. In a Phase 1 drug-drug interaction study, the tolperisone plasma exposure increased approximately 2 fold following concomitant administration with paroxetine (a CYP2D6 inhibitor) and increased by 3- to 4- fold following concomitant administration with

fluvoxamine (a CYP2C19 inhibitor). The CYP2D6 genotype (conferring ultra-fast, fast, intermediate and slow metabolizer phenotypes) influences tolperisone bioavailability. In one pharmacokinetic study, subjects who were classified as CYP2D6 intermediate metabolizers had approximately 50% higher exposure to tolperisone following oral dosing than fast metabolizers. Overall, the bioavailability increased with decreasing metabolic activity among the four genotypes.

In a driving simulation, Study 115, assessed the sedation risk tolperisone. Study 115 was a randomized, placebo-controlled, multiple-dose 3-way cross-over study of safety and cognitive effects of multiple doses of 150 mg tolperisone administered three times daily (*TID*) in 35 male and female healthy volunteers. Treatment groups included 450 mg tolperisone (150 mg *TID*), 30 mg cyclobenzaprine (i.e., 10 mg administered three times daily), and placebo. Subjects received 3 days of each treatment. In this study, tolperisone was equivalent to placebo at T_{max}, showed no drug accumulation or sedation effects following multiple doses, and showed no next day residual effects.

The most common AE across all studies was headache, occurring in 14.2% of subjects in healthy volunteer studies and 15.3% of subjects in patient studies. No other AEs occurred in more than 5% of subjects in either group of studies.

This Phase 2 study will explore the efficacy and safety of tolperisone at doses up to 600 mg administered *TID* for 14 days in patients with acute and painful back muscle spasms.

7.2. Drug Profile

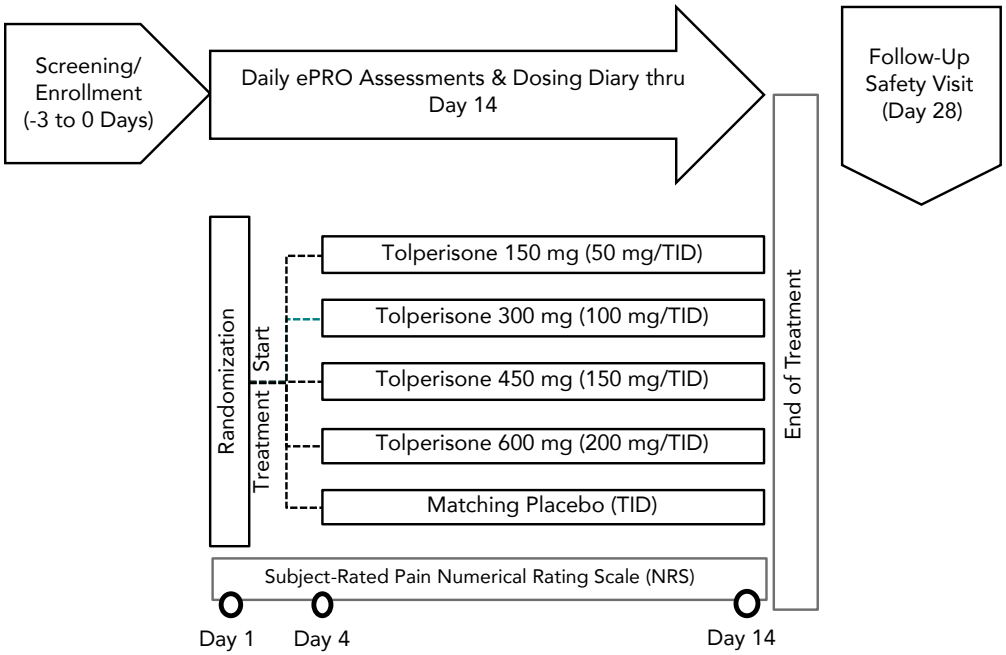
Full details of tolperisone pre-clinical and clinical safety and tolerability data are contained in the Investigator's Brochure.

7.3. Rationale

7.3.1. Study Design

This is a double-blind, randomized, placebo-controlled, parallel group study of the efficacy and safety of tolperisone or placebo administered as multiple doses TID in approximately 400 male and female subjects experiencing back pain due to or associated with muscle spasm. The tolperisone groups consist of dose levels of 150, 300, 450, and 600 mg administered TID in doses of 50, 100, 150, or 200 mg for 14 days, with a visit at 28 days as follow-up. Subjects randomized to the placebo group will receive matching placebo tablets TID for 14 days with a follow-up visit at Day 28. Subject participation will be approximately 4 weeks.

The study design provides unbiased (through randomization) observations of the efficacy and safety of tolperisone over a range of doses (150 to 600 mg/day) administered for two weeks, as appropriate for acute back spasms and based on prior studies.



See the Schedule of Procedures in Table 2.

7.3.2. Tolperisone Dose Levels

Tolperisone 50, 100, 150, and 200 mg tablets and matching placebo will be provided for the study by the Sponsor. Dosing will be three times a day/TID, with a single tablet administered at each dose for a total daily dose of 150, 300, 450, and 600 mg per day. Subjects should be instructed to dose at 6-8 am, 12-2 pm, and 6-8 pm daily for 14 days. Subjects who are experiencing significant pain following randomization will be allowed to take a single tablet of acetaminophen 500 mg up to three (3) times per day as a rescue medication. Rescue medication will be captured on the study-provisioned smartphone/trial application. **Subjects are not to take rescue medication on clinic visit days, Day 4 (Visit 2) and Day 14 (Visit 3).**

Doses for the Phase 2 study are based on many years of historical use of tolperisone for treatment of painful muscle spasms where the therapeutic dose is generally 300 to 450 mg per day. In addition, the total daily dose of 600 mg was selected to explore a higher dose range to optimize efficacy without impacting safety. A previous clinical study (AV650-018) conducted in subjects with multiple scelerosis-associated spasticity using doses up to 900 mg/day for up to 48 weeks did not show an increase in adverse events.

See Investigator's Brochure for further information.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1. Primary Objective

The primary objective of this study is to assess the efficacy of tolperisone daily doses 150, 300, 450, and 600 mg for relief of pain due to acute back muscle spasm.

8.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of tolperisone in subjects with pain due to acute back spasm.
- To determine the onset of action of tolperisone in treatment of pain due to acute back spasm.
- To determine the duration of pain relief of tolperisone in treatment of pain due to acute back spasm.
- To determine the need for rescue medication when treated with various doses of tolperisone for pain due to acute back spasm.

8.3. Primary Endpoint

The primary endpoint for this study is subject-rated pain due to acute back spasm using a Numerical Rating Scale (NRS; 0-10 scale, from no pain to worst possible pain) on Day 14 ("right now" time point).

8.4. Secondary Endpoints

The secondary endpoints for this study include the following. For these endpoints, baseline is defined as the last assessment prior to the first dose of study drug.

Efficacy Endpoints:

- Subject-rated pain due to acute back spasm using an NRS (0-10 scale, from no pain to worst possible pain) on Day 4 "right now".
- Subject rating of medication helpfulness (SRMH; 1-5 scale, from poor to excellent) on Days 4 and 14.
- Subject-rated NRS (0-10 scale) of pain due to acute back spasm on Days 1 to 14; average over the past 12 hours.
- Subject-rated NRS (0-10 scale) of pain due to acute back spasm on Days 1 to 14; average over the past hour.
- Subject-rated NRS (0-10 scale) of average pain due to acute back spasm on rest or movement, rated at the end of the day on Days 1 to 14.
- Time to relief of pain from baseline due to acute back spasm using subject-rated NRS (0-10 scale) on Days 1 to 14.

- Clinician's Global Impression of Severity (CGI-S) (1–5 scale) at baseline (Day 1).
- Clinician's Global Impression of Change (CGI-C) 1-7 scale from worse to marked improvement) on Days 4 and 14.
- Patient's Global Impression of Severity (PGI-S) (1-5 scale) at baseline (Day 1).
- Patient's Global Impression of Change (PGI-C) based on subject's global assessment (1-7 scale, from worse to marked improvement) on Days 4 and 14.
- Functionality assessment: fingers to floor distance (FFD) is an index of mobility of the spinal cord and is measured as distance in cm when standing with the spinal cord flexed with complete extension of knee joint, on Days 4 and 14 compared to baseline (Day 1) (assessments should be conducted at the same time of day for all three time points).
- Disability assessment at baseline (Day 1), Day 4, and Day 14:
  - Oswestry Pain and Disability (ODI) questionnaire (10 questions with one answer each for pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling).
- Use of rescue medications (measured daily, assessed as number of rescue tablets administered by the subject via smartphone/use of trial application). Patients are instructed not to take rescue medications on the day of clinic visits on Day 4 and 14.
- Quality of sleep rated by subjects starting at baseline (Day 1) and on Days 2 to 14.
- Visual Analogue Scale (VAS) score for subject-reported sleepiness measured in the clinic on at Day 4.

