CLINICAL TRIAL PROTOCOL: 115

Title:	Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo
Substance Identifier	Tolperisone hydrochloride, NR100
IND number	69,169
Protocol Number	115
Sponsor	Neurana Pharmaceuticals, Inc. 3525 Del Mar Heights Rd, #609 San Diego, CA 92130
Principal Investigator	Russell Rosenberg, Ph.D. NeuroTrials Research 1100 Johnson Ferry Rd, Suite 420 Atlanta, GA 30342 (678) 651-2006
Date of Protocol	28 April 2017
Sponsor Representative	Judy Caron, Ph.D., Chief Operating Officer Neurana Pharmaceuticals, Inc. 3525 Del Mar Heights Rd, #609 San Diego, CA 92130 (617) 640-5043
Amendment #	NA

1 SIGNATURES

1.1 Sponsor's Representative

Judy Caron, Ph.D.
Chief Operating Officer
Neurana Pharmaceuticals, Inc.

SIGNATURE

DATE

4/28/17

1.2 Investigator

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with Good Clinical Practice guidelines. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in this protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol.

It is obligatory that the Investigator become familiar with all the sections of the tolperisone Investigator's Brochure prior to initiation of the study.

SIGNATURE DATE

_____ _____

PRINTED NAME

_____

2 SYNOPSIS

Sponsor: Neurana Pharmaceuticals, Inc.
Name of Finished Product: Tolperisone hydrochloride, NR100
Name of Active Ingredient: Tolperisone hydrochloride
Study Title: Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo
Study Number: 115
Study Phase: Phase 1
Primary Objective: • To assess the sedative effect of 150 mg TID tolperisone and 10 mg TID cyclobenzaprine compared to placebo on simulated driving performance and cognitive functioning in healthy adult volunteers. In this crossover study, treatment effects will be assessed following the second initial dose, the morning following nighttime dosing (to assess residual next day effects), and at steady state (i.e., following AM dosing on Day 3). **Secondary Objectives:** • To assess the safety of 150 mg TID tolperisone dosing for 3 days in healthy volunteers.

Endpoints:

Primary Endpoint:

- Standard Deviation of Lateral Position (SDLP), measured by simulated driving performance using CRCDS-MiniSim, of tolperisone compared to placebo

Secondary Endpoints:

- SDLP measured by simulated driving performance using CRCDS-MiniSim of tolperisone compared to cyclobenzaprine
- Sleepiness Endpoint – Karolinska Sleepiness Scale (KSS)
- Self-reported readiness to drive (Response to: "Right now do you feel safe to drive?")
- Visual Analog Scales (VAS) to assess self-reported motivation and appraisal of driving performance
- Cognitive Performance Endpoints
  - CogScreen Symbol Digit Coding (SDC) test
    - Number of correct responses
    - Response Accuracy
    - Standard deviation of reaction time
- Driving Performance Endpoints
  - Lane exceedance; including number, maximum, and duration
  - Speed related measures; including speed deviation, average speed, excessive speed count, and speedings ratio
  - Driving safety measures; including excessive Ay (cornering speed threshold -exceeded), and total collisions
  - Divided attention measures; including correct responses, omission errors, commission errors, reaction time, and standard deviation of reaction time
- Plasma drug levels and driving performance
- Safety Endpoints
  - Clinical Evaluations
    - Vital signs
    - Orthostatic effects
    - Physical examinations
    - 12-lead electrocardiograms (ECGs)
  - Laboratory safety tests (blood chemistry, hematology, urinalysis, serum and urine pregnancy tests for women of childbearing potential)
  - Adverse events (AEs)

Study Design:

This will be a randomized, placebo-controlled, multiple-dose 3-way cross-over study of the safety and cognitive effects of multiple doses of 150 mg tolperisone administered TID in 30 male and female healthy volunteers. Treatment groups include 450 mg tolperisone (i.e., 150

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mg administered three times daily), 30 mg cyclobenzaprine (i.e., 10 mg administered three times daily), and placebo. Subjects will receive 3 days of each treatment. Subject participation will be approximately 3 weeks as outpatients with 3 days each week as overnight clinic participants. Subjects will be screened within 28 days prior to Treatment Period 1 (Visit 2) for eligibility for participation in the study. The Familiarization and Practice drives on the driving simulator must be completed no more than 21 days prior to Treatment Period 1. Subjects meeting all inclusion/exclusion criteria will then be admitted to the clinic on Day -1 to be evaluated for continued eligibility. Subjects will perform a practice trial with the driving simulator and the cognitive function test. Subjects will be dosed on the morning of Day 1. Approximately one hour after the second dose on Day 1, subjects will be administered the cognitive test, followed by the driving simulator examination. On the morning of Day 2, prior to dosing, subjects will be readministered the cognitive test and driving examination to assess residual next day effects. Subjects will repeat cognitive testing and the driving examination on the morning of Day 3, after administration of the AM study medication, to evaluate the cumulative effects of 3 days of dosing. Subjects will be discharged on Day 3 with instructions to return to the clinic on Day 7 and Day 14 to repeat the above procedure with the second and third treatments. A follow-up phone call will be conducted 1 week (±3 days) following discharge from the clinic on Day 17 to assess for continued safety.

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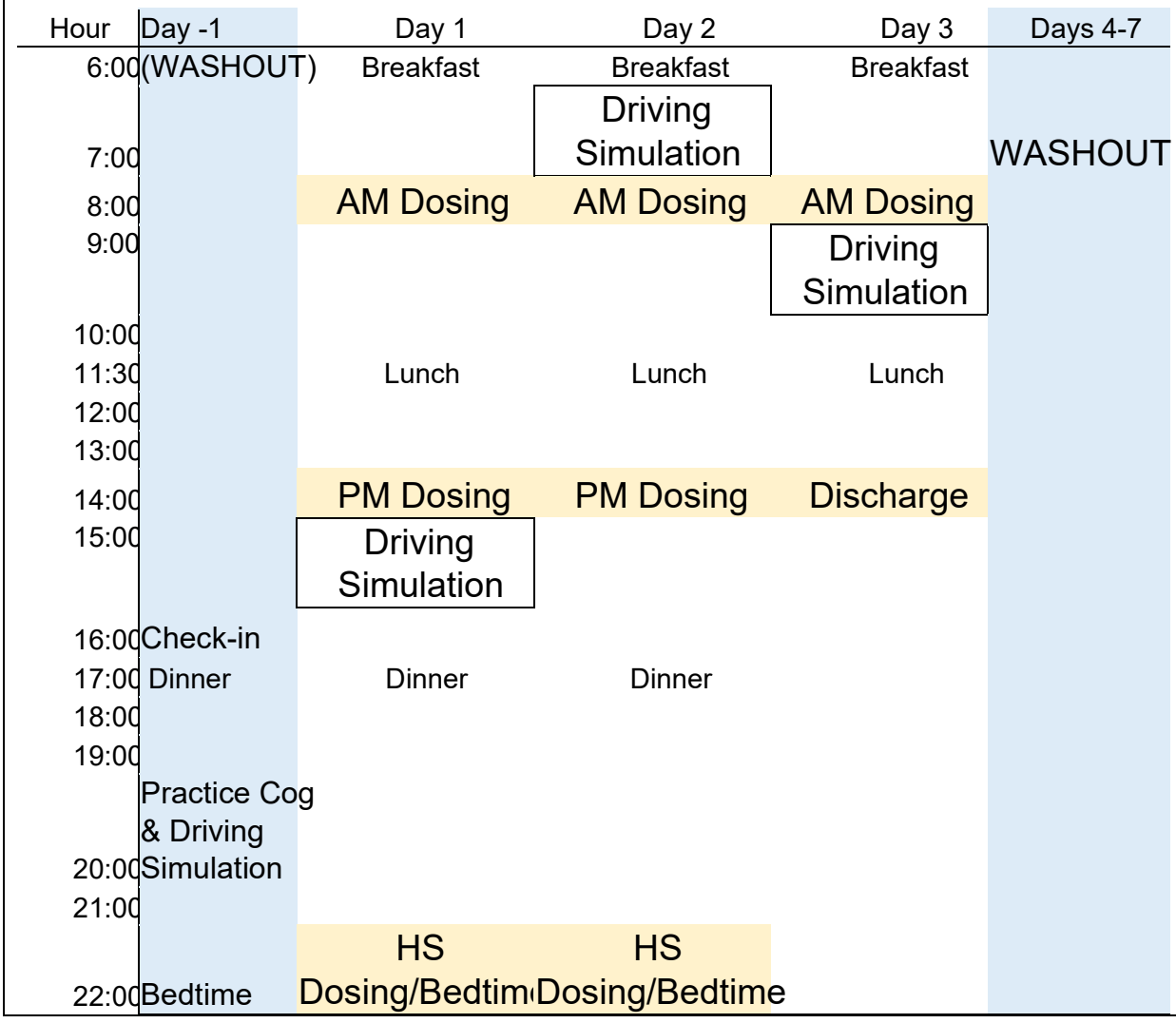
Schematic of Design:



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Subject Population:

Inclusion Criteria:

1. All healthy volunteer subjects must be in general good health based on screening physical examination (defined as the absence of any clinically relevant abnormalities), medical history, 12-lead ECG, and clinical laboratory values (hematology, serum chemistry and urinalysis).
2. Male and female subjects must be between 21 and 55 years of age, inclusive, at the time of consent.
3. All subjects must be capable of understanding and complying with the protocol and have signed the informed consent document. Female subjects of childbearing potential must sign the Women of Childbearing Potential Addendum to the informed consent form.
4. Subjects are required to have a body mass index (BMI) of 18 to 32 kg/m^2, inclusive, at Screening.
5. Subject must be able to reliably perform study assessments (i.e., SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the CVDA practice scenario; and number correct on CogScreen Symbol Digit Coding no less than 1 standard deviation below the mean for healthy adults in the 21-55 year age range); demonstrates the ability to understand task instructions (in English), and be physically capable (e.g., adequate manual dexterity, vision, and hearing), cognitively capable and motivated to perform study tasks.
6. Subject must possess a valid driver's license and be an active driver, and have driven a minimum of 10,000 miles (about 16,000 km) per year for the previous 3 years.
7. Subject must also demonstrate simulator sickness questionnaire scores which are not indicative of simulator sickness as defined in the driving simulation operations manual.
8. Subject must have a regular sleep pattern, not be engaged in shift-work, and in general, have at least 7 hours of sleep each night (bedtime occurs between 21:00 and 24:00 hours).
9. Subject has a score < 10 on the Epworth Sleepiness Scale (ESS).
10. Female subjects must have a negative serum 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 one month after the end of the study by

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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, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double-barrier method (e.g., condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

11. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

1. Subjects who have any clinically significant unstable medical abnormality, chronic disease or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems.
2. Subjects who test positive at screening for hepatitis B surface antigen, hepatitis C antibody or have a history of a positive result.
3. Subjects who are known to be seropositive or test positive at Screening for Human immunodeficiency virus (HIV).
4. Female subjects who are pregnant or lactating.
5. Subjects who have a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion.
6. A history within 2 years of, or current treatment for a sleeping disorder (including excessive snoring, obstructive sleep apnea), or a chronic painful condition that interferes with the subject's sleep.
7. A history of difficulty in falling asleep or staying asleep in the previous 3 months, that is considered clinically significant by the investigator.
8. Subjects who have a history or diagnosis of any of the following conditions:
    a. Primary or secondary insomnia
    b. Narcolepsy
    c. Cataplexy (familial or idiopathic)
    d. Circadian Rhythm Sleep Disorder
    e. Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and rapid eye movement behavior disorder
    f. Sleep-related Breathing Disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome)

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g. Periodic Limb Movement Disorder
h. Restless Legs Syndrome
i. Primary Hypersomnia
j. Excessive Daytime Sleepiness (EDS)
k. Subject has visual or auditory impairment which in the opinion of the investigator would interfere with study related procedures or study conduct.

9. Subjects expected to use any other medication or dietary supplement to promote sleep including over-the-counter sleep medications, during their participation in the study.
10. Subjects who have participated in any investigational study within 30 days prior to screening or are currently participating in another clinical trial.
11. 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.
12. Subjects who have a history of allergic reaction to tolperisone or cyclobenzaprine or any components of these study medications.
13. Use of psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of admission to the Clinical Research Unit (CRU) on Day 1.
14. Presence of a medical or psychiatric condition which could jeopardize the safety of the subject or validity of study results
15. Subjects who consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings per day (where 1 serving is approximately equivalent to 120 mg of caffeine).
16. Subjects who will be working a night shift within 1 week of a visit.
17. Subject who have traveled across 1 or more time zones (transmeridian travel) in the last 2 weeks prior to randomization or is expected to travel across 1 or more time zones during the study.
18. Current smoker (>10 cigarettes or eCigarettes, 3 cigars, or 3 pipes per day) and unwilling to refrain from smoking while confined to the CRU for periods of 3 days.
19. Subjects who have an inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator or designee.
20. Subjects who are a staff member or relative of a staff member.

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21. Inability or unwillingness to use adequate contraception (as defined in item 10 of the Inclusion Criteria) during and for 1 month following completion of the study.
22. Has a positive screen for alcohol or other drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates).

Planned Number of Subjects:

A sufficient number of subjects will be enrolled to ensure a total of 30 normal, healthy, male and female subjects between the ages of 21 and 55 years (at the time of informed consent) will complete all dosing periods, including the driving assessment.

Test Product; Dose; and Mode of Administration:

Tolperisone 150 mg tablets and matching placebo will be provided for the study by the Sponsor.

Cyclobenzaprine 10 mg tablets will be procured by the individual sites or by the CRO on behalf of the sites.

The subjects will be instructed to swallow the tablets whole, with approximately 4-6 ounces of water. Study drug will be administered by qualified unblinded CRU personnel and a mouth and hand check performed.

Duration of Treatment:

The total duration of study participation will be approximately 4 weeks (range 4-8 weeks), including Screening and Follow-up.

Safety Assessments:

Adverse Events (AEs):

AEs will be captured from the time of obtaining informed consent until discharge from the study.

Pregnancy Test:

A serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed upon each admission to the unit for females of childbearing potential. A positive pregnancy test at any time during the study 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 visit and end of study (EOS) (Day 17).

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Vital Signs:

Vital signs, including supine and standing blood pressure and heart rate, temperature and respiration rate will be collected at the following visits/time points:

- Screening,
- Day -1, 7, and 14 upon clinic check-in,
- Day 1, 2, 3, 8, 9, 10, 15, 16, and 17 prior to and 4 hours post AM dosing.
- Weight and height will be measured at Screening only.

Electrocardiogram

Twelve-lead ECG recording will be collected at Screening and EOS (Day 17).

Pharmacokinetic (PK) Blood Sampling:

Blood samples for the determination of plasma tolperisone concentrations will be drawn prior to each AM dosing on Days 1-3 and post-driving test (15-30 minutes after the drive) on Days 1 and 3.

Statistical Plan and Methods:

Doses of tolperisone will be considered non-inferior (NI) to placebo if the upper 95% confidence limit on the difference in SDLP between that dose and placebo is less than 4.4 cm (the NI margin). Cyclobenzaprine comparisons to placebo are to assess assay sensitivity and no adjustment to alpha levels will be made for either the comparison of cyclobenzaprine to placebo or tolperisone, or for secondary endpoints or analyses. Formal statistical tests (where performed) will be two-sided and testing at the alpha=0.05 level of significance.

The sequence of testing to control for multiplicity associated with comparisons of tolperisone to placebo (to assess NI) on multiple days is Day 1 (single-dose), followed by Day 3 (steady-state), followed by Day 2 (residual effect). Tolperisone will be considered NI to placebo if prior comparisons (at time points in the sequence provided, above) also indicate non-inferiorty.

In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation (SD), median, minimum, and maximum values.

All study data will be displayed in the data listings.

Safety:

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

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Safety analysis will be based on all subjects enrolled who receive at least 1 dose of the study medication. The safety analysis will evaluate adverse events 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. 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 EOS 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.

Pharmacokinetics:

The correlations between plasma drug concentrations and key secondary end points will be evaluated.

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be determined by Neurana Pharmaceuticals, Inc. The relationship between plasma drug levels and driving performance will be evaluated, data permitting. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Pharmacodynamics:

The primary endpoint, SDLP, will be analyzed using a normal theory mixed effects model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used.

Pair-wise comparisons (hypothesis tests) of differences in least squares means, and 95% confidence intervals on differences will be provided for:

Initial dose effect

1. cyclobenzaprine versus placebo following Day 1 PM dose
2. tolperisone versus placebo following Day 1 PM dose
3. tolperisone versus cyclobenzaprine following Day 1 PM dose

Next day residual dose effect

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4. cyclobenzaprine versus placebo following Day 2 AM dose
5. tolperisone versus placebo following Day 2 AM dose
6. tolperisone versus cyclobenzaprine following Day 2 AM dose

Steady-state dose effect

7. cyclobenzaprine versus placebo following Day 3 AM dose
8. tolperisone versus placebo following Day 3 AM dose
9. tolperisone versus cyclobenzaprine following Day 3 AM dose

In addition, pair-wise within-subject differences in SDLP greater than 4.4 cm in absolute value (equal to the previously found difference between placebo and 0.05% Blood Alcohol Content (BAC) for the CRCDS) will be compared using McNemar's test. These pair-wise, within subject differences in SDLP will also be tested for symmetry about zero [6] using the maximally selected McNemar test.

Summary statistics will be provided (mean, SD, median, minimum, maximum) for SDLP for each time point and treatment group.

Additional details of analysis for secondary endpoints of VAS, SDC, KSS, and driving performance endpoints will be specificed in the Statistical Analysis Plan (SAP).

The relationship between tolperisone plasma drug levels and driving performance (i.e., the primary endpoint of SDLP) will be assessed by correlational analyses.

All pharmacodynamic results will be summarized in tabular format, with summary statistics (number [n], mean, SD, median, minimum, and maximum) and change from baseline, as appropriate by time point.

3 TABLE OF CONTENTS

4 ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	Adverse event(s)
ALT	Alaninie aminotransferase
AST	Aspartate aminotransferase
BAC	Blood Alcohol Content
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
	degrees Celcius
CFR	Code of Federal Regulations
cm	Centimeter
CNS	Central Nervous System
CRCDS-MiniSim	Cognitive Research Corporation Driving Simulator-MiniSim
CRF	Case report form
CRU	Clinical research unit
CVDA	Country Vigilance-Divided Attention
DA	Divided attention
E	number of events
ECG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
EOS	End of study
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HCl	Hydrochloride
HIV	Human immunodeficiency virus
HR	Heart Rate
IATA	International Air Transport Association
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device

kg	Kilogram
kg/m^2	Kilogram per meter squared
km	Kilometer
KSS	Karolinska Sleepiness Scale
LLC	Limited Liability Company
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
N	Number
NI	Non-inferiority
pH	Potential of hydrogen
PK	Pharmacokinetic
PT	Preferred term
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDC	Symbol Digit Coding
SDLP	Standard deviation of lateral position
SOC	System Organ Class
SOPs	Standard operating procedures
TEAE	Treatment Emergent Adverse Event
TID	Three times a day
TSH	Thyroid stimulating hormone
VAS	Visual analog scale

5 STUDY ADMINISTRATION SCHEDULE

5.1 Principal Investigator

Russell Rosenberg, Ph.D.
NeuroTrials Research
1100 Johnson Ferry Rd, Suite 420
Atlanta, GA 30342
(678) 651-2006

5.2 Study Director

Gary Kay, Ph.D.
President
Cognitive Research Corporation
200 Central Avenue, Suite 1230
Saint Petersburg, FL 33701
Office: (727) 897-9000
Mobile: (202) 256-5617

5.3 Medical Monitor

Gerald M. Penn, M.D.
Medical Director
Mary Rutan Hospital Dept. of Pathology
205 Palmer Rd.
Bellfontaine, OH 43311
Email: gerald.penn@maryrutan.org
Office: 937-651-6632
Mobile: 614-563-7543

5.4 SAE Reporting Contact Information - Sponsor

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

6 BACKGROUND AND RATIONALE FOR THE STUDY

6.1 Introduction

Tolperisone hydrochloride (HCl), a centrally acting muscle relaxant, is widely used in Europe, Asia, and South America for the treatment of abnormally increased muscle tone. NR100, an oral formulation of tolperisone HCl as film-coated tablets, is being developed by Neurana Pharmaceuticals, Inc. as a novel muscle relaxant for the treatment of acute and painful symptoms associated with muscle spasms resulting from occupational and sports-related injury or myofascial pain. Future development of NR100 will be for the separate indication of treatment of spasticity associated with neurological conditions such as multiple sclerosis and spinal cord injury.

While the mode of action of tolperisone HCl is not fully characterized, the most prominent effect of tolperisone HCl 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 HCl has sodium (Na^+) and, to a lesser extent, calcium ($Ca2^+$) channel blocking activity. It inhibits, in a relatively selective manner, voltage-gated Na^+ channels. However, even with high tolperisone HCl concentrations, channel blockade remains incomplete and reversible. Tolperisone has been shown to have unique analgesic effects and a lack of sedation effects.

The centrally acting muscle relaxants reduce the increased muscle tonus and are typically sedative when used. The avoidance of drug-induced central depression, e.g., dizziness, drowsiness and excessive loss of muscle strength, is important in the medical care of patients.

The Study 115 will explore the sedative effects of tolperisone HCl after single and multiple doses of NR100 compared to placebo, and to a widely prescribed agent for muscle relaxation used as a positive control, cyclobenzaprine.

6.2 Drug Profile

6.2.1 Tolperisone

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

6.2.2 Cyclobenzaprine

Full details of cyclobenzaprine pre-clinical and clinical safety and tolerability data are contained in the Package Insert.

6.3 Rationale

6.3.1 Study Design

This will be a randomized, placebo-controlled, multiple-dose 3-way cross-over study of the safety and cognitive effects of multiple doses of tolperisone administered TID in 30 male and

female healthy volunteers. Treatment groups include 450 mg tolperisone (i.e., 150 mg administered three times daily), 30 mg cyclobenzaprine (i.e., 10 mg administered three times daily), and placebo.

Subjects meeting all inclusion/exclusion criteria at Screening will be admitted to the clinic on Day -1 to be evaluated for continued eligibility. Subjects will perform a practice trial with the driving simulator and the cognitive function test.

Subjects will be dosed on the morning of Day 1. Approximately one hour after the second dose on Day 1, subjects will be administered the cognitive test, followed by the driving simulator examination.

On the morning of Day 2, prior to dosing, subjects will be readministered the cognitive test and driving examination to assess residual next day effects.

Subjects will repeat cognitive testing and the driving examination on the morning of Day 3, after administration of the AM study medication, to evaluate the cumulative effects of 3 days of dosing.

Subjects will be discharged on Day 3 with instructions to return to the clinic on Day 7 and Day 14 to repeat the above procedures with the second and third treatments.

A follow-up phone call will be conducted 1 week (±3 days) following discharge from the clinic on Day 17 to assess for continued safety.

6.3.2 Tolperisone Dose Level

For the tolperisone treatment arm, tolperisone will be administered three times per day, with 1 tablet administered at 8:00 AM (AM dose), 2:00 PM (PM dose), and 10:00 PM (HS dose) daily for 2 days and 1 tablet at 8:00 AM on Day 3. Depending upon randomization sequence tolperisone dosing will take place at Visit 1, 2, or 3. Each dose will be a 150 mg tablet of tolperisone, for a total daily dose of 450 mg on Days 1 and 2, and a total dose of 150 mg on Day 3.

6.3.3 Positive Control Dose Level

Cyclobenzaprine will serve as the positive control to demonstrate assay sensitivity. For the cyclobenzaprine treatment arm, cyclobenzaprine will be administered three times per day, with 1 tablet administered at 8:00 AM (AM dose), 2:00 PM (PM dose), and 10:00 PM (HS dose) daily for 2 days and 1 tablet at 8:00 AM on Day 3. Depending upon randomization sequence, cyclobenzaprine dosing will take place at Visit 1, 2, or 3. Each dose will be a 10 mg tablet of cyclobenzaprine, for a total daily dose of 30 mg on Days 1 and 2, and a total dose of 10 mg on Day 3.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

The primary objective of this study is to assess the sedative effect of 150 mg TID tolperisone and 10 mg TID cyclobenzaprine compared to placebo on simulated driving performance and cognitive functioning in healthy adult volunteers. In this crossover study, treatment effects will be assessed following the second initial dose, the morning following nighttime dosing (to assess residual next day effects), and at steady state (i.e., following AM dosing on Day 3).

7.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of 150 mg TID tolperisone dosing for 3 days in healthy volunteers.

7.3 Primary Endpoint

The primary endpoint for this study is simulated driving performance, as measured by Standard Deviation of Lateral Position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim) CVDA (100 km) driving scenario, of tolperisone compared to placebo.