Safety Endpoints

- Clinical evaluations include:
  - Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
  - Orthostatic effects on blood pressure
  - Physical examinations
  - 12-lead electrocardiograms (ECGs)
- Laboratory safety tests include blood chemistry, hematology, urinalysis, and urine pregnancy tests for women of childbearing potential
- Adverse events (AEs)

9. SUBJECT DEFINITION

A sufficient number of subjects will be screened to ensure the enrollment of approximately 400 subjects. Individuals are eligible for this study if they meet all inclusion and no exclusion criteria. The criteria below will be assessed at the Screening/Baseline visit.

9.1. Inclusion Criteria

1. Ambulatory male or female, 18 to 65 years of age.
2. Current acute back pain and/or stiffness due to acute and painful muscle spasm starting within 7 days prior to study entry and more than 8 weeks after the last episode of acute back pain.
3. Subjects must have pain of 4 or more on the subject "right now" rating of pain intensity NRS scale of 0 – 10 points at baseline.
4. Must be willing to discontinue all medication used for the treatment of pain or muscle spasm on study entry at Day 1 including but not restricted to:
    a. Ibuprofen (Motrin)
    b. Diclofenac (Voltaren)
    c. Celocoxib (Celebrex)
    d. Naproxen (Aleve)
    e. Tolmetin (Tolectin)
    f. Cyclobenzaprine (Flexeril)
    g. Cyclobenzaprine (Amrix)
    h. Metaxolone (Skelaxin)
    i. Methocarbamol (Robaxin)
    j. Other nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin)
    k. Carisoprodol (Soma)
    l. Tizanidine (Zanaflex, Sirdalud)
5. Pain localized below the neck and above the inferior gluteal folds.
6. Body mass index ranging between 18 and 35 kg/m^2.
7. All subjects must be capable of understanding and complying with the protocol and have signed the informed consent document.
8. Female subjects must have a negative urine pregnancy test at screening, must be postmenopausal (amenorrhea for at least 2 years), surgically sterile, or practicing or agree to practice an effective method of birth control if they are sexually active before study entry, during the study and for 2 weeks after the end of the study by using an acceptable method of contraception. Acceptable methods of birth control must be used for at least 14 days prior to the use of study drug. Acceptable methods of birth control include oral, injectable, subdermal implant, vaginal or patch contraceptives, intrauterine device (IUD; copper or hormonal IUD), or double-barrier method (e.g., condom, diaphragm or cervical cap with spermicidal foam, cream, gel, or suppository).
9. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

9.2. Exclusion Criteria

1. Unwillingness to stop taking pain or antispasmodic medication other than the study medication (specifically opioid use [e.g., Vicodin], barbiturates, and cannabis).
2. Chronic pain for the previous 3 months or longer, on more days than not.
3. Radicular pain in the lower extremity (i.e. pain radiating below the knee), sciatica pain down the leg, or pain below the knee (indicating a lumber radiculopathy); radicular pain in the upper extremity, radiating into the forearm or hand (indicating a cervical radiculopathy).
4. Concomitant severe pain in a region other than the back.
5. Spinal surgery within 1 year of study entry.
6. Back pain due to major trauma (e.g., motor vehicle accident, fracture of bone) unless resolved for more than 1 year.
7. Treatment of back pain ongoing with non-pharmacological therapy (e.g., acupuncture, chiropractic adjustment, massage, Transcutaneous Electrical Nerve Stimulation [TENS], physiotherapy).
8. Female subjects who are pregnant or lactating.
9. Subjects who are taking Baclofen (Lioresal, Liofen, Gablofen, etc.) or Botox (onabotulinumtoxin A) for pain.
10. Subjects who test positive for alcohol by breathalyzer test.
11. Known history or symptoms suspicious of:
    a. Spinal fracture within previous 3 years
    b. Osteoporosis with fracture
    c. Cancer except cutaneous cancers (e.g., melanoma, squamous cell carcinoma)
    d. Constitutional symptoms such as recent unexplained chills or weight loss
    e. Spinal infection
    f. Intravenous drug abuse
    g. Immunosuppression
    h. Cauda equine syndrome
    i. History of chronic severe scoliosis (childhood)
12. Myasthenia gravis.
13. Recent history of severe hepatic insufficiency, i.e., aspartate aminotransferase (AST)/alanine aminotransferase (ALT) above 3 times the upper limit of normal (ULN).
14. Recent history of severe renal insufficiency, i.e., serum creatinine value above 2.5 mg/dL.
15. History or presence of a severe infection, major surgery or trauma, severe metabolic, endocrine or electrolyte disturbances.
16. A major illness, requiring hospitalization during the 3 months before commencement of the screening period.
17. Inflammatory arthritis, or other diseases known to cause intermittent or chronic pain.

18. Subjects who have had a recent history (less than 2 years before entering the study) of drug or alcohol abuse, or current positive urine drug screen. Alcohol abuse is defined as current consumption of more than three alcoholic beverages per day.
19. History of seizure disorder other than Infantile Febrile Seizures, family history of seizure, or history of head trauma with loss of consciousness.
20. Disability claim for back pain, or pending legal issue regarding back pain.
21. Subjects who have received treatment with an investigational product/device within 30 days prior to study entry.
22. Subjects who have a history of allergic reaction to tolperisone, eperisone, or other skeletal muscle relaxants, lidocaine, acetaminophen or NSAIDs or any components of these study medications.
23. Any other condition that, in the opinion of the Investigator, would adversely affect the subject's ability to complete the study or its measures.
24. Subjects who are unwilling to stop taking moderate to potent inhibitors of cytochrome P450 (CYP) isozymes CYP2D6 and CYP2C19, which are likely to cause drug interactions with tolperisone HCl (e.g., medications such as paroxetine and fluvoxamine).
25. Subjects who are a site staff member, relative, or friend of a site staff member or subjects in same household or who are related to each other.
26. Subjects with clinically significant cardiovascular disorders, such as ischemic heart disease, arrhythmias, poorly controlled hypertension, or history of acute myocardial infarction.
27. Subjects with QT interval greater than 480 milliseconds (msec) or greater than 450 msec if accompanied by a partial bundle branch block, or other clinically significant ECG abnormaility at Screening in the judgement of the Investigator.
28. Subjects with diastolic blood pressure less than 50 mmHg or greater than 105 mmHg; sitting heart rate less than 50 beats per minute (bpm) or greater than 110 bpm (after approximately 3 minutes at rest); or heart rate by ECG less than 50 or greater than 110 bpm at Screening.

9.3. Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time. Reasons that subjects may discontinue or be withdrawn from the study may include, but are not limited to:

- AEs
- Subject request
- Investigator decision
- Protocol non-compliance
- Study termination by the Sponsor or Institutional Review Board (IRB).

If a subject is withdrawn from the study, all efforts will be made to complete the Visit 3 (EOT) procedures at an Early Termination visit (see Section 11.2.4). All information, including the reason for withdrawal, should be reported on the applicable pages of the electronic case report form (eCRF).

For subjects who are lost to follow-up, three documented attempts will be made to contact the subject for follow-up information, including reason for discontinuation and follow-up of AEs.

Subjects who withdraw from the study will not be replaced.

10. STUDY DESIGN

10.1. Summary of Study Design

This is a double-blind, randomized, placebo-controlled, parallel group study of the efficacy and safety of multiple doses of tolperisone administered TID in approximately 400 male and female subjects experiencing back pain due to or associated with muscle spasm. The tolperisone groups consist of dose levels of 150, 300, 450, and 600 mg administered TID in doses of 50, 100, 150, or 200 mg for 14 days, with a visit at 28 days as follow-up. Subjects randomized to the placebo group will receive matching placebo tablets TID for 14 days. Subject participation will be approximately 4 weeks.