7.4 Secondary Endpoints

The secondary endpoints for this study include:

- SDLP measured by simulated driving performance using CRCDS-MiniSim of tolperisone compared to cyclobenzaprine
- Sleepiness Endpoint – Karolinska Sleepiness Scale (KSS)
- Self-reported readiness to drive (Response to: “Right now do you feel safe to drive?”)
- Visual Analog Scales (VAS) to assess self-reported motivation and appraisal of driving performance
- Cognitive Performance Endpoints
  CogScreen Symbol Digit Coding (SDC) test
  - Number of correct responses
  - Response Accuracy
  - Standard deviation of reaction time
- Driving Performance Endpoints
  Lane exceedance; including number, maximum, and duration
  Speed related measures; including speed deviation, average speed, excessive speed count, and speedings ratio
  Driving safety measures; including excessive Ay (cornering speed threshold -exceeded), and total collisions

Divided attention measures; including correct responses, omission errors, commission errors, reaction rime, and standard deviation of reaction time

- Plasma drug levels and driving performance
- Safety Endpoints

  Clinical Evaluations
  - Vital signs
  - Orthostatic effects
  - Physical examinations
  - 12-lead electrocardiograms (ECGs)

  Laboratory safety tests (blood chemistry, hematology, urinalysis, serum and urine pregnancy tests for women of childbearing potential)

  Adverse events (AEs)

8 SUBJECT DEFINITION

A sufficient number of subjects will be enrolled to ensure a total of 30 subjects will complete all dosing periods, including the driving assessment. Individuals are eligible for this study if they meet all inclusion and no exclusion criteria. The criteria below will be assessed at the Screening visit.

8.1 Inclusion Criteria

1. All healthy volunteer subjects must be in general good health based on screening physical examination (defined as the absence of any clinically relevant abnormalities), medical history, 12-lead ECG, and clinical laboratory values (hematology, serum chemistry and urinalysis).

2. Male and female subjects must be between 21 and 55 years of age, inclusive, at the time of consent.

3. All subjects must be capable of understanding and complying with the protocol and have signed the informed consent document. Female subjects of childbearing potential must sign the Women of Childbearing Potential Addendum to the informed consent form.

4. Subjects are required to have a body mass index (BMI) of 18 to 32 kg/m2, inclusive, at Screening.

5. Subject must be able to reliably perform study assessments (i.e., SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the CVDA practice scenario; and number correct on CogScreen Symbol Digit Coding no less than 1 standard deviation below the mean for healthy adults in the 21-55 year age range); demonstrates the ability to understand task instructions (in English), and is physically capable (e.g., adequate manual dexterity, vision, and hearing), cognitively capable and motivated to perform study tasks.

6. Subject must possess a valid driver's license and be an active driver, and have driven a minimum of 10,000 miles (about 16,000 km) per year for the previous 3 years.

7. Subject must also demonstrate simulator sickness questionnaire scores which are not indicative of simulator sickness as defined in the driving simulation operations manual.

8. Subject must have a regular sleep pattern, not be engaged in shift-work, and in general, have at least 7 hours of sleep each night (bedtime occurs between 21:00 and 24:00 hours).

9. Subject has a score < 10 on the Epworth Sleepiness Scale (ESS).

10. Female subjects must have a negative serum 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 one month 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, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double barrier method (e.g., condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

11. Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

8.2 Exclusion Criteria

1. Subjects who have any clinically significant unstable medical abnormality, chronic disease or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems.

2. Subjects who test positive at screening for hepatitis B surface antigen, hepatitis C antibody or have a history of a positive result.

3. Subjects who are known to be seropositive or test positive at Screening for Human immunodeficiency virus (HIV).

4. Female subjects who are pregnant or lactating.

5. Subjects who have a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion.

6. A history within 2 years of, or current treatment for a sleeping disorder (including excessive snoring, obstructive sleep apnea), or a chronic painful condition that interferes with the subject's sleep.

7. A history of difficulty in falling asleep or staying asleep in the previous 3 months, that is considered clinically significant by the investigator.

8. Subjects who have a history or diagnosis of any of the following conditions:

    a. Primary or secondary insomnia

    b. Narcolepsy

    c. Cataplexy (familial or idiopathic)

    d. Circadian Rhythm Sleep Disorder

    e. Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and rapid eye movement behavior disorder

    f. Sleep-related Breathing Disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome)

    g. Periodic Limb Movement Disorder

h. Restless Legs Syndrome

i. Primary Hypersomnia

j. Excessive Daytime Sleepiness (EDS)

k. Subject has visual or auditory impairment which in the opinion of the investigator would interfere with study related procedures or study conduct.

9. Subjects expected to use any other medication or dietary supplement to promote sleep including over-the-counter sleep medications, during their participation in the study.

10. Subjects who have participated in any investigational study within 30 days prior to screening or are currently participating in another clinical trial.

11. 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.

12. Subjects who have a history of allergic reaction to tolperisone or cyclobenzaprine or any components of these study medications.

13. Use of psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of admission to the Clinical Research Unit (CRU) on Day 1.

14. Presence of a medical or psychiatric condition which could jeopardize the safety of the subject or validity of study results

15. Subjects who consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings per day (where 1 serving is approximately equivalent to 120 mg of caffeine).

16. Subjects who will be working a night shift within 1 week of a visit.

17. Subject who have traveled across 1 or more time zones (transmeridian travel) in the last 2 weeks prior to randomization or is expected to travel across 1 or more time zones during the study.

18. Current smoker (>10 cigarettes or eCigarettes, 3 cigars, or 3 pipes per day) and unwilling to refrain from smoking while confined to the CRU for periods of 3 days.

19. Subjects who have an inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator or designee.

20. Subjects who are a staff member or relative of a staff member.

21. Inability or unwillingness to use adequate contraception (as defined in item 10 of the Inclusion Criteria) during and for 1 month following completion of the study.

22. Has a positive screen for alcohol or other drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates).

9 STUDY DESIGN

9.1 Summary of Study Design

This will be a randomized, placebo-controlled, multiple-dose 3-way cross-over study of the safety and cognitive effects of multiple doses of tolperisone administered TID in 30 male and female healthy volunteers. Treatment groups include 450 mg tolperisone (i.e., 150 mg administered three times daily), 30 mg cyclobenzaprine (i.e., 10 mg administered three times daily), and placebo.

Subject participation will be approximately 3 weeks as outpatients with 3 days each week as overnight clinic participants.

Subjects will be screened within 28 days prior to Treatment Period 1 (Visit 2) for eligibility for participation in the study. The Familiarization and Practice drives on the driving simulator must be completed no more than 21 days prior to Treatment Period 1.

Subjects meeting all inclusion/exclusion criteria will then be admitted to the clinic on Day -1 to be evaluated for continued eligibility. Subjects will perform a practice trial with the driving simulator and the cognitive function test.

Subjects will be dosed on the morning of Day 1. Approximately one hour after the second dose on Day 1, subjects will be administered the cognitive test, followed by the driving simulator examination.

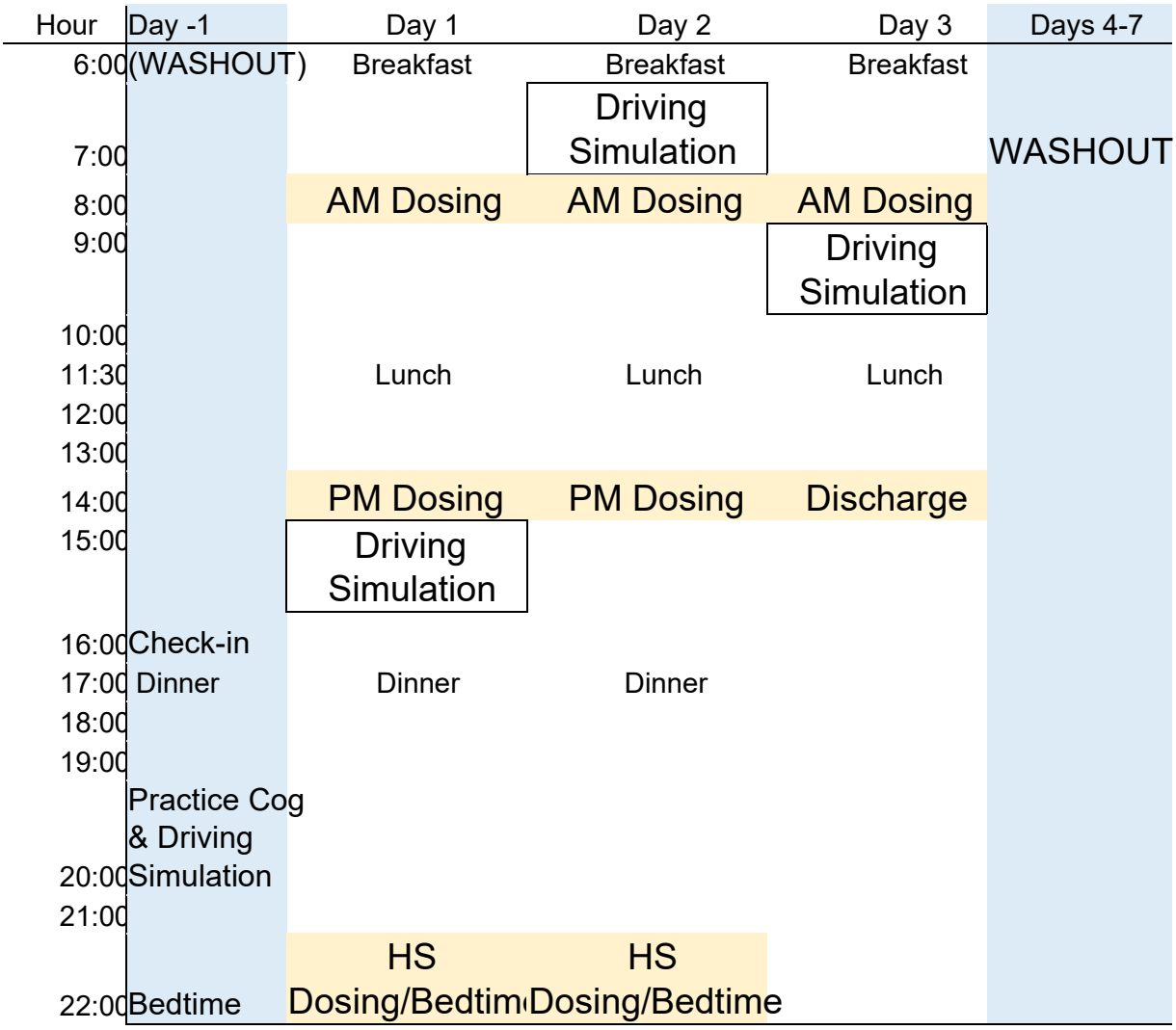
On the morning of Day 2, prior to dosing, subjects will be readministered the cognitive test and driving examination to assess residual next day effects.

Subjects will repeat cognitive testing and the driving examination on the morning of Day 3, after administration of the AM study medication, to evaluate the cumulative effects of 3 days of dosing.

Subjects will be discharged on Day 3 with instructions to return to the clinic on Day 7 and Day 14 to repeat the above procedures with the second and third treatments.

A follow-up phone call will be conducted 1 week (±3 days) following discharge from the clinic on Day 17 to assess for continued safety.

Schematic of Design:



9.2 Meals

During each confinement period, subjects will consume only food and beverages that are provided to them by the CRU staff. Standard meals (e.g. breakfast, lunch, dinner, and evening snack) will be provided to the subjects while confined to the CRU.

9.3 Subject Assignment

Prior to dosing, subjects will be randomly assigned to one of 6 treatment sequences (one for each permutation of treatment groups) and dosed with study medication (tolperisone, cyclobenzaprine or placebo) based upon a randomization scheme provided by Cognitive Research Corporation. Only the qualified person(nel) assigned to prepare and administer the study treatment will have access to the randomization schedule and dispensing records during the study period.

10 DAILY STUDY ACTIVITIES

A complete Schedule of Events can be found in Section 26.

10.1 Screening

Screening (Visit 1) will include procedures as described in the Schedule of Activities and further in the protocol. Prior to randomization, subjects will be screened for simulator sickness and will receive standardized training on the driving simulator and CogScreen Symbol Digit Coding subtest. Screening procedures and screening assessments may be performed on different days but must be completed within 28 days before Period 1 (Visit 2). The Familiarization and Practice drives on the driving simulator must be completed no more than 21 days prior to Period 1.

In addition, each potential study participant will have the following assessments done by the Investigator or designee within 28 days prior to study start: medical and social history and demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and smoking habits. Each potential participant will receive a physical examination, vital signs (including supine and standing blood pressure and heart rate, respiration rate, and body temperature), ECG, ESS, and laboratory tests including hematology, serum chemistry, and urinalysis. Urine drug and alcohol breathalyzer tests will be conducted on all potential subjects. Serum pregnancy tests will be conducted on all females of childbearing potential. AEs will be assessed, and prior and concomitant medication use will be recorded.

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs will be enrolled in the study. The informed consent documents 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.

10.2 Study Periods

10.2.1 CRU Admission Days (Visits 2, 6, and 10: Days -1, 7, and 14)

Within 28 days after the Screening visit, eligible subjects will return for Period 1 (Visit 2). Subjects who meet the inclusion and no exclusion criteria will be instructed to return to the clinic on Day -1 at approximately 4:00 PM. The following will be done on Days -1, 7, and 14:

- A urine pregnancy test will be performed for all females of childbearing potential upon admission to the unit.
- The alcohol breathalyzer and drug screen will be repeated.
- Continued subject eligibility will be verified.
- Dinner will be served at 5:00 PM.