Subjects will be screened for eligibility for participation in the study at Screening/Baseline Visit 1 (Day 1) after reviewing and signing the informed consent form. Subjects meeting all inclusion/exclusion criteria will then be randomized into the study (Day 1) and begin dosing this same day. If needed, screening assessments may be completed up to 3 days prior to Day 1 (first dose) as described below.

It is highly recommended to complete all screening and baseline assessments on the same day the subject presents at the site due to their acute pain relief needs. However, to accommodate real world logistical issues and time constraints of either the subject or site, the site has the flexibility to allow completion of screening assessments within 3 days (-3 days) prior to Day 1 baseline assessments, deployment of study-provisioned smartphone/download of trial application on subject's smartphone, randomization, and first dose (in that order).

After completing all screening and baseline assessments by/on Day 1, subjects will receive all study drug and rescue medication (acetaminophen 500 mg) and will be instructed to begin taking their study drug that same day. Depending on the time of their clinic visit, they should be instructed to begin dosing with either the midday dose (12-2 pm) or the evening dose (6-8 pm). Subjects will be instructed to continue taking study drug TID through Day 14 and complete dosing diary and daily ePRO assessments.

Subjects will return to the clinic to complete the procedures listed in the Schedule of Procedures on Day 4 (±1 day; Visit 2) and Day 14 (+1 day, End of Treatment [EOT] visit, Visit 3). Subjects must also return to the clinic for a follow-up visit on Day 28 (+3 days, 2-week follow-up visit, Visit 4).

For all subjects, safety laboratory assessments will be performed on Day 1 (Screening/Baseline visit, -3 to 0 days) and Day 14 (Visit 3). In addition, a sample for genotyping will be collected on Day 1 (Screening/Baseline visit). For select sites with additional consenting subjects, pharmacokinetic samples will be collected on Day 4 (Visit 2).

Please refer to Schedule of Procedures, Table 2.

10.2. Subject Assignment

Randomization will occur only after the subject has been determined to be eligible for study participation based on the inclusion and exclusion criteria. Subjects will be randomly assigned to one of the following five treatment groups in a 1:1:1:1:1 ratio: tolperisone 50 mg TID (150 mg/day), tolperisone 100 mg TID (300 mg/day), tolperisone 150 mg TID (450 mg/day), tolperisone 200 mg TID (600 mg/day), matching placebo TID. Prior to each eligible subject's participation, the next unique, sequentially available randomization number will be assigned to the subject using an interactive web response system.

10.2.1. Unblinding

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat a medical emergency of the subject. The decision to break the blind in emergency situations remains the responsibility of the Investigator, which will not be delayed or refused by the Sponsor. However, the Investigator should contact the Medical Monitor and Sponsor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject. If it is medically imperative to know what study drug the subject is receiving, study drug should be temporarily discontinued if, in the opinion of the Investigator, continuing study drug can negatively affect the outcome of the subject's treatment.

The Principal Investigator has the ability to unblind single subjects within EDC system for emergency unblinding purposes. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the patient's source documentation.

10.3. Treatment Compliance

Each subject will be instructed on the importance of returning his or her study drug and rescue medication at each applicable study visit (i.e., Visits 2 and 3). The subject will also be asked to enter daily dosing information on the smartphone/trial application and study staff will review this information with the subject at each site visit to assess the subject's compliance with the study drug and rescue medication. Any missed doses will be noted by the subject on the smartphone/trial application.

11. DAILY STUDY ACTIVITIES

A complete Schedule of Procedures can be found in Table 2.

11.1. Screening

The Screening/Baseline visit (Visit 1) will include procedures as listed in Table 2.

The informed consent document will be discussed with each potential participant, and each individual will sign an informed consent document for the study prior to any study-specific procedures being performed. A positive test result for pregnancy, urine drug or alcohol breathalyzer will end the screening process.

11.2. Study Periods

See Table 2 in Section 29 for the schedule of procedures and assessments across the time points for the study.

11.2.1. Clinic Visit 1: Day 1 (Screening/Baseline) and up to Day -3 (Additional Screening Days, If Needed)

Subjects will visit the clinic site for their Screening/Baseline visit (Visit 1, -3 to 0 days) and undergo screening processes for entry into the study. Subjects who meet the inclusion and no exclusion criteria will be entered into the study.

The following screening assessments will be conducted by the Investigator or designee prior to subject enrollment. If needed, the following screening assessments may be completed within 3 days prior to Day 1 (-3 to 0 days):

- Informed consent to be signed
- A urine pregnancy test for all females of childbearing potential
- Medical history and demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and smoking habits
- Physical examination
- Neurological examination
- The alcohol breathalyzer and urine drug screen
- Laboratory tests (serum chemistry, hematology, and urinalysis)
    - blood sample for DNA genotyping for CYP450 2D6 polymorphism would be collected at same time of other required blood draw
- Vital signs (supine and standing blood pressure [including orthostatic pressure]), sitting heart rate (after approximately 3 minutes at rest), respiratory rate, and body temperature,)
- A 12-lead ECG
- Prior and/or concomitant medications during the study will be recorded, as well as those that qualify as rescue medications (see Section 12.8)
- Inclusion/exclusion criteria to be reviewed for qualification of the subject's enrollment into the study

The following baseline assessments will be conducted by the Investigator or designee prior to dosing on Day 1. If any screening assessments were completed prior to Day 1, inclusion/exclusion criteria are to be re-reviewed for qualification of the subject's enrollment into the study:

- Baseline assessments for study efficacy endpoints:
    - Subject rating of pain "right now" (NRS), must be 4 or greater

- Global severity of pain assessment by the physician and the subject on a scale of 1-5, with 1=none, 2=mild, 3=moderate, 4=severe, 5=very severe
- Functionality assessment:
  - Fingers to Floor Distance (FFD)
- Disability assessment:
  - Oswestry Pain and Disability Index (ODI) via the site study-provisioned tablet
- Deploy subject smartphone/use of trial application to subject
- Quality of sleep via the subject smartphone/use of trial application
- Randomization
- Dispense study drug (for 14 days of dosing) and rescue medication; sufficient for use by subjects for the entire duration of the study
- AEs occurring after the first dose of study medication will be reported. Any concurrent medication use will be recorded.

Subjects will receive all study drug and rescue medication on Day 1. Subjects will begin taking their study drug that same day. Depending on the time of their clinic visit, they should be instructed to begin dosing with either the midday dose (12-2 pm) or the evening dose (6-8 pm).

Subjects will be provided a smartphone/use of trial application on Day 1, just prior to randomization. Subjects will be instructed on how to perform the assessments to be conducted by the subject at home/away from clinic and how to record the results on the smartphone/trial application.

Subjects will be instructed to return to the clinic on Day 4 (Visit 2) and on Day 14 (EOT visit, Visit 3) and to bring all study drug and rescue medication with them as well as smartphone device. Subjects must also return to the clinic for a safety follow-up visit on Day 28 (2-week follow-up visit, Visit 4).

Subjects will be asked and reminded not to consume alcoholic beverages prior to their study visit on Days 1, 4, and 14 and to restrict their consumption during the study duration. At all other times, alcohol consumption is limited to no more than 2 alcoholic drinks or equivalent (beer [24 ounces or 710 mLs], wine [12 ounces or 355 mLs], or distilled spirits [3 ounces or 89 mLs]) per day.

Subjects will be reminded to restrict their consumption of caffeinated beverages to no more than 4 units per day amounts (1 unit =120 mg caffeine or about one eight-ounce cup of coffee).

Subjects will be reminded to refrain from vigorous physical activity, heat and ice packs, and non-pharmacological therapies (e.g., acupuncture, chiropractic adjustment, massage therapy, TENS, physiotherapy) during Days 1 to 14.

11.2.2. Outpatient Assessments: Days 1-14

The following subject assessments and procedures will be conducted by the subjects at home/away from the clinic in the morning, at midday, and in the evening. For Days 1, 4 and 14, these assessments are in addition to the clinic visit assessments. Throughout the study, site staff

will be instructed to review the ePRO/eDiary administration portal to ensure subject compliance with completion of the following ePRO assessments, study drug dosing, and use of rescue medications.