- Subjects will be administered a practice trial of the CogScreen SDC test beginning at approximately 7:40 PM.
- A practice drive (approximately 20 minutes) will be performed on the driving simulator beginning at approximately 8:00 PM.
- Vital signs will be measured.
- Any concurrent medication use will be recorded.
- AEs will be assessed

Subjects will spend the night at the CRU and will go to bed at 10:00 PM.

10.2.2 CRU Inpatient Day 1 (Visits 3, 7, and 11: Days 1, 8, and 15)

On Days 1, 8, and 15, subjects will be awakened and fed a standard breakfast at approximately 6:00 AM. A pre-dose pharmacokinetic (PK) blood sample will be taken within 30 minutes before the first dose. Vital signs will be taken at 7:55 AM (±5 minutes). Subjects will be randomized to a treatment sequence on Day 1 and will be dosed with study medication (tolperisone 150 mg, cyclobenzaprine 10 mg, or placebo) according to the randomization schedule at 8:00 AM (±5 minutes) on Days 1, 8, and 15.

Subjects will be fed a standard lunch at approximately 11:30 AM. Prior to receiving the 2nd dose, vital signs will be taken at 1:55 PM (±5 minutes). Subjects will then be dosed with study medication (tolperisone 150 mg, cyclobenzaprine 10 mg, or placebo) at approximately 2:00 PM. At approximately 2:40 PM, subjects will perform the CogScreen SDC Test and KSS, and indicate their self-perceived safety to drive. Subjects will then be tested (approximately 1 hour after the 2nd dose) with the Country Vigilance-Divided Attention (CVDA) driving scenario on the CRCDS-MiniSim. Upon completion of the driving scenario, subjects will be administered visual analog scales to assess their motivation and self-appraisal of their driving performance. A PK blood sample will be taken post-driving test (15-30 minutes after the drive). A standard dinner will be provided at approximately 5:00 PM.

During the period between the time of awakening and completion of all assessments on dosing days during each treatment period, subjects must stay out of bed. They are permitted to engage in non-strenuous activities. For example, they may read, play games, socialize, work on the computer, or walk around the room.

Subjects are prohibited from having their cellphone turned on during any of the cognitive procedures (eg, driving, CogScreen, forms) throughout the trial (eg, including screening), and from the time of dosing until completion of cognitive testing during each of the treatment periods.

Subjects will receive their 3rd dose of study drug at 10:00 PM (±5 minutes). They will spend the night at the CRU and will go to bed immediately following the 3rd dose. AEs and concurrent medication use will be recorded each day.

10.2.3 CRU Inpatient Day 2 (Visits 4, 8, and 12: Days 2, 9, and 16)

On Days 2, 9, and 16, subjects will be awakened and fed a standard breakfast at approximately 6:00 AM. Beginning at approximately 6:30 AM, subjects will be administered the CogScreen SDC Test and KSS, and indicate their self-perceived safety to drive. Subjects will then be tested

with the CVDA driving scenario on the CRCDS-MiniSim. Upon completion of the driving scenario, subjects will be administered visual analog scales to assess their motivation and self-appraisal of their driving performance. Following completion of the VAS, a pre-dose PK blood sample will be drawn. Vital signs will be taken at 7:55 AM (±5 minutes). Subjects will then be dosed with study medication (tolperisone, cyclobenzaprine, or placebo) at 8:00 AM (±5 minutes).

Subjects will be fed a standard lunch at approximately 11:30 AM. Prior to receiving the 2nd dose, vital signs will be taken at 1:55 PM (±5 minutes). Subjects will then be dosed with study medication (tolperisone, cyclobenzaprine, or placebo) at approximately 2:00 PM. A standard dinner will be provided at approximately 5:00 PM.

Subjects will receive their 3rd dose of study drug at 10:00 PM (±5 minutes). They will spend the night at the CRU and will go to bed immediately following the 3rd dose. AEs and concurrent medication use will be recorded each day.

10.2.4 Clinic Discharge Days (Visits 5, 9, and 13: Days 3, 10, and 17)

On Days 3, 10, and 17, subjects will be awakened and fed a standard breakfast at approximately 6:00 AM. A pre-dose PK blood sample will be taken within 30 minutes before the first dose. Prior to dosing, vital signs will also be taken at 7:55 AM (±5 minutes). Subjects will then be dosed with study medication (tolperisone, cyclobenzaprine, or placebo) at 8:00 AM (±5 minutes).

At approximately 8:40 AM, subjects will be administered the CogScreen SDC Test and KSS, and indicate their self-perceived safety to drive. Subjects will then be tested (approximately 1 hour after the 1st dose) on the CVDA driving scenario on the CRCDS-MiniSim. Upon completion of the driving scenario, subjects will be administered visual analog scales to assess their motivation and self-appraisal of their driving performance. A PK blood sample will be taken between 1.5 and 2 hours after the start of the drive (approximately 10:30 AM to 11:00 AM). Subjects will be fed a standard lunch at approximately 11:30 AM.

Prior to discharge from the CRU, the following will be performed:

- AEs will be recorded.
- Any concurrent medication use will be recorded.
- Vital signs will be measured at 1:55 PM (±5 minutes).

Subjects will leave the clinical site at approximately 2:00 PM. However, they will be advised to stay at the clinical site, if judged necessary by the physician in charge, for safety reasons.

On Day 17, the following will also be done prior to discharge from the CRU:

- Physical Exam.
- Twelve-lead ECG recording will be collected.
- Blood samples for chemistry and hematology will be drawn.
- Urine samples will be collected for urinalysis.

10.3 Day 24 ±3 Days (Visit 14: Follow-up Phone Call)

Approximately 1 week after discharge from the CRU at Visit 13, site staff will conduct a follow up safety phone call. The site staff will ask the subject about their health and any medications they have taken since completing Visit 13.

11 STUDY PROCEDURES

11.1 CVDA Driving Scenario on the CRCDS-MiniSim

The present study employs the CVDA driving scenario, a 62.1 mile (100 km), monotonous, two-lane highway driving task that includes a secondary visual vigilance task (DA). The monotonous Country Vigilance scenario has been demonstrated to be sensitive to detect the effects of fatigue or sleepiness on driving performance [1]. This scenario has been useful in measuring the effects of sleep deprivation, Obstructive Sleep Apnea, chronic primary insomnia, and is sensitive to central nervous system (CNS) depressants (e.g., alcohol and sedating antihistamines). Results obtained using this methodology are comparable to those obtained using over-the-road driving tests [2].

Subjects will perform the driving simulator test at the times specified in Section 10. Data will be captured in electronic format. Details are provided in the Cognitive Research Corporation CRCDS Testing Operations Manual.

11.2 Karolinska Sleepiness Scale

The KSS [3] will be used to assess subjective level of sleepiness. This is a subject self-report measure of situational sleepiness and provides an assessment of alertness/sleepiness at a particular point in time. The KSS has been found to correlate with electroencephalogram and behavioral variables [4]. Subjects indicate their level of alertness versus sleepiness according to the following scale:

Karolinska Sleepiness Scale

1=extremely alert
2
3=alert
4
5=neither alert nor sleepy
6
7=sleepy - but no difficulty remaining awake
8

9=extremely sleepy – fighting sleep

Subjects will self-report their KSS assessments at the times specified in Section 10. The subject's self-reported scores will be recorded in the case report form (CRF).

11.3 Self-perceived Safety to Drive Question

Prior to driving, the subject will be asked a simple question as to whether they feel safe to drive ("Right now do you feel safe to drive?"). The subject will answer "yes" or "no". The answer will be recorded in the CRF.

11.4 Digit Symbol Substitution Test (CogScreen Symbol Digit Coding; SDC)

The CogScreen SDC subtest will be used in this study to measure attention, visual scanning, working memory, and speed of information processing. SDC is a computer analogue of the conventional symbol-substitution task found in the WAIS-R Digit Symbol subtest and the Symbol Digit Modalities Test [5].

SDC will be administered by trained study site personnel. Subjects will perform the test prior to the driving simulation test at the times specified in Section 10. The subject will perform the test by interacting with a touchscreen monitor. Data will be captured in electronic format. Details are provided in the CogScreen® Examiner Manual, CogScreen LLC, 2016.

11.5 Visual Analog Scales (VAS) to Assess Subject's Motivation and Self-Appraisal

After completing the driving simulation, subjects will assess their own performance and their level of motivation to perform at their best during the driving simulation.

Subjects will respond to 2 questions:

1. How well you think you drove for the last 60 minutes?

2. How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects will record their response to each question by drawing a vertical line on a 100 mm horizontal, linear visual analog scale. For the self-assessment of driving performance, one end of the line is marked "Not Satisfactory" and the other end of the line is marked "Satisfactory". For the motivation item, one end of the line is marked "Not Motivated" and the other end is marked "Motivated". Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left. The subject's scores will be recorded in the CRF.

11.6 Vital Signs

Vital signs will include the measurement of supine and standing blood pressure and heart rate, respiration rate, and body temperature. Weight and height will be measured at Screening only.

11.7 Clinical Laboratory Assessments

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

Category	Test Name
Hematology	Hemoglobin Hematocrit Platelets Prothrombin Time (PT)[c] 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)[c]
Urinalysis	Bilirubin Erythrocytes Glucose Ketones Leukocytes Nitrite pH Protein Specific gravity Urobilinogen
Other	Urine drug and alcohol breathalyzer[a,b] Serum/urine Pregnancy[d]

[a] Screening and end of study (EOS) (Day 17).
[b] Includes testing for amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol and opiates – ethanol will be determined by breathalyzer.
[c] Screening only.
[d] Serum pregnancy at Screening and urine pregnancy test at check-in for each period (Days -1, 7, and 14) for females of childbearing potential.
Note: The complete panel of safety labs (other than where footnoted) will be completed at Screening and EOS (Day 17).

11.8 Blood Collection for Tolperisone Plasma Concentrations

Blood samples for the determination of plasma tolperisone concentrations will be drawn prior to each AM dosing on Days 1-3 and post-driving test (15-30 minutes after the drive) on Days 1 and 3.

Blood samples will be collected into heparinized polypropylene tubes (~5.0 mL). The tubes should be mixed immediately after filling by gently inverting the tubes at least 8 to 10 times. Thereafter, the tubes will be centrifuged as soon as possible (within 30 minutes of collection) at a minimum of 1500 g for 15 minutes until cells and plasma are well separated. The resulting

plasma samples will be transferred into two (duplicate) 2 ml cryovial tubes and labeled appropriately.

Plasma samples will be analyzed for tolperisone at Pharm-analyt Labor GmB, Ferdinand-Pichler-Gasse 2, 2500 Baden, Austria, using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method (limit of quantification (LOQ): 1 ng/mL). A detailed method description, including validation, calibration and quality assurance procedures will be included in the bioanalytical report which will be part of the Final Study Report.

11.8.1 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 Pharm-Analyt Labor, GmB, Ferdinand-Pichler-Gasse 2, 2500 Baden, Austria for analysis. 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 analytical laboratory. Detailed shipping instructions will be provided separately.

11.9 Blood Collection Volume for the Study

For Periods 1-3, a total of approximately 25 mL (5 x 5 mL samples) will be collected from each subject for PK analysis. In addition, up to 48 mL of blood will be collected for screening and EOS clinical laboratory evaluations.

11.10 Medical and Social History

A medical and social history will be performed at Screening. Each subject's history of alcohol and drug use will be evaluated. Subject's caffeine consumption and tobacco use will be evaluated to ensure that the protocol will be followed during the course of the study. Continued eligibility will be evaluated on Day -1 and adherence to protocol restrictions will be confirmed throughout the study.

11.11 Physical Examination

A physical examination will be performed at Screening and EOS.

11.12 Epworth Sleepiness Scale

The ESS will be used to exclude subjects who demonstrate excessive sleepiness prior to randomization.

The ESS is an 8-item self-administered questionnaire which measures general level of daytime sleepiness. Individual items on the scale refer to daytime events likely to lead to sleepiness. For each item, the subject rates how likely they are to fall asleep. Subjects are asked to rate how likely they would be to doze off or fall asleep in each situation in contrast to feeling just tired based on their usual way of life in recent times. Each item (or situation such as sitting and reading) is rated on a 4-point scale that ranges from "0 = Would never doze" to "3 = High chance

of dozing." The total score on the ESS is the sum of the responses to each of the 8 items. The range of possible scores for each responder is 0 to 24. A total score of <10 indicates that the individual is not likely suffering from excessive daytime sleepiness. Individual items are not analyzed and have no independent, valid interpretations.

Subjects will complete the ESS at Screening.

11.13 Pregnancy Test

A serum pregnancy test will be performed at Screening for all females of childbearing potential. A urine pregnancy test will also be collected at each CRU check-in visit (Days -1, 7, and 14) 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.