Morning: Subjects should take the first daily dose of study drug (am dose; 6-8 am) with approximately 4-6 ounces of water, and then perform the following assessments between 8-10 am:

- Subject rating of pain (NRS) for the average level of pain over the last 12 hours
- Subject rating of pain (NRS) for the average level of pain over the past 1 hour
- Quality of sleep

Midday: Subjects should take the second daily dose of study drug (midday dose; 12-2 pm) with approximately 4-6 ounces of water.

Evening: Subjects should take the third daily dose of study drug (evening dose; 6-8 pm) with approximately 4-6 ounces of water, and perform the following assessments between 8-10 pm:

- Subject rating of pain (NRS) for the average level of pain over the last 12 hours
- Subject rating of pain (NRS) average pain over the past 1 hour
- Rating of pain using NRS, for average pain at rest or movement
- Daily activities (sedentary, walking activities, etc.) to be recorded by the subject at the end of the day
- Use of any rescue medications throughout the day

11.2.3. Clinic Visit 2: Day 4 (±1 Day)

On Day 4, subjects return to the clinic to undergo the following assessments:

- Alcohol breathalyzer and urine drug screen. A positive test result for urine drug or alcohol breathalyzer at any time during the study will terminate the subject from further participation in the study.
- Abbreviated physical examination
- Neurological examination
- Vital signs
- Document AEs
- Subject rating of pain (NRS) “right now” via the site study-provisioned tablet
- Subject rating of medication helpfulness via the site study-provisioned tablet
- Global clinical impression of improvement by the physician (CGI-C) via the site study provisioned tablet

- Global impression of improvement by the subject (PGI-C) via the site study-provisioned tablet
- Functionality assessment:
  - Fingers to Floor Distance (FFD)
- VAS via the site study-provisioned tablet
- Disability assessment at Day 4:
  - Oswestry Disability Index (ODI) via the site study provisioned tablet
- For the select group of sites and subjects who will undergo PK assessments, a single blood sample will be drawn on Day 4 after all other assessments have been completed.
- Any changes or additions to prior concurrent medication use will be recorded. Confirm that no rescue medications were taken on Day 4 (Visit 2).
- Site staff to review returned study drug and rescue medication against the eDiary dosing information to evaluate compliance.

11.2.4. Clinic Visit 3: Day 14 (+ 1 Day, End of Treatment/Early Termination)

On Day 14, subjects return to the clinic to undergo the following assessments:

- Abbreviated physical examination
- Neurological examination
- Vital signs
- Document AEs
- Subject rating of pain (NRS) “right now” via the site study-provisioned tablet
- Subject rating of medication helpfulness via the site study-provisioned tablet
- Global clinical impression of improvement by the physician (CGI-C) via the site study-provisioned tablet
- Global impression of improvement by the subject (PGI-C) via the site study-provisioned tablet
- Functionality assessment:
  - Fingers to Floor Distance (FFD)
- Alcohol breathalyzer and urine drug screen
- Disability assessment:
  - Oswestry Disability Index (ODI) via the site study-provisioned tablet
- Urine pregnancy test for all females of childbearing potential
- Laboratory evaluations

- 12-Lead ECG
- Any changes or additions to prior concurrent medication use will be recorded. Confirm that no rescue medications were taken on Day 14 (Visit 3).
- Site staff to review returned study drug and rescue medication against the eDiary dosing information to evaluate compliance.
- Site staff to collect smartphone, if provisioned

In the event that a subject discontinues or is withdrawn from the study early, the Day 14/EOT assessments should be completed at an Early Termination visit.

11.2.5. Clinic Visit 4: Day 28 (+3 Days, Follow-Up Visit)

Prior to discharge from the clinical study, the following procedures should be performed:

- AEs will be recorded.
- Any changes or additions to prior concurrent medication use will be recorded.
- Vital signs
- Abbreviated physical examination
- Urine pregnancy test for all females of childbearing potential

12. STUDY PROCEDURES

12.1. Numerical Rating Scale to Assess Subject's Pain Level due to Muscle Spasm

The NRS is a scale of 0 to 10 (0=no pain, 10=worst possible pain). Subjects will use the NRS to evaluate their pain ("right now") on Day 1 (baseline assessment) and on Days 4 (Visit 2) and 14 (Visit 3) during the clinic visit via the site study-provisioned tablet.

In addition, the NRS scale will be used by subjects for pain assessment at rest and upon movement in the evening (8–10 pm) on Days 1 to 14 recorded via the subject smartphone/use of trial application. Subjects will also be asked to rate their average pain level (NRS scale) over the past hour and the past 12 hours in the morning (8-10 am) and evening (8-10 pm) via the subject smartphone/use of trial application.

12.2. Subject Rated Medication Helpfulness (SRMH)

The SRMH is a categorical scale for subjects to assess medication helpfulness, where 1=poor, 2=fair, 3=good, 4=very good, and 5=excellent. Medication helpfulness will be administered via the site study-provisioned tablet ePRO during the clinic visit on Days 4 and 14.

12.3. Clinical Global Assessments (Clinician's Global Impression of Severity, CGI-S and Clinician's Global Impression of Change, CGI-C)

On Day 1, the CGI-S will be conducted by the physician using a 1-5 scale (1=no pain, 2=mild pain, 3=moderate pain, 4=severe pain, and 5=worst possible pain).

The CGI-C will be conducted by the physician on Days 4 (Visit 2) and 14 (Visit 3) to assess global improvement using a 7-point scale (1=Very Much Worse, 2=Much Worse, 3=Minimally Worse, 4=No Change, 5=Minimally Improved, 6=Much Improved, and 7=Very Much Improved).

The Investigator/evaluator will be provided with training to ensure consistent CGI-S and CGI-C assessments across investigational centers. To the greatest extent possible, the assessments for a particular subject should be performed by the same rater/evaluator at all study visits.

12.4. Subject-Rated Global Assessments (Patient's Global Impression of Severity, PGI-S and Patient's Global Impression of Change, PGI-C)

On Day 1 (Screening/Baseline visit), the PGI-S will be administered to assess the subject's impression of severity of pain using a 1-5 scale (1=no pain, 2=mild pain, 3= moderate pain, 4=severe pain, and 5=worst possible pain).

The PGI-C will be administered on Days 4 (Visit 2) and 14 (Visit 3) to assess the subject's global impression of improvement using a 7-point scale (1=Very Much Worse, 2=Much Worse, 3=Minimally Worse, 4=No Change, 5=Minimally Improved, 6=Much Improved, and 7=Very Much Improved).

12.5. Visual Analogue Scale (VAS)

The VAS for subject-reported sleepiness will be measured in the clinic on Day 4 (Visit 2) using a visual analog scale from 0 = alert, wide awake; to 10 = very sleepy, difficulty remaining awake.

12.6. Functionality Assessment

On Day 1 (Screening/Baseline visit) and on Days 4 (Visit 2) and 14 (Visit 3), the subject's functionality based on the Fingers to Floor Distance (FFD) test will be assessed at the clinical site. FFD is measured as the distance in cm from the patients right long finger to the floor when standing with the spinal cord flexed with complete extension of knee joint. The FFD should be conducted at the same time of day for each test on Days 1, 4, and 14. The Investigator/evaluator will be provided with training to ensure consistent FFD assessments across investigational centers. To the greatest extent possible, the assessments for a particular subject should be performed by the same evaluator at all study visits.

12.7. Oswestry Disability Index (ODI)

Disability will be assessed by the subject using the Oswestry Disability Index, which is based on 10 questions with one answer each for: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling). This will be conducted on

Day 1 (Screening/Baseline visit) and on Days 4 (Visit 2) and 14 (Visit 3) via the site study-provisioned tablet .

12.8. Use of Rescue Medications

Concomitant use of rescue analgesia used during the study will be recorded as concomitant medications on the eCRF (see Section 14 for allowed and disallowed medications during the study) and will be analyzed at the time of report following dosing of study drug through Visit 4 (Day 28). Subjects will receive acetaminophen (500 mg tablets) (Tylenol) for use as rescue medication if needed for pain during the study. Use of rescue medication will be recorded daily via smartphone/use of trial application . Subjects are instructed to not take any rescue medications on the day of the clinic visits, Days 4 (Visit 2) and 14 (Visit 3).

12.9. Vital Signs

Vital signs will include the measurement of supine and standing blood pressure, orthostatic assessments, sitting heart rate (after approximately 3 minutes at rest), respiratory rate, and body temperature. Vital signs will be measured on Day 1 (Screening/Baseline visit) and on Days 4, 14, and 28 (All Visits). Weight and height will be measured at Screening/Baseline only.