11.14 Study Drug Preparation and Dispensing

The Sponsor will supply Tolperisone 150 mg tablets and matching placebo in an unblinded fashion. The sites or CRO on behalf of the sites will procure the cyclobenzaprine 10 mg tablets. To maintain the double-blind status of the study, the following dispensing and dosing procedures will be followed. The site will identify a qualified unblinded dispenser and alternate(s) who will be responsible for dispensing and administering the study treatment. Aside from dispensing and administering the study treatment, the qualified unblinded dispenser will not be otherwise involved in the study. Cognitive Research Corporation will provide randomization codes directly to the individual identified by the study site. The randomization codes will be kept in a secured area with access limited to only the assigned unblinded dispenser.

The qualified unblinded dispenser will prepare study treatment for each subject in a designated dispensing room. Prior to administering the first dose, the qualified unblinded dispenser will assign the next available randomization number. For each dose administered, the unblinded dispenser will dispense the appropriate tablet into a dispensing cup and complete the study treatment dispensing record. The study treatment dispensing record will remain in a secure locked area with access limited to the qualified unblinded dispenser and the alternate(s). No other study personnel will be present in the designated dispensing room at the time of study treatment dispensing.

11.15 Study Drug Administration

To maintain the study blind for tolperisone 150 mg, cyclobenzaprine 10 mg, and placebo, subjects will be blindfolded during dosing in each Period. Subjects will be given one tablet at approximately 8:00 AM, 2:00 PM, and 10:00 PM daily on Days 1, 2, 8, 9, 15, and 16 and at 8:00 AM on Days 3, 10, and 17. Dosing will be observed by a study staff member (qualified unblinded dispenser); no other study personnel will be present at the time of dosing.

The qualified unblinded dispenser will place the tablet into a dispensing cup. The blindfolded subject will transfer the study treatment directly from the cup into their mouth. All study medications will be administered orally with 4-6 ounces of room temperature water. The subjects

will be instructed to swallow the study tablet whole, without chewing the tablet. Mouth and hand checks will be performed by CRU personnel for each dose of study drug administered.

11.16 Concurrent Medication

- Subjects are to abstain from using psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of Day 1.
- Subjects are to abstain from using any other 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.
- No other medications (with the exception of birth control) are to be taken by the subjects without prior approval from the Principal Investigator and the Sponsor unless it is a medical emergency. All concomitant medication taken during the trial should be recorded with indication, daily dose, and start and stop dates of administration.

11.17 Fluid, Food, and Lifestyle Restrictions

- Subjects are not allowed to consume alcoholic beverages from 48 hours prior to admission to the CRU on Days -1, 7, and 14 until discharged from the CRU following completion of all procedures of each Period on Days 3, 10, and 17. At all other times, alcohol consumption is limited to no more than 3 alcoholic beverages or equivalent (beer [284 mL], wine [125 mL], or distilled spirits [25 mL]) per day.
- The subject will be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Subjects should also be cautioned that the CNS effects of tolperisone and or cyclobenzaprine may be additive to those of alcohol and other CNS depressants.
- Subjects are not allowed to consume caffeine containing products from approximately 1 pm on the days of admission to the CRU (Days -1, 7, and 14) until discharged from the CRU following completion of all procedures on Days 3, 10, and 17. At all other times, caffeinated beverages will be permitted to no more than 4 units per day amounts (1 unit = 120 mg caffeine).
- Subjects are to refrain from vigorous physical activity from 24 hours prior to admission to the CRU on Days -1, 7, and 14 until discharged from the CRU following completion of all procedures on Days 3, 10, and 17.

11.18 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.

11.18.1Premature Termination of Study/Closure of Study Sites

The study may be terminated prematurely if new toxicological findings or 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 Institutional Review Board (IRB).

12 EVALUATION AND REPORTING OF ADVERSE EVENTS

12.1 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 medical qualified designate considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required 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 conditions(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.

A serious adverse event (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).

12.1.1 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.

12.1.2 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.

12.2 Routine Reporting

For the purposes of this study, the period of observation of AEs extends from the signing of the consent at the screening visit until the follow-up call. 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 CRF.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

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 clinical site. Open-ended questions will be asked.

Classification will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 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 CRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF.

Pregnancy in a female subject on the study shall be reported to the sponsor within 24 hours of the knowledge of its occurrence by the Principal Investigator or designee (for pregnancies occurring during the course of the study or immediately following the end 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. 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 SAE experienced during pregnancy will be reported on a SAE Report Form.

12.3 Serious Adverse Event Reporting

The sites will notify the sponsor 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 info is available.

The notification should be directed to the following sponsor representatives:

Gerald M. Penn, M.D.
Medical Director, Mary Rutan Hospital Department of Pathology
205 Palmer Rd.
Bellefontaine, OH 43311
gerald.penn@maryrutan.org
Office: (937) 651-6632
Mobile: (614) 563-7543

An SAE will be considered "unexpected" if the AE is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator 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 within 15 calendar days of the investigator or staff becoming 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.

13 STATISTICAL METHODS

13.1 Determination of Sample Size

This study is designed to test non-inferiority of tolperisone doses relative to placebo, with a cyclobenzaprine test versus placebo to confirm the sensitivity of the simulator to detect treatment effects. The following assumptions were made in the sample size computation: (a) within-subject standard deviation for SDLP is approximately 6 cm; (b) the true difference between tolperisone doses and placebo is 0; and, (c) the non-inferiority (NI) margin is proposed to be 4.4 cm, which is the effect seen with 0.05% of BAC with this driving simulator scenario. Under these assumptions, a sample of 30 subjects would provide in excess of 90% power to establish non-inferiority of tolperisone compared to placebo on any given dosing day in terms of the primary end point, SDLP. This sample size is considered more than adequate to detect cyclobenzaprine differences from placebo, which are anticipated to exceed the NI margin.

13.2 Analysis Populations

- PK Population – All subjects with evaluable plasma concentration data will be included in the pharmacokinetic population.

- Intent-to-Treat (ITT) Population – The ITT Population includes all randomized subjects who receive at least 1 dose of study drug in a given treatment period. This is the analysis population for efficacy analysis. Subjects will (in general) be included in all analyses for which data are non-missing.

- Safety Population – The Safety Population includes all subjects who received at least 1 dose of study drug.

13.3 Statistical Analysis – General Considerations

This section describes the general approaches planned to analyze the data from this study. Additional details of the planned analyses outlined here, will be further described in the SAP.

Doses of tolperisone will be considered non-inferior to placebo if the upper 95% confidence limit on the difference in SDLP between that dose and placebo is less than 4.4 cm (the NI margin). Cyclobenzaprine comparisons to placebo are to assess assay sensitivity and no adjustment to

alpha levels will be made for either the comparison of cyclobenzaprine to placebo or tolperisone, or for secondary endpoints or analyses. Formal statistical tests (where performed) will be two-sided and testing at the alpha=0.05 level of significance.

The sequence of testing to control for multiplicity associated with comparisons of tolperisone to placebo (to assess NI) on multiple days is Day 1 (single-dose) , followed by Day 3 (steady-state), followed by Day 2 (residual effect). Tolperisone will be considered NI to placebo if prior comparisons (at time points in the sequence provided, above) also indicate non-inferiorty.

In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation (SD), median, minimum, and maximum values.

All study data are to be displayed in the data listings.

13.4 Safety Analysis

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

Safety analysis will be based on all subjects enrolled who receive at least 1 dose of the study medication. The safety analysis will evaluate adverse events 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. 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 EOS 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.

13.4.1 Adverse Events

Adverse events will be summarized by treatment, MedDRA terminology (latest version), severity and relation to study drug. The descriptive statistics presented for each system-organ class and preferred term will be the number of subjects with event (N), the percent of subjects exposed with event (%), and the number of events (E). All AEs will be listed by subject, including demographic information, dose, MedDRA latest version, system organ class, and preferred term.

13.4.2 Clinical Laboratory

Clinical laboratory values will be summarized by descriptive statistics by dose. Changes from baseline in clinical laboratory values will be summarized by descriptive statistics. All clinical laboratory values outside normal range (including Screening/Visit 1 and EOS/Day 17

examination) will be listed by treatment and subject number, including demographic information and flagging of values.

13.4.3 Vital Signs

Vital signs (BP, HR and body temperature) will be summarized by dose using descriptive statistics. Changes from baseline in vital signs will be summarized by descriptive statistics for each dose.

13.4.4 Twelve-lead ECG

All ECG endpoints will be listed by dose, subject and time of assessment and summarized by descriptive statistics. Changes from baseline in ECG parameters will be summarized by descriptive statistics by dose.

13.4.5 Physical Examination

Subjects with any changes in the physical examination evaluation from Screening/Visit 1 to EOS/Day 17 will be listed. A description of the study population in terms of baseline measures and demographics will be presented.

13.5 Pharmacokinetic Analysis

The correlations between plasma drug concentrations and key secondary end points will be evaluated. Details of the PK and associated statistical analyses will be included in the Statistical Analysis Plan.

13.6 Pharmacodynamic Analyses

The primary endpoint, SDLP, will be analyzed using a normal theory mixed effects model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used.

Pair-wise comparisons (hypothesis tests) of differences in least squares means, and 95% confidence intervals on differences will be provided for:

Initial dose effect

1. cyclobenzaprine versus placebo following Day 1 PM dose
2. tolperisone versus placebo following Day 1 PM dose
3. tolperisone versus cyclobenzaprine following Day 1 PM dose

Next day residual dose effect

4. cyclobenzaprine versus placebo following Day 2 AM dose
5. tolperisone versus placebo following Day 2 AM dose

6. tolperisone versus cyclobenzaprine following Day 2 AM dose

Steady-state dose effect

7. cyclobenzaprine versus placebo following Day 3 AM dose
8. tolperisone versus placebo following Day 3 AM dose
9. tolperisone versus cyclobenzaprine following Day 3 AM dose

In addition, pair-wise within-subject differences in SDLP greater than 4.4 cm in absolute value (equal to the previously found difference between placebo and 0.05% Blood Alcohol Content (BAC) for the CRCDS) will be compared using McNemar's test. These pair-wise, within subject differences in SDLP will also be tested for symmetry about zero [6] using the maximally selected McNemar test.

Summary statistics will be provided (mean, SD, median, minimum, maximum) for SDLP for each time point and treatment group.

Additional details of analysis for secondary endpoints of VAS, SDC, KSS, and driving performance endpoints will be specified in the SAP.

The relationship between tolperisone plasma drug levels and driving performance (i.e., the primary endpoint of SDLP) will be assessed by correlational analyses.

All pharmacodynamic results will be summarized in tabular format, with summary statistics (number [n], mean, SD, median, minimum, and maximum) and change from baseline, as appropriate by time point.

14 CLINICAL SUPPLIES

14.1 Product Description

Tolperisone:

Tolperisone 150 mg tablets will be provided by the Sponsor. Matching placebo tablets will also be provided.

Cyclobenzaprine:

The positive control product, cyclobenzaprine 10 mg tablets, will be procured for the study by the individual sites or CRO on behalf of the sites.

14.2 Storage Requirements

Study drug supplies should be stored at room temperature and locked in a secure cabinet or room. Only the Investigator or designated third party study personnel will have access to study drug. Only the qualified unblinded dispenser(s) will have access to randomization codes and study treatment assignments.

14.3 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.

In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel when directly handling investigational products.

15 BIOLOGICAL SPECIMENS

Whole blood samples and urine samples will be collected as outlined in the study flow chart for clinical chemistry, hematology, pharmacokinetics, and urinalysis.

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.

16 CLINICAL AND LABORATORY DATA COLLECTION

16.1 Case Report Forms

A CRF 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 a CRF should be completed. If information is not available, it should be documented as such.

The completed CRFs 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.

16.2 Laboratory Results

Laboratory tests (clinical chemistry, hematology and urinalysis) will be analyzed by a certified laboratory and reported to the clinical 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 kept in the study subject file at the site for the Sponsor and will represent the source data.

17 STUDY DOCUMENTATION

17.1 Source Documents

Source documents may include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, biopsy reports, ultrasound photographs, 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 CRFs 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.

17.2 Access to Records

As required by the International Conference on Harmonization-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 CRFs 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.

17.3 Retention of Records

All essential documents and records will be maintained at the study site for a period of 5 years. These documents may be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

18 INSTITUTIONAL REVIEW BOARD (IRB)

The Investigator is responsible for obtaining an approval for conduct of the study from the IRB, as well as approval of all subsequent major changes to the study, in compliance with local law. These approvals must be forwarded to the Sponsor. The IRB will comply with all federal, state, and local laws. Particular attention is drawn to the Food and Drug Administration (FDA) Regulation for IRB (21 CFR, Part 56 and ICH GCP guidelines).

The Investigator shall also obtain from the IRB and submit to the Sponsor, a signed statement indicating that it complies with Good Clinical Practices.