12.10. 12-Lead Electrocardiograms

Standard 12-lead ECGs will be administered at the clinic on Day 1 (Screening/Baseline visit) and on Day 14 (Visit 3). Normal, abnormal (not clinically significant or clinically significant) are collected.

12.11. Clinical Laboratory Assessments

A certified laboratory will be used as a central laboratory to perform all routine hematology, clinical chemistry, and urinalysis assessments. Planned laboratory analyses include:

Category	Test Name
Hematology	Hemoglobin Hematocrit Platelets Prothrombin Time (PT)[a] Red blood cells White blood cells with differential (absolute)
Chemistry	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Blood urea nitrogen (BUN) Creatinine Gamma glutamyltransferase (GGT) Glucose Potassium Sodium Total and direct bilirubin Thyroid stimulating hormone (TSH)[a]
Urinalysis	Bilirubin Occult blood Glucose Ketones Leukocytes Nitrite pH Protein Specific gravity Urobilinogen
Other	Urine drug and alcohol breathalyzer[b,c] Urine pregnancy[d]

Note: The complete panel of safety labs (other than where footnoted) will be completed on Day 1 (Screening/Baseline visit) and Day 14.

[a] Screening only.
[b] Day 1 (Screening/Baseline), Day 4, and Day 14 (End of Treatment).
[c] Includes testing for amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates – ethanol will be determined by breathalyzer.
[d] Urine pregnancy test at Days 1, 14, and 28 for females of childbearing potential.

12.12. Blood Collection for Tolperisone Plasma (PK) Concentrations (Optional)

In a subset of subjects (approximately 120) at select sites, blood samples for the determination of plasma tolperisone concentrations will be drawn on Day 4 (Visit 2) after completion of all study assessments. The results from the analyses will be used for determination of population PK of tolperisone.

Plasma samples will be analyzed for tolperisone using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method (limit of quantification [LOQ]: 1 ng/mL).

Results will not be included in the Clinical Study Report.

12.12.1. Sample Storage and Shipment

The samples will be frozen as soon as possible (within 4 hours) of collection and stored frozen at –20°C until time of shipment to the central laboratory (ACM). All samples will be shipped frozen with sufficient dry ice to maintain frozen conditions for at least 72 hours at times arranged between the study site and the laboratory. Please refer to the ACM Laboratory Manual for detailed instructions.

12.13. DNA Genotype

A blood sample will be collected at baseline for DNA genotype screening for CYP450 2D6 polymorphism. No other DNA testing will be performed. Samples will be shipped to the genotyping laboratory (Machaon) and stored until ready for use by the Sponsor. Samples will be labeled with a unique sample identification label and will not include any protected subject health information. Any results from future testing will not be provided to the site or subjects. Samples will be stored in a secure, limited access facility indefinitely, or disposed. Samples will be inventoried and traceability will be maintained as to where samples are stored and how samples are used (assay validation, or research and development). Please refer to the Machaon Laboratory Manual for detailed instructions.

12.14. Blood Collection Volume for the Study

Up to 48 mL of blood will be collected for screening and EOT/ET clinical laboratory evaluations. In addition, a blood sample (approximately 5 mL) will be collected at baseline for DNA genotype screening for CYP450 2D6 polymorphism. In a subset of subjects (N=80), approximately 5 mL (1 x 5 mL samples) will be collected for PK analysis.

12.15. Medical History

A medical history will be performed at Screening/Baseline (Day 1). Each subject's history of alcohol and drug use will be evaluated. Continued eligibility and adherence to protocol restrictions will be confirmed throughout the study.

12.16. Physical and Neurological Examination

A physical and neurological examination will be performed at Screening/Baseline (Day 1), on Day 4, and on Day 14. Only a physical examination will be performed on Day 28 (Visit 4). A physical examination will be performed at Screening/Baseline (Day 1). All other physical examinations may be abbreviated (i.e. disease-specific and symptom directed).

12.17. Pregnancy Test

A urine pregnancy test will be performed at Screening/Baseline for all females of childbearing potential. A urine pregnancy test will also be collected at Days 14 (Visit 3) and 28 (Visit 4) for females of childbearing potential. A positive pregnancy test at any time during the study will immediately terminate the subject from further participation in the study.

13. STUDY DRUG

The Sponsor will supply tolperisone 50, 100, 150, and 200 mg tablets and matching placebo in a blinded fashion. Each subject will be provided with one bottle of study drug containing 42 tablets for 14 days of TID dosing. The study drug will be self-administered (TID) by the subjects. Each subject will also be provided with one bottle of rescue medication (acetaminophen 500 mg) containing 50 caplets (as is standard commercial packaging).

Study drug and rescue medication should be stored at controlled room temperature (15-30 °C [59-86 °F]) and locked in a secure cabinet or room.

13.1. Study Drug Administration

Tolperisone 50, 100, 150, and 200 mg, or matching placebo should be taken by the subjects TID, at 6-8 am, 12-2 pm, and 6-8 pm on Days 2 to 14; the first dose of study drug will be administered by the subject on Day 1.

All study medications will be administered orally with approximately 4-6 ounces of water. The subjects will be instructed to swallow the study tablet whole, without chewing the tablet. The subjects may take the study drug with or without food.

Subjects will be prompted via reminders on their smartphone/trial application to take their study drug at least 1 hour before and within 2 hours of the morning and evening assessments.

- Subjects in Group A (n=80) will be randomized to receive (1) 50 mg tolperisone tablet, TID for 14 days, for a total daily dose of 150 mg.
- Subjects in Group B (n=80) will be randomized to receive (1) 100 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 300 mg.
- Subjects in Group C (n=80) will be randomized to receive (1) 150 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 450 mg.
- Subjects in Group D (n=80) will be randomized to receive (1) 200 mg tolperisone tablet administered TID for 14 days, for a total daily dose of 600 mg.
- Subjects in Group E (n=80) will be randomized to receive (1) placebo tablet administered TID for 14 days.

13.2. Accountability

The Investigator or designated study personnel is responsible for keeping accurate records of the clinical supplies received from the Sponsor and the study drug administered to each subject. The study monitor(s) will review study drug records periodically during the conduct of the study. At the end of the study, all partial and empty containers must be returned to the Sponsor or they must be destroyed at the clinical study site according to site standard operating procedures (SOPs). Records of destruction of study drug at the study site must include bottle identifying information and number of tablets in each bottle.

14. SUBJECT RESTRICTIONS

Subjects are to abstain from using psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations during their participation in the study.

Subjects are to abstain from using any medication or dietary supplement to promote sleep, including over the counter sleep medications, during their participation in the study.

Subject will abstain from using antihistamine or any other drugs that can cause drowsiness, and will discuss any new prescription with the Investigator.

Other medications that the subject routinely takes will be discussed and reviewed by the PI. All concomitant medication taken during the trial should be recorded with indication, daily dose, and start and stop dates of administration.

Subjects will receive study-provided rescue medication of acetaminophen tablets (500 mg) that can be taken up to 3 times per day as rescue medications if their pain is severe. All rescue medication should be entered via the smartphone/use of trial application daily through Day 14 (Visit 3). Rescue medication is not to be taken on Days 4 (Visit 2) or 14 (Visit 3).

14.1. Fluid, Food, and Lifestyle Restrictions

Subjects are not allowed to consume alcoholic beverages prior to their study visit on Days 1, 4, and 14. At all other times, alcohol consumption is limited to no more than 2 alcoholic drinks or equivalent (beer [24 ounces or 710 mLs], wine [12 ounces or 355 mLs], or distilled spirits [3 ounces or 89 mLs]) per day.

Caffeinated beverages will be permitted to no more than 4 units per day amounts (1 unit = 120 mg caffeine or about one eight-ounce cup of coffee).

Subjects are to refrain from vigorous physical activity, heat and ice packs and non-pharmacological therapies (e.g. acupuncture, chiropractic adjustment, massage, TENS, physiotherapy, etc.) during Days 1 to 14.

15. DISCONTINUATION CRITERIA AND PROCEDURES

According to the Declaration of Helsinki, all subjects have the right to withdraw from a study at any time, regardless of their reasons. In addition, it is the right of the Investigator to remove subjects from the study as a result of AEs, protocol violation, or any other reason.