19 ETHICAL CONDUCT OF THE STUDY

The study will be performed according to the Declaration of Helsinki, latest edition (Edinburgh, Scotland, October 2000) with approval from the IRB.

20 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 trial.

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.

21 CONFIDENTIALITY

21.1 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 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.

21.2 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.

22 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 trial-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 CRFs.

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.

23 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 Good Clinical Practices.

24 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.

25 REFERENCES

1. CRCDS Operations Manual. Cognitive Research Corporation. Data on file.
2. Siemen A, Gargano C, Cha J, Drexel M, Bautmans A, Heirman I, Laethem T, Hochadel T, Gheyle L, Bleys K, Beals C, Stoch A, Kay G, & Struyk A. (2015). A randomized, crossover, placebo-controlled clinical trial to assess the sensitivity of the CRCDS Mini-Sim to the next-day residual effects of zopiclone. Therapeutic Advances in Drug Safety, 6 (3), 86-97.
3. Akerstedt T, Gillberg M. (1990). Subjective and objective sleepiness in the active individual. International Journal of Neuroscience, 52, 29–37.
4. Kaida M, Takahashi T, Åkerstedt A, Nakata Y, Otsuka T, Haratani K, et al. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. Clinical Neurophysiology, 117, 1574–81.
5. Wechsler, D. (1981). Wechsler Adult Intelligence Scale-Revised. San Antonio: Psychological Corporation.
6. Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med 2012;31:3178-91.

26 SCHEDULE OF ACTIVITIES

	Screening	Period 1				Period 2				Period 3				Follow-up Phone Call
Procedures	**Day -28 to -2 (V1)**	**Day -1 (V2)**	**Day 1 (V3)**	**Day 2 (V4)**	**Day 3 (V5)**	**Day 7 (V6)**	**Day 8 (V7)**	**Day 9 (V8)**	**Day 10 (V9)**	**Day 14 (V10)**	**Day 15 (V11)**	**Day 16 (V12)**	**Day 17 (V13)**	**Day 24 (±3 days) (V14)**
Informed Consent	X													
Inclusion/Exclusion Review	X	X				X				X				
Medical/Social History	X													
Physical Examination	X												X	
Epworth Sleepiness Scale	X													
Simulator Sickness Questionnaire	X													
Driving Simulation & Cognitive Testing practice	X	X				X				X				
Driving Simulation & Cognitive Testing			X	X	X		X	X	X		X	X	X	
KSS			X	X	X		X	X	X		X	X	X	
Self-Perceived Questionnaire			X	X	X		X	X	X		X	X	X	
VAS			X	X	X		X	X	X		X	X	X	
Vital Sign Measurements[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Standard 12-Lead ECG	X												X	
Laboratory Evaluations[b]	X												X	
Serum/Urine Pregnancy Test[c]	X	X				X				X				
Urine Drug Screening / Breathalyzer	X	X				X				X				
Pharmacokinetic Sampling[d]			X	X	X		X	X	X		X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration			X	X	X		X	X	X		X	X	X	
Discharge from Clinic					X				X				X	

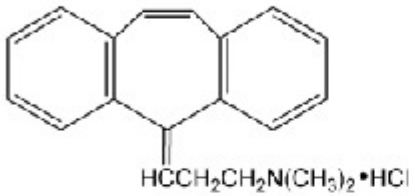
a Vital signs include supine and standing blood pressure and heart rate; respiration rate; and body temperature. Weight and height collected at Visit 1 only.
b Laboratory Evaluations include hematology, serum chemistry, and urinalysis.
c A serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed upon each admission to the unit.
d Blood samples for the determination of plasma tolperisone concentrations will be drawn prior to each AM dosing on Days 1-3 and post-driving test (15-30 minutes after the drive) on Days 1 and 3.

Appendix 1 Prescribing Information for Cyclobenzaprine

CYCLOBENZAPRINE HYDROCHLORIDE- cyclobenzaprine hydrochloride tablet, film coated
Mylan Institutional Inc.

DESCRIPTION

Cyclobenzaprine hydrochloride, USP is a white, crystalline tricyclic amine salt with the molecular formula $C_{20}H_{21}N \cdot HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine hydrochloride is designated chemically as 3-(5 *H* -dibenzo[*a,d*] cyclohepten-5-ylidene) -*N*, *N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Cyclobenzaprine hydrochloride tablets, USP are available as 5 mg, 7.5 mg and 10 mg tablets for oral administration. Each 5 mg, 7.5 mg and 10 mg tablet contains cyclobenzaprine hydrochloride and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate, titanium dioxide, and triacetin. In addition, the 5 mg tablet contains FD&C Blue No. 2 Aluminum Lake and the 10 mg tablet contains lecithin, sodium alginate and yellow iron oxide.

CLINICAL PHARMACOLOGY

Cyclobenzaprine hydrochloride relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

Estimates of mean oral bioavailability of cyclobenzaprine range from 33% to 55%. Cyclobenzaprine exhibits linear pharmacokinetics over the dose range 2.5 mg to 10 mg, and is subject to enterohepatic circulation. It is highly bound to plasma proteins. Drug accumulates when dosed 3 times a day, reaching

steady-state within 3 to 4 days at plasma concentrations about 4-fold higher than after a single dose. At steady-state in healthy subjects receiving 10 mg t.i.d. (n = 18), peak plasma concentration was 25.9 ng/mL (range, 12.8 to 46.1 ng/mL), and area under the concentration-time (AUC) curve over an 8-hour dosing interval was 177 ng·hr/mL (range, 80 to 319 ng·hr/mL).

Cyclobenzaprine is extensively metabolized, and is excreted primarily as glucuronides via the kidney. Cytochromes P450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine is eliminated quite slowly, with an effective half-life of 18 hours (range 8 to 37 hours; n = 18); plasma clearance is 0.7 L/min.

The plasma concentration of cyclobenzaprine is generally higher in the elderly and in patients with hepatic impairment (see PRECAUTIONS: Use in the Elderly and PRECAUTIONS: Impaired Hepatic Function).

Elderly

In a pharmacokinetic study in elderly individuals (≥ 65 yrs old), mean (n = 10) steady-state cyclobenzaprine AUC values were approximately 1.7-fold (171 ng·hr/mL, range 96.1 to 255.3) higher than those seen in a group of 18 younger adults (101.4 ng·hr/mL, range 36.1 to 182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4-fold (198.3 ng·hr/mL, range 155.6 to 255.3 vs. 83.2 ng·hr/mL, range 41.1 to 142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2-fold (143.8 ng·hr/mL, range 96.1 to 196.3 vs. 115.9 ng·hr/mL, range 36.1 to 182.9 for younger females).

In light of these findings, therapy with cyclobenzaprine in the elderly should be initiated with a 5 mg dose and titrated slowly upward.

Hepatic Impairment

In a pharmacokinetic study of 16 subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. Based on the findings, cyclobenzaprine should be used with caution in subjects with mild hepatic impairment starting with the 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of cyclobenzaprine or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of cyclobenzaprine and naproxen or diflunisal was well tolerated with no reported unexpected adverse effects. However combination therapy of cyclobenzaprine with naproxen was associated with more side effects than therapy with naproxen alone, primarily in the form of drowsiness. No well-controlled studies have been performed to indicate that cyclobenzaprine enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of cyclobenzaprine in acute musculoskeletal conditions.

Clinical Studies

Eight double-blind controlled clinical studies were performed in 642 patients comparing cyclobenzaprine hydrochloride 10 mg, diazepam, and placebo. Muscle spasm, local pain and tenderness, limitation of motion, and restriction in activities of daily living were evaluated. In three of these studies there was a significantly greater improvement with cyclobenzaprine than with diazepam, while in the other studies the improvement following both treatments was comparable.

Although the frequency and severity of adverse reactions observed in patients treated with cyclobenzaprine were comparable to those observed in patients treated with diazepam, dry mouth was observed more frequently in patients treated with cyclobenzaprine and dizziness more frequently in those treated with diazepam. The incidence of drowsiness, the most frequent adverse reaction, was similar with both drugs.

The efficacy of cyclobenzaprine hydrochloride 5 mg was demonstrated in two 7-day, double-blind, controlled clinical trials enrolling 1,405 patients. One study compared cyclobenzaprine hydrochloride 5 mg and 10 mg t.i.d. to placebo; and a second study compared cyclobenzaprine hydrochloride 5 mg and 2.5 mg t.i.d. to placebo. Primary endpoints for both trials were determined by patient-generated data and included global impression of change, medication helpfulness, and relief from starting backache. Each endpoint consisted of a score on a 5-point rating scale (from 0 or worst outcome to 4 or best outcome). Secondary endpoints included a physician's evaluation of the presence and extent of palpable muscle spasm.

Comparisons of cyclobenzaprine hydrochloride 5 mg and placebo groups in both trials established the statistically significant superiority of the 5 mg dose for all three primary endpoints at day 8 and, in the study comparing 5 mg and 10 mg, at day 3 or 4 as well. A similar effect was observed with cyclobenzaprine hydrochloride 10 mg (all endpoints). Physician-assessed secondary endpoints also showed that cyclobenzaprine hydrochloride 5 mg was associated with a greater reduction in palpable muscle spasm than placebo.

Analysis of the data from controlled studies shows that cyclobenzaprine produces clinical improvement whether or not sedation occurs.

Surveillance Program

A postmarketing surveillance program was carried out in 7,607 patients with acute musculoskeletal disorders, and included 297 patients treated with cyclobenzaprine hydrochloride 10 mg for 30 days or longer. The overall effectiveness of cyclobenzaprine was similar to that observed in the double-blind controlled studies; the overall incidence of adverse effects was less (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Cyclobenzaprine hydrochloride tablets, USP are indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

Cyclobenzaprine hydrochloride tablets should be used only for short periods (up to 2 or 3 weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine hydrochloride tablets have not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Concomitant use of monoamine oxidase MAO inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures, and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.

Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

Hyperthyroidism.

WARNINGS

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine hydrochloride when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or (MAO) inhibitors. The concomitant use of cyclobenzaprine hydrochloride with MAO inhibitors is contraindicated (see CONTRAINDICATIONS). Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with cyclobenzaprine hydrochloride and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with cyclobenzaprine hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see PRECAUTIONS: Drug Interactions).

Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, cyclobenzaprine should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Impaired Hepatic Function

The plasma concentration of cyclobenzaprine is increased in patients with hepatic impairment (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Hepatic Impairment). These patients are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine. Cyclobenzaprine hydrochloride should be used with caution in subjects with mild hepatic impairment starting with a 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine in subjects with moderate to severe impairment is not recommended.

Information for Patients

Cyclobenzaprine, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. In the elderly, the frequency and severity of adverse events associated with the use of cyclobenzaprine, with or without concomitant medications, is increased. In elderly patients, cyclobenzaprine hydrochloride should be initiated with a 5 mg dose and titrated slowly upward.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of cyclobenzaprine hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Patients should be advised of the signs and symptoms of

serotonin syndrome, and be instructed to seek medical care immediately if they experience these symptoms (see WARNINGS and PRECAUTIONS: Drug Interactions).

Drug Interactions

Cyclobenzaprine may have life-threatening interactions with MAO inhibitors (see CONTRAINDICATIONS). Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. If concomitant treatment with cyclobenzaprine hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see WARNINGS).

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after 26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Reproduction studies have been performed in rats, mice and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when cyclobenzaprine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of cyclobenzaprine in pediatric patients below 15 years of age have not been established.

Use in the Elderly

The plasma concentration of cyclobenzaprine is increased in the elderly (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elderly). The elderly may also be more at risk for CNS adverse events such as hallucinations and confusion, cardiac events resulting in falls or other sequelae,

drug-drug and drug-disease interactions. For these reasons, in the elderly, cyclobenzaprine should be used only if clearly needed. In such patients cyclobenzaprine hydrochloride should be initiated with a 5 mg dose and titrated slowly upward.

ADVERSE REACTIONS

Incidence of most common adverse reactions in the two double-blind*, placebo-controlled 5 mg studies (incidence of > 3% on cyclobenzaprine hydrochloride 5 mg):

	Cyclobenzaprine Hydrochloride 5 mg N = 464	Cyclobenzaprine Hydrochloride 10 mg N = 249	Placebo N = 469
Drowsiness	29%	38%	10%
Dry Mouth	21%	32%	7%
Fatigue	6%	6%	3%
Headache	5%	5%	8%

*Note: Cyclobenzaprine hydrochloride 10 mg data are from one clinical trial. Cyclobenzaprine hydrochloride 5 mg and placebo data are from two studies.

Adverse reactions which were reported in 1% to 3% of the patients were: abdominal pain, acid regurgitation, constipation, diarrhea, dizziness, nausea, irritability, mental acuity decreased, nervousness, upper respiratory infection, and pharyngitis.