15.1. Premature Termination of Study/Closure of Study Sites

The study may be terminated prematurely if results affecting the safety of the subjects become available. A site may be closed prematurely if recruitment is too slow, poor quality data is produced, or there is evidence of attempted or proven fraud.

In the event the Sponsor prematurely terminates the study, the Investigator will promptly notify the IRB.

16. EVALUATION AND REPORTING OF ADVERSE EVENTS

16.1. Adverse Event (AE) Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. AEs occurring after the initiation of the treatment are referred to as treatment-emergent adverse events (TEAEs). An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study medication including comparator; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the Principal Investigator or medically qualified designate considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the Principal Investigator).

16.1.1. Severity Assessment

All AEs will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Every effort will be made to obtain an adequate evaluation of the severity.

16.1.2. Causality Assessment

Investigators are required to assess the causal relationship (i.e., whether there is reasonable possibility that the study drug caused the event) using the following definitions:

- Unrelated: another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the study agent; or a causal relationship is considered biologically implausible.
- Possibly Related: There is a clinically plausible time sequence between onset of the adverse event and administration of the study agent, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possible related should be used when the study agent is one or several biologically plausible adverse event causes.
- Definitely Related: The adverse event is clearly related to use of the study agent.

16.2. Routine Reporting

For the purposes of this study, the period of observation of AEs extends from the time of first dose (Day 1) until the final clinic visit (i.e., Day 28 follow-up visit [Visit 4] or, if applicable, Early Termination). During this period, all AEs spontaneously reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded and reported in the eCRF.

Any AE that remains unresolved as of the last visit, the Investigator will attempt to resolve the event or determine the status of the event.

In the case of AEs deemed related to the Investigational Product, every effort will be made to determine the final outcome.

It is the Investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Subjects will be questioned on their health status at the beginning of the study period and before the departure from the clinic site. Open-ended questions will be asked.

Classification will be performed by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or higher.

In general, AEs occurring secondary to other events (e.g., clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as SAE or AE in the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF.

Pregnancy in a female subject on the study shall be reported to the Sponsor's designee within 24 hours of the knowledge of its occurrence by the Principal Investigator or designee (for pregnancies occurring during the course of the study). Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the Principal Investigator or designee to the Sponsor's designee. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any pregnancy will be reported on a Pregnancy Report Form.

16.3. Serious Adverse Event Reporting

The sites will notify the sponsor and sponsor's designee of any SAE, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant information is available.

The SAE notification should be reported by completing the SAE report form in the EDC.

An SAE will be considered "unexpected" if the AE is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The sites will determine whether any serious unexpected related AE must be reported to the IRB. If so, the event will be reported via fax or email or as required per IRB once the Investigator or staff becomes aware of the event.

The sponsor will determine whether the SAE must be reported in an expedited manner to the appropriate regulatory agencies. If so, the Sponsor will report the event to the appropriate regulatory agencies, and all participating Investigators.

If reports of any new and unexpected AEs become available to the Sponsor during the clinical portion of this study (related or not to the present study), the Sponsor must advise the sites of those events.

17. STATISTICAL CONSIDERATIONS

17.1. General Considerations

This section describes the general approaches planned to analyze the data from this study.

All efficacy and safety data will be displayed in subject data listings. Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to study drug administration. All safety and efficacy endpoints will be summarized by dose level.

In general, categorical variables will be summarized by the frequency counts and percentages. Continuous variables will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum values.

Unless otherwise specified, all statistical hypothesis testing will be two-sided using $\alpha = 0.05$.

Additional details of the planned analyses outlined here will be further described in the Statistical Analysis Plan.

17.2. Determination of Sample Size

The sample size for this study was determined from results of two previous studies. The first was a study in subjects with acute upper back, neck, or shoulder spasm and pain, which showed a difference of 0.4 in the average of Day 1 through Day 7 between the placebo and active groups, and SDs between 1.76 and 1.93 (across placebo and active groups respectively) (Collaku, 2017). A sample size of 400 subjects (80 per group) would provide at least 80% power to detect a difference of 0.9 between the placebo and treatment groups in the NRS scale, assuming a two-sample t-test at the 5% level of significance and a pooled SD of 2.0. This sample size assumes an effect size of 0.45 (0.9/2.0 = 0.45), using the formula Effect Size = Mean/SD), which is larger than that seen in the reference study but consistent with that seen in a second study.

A second previous study in subjects with acute musculoskeletal spasm associated with back pain showed effect sizes ranging from 0.57 to 0.62 for lumbar cinelgasia, based on a treatment difference of 9.6 at Day 3, with SDs of 15.5 (treated group) and 16.7 (placebo group) (Chandanwale, 2011). This study demonstrated effect sizes ranging from 1.1 to 1.6, based on a difference of 24.2 at Day 14 with SDs of 15.1 (treated group) and 23.0 (placebo group). The effect size of the current study is expected to be similar to that in Chandanwale, though sample size estimates have been made more conservative to provide sufficient power to detect smaller differences. Though the primary comparison of interest in this study is Day 14, the study is sufficiently powered to detect a treatment difference at Day 4 based on effect sizes ranging from 0.35 to 0.45.

The power for this range of effect sizes across six different scenarios for a test of linear trend, as well as a comparison between the high dose and placebo only, is provided below, assuming n=80 in each group. Assuming an effect size of 0.4 (averaging the lowest and highest effects sizes)

yields power estimates that are greater than 80% for each scenario tested, except when all treatment groups have identical differences from placebo.

Sample size considerations are provided in Table 1.

Table 1 Sample Size Considerations

	Hypothesized Difference from Placebo					
Effect Size (High Dose vs. Placebo)	**Dose Group 1**	**Dose Group 2**	**Dose Group 3**	**Dose Group 4**	**Power: Linear Contrast**	**Power: High Dose vs. Placebo**
0.35	0	0	0.35	.35	84%	60%
	0	0	0.25	0.35	76%	60%
	0	0.08	0.25	0.35	76%	60%
	0	0.12	0.24	0.35	76%	60%
	0.08	0.16	0.24	0.35	68%	60%
	0.35	0.35	0.35	0.35	51%	60%
0.4	0	0	0.4	0.4	92%	71%
	0	0	0.2	0.4	81%	71%
	0	0.1	0.3	0.4	87%	71%
	0	0.13	0.26	0.4	85%	71%
	0.05	0.1	0.26	0.4	81%	71%
	0.1	0.2	0.3	0.4	81%	71%
	0.4	0.4	0.4	0.4	62%	71%
0.45	0	0	0.45	0.45	97%	81%
	0	0	0.23	0.45	89%	81%
	0	0.1	0.3	0.45	92%	81%
	0	0.14	0.28	0.45	91%	81%
	0.05	0.1	0.28	0.45	89%	81%
	0.11	0.22	0.33	0.45	88%	81%
	0.45	0.45	0.45	0.45	72%	81%

17.3. Analysis Populations

The analysis populations will be defined as follows:

- Intent-to-Treat (ITT) Population: All randomized subjects who receive any amount of study drug. This population will be used as the primary analysis population for all efficacy endpoints. Subjects will be included in this population based on their randomized treatment assignment.
- Safety Population: All subjects who receive any amount of study drug. This population will be used for all summaries of safety data. Subjects will be included in this population based on the actual treatment received.
- Per-Protocol (PP) Population: All randomized subjects who complete the study with no significant protocol violations that would affect the efficacy analyses. The

PP Population will be determined prior to database lock and will be used for sensitivity analyses on the primary and select secondary endpoints.

17.4. Statistical Analysis Methods

17.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects randomized, dosed, completing the Day 14 visit, and not completing the Day 14 visit by reason for withdrawal will be summarized for the ITT Population. Subject demographics and baseline characteristics will also be summarized for the ITT Population and will include age, sex, race, ethnicity, height, and weight.

17.4.2. Efficacy Analysis

17.4.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is subject-rated pain "right now" due to acute back spasm using an NRS (0-10 scale, from no pain to worst possible pain) for the clinic visit on Day 14. This analysis will be performed using a linear test of trend across doses, using a mixed effect model for repeated measures. The model will include treatment and time as fixed effects, the treatment by time interaction, and the baseline NRS rating as a covariate. Differences in linear trend for each dose level versus placebo will be presented with 95% confidence intervals and associated p-values.