The following list of adverse reactions is based on the experience in 473 patients treated with cyclobenzaprine hydrochloride 10 mg in additional controlled clinical studies, 7,607 patients in the postmarketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with cyclobenzaprine were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies with Cyclobenzaprine hydrochloride 10 mg	Surveillance Program with Cyclobenzaprine hydrochloride 10 mg
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg tablet:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice and cholestasis.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Musculoskeletal: Local weakness.

Nervous System and Psychiatric: Seizures; ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis; abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia, serotonin syndrome.

Skin: Sweating.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown

Other reactions, reported rarely for cyclobenzaprine under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a Whole: Chest pain; edema.

Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.

Digestive: Paralytic ileus; tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Myalgia.

Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Photosensitization; alopecia.

Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

DRUG ABUSE AND DEPENDENCE

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when cyclobenzaprine is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Although rare, deaths may occur from overdosage with cyclobenzaprine. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.** Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible. The acute oral LD_{50} of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats, respectively.

Manifestations

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome.

Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under ADVERSE REACTIONS.

Management

General

As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.

In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.

Gastrointestinal Decontamination

All patients suspected of an overdose with cyclobenzaprine should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a pCO_2 < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose of cyclobenzaprine hydrochloride tablets is 5 mg three times a day. Based on individual patient response, the dose may be increased to 10 mg three times a day. Use of cyclobenzaprine hydrochloride tablets for periods longer than 2 or 3 weeks is not recommended (see INDICATIONS AND USAGE).

Less frequent dosing should be considered for hepatically impaired or elderly patients (see PRECAUTIONS: Impaired Hepatic Function, and Use in the Elderly).

HOW SUPPLIED:

Cyclobenzaprine Hydrochloride Tablets, USP are available containing 10 mg of cyclobenzaprine hydrochloride, USP.

The 10 mg tablets are butterscotch yellow film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **751** on the other side. They are available as follows:

NDC 51079-644-20 – Unit dose blister packages of 100 (10 cards of 10 tablets each).
NDC 51079-644-19 – Robot Ready blister packages of 25 (25 cards of 1 tablet each).

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Manufactured by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Distributed by:
Mylan Institutional Inc.
Rockford, IL 61103 U.S.A

S-12205 R1
9/15

PRINICIPAL DISPLAY PANEL - 10 mg

NDC 51079-644-20

Cyclobenzaprine
Hydrochloride
Tablets, USP
10 mg

100 Tablets (10 x 10)

Each film-coated tablet
contains: Cyclobenzaprine
hydrochloride, USP 10 mg

Usual Adult Dosage: See accompanying prescribing information.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]

Manufactured by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Rx only

S-4589 R7

Packaged and Distributed by:

Mylan Institutional Inc.

Rockford, IL 61103 U.S.A.

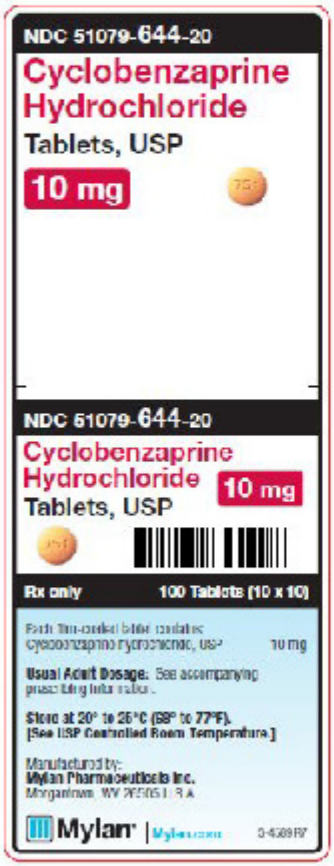
This unit dose package is not child resistant.

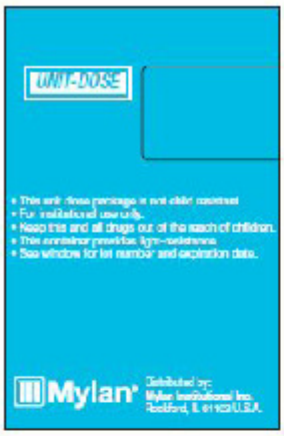
For institutional use only.

Keep this and all drugs out of the reach of children.

This container provides light-resistance.

See window for lot number and expiration date.





CYCLOBENZAPRINE HYDROCHLORIDE

cyclobenzaprine hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51079-644(NDC:0378-0751)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
CYCLOBENZAPRINE HYDROCHLORIDE (UNII: 0VE05JYS2P) (CYCLOBENZAPRINE - UNII:69O5WQQ5TI)	CYCLOBENZAPRINE HYDROCHLORIDE	10 mg

Inactive Ingredients	
Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYDEXTROSE (UNII: VH2XOU12IE)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	
SODIUM ALGINATE (UNII: C269C4G2ZQ)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	

Product Characteristics			
Color	yellow (butterscotch yellow)	Score	no score
Shape	ROUND	Size	8mm
Flavor		Imprint Code	M;751
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51079-644-20	100 in 1 BOX, UNIT-DOSE	08/25/1997	
1	NDC:51079-644-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:51079-644-19	25 in 1 BOX, UNIT-DOSE	10/01/1997	
2	NDC:51079-644-17	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA073144	08/25/1997	

Labeler - Mylan Institutional Inc. (039615992)

Revised: 9/2016 Mylan Institutional Inc.

16.1.3 List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) and Sample Consent Form

Chesapeake IRB
6940 Columbia Gateway Drive, Suite 110
Columbia, MD 21046
IRB Chairperson: Joy Cavagnaro, Ph.D., DABT, RAC

The IRB membership roster dated 04/06/2017 and sample informed consent forms are provided.

CONSENT TO TAKE PART IN A RESEARCH STUDY
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Name of Research Study:	**Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo**
Protocol Number:	**115**
Name of Company Sponsoring the Research Study:	**Neurana Pharmaceuticals, Inc.**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Additional Contact(s): (Study Staff)	**«AdditionalStaffMemberContacts»**
Address:	**«PiLocations»**

You have been asked to take part in a research study. First, we want you to know that taking part in a research study is entirely voluntary. Second, you need to know that there are important differences between being cared for in a research study and being cared for by your doctor outside of a research study. Participating in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information. Being in this study does not replace your regular medical care. Therefore, it is important that you understand the difference between the regular care you get from your doctor and what is involved in this research study.

This consent document gives you important information about the research study. Please read this information carefully before deciding to take part. No one can make you take part and you can stop at any time. If you choose to take part in this research study, you will need to sign and date this consent document and you will receive a copy of this signed and dated document for your records.

This research study is being conducted for Neurana Pharmaceuticals, Inc. Neurana Pharmaceuticals, Inc. is sponsoring the study and will be paying the study doctor and the study site to conduct the study.

The following sections describe the research study. Before you decide to take part, please take as much time as you need to ask questions with the study team, with family and friends, or with your personal physician or other healthcare professionals. The study team will fully answer any questions you have before you make a decision.

1. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this research study is to compare how certain drugs affect how you feel, how you perform on a simulated driving task, and your cognitive functioning after taking the drug. This research study will compare the effects of the following study drugs: tolperisone, cyclobenzaprine, and placebo.

During the study, subjects will receive oral doses of 450 mg tolperisone (150 mg administered three times daily), 30 mg cyclobenzaprine (10 mg administered three times daily), and placebo. Subjects will receive each study treatment for the 3 days, with only 1 dose being administered on the 3rd day.

Tolperisone is marketed in multiple countries in Europe, and Asia, for muscle spasticity (tightness or stiffness) and muscle spasms. It will be studied in the United States to determine its safety and efficacy (how well it works).

Cyclobenzaprine has been approved by the Food and Drug Administration in the USA as Flexiril®. It is available by prescription to relax muscles. The 10 mg dose three times per day represents the highest dose typically administered for adults with muscle spasms.

Researchers use a placebo (sugar pill) to see if the study drug works better or is safer than not taking any drug.

Because this is a research study, the study drugs will be given to you only during this study and not after the study is over.

2. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY?

There will be about 30 male and female participants between the ages of 21-55 years enrolled in this study. The study is being conducted at 1 or 2 different research sites in the USA. About 15-30 people will be enrolled at this site.

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

If you decide to participate, you will be in this study for at least 3 weeks but no longer than 7 weeks. You will need to visit the research site 5 times during the study, including 3 visits with 3 overnight stays.

4. WHAT WILL HAPPEN BEFORE THE RESEARCH STUDY BEGINS?

If you decide to take part in this study, we will ask you to sign this consent document before we conduct any study-related activities.

5. WHAT WILL HAPPEN DURING THE RESEARCH STUDY?

Screening Visit (Visit 1)
After signing and dating this consent document, you will begin in the study with a screening visit. The purpose of the screening visit is to find out if you meet all of the requirements to take part in this research study.

During the screening visit, you will be asked to have the following tests and activities or assessments:

- Provide a social and medical history;
- An electrocardiogram (ECG, a recording of the heart's rhythm) will be performed;
- You will also be asked about any medications and treatments you are currently taking. It is important to tell the study site staff if you are taking any "over the counter" medications, herbal or natural remedies or dietary supplements;
- Physical examination and vital signs (includes an examination of major body systems, height, weight, blood pressure while lying down and standing, pulse [heartrate], oral temperature, and respiratory [breathing] rate);
- You will provide a urine sample and be given a breathalyzer test. The urine sample will be used for safety laboratory assessments (urinalysis) and to detect drugs and alcohol that are not allowed in this study, including illegal drugs (such as: amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates). Your urine sample must test negative for all of these drugs, and your breathalyzer must test negative for alcohol to participate in the study;
- You will be required to complete a questionnaire regarding your sleep habits;
- Collection of about 2 teaspoons of blood. This blood sample will be used to determine if you have HIV (Human Immunodeficiency Virus) or hepatitis (liver problem), and will also measure blood counts (hematology) and organ function (blood chemistry). For females who could become pregnant, the sample will also be used to help confirm if you are pregnant. If the HIV or hepatitis result is positive, the physician in charge of the study or designee will personally inform you and at that moment he or she will indicate the procedure to follow. Note that a positive result for HIV, hepatitis B, or hepatitis C must be reported to the public health department as required by law. If you have any questions about what information is required to be reported, please ask the Study Doctor or study staff.

  All blood collections for this study will be taken by individual needle sticks into one of the veins in your arm.

The following assessments may also be done while you are at the site for your screening visit or the study staff may ask that you come back to the site within the next 4 weeks to complete them. If you return within 4 weeks to complete the following assessments, this will be an extra study visit (so you will have 6 visits in total).

- You will learn more about driving simulators and practice for about 20 minutes. A driving simulator is an open booth with a steering wheel and computer screens. You will then complete a questionnaire that asks you how you feel after driving the simulator. Once you have completed the questionnaire you will complete another drive in the simulator for about 20 minutes.
- You will complete a practice test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The practice test will be completed on a computer.

By the end of the screening period, the study doctor will determine if you are eligible to continue into the study. If you will not be able to continue in the study, the study doctor will explain why.

Study Treatment Period 1

Visit 2 (Day -1 to Day 3)

Day -1

You will return to the site for your next visit (visit 2) in the evening (4:00 PM) before the first drug administration.

When you arrive, the following tests, activities or assessments will be performed:

- Review of any changes to your health;
- You will be asked how you are feeling and if there have been any changes in your medications since the last visit. It is important to tell your study doctor if you are taking any “over the counter” medication, herbal or natural remedies or dietary supplements, including multi-vitamins;
- You will provide a urine sample. The urine sample will be used to determine if you are pregnant (if you are a female who can become pregnant) and to test for certain drugs that are not allowed in this study, including illegal drugs. Your urine sample must test negative for all of these drugs to participate in the study;
- You will take a breathalyzer test;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff;
- You will complete a practice test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The practice test will be completed on a computer;
- You will be required to complete a 20-minute practice drive in the driving simulator;

- You will be served dinner.

After completing the assessments, the Study Doctor will determine if you are eligible to continue in the study. If you are not eligible, the Study Doctor will explain why. If you are eligible for the study, you will stay at the clinical site overnight and continue with the visit 2 procedures (Day 1). If you enroll in the study, you will receive each of the study drugs (tolperisone, cyclobenzaprine, and placebo) for 3 days, but at different study visits.

Day 1

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast;
- You will be asked how you are feeling and if there have been any changes in your medications since yesterday. It is important to tell your study doctor if you are taking any "over the counter" medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- About one teaspoon of blood will be collected prior to study drug administration to compare how much study drug is in your system later;
- You will be randomly assigned (by chance) and administered a study drug. This is a double-blind study, which means neither you nor the study team will know to which study drug you are assigned at each study visit. This is done to make sure the results of the study cannot be unfairly influenced by anyone. In case of urgent need, the study team can get this information quickly. At each visit, you will be blindfolded while you take your study drug and will not know what study drug you took.
- You will be fed lunch;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your afternoon dose;
- You will receive your afternoon dose of study drug;
- You will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;

- You will be fed dinner;
- You will receive your evening dose of study drug at about 10:00 PM;
- You will spend the night at the clinical site and will go to bed immediately after taking your evening dose of study drug.