17.4.2.2. Secondary Efficacy Analyses

The analysis performed for the primary endpoint will be repeated for the NRS at Day 4.

In addition to the primary efficacy analysis, subjects will also use the NRS scale to record pain intensity due to back spasm each day on an outpatient basis. Ratings will be averaged for both morning and evening recordings on Days 1 through Day 14 and summarized by dose level and day using descriptive statistics. Mean NRS pain intensity scores will also be plotted in a line graph over time, with associated standard errors (SEs) for Days 1 through 14. The analysis will be repeated using the evening values only for NRS scores on rest and also on movement. The comparison of each group to placebo will be conducted using a mixed effects model as described for the primary analysis.

The SRMH and the Functionality Assessment: FFD will be analyzed using the same methods described for the primary endpoint.

Global symptom assessments (CGI and PGI) will be summarized by the percentage of subjects reporting each individual response. The proportion of subjects in each category will be recorded at each day. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test.

Quality of sleep will be analyzed using the same methods described for the global symptom assessments.

Median time (in hours) to relief of pain on Days 1 and 14 compared to baseline will be plotted using Kaplan-Meier (K-M) curves. Estimates of the median times will be presented along with

their associated 95% confidence interval (CI) in a corresponding table. Treatment group comparisons will be summarized with hazard ratios and their associated 95% CI from a Cox Proportional Hazards regression model with treatment as the main effect and p-values from the generalized Wilcoxon test.

Use of rescue medications will be summarized using frequency counts and percentages by generic drug name. Average daily use and total use will be tabulated using descriptive statistics. The Shapiro-Wilk test will be used to examine the assumption of normality. If this test is statistically significant (i.e., $p \leq 0.05$) then the assumption of normality is violated and the total rescue medication consumption will be analyzed using a Wilcoxon Rank Sum test. Results will be expressed as median (range) and p-values. However, if the assumption of normality holds (i.e., Shapiro-Wilk p-value > 0.05), then the total rescue medication consumption will be analyzed using an analysis of variance (ANOVA) model with randomized treatment as the main effect. Results will be expressed as means, SDs, and least squares mean difference (LSMD) and SEs with associated 95% CI, and p-values.

All other secondary endpoints will be summarized by dose using descriptive statistics. In addition, the comparison of each group to placebo will be conducted using an ANCOVA model, adjusting for baseline.

17.4.2.3. Handling of Dropouts or Missing Data

Efficacy analyses on the ITT Population will use the last observation carried forward (LOCF) method for handling missing data. Only post-baseline values will be carried forward. Efficacy analyses on the ITT Population will also be performed using observed data only. All other analyses will be based on observed data only.

17.4.3. Safety Analysis

Safety analysis will be based on all subjects randomized who receive at least one dose of the study drug. The safety analysis will evaluate adverse events and additional safety parameters.

Additional safety parameters will be assessed from summaries of physical examinations, 12-lead ECGs and vital signs.

17.4.3.1. Adverse Events

Adverse events will be summarized by dose level. All adverse events will be coded from the verbatim text to the lower level term and mapped to preferred term and primary system organ class using the latest version of MedDRA. The number and percentage of subjects experiencing at least one AE will be summarized by body system, preferred term, and dose level. If appropriate, AEs will also be summarized by severity and relationship to study drug. Serious AEs, if any, will be tabulated. Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term.

Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and subject incidence of TEAEs meeting various criteria;

- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs by severity, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term;
- Subject incidence of SAEs by MedDRA system organ class and preferred term.

Adverse events will also be presented in subject listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome.

17.4.3.2. Extent of Exposure to Study Drug

The total amount of study drug used by each subject as well as the mean daily amount of study drug used by each subject will be calculated. Total amount and mean daily amount of study drug will be summarized by dose level using descriptive statistics.

17.4.3.3. Clinical Laboratory

Clinical laboratory results and changes from baseline will be summarized by dose using descriptive statistics for all regularly scheduled visits. For each laboratory test, individual subject values will be listed and values outside of the standard reference range will be flagged. A separate listing will be provided to include all clinical laboratory values outside normal range (including Screening/Baseline Visit 1 and Day 14/ EOT examination) and will also include relevant demographic information.

17.4.3.4. Vital Signs

Vital sign (blood pressure, heart rate, respiratory rate, and body temperature) measurements and changes from baseline will be summarized by dose using descriptive statistics for regularly scheduled visits. Measurements will also be presented in a subject data listing.

17.4.3.5. Twelve-lead Electrocardiogram (ECG)

Individual subject results will be summarized categorically as normal, clinically significant abnormal, and not clinically significant abnormal by dose and presented in the subject data listings.

17.4.3.6. Physical and Neurological Examination

Neurological examination results will summarized in frequency tables by dose. Physical and neurological examination results will be presented in subject data listings.

17.4.4. DNA Genotyping

Results will be examined and summarized for CYP450 2D6 polymorphism, dose-response, and AE profile.

17.4.5. Pharmacokinetic Analysis

Details of the PK and associated statistical analyses will be included in a separate population PK Statistical Analysis Plan.

18. BIOLOGICAL SPECIMENS

Whole blood samples and urine samples will be collected as outlined in the Schedule of Procedures (Table 2) for clinical chemistry, hematology, urinalysis, and optional PK and DNA genotyping.

It is the responsibility of the Investigator to ensure that all personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

19. CLINICAL AND LABORATORY DATA COLLECTION

19.1. Electronic Case Report Forms (eCRF)

An eCRF will be completed for each subject. All appropriate subject data gathered during the study will be recorded in English on these forms.

Whenever possible, all information requested on an eCRF should be completed. If information is not available, it should be documented as such.

The completed eCRFs for this study are the property of Neurana Pharmaceuticals, Inc. and should not be made available to third parties, except for authorized representatives of appropriate health/regulatory authorities, without written permission from Neurana Pharmaceuticals, Inc.

19.2. Electronic Patient Reported Outcomes (ePRO)

The ePROs will be collected in an electronic capture device (tablet and smartphone/use of trial application) that will be used at the clinic and by the subject at home/away from clinic to record pain assessments and other secondary endpoint assessments. A study-provisioned tablet will be used to document results at the clinic visits and a study-provisioned smart phone or study application on the subject's own smartphone will be used to document results at the subject's home/away from clinic over 14 days of study drug treatment.

19.3. Laboratory Results

Laboratory tests (clinical chemistry, hematology and urinalysis) will be analyzed by a certified laboratory (ACM) and reported to the clinic site as results are generated. The Investigator will review and comment on any laboratory value reported outside the normal range provided by the laboratory. The laboratory data must be signed and dated and kept in the study subject file at the site for the Sponsor and will represent the source data.

20. STUDY DOCUMENTATION

20.1. Source Documents

Source documents may include, but are not limited to, laboratory reports, ECG tracings, clinic notes or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Source documents may also include eCRFs or electronic devices when information is recorded directly onto such forms or devices.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

20.2. Access to Records

As required by the International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and regulatory authorities the Investigator will allow Sponsor's representative(s) direct access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The records, including source documentation, must also be available for inspection by relevant regulatory health authorities.

20.3. Retention of Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

21. INSTITUTIONAL REVIEW BOARD (IRB)

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

22. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and the Neurana Pharmaceuticals, Inc. policy on bioethics.

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Neurana Pharmaceuticals, Inc., its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

23. INFORMED CONSENT

It is the responsibility of the Investigator to give each potential study subject, prior to inclusion into the study, full and adequate verbal and written information regarding the objectives and procedures of the study. The study subjects must be informed about their right to withdraw from the study at any time. It is the responsibility of the Investigator (who may delegate this task to other members of the study team) to obtain signed informed consent from all study subjects before any study related assessments are performed. Consent must be documented by the subject's dated signature on an informed consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. In the event of a revised informed consent, all ongoing subjects and newly enrolled subjects should be administered and sign the most current IRB-approved ICF.

24. CONFIDENTIALITY

24.1. Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB and Food and Drug Administration (FDA), or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication with prior approval of the Sponsor.

24.2. Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), IRB or regulatory agency representatives may consult and/or copy study documents in order to verify case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying case report form information, the subject will be identified by subject number only, full names/initials will be masked prior to transmission to the Sponsor, IRB or regulatory agency.

25. COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The Investigator also agrees to allow monitoring, audits, IRB review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents including access to the electronic data base for the study.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and eCRFs.

ICH-GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study and provide the final results (i.e., final observations and responses) to the Sponsor.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study. The Investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify the IRB.

26. QUALITY CONTROL AND QUALITY ASSURANCE

Designated personnel from the study site and the Sponsor or designee will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for GCP.

27. PUBLICATIONS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

28. REFERENCES

Chandanwale AS, Chopra A, Goregaonkar A, et al. Evaluation of eperisone hydrochloride in the treatment of acute musculoskeletal spasm associated with low back pain: A randomized, double-blind, placebo-controlled trial. Journal of Postgraduate Medicine, 2011; 57 (4):278-285.

Collaku A, Yue Y, Reed K. Efficacy and safety of guaifenesin for upper back, neck, and shoulder pain: a Phase II proof-of-concept, multicenter, placebo-controlled, repeat-dose, parallel-group study. Journal of Pain Research, 2017; 10:669-678.

Dulin J, Kovacs L, Ramm S, et al. Evaluation of sedative effects of single and repeated doses of 50 mg and 150 mg Tolperisone Hydrochloride. Results of a prospective, randomized, double-blind, placebo-controlled trial. Pharmacopsychiat, 1998; 31:137-142.

Kohnen R, Krüger H P, Dulin J. The human-experimental investigation of sedative effects from drugs in combination with alcohol. Psycho, 1995; 21:768-775.

29. SCHEDULE OF PROCEDURES

Table 2 Schedule of Procedures

	Visit 1 Screening /Baseline Clinic Visit		**Visit 2 Clinic Visit**		**Visit 3 EOT/Early Termination Clinic Visit**	**Visit 4 2-Week Follow-up Clinic Visit**
	Day 1 (and if needed up to Day -3 [a]**)**	**Outpatient Days 2, 3**	**Day 4 ±1 day**	**Outpatient Days 5 - 13**	**Day 14 +1 day**	**Day 28 +3 days**
Informed consent	X [a]					
Medical history and demographics [b]	X [a]					
Physical and neurological examination [c]	X [a]		X		X	X
Urine pregnancy test	X [a]				X	X
Urine drug screening and alcohol breathalyzer	X[a]		X		X	
Laboratory evaluations (serum chemistry, hematology, urinalysis) [d]	X [a]				X	
DNA genotyping [e]	X					
Pharmacokinetics (optional) [f]			X			
Inclusion/exclusion review	X [a]					
Randomization	X					
Study drug and rescue medication dispensing	X					
Subject smartphone/application deployment	X					
Study drug dosing[g]	X	X	X	X	X	
Study drug and rescue medication collection					X	
Subject smartphone returned, if applicable					X	
NRS, subject rating of pain “right now” [h]	X		X		X	
Subject-rating of medication [study drug] helpfulness (SRMH)[i]			X		X	
NRS, subject rating of average pain over time [j]	X	X	X	X	X	
NRS, subject rating of average pain on rest or movement [k]	X	X	X	X	X	
Clinician’s Global Impression of Severity of pain (CGI-S)	X					
Clinician’s Global Impression of Change of pain (CGI-C)			X		X	
Patient’s Global Impression of Severity of pain (PGI-S)	X					

	Visit 1 Screening /Baseline Clinic Visit		**Visit 2 Clinic Visit**		**Visit 3 EOT/Early Termination Clinic Visit**	**Visit 4 2-Week Follow-up Clinic Visit**
	Day 1 (and if needed up to Day -3 [a]**)**	**Outpatient Days 2, 3**	**Day 4 ±1 day**	**Outpatient Days 5 - 13**	**Day 14 +1 day**	**Day 28 +3 days**
Patient's Global Impression of Change of pain (PGI-C)			X		X	
Visual Analogue Scale (VAS) of sleepiness			X			
Functionality assessment: • Fingers to floor distance (FFD) [l]	X		X		X	
Disability assessment: [l] • Oswestry Disability Index (ODI)[m]	X		X		X	
Use of rescue medication [n]	X	X	X	X	X	
Daily activities (sedentary, walking activities, etc.)	X	X	X	X	X	
Quality of sleep [o]	X	X	X	X	X	
Vital sign measurements [p]	X [a]		X		X	X
Standard 12-lead electrocardiogram	X [a]				X	
Adverse events	X		X		X	X
Concomitant Medications	X [a]		X		X	X
Drug Accountability			X		X	

Note: All **darker shaded** rows are to be completed on the **subject's study-provisioned smartphone or on their own phone** using the trial application.

All **lighter shaded** rows are to be completed **at the clinic site and on the study-provisioned tablet** by the Investigator Rater/Evaluator or subject, as applicable for assessments.

All non-shaded rows are not captured in a study-provisioned site tablet or a subject smartphone/trial application; applicable information should be entered into the eCRF.

EOT = End of Treatment; ePRO = electronic Patient Reported Outcomes; PK = pharmacokinetic

[a] Screening assessments may be completed within 3 days prior to Day 1 (-3 to 0 days). If screening assessments are completed prior to Day 1, inclusion/exclusion criteria to be re-reviewed for qualification of the subject's enrollment into the study prior to dosing on Day 1.

[b] Including sex, age, race, ethnicity, body weight (kg), height (cm), body mass index (BMI) (kg/m^2), and smoking habits.

[c] Physical and neurological examination will be performed at Screening/Baseline (Day 1), on Day 4, and on Day 14. A physical examination only will be performed on Day 28. A complete physical examination will be performed at Screening/Baseline (Day 1). All other physical examinations may be disease-specific and symptom directed.

[d] Laboratory Evaluations include hematology, serum chemistry, and urinalysis on Days 1 and 14**.** (See ACM lab manual for further instructions.)

[e] DNA genotyping for CYP450 2D6 polymorphism will be collected at same time of other required blood draw on Day 1. (See Machaon lab manual for further instructions.)

[f] For the select group of sites and subjects who will undergo PK assessments, blood samples will be drawn on Day 4. (See ACM lab manual for further instructions.)

[g] Dosing will be three times per day, with a single tablet administered at each dose. Subjects should be instructed to dose at 6-8 am, 12-2 pm, and 6-8 pm for 14 days and will enter their dosing information in the eDiary on the subject's smartphone/trial application.

[h] Subject rating of pain using Numerical Rating Scale (NRS, a scale of 0 to 10 where 0 = no pain, and 10=worst possible pain) for the level of pain that the subject is feeling "right now" due to back spasm (**primary efficacy endpoint**) administered by study-provisioned tablet ePRO at baseline, and on Days 4 and 14 in the clinic.

[i] Subject rating of medication helpfulness (SRMH): a five point scale from 1=poor to 5=excellent, administered by study-provisioned tablet ePRO on Days 4 and 14 in the clinic.

[j] Subject rating of pain using NRS due to back spasm, measured daily in the morning 8 to 10 am and in the evening between 8 to 10 pm from Days 1 through 14, for intensity of average pain due to spasm over last 12 hours, and subject rating of average pain over the past 1 hour, all on the subject's smartphone/trial application.

[k] Subject rating of average pain using NRS at rest and upon movement at the end of the day (between 8 to 10 pm) on Days 1 to 14 on the subject's smartphone/trial application.

[l] Functionality assessments to be administered in the clinic on Days 1, 4 and 14. FFD is measured as distance in cm from the tips of the fingers to the floor when standing with the spinal cord flexed with complete extension of knee joint. This is not captured in an electronic device. Enter score in eCRF.

[m] The Oswestry Disability Index (10 sections with one answer each for: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling) will be captured by study-provisioned tablet ePRO on Days 1, 4, and 14 in the clinic.

[n] The use of study-provided rescue medication (acetaminophen 500 mg) taken to control their pain throughout the day will be captured in the subject's smartphone/trial application daily from Day 1 through 14, at the end of the day. Subjects are not to take rescue medications on clinic visits on Days 4 and 14.

[o] The subject's quality of sleep will be captured on their smartphone/trial application starting at baseline visit in clinic and on a daily basis at home/away from clinic between 8 to 10 am for Days 1 to 14. In response to the question of "how did you sleep last night", subject responses will be captured on a 5-point scale (from 1=not at all to 5=slept all night).

[p] Vital signs include supine and standing blood pressure; sitting heart rate (after approximately 3 minutes at rest); respiratory rate; and body temperature on Days 1, 4, 14, and 28 (All Visits). Weight and height will be assessed at Visit 1 only.