Day 2

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast;
- You will be asked how you are feeling and if there have been any changes in your medications since the previous day. It is important to tell your study doctor if you are taking any "over the counter" medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- You will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much drug is in your system;
- You will receive your morning dose of study drug at about 8:00 AM;
- You will be fed lunch at about 11:30 AM;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your afternoon dose;
- You will receive your afternoon dose of study drug;
- You will be fed dinner at about 5:00 PM;
- You will receive your evening dose of study drug at about 10:00 PM;
- You will spend the night at the clinical site and will go to bed immediately after taking your evening dose of study drug.

Day 3

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast;

- You will be asked how you are feeling and if there have been any changes in your medications since the previous day. It is important to tell your study doctor if you are taking any “over the counter” medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;
- You will receive your morning dose of study drug at about 8:00 AM;
- About 30 minutes after your morning dose, you will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;
- You will be fed lunch at about 11:30 AM;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff at about 1:55 PM;

When all assessments in Study Treatment 1 have been completed, a study staff member will schedule your next visit, which will occur in about 4 days. You will leave the clinical site at approximately 2:00 PM and can go home. However, you will be advised to stay at the clinical site, if the study doctor in charge feels it is necessary, for safety reasons. You will not be allowed to drive yourself home. You must arrange for someone to take you home.

Study Treatment Periods 2 and 3

Study Treatment Periods 2 and 3 will be exactly the same as Study Treatment Period 1. In between each visit (Study Treatment Period), you will not take any study drug while you are at home.

At the end of the Study Treatment Period 3, after you have completed all study procedures and prior to discharge, the following tests, activities or assessments will be performed:

- An ECG will be performed;

- You will be asked how you are feeling and if there have been any changes in your medications since the last visit. It is important to tell your study doctor if you have taken any "over the counter" medication, herbal or natural remedies or dietary supplements, including multi-vitamins;
- Physical examination and vital signs (includes an examination of major body systems, weight, blood pressure while lying down and standing, pulse [heart rate], oral temperature, and respiratory [breathing] rate);
- About 2 teaspoons of blood will be collected. This blood sample will be used to measure blood counts (hematology) and organ function (blood chemistry).
- You will provide a urine sample. The urine sample will be used for safety laboratory assessments (urinalysis).

Follow-Up

Approximately 1 week after discharge from the clinical site after Study Treatment Period 3, site staff will conduct a follow-up safety phone call. The site staff will ask you subject about your health and any medications you have taken since being discharged from the clinical site. Following this phone call, your participation in the study will be complete.

6. HOW WILL I RECEIVE THE STUDY DRUG?

This study involves 3 different study treatments (tolperisone, cyclobenzaprine, and placebo). You will receive a different study treatment during each of the 3 Study Treatment Periods. You will receive study drug 3 times on Day 1, 3 times on Day 2, and 1 time on Day 3 of each Study Treatment Period. Prior to receiving study drug, you will be blindfolded so that you will not see which study drug you are taking. Each dose of study drug will consist of 1 tablet. You will take each dose of study drug with water.

7. WHAT HAPPENS WHEN I FINISH TAKING THE STUDY DRUG?

About 1 week after you have taken the last dose of study drug and completed the Study Treatment Period 3 assessments, you will receive a follow-up safety phone call from the clinical site staff. Following this phone call, your participation in the study will be complete.

8. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS OF BEING IN THIS RESEARCH STUDY?

Any clinical research may have some risks, which may include things that could make you sick, make you feel uncomfortable, or harm you. You might experience negative effects related to the study drug while participating in the study. All research participants taking part in the study will be watched carefully for any negative effects; however, the study team does not know all the effects that the study drug may have on you. The study team may give you medicines to help reduce negative effects. These effects may be mild or serious. In some cases, these effects might be long lasting, or permanent, and may even be life threatening.

The negative events that are the most likely to happen to you if you take part in this study are listed below.

For tolperisone:

Common Side Effects:

- Muscle weakness
- Headache
- Dizziness
- Somnolence (drowsiness)
- Vertigo (loss of balance)
- Low blood pressure
- Nausea
- Vomiting
- Abdominal (stomach) discomfort
- Indigestion
- Dry mouth

For cyclobenzaprine:

Common Side Effects:

- Drowsiness
- Somnolence ("sleepiness" or "drowsiness" – a state of strong desire for sleep, or sleeping for unusually long periods)
- Dry mouth
- Fatigue (tiredness)
- Headache
- Dizziness
- Abdominal pain
- Acid reflux
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Irritability
- Decreased mental sharpness
- Nervousness
- Upper respiratory infection
- Pharyngitis (sore throat)
- Asthenia (weakness or lack of energy)
- Indigestion
- Unpleasant taste
- Blurred vision

Placebo Risk:
Taking a placebo may be similar to not taking any medication.

Risks and possible discomforts you might experience from the study procedures include:

Other Risks

Since the use of the study drug is investigational when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. You should get medical help and contact the Study Doctor right away if you think you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck. Other allergic reactions may include rash, hives, or blisters.

If you experience the symptoms of an allergic reaction while outside the clinic, please go to the nearest hospital emergency department. If you experience these symptoms while inside the clinic, please tell the study staff.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

Blood draws: A blood draw may cause faintness, swelling of the vein, pain, redness, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

Simulator Sickness: You may feel sick after driving the simulator. This is a feeling similar to motion sickness.

HIV/Hepatitis Testing: Some of your blood will be tested for HIV, hepatitis B, and hepatitis C. The study doctor may be required by law to report the result of these tests to the local health authority.

Pregnancy Related Risks / Use of Birth Control

Women who are pregnant or nursing a child may not participate in this study. To participate in the study, you must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant during the study or for at least one month after you complete the study. If there is any possibility that you may become pregnant during the study, you will not be able to participate in the study. If you suspect that you have become pregnant during the study, you must notify the study doctor immediately. You will not be able to participate in the study if you become pregnant.

Acceptable methods of birth control must be used for 14 days before taking the study drug and for 30 days after the end of the study. Acceptable methods of birth control include oral, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double-barrier method (for example, condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

Pregnancy Follow Up

If you become pregnant during the study or within 1 month after your last dose of study drug, please tell the Study Doctor immediately. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this study. The Study Doctor will ask if your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you agree, this information will be provided to the study sponsor for safety monitoring follow-up.

9. ARE THERE ANY SPECIAL INSTRUCTIONS TO FOLLOW WHILE PARTICIPATING IN THIS STUDY?

During this study, it is important that you:

- Do not travel across time zones or work on a rotating shift during the study;
- Do not work a night shift for one week before each study visit;
- Do not consume alcohol for 48 hours prior to any study visit;
- Do not consume caffeine or caffeinated products (medicines, supplements, foods, beverages or confections) from 1:00 PM on the day of each study visit until you return home after the visit;
- Nicotine-containing products may not be used while at the research site;
- Do not practice vigorous physical activity for 24 hours prior to any study visit;
- The study doctor will tell you what medications are not allowed during the study. They include:
    - Do not use any sleep aids [for example, diphenhydramine hydrochloride (Benadryl, Unisom SleepGels, Tylenol PM, Nyquil ZZZ, Advil PM, others), doxylamine succinate (Unisom SleepTabs, Kirkland, others), melatonin, and valerian];
    - Do not use any cold or allergy products containing an antihistamine (for example, Dimetapp® Cold and Allergy Elixir, Chlor-Trimeton®, Dramamine®, Benadryl® Allergy, Nytol®, Sominex®, Vicks NyQuil®, Alka-Seltzer® Plus Night-Time Cold Medicine);
- Go to bed between 9:00 pm and 12:00 am on the night before every study visit.

10. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

This research study is for research purposes only. The only alternative is to not take part in this study.

11. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

This study is for research purposes only. There is no direct benefit to you from your participation in the study. Information learned from the study may help other people in the future.

12. WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH STUDY?

If you become ill or are hurt while you are in the study, get the medical care that you need right away. You must notify the study doctor immediately of any injury. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact the study doctor using the contact information on the first page of this form.

If you experience a research injury, the study doctor or study site will provide or arrange for medical treatment at no cost to you. Neurana Pharmaceuticals, Inc. will cover the costs of this treatment. A research injury is any physical injury or illness caused by your taking part in this study. If you are injured by a medical treatment or procedure that you would have received even if you were not in this study, that is not a research injury. To help avoid injury, it is very important to follow all study directions. The sponsor has no plans for other financial compensation.

To pay these medical expenses, the sponsor will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

You still have the right to make a claim through the legal system even if you sign this form, accept medical care, or accept payment for medical expenses.

13. IS BEING IN THE STUDY VOLUNTARY?

Yes. Taking part in this research study is up to you. You may choose not to take part, or you can change your mind and withdraw (drop out) later. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could change your mind about taking part or continuing in this research study. If you want to drop out, you should tell us. We will make sure you can end the study in the safest way. We will also talk to you about follow-up care, if needed.

The study doctor or the study sponsor may decide to take you out of the study without your agreement if:

- You do not follow the directions of the study team;
- The study doctor decides that the study is not in your best interest;
- The study is stopped by the study sponsor, the institutional review board (IRB) (a group of people who review the research to protect your rights), or by a regulatory agency;
- You become pregnant, intend to become pregnant or are nursing a child during this study.

If you withdraw or are removed from the study, biological samples (for example, blood or urine samples) that have been collected from you (but not yet fully analyzed) can be destroyed by making a request to the study doctor in person or at the telephone number listed on the first page of this form. However, any data already generated from your samples will be kept to preserve the value of the study.

14. WHAT WILL I HAVE TO PAY FOR IF I TAKE PART IN THIS RESEARCH STUDY?

There will be no charge to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

The study drugs (tolperisone, cyclobenzaprine, and placebo) and all other study procedures will be provided at no charge while you are participating in this study.

Will I Be Paid For Taking Part In This Study?

You will be paid [total amount] to cover your out-of-pocket expenses. You will get $_____ for each study visit you complete. You will be paid at the end of each study visit / monthly for completed study visits / quarterly (every 3 months) for completed study visits. If you leave the study early for any reason, you will be paid for each study visit you have already completed. You will not be compensated for any delay or cancellation occurring before the first visit of this study.

Neurana Pharmaceuticals, Inc. may use information from your sample(s) to develop products or processes from which they may make a profit. There are no plans to pay you or provide you with any products developed from this research. Neurana Pharmaceuticals, Inc. will own all products or processes that are developed using information from your sample(s).

15. CONFIDENTIALITY

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location. Please understand that representatives of the Food and Drug Administration (FDA), the sponsor of this study, and any other entities included in the section below, may review your study data for the purposes of verifying research data, and will see personal identifiers.

16. IF I TAKE PART IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

A federal regulation, known as the Privacy Rule, gives you certain rights concerning the privacy of your health information. The Privacy Rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. However, if you do not, you will not be able to take part in the study.

Who Will Use and Disclose My Health Information?

The study team may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication.

What Health Information will be Used and Disclosed?

During the study, the study team will use, collect, and record health information about you (your “records”). Your records will include any information about you that the study team needs to do the study, including information from the procedures described above. Your records may include other health information about you and will include identifying information such as your name and address. The study team will record some of this information on “study forms” provided by the study sponsor. Your name or address will not appear on the study forms. Instead, you will be assigned a participant identification number.

The study team will send the completed study forms to the study sponsor and may share this information with others, as described below.

Representatives from the groups identified below may also need to look at your records (which identify you) to make sure that the information on the study forms is correct or that the study was conducted properly. Reviews like that will take place at the research site or where the records are stored and can take place after the study is over.

Who Will Receive My Health Information?

Your study information may be shared with the following people or groups:

- The study sponsor (Neurana Pharmaceuticals, Inc.) or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other research sites
- The Institutional Review Board (ethics committee) that approved this study and any other committees responsible for overseeing the research
- Government health agencies (such as the Food and Drug Administration) in the US or other countries
- Your study doctor may inform your primary physician about your participation in the study if you have a primary physician and you agree to the primary physician being informed.

Will My Information Be Protected by the Privacy Rule After it is Disclosed to Others?

The study site is required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. However, the study sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the study sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs or diseases or to help design better studies in the future. When using your information in these ways, the study sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services. This could result in transfer of your information outside the United States. **However, your name will never appear in any study sponsor reports or publications, or in any future disclosures by the study sponsor.**

What Happens if I Leave the Study Early?

If you stop participating in the study early for any reason, the study team will tell the study sponsor why. If the study team asks you to come to any more study visits and if you agree, the study team will send the study sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire?

This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over. The review of your medical records (described above) may also take place after the study is over.

May I Take Back My Authorization?

You have the right to take back (revoke) your Authorization at any time by writing to the study doctor at the address listed on the first page of this form.

If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already collected information if that is necessary for the reliability (the scientific value) of the study. The study sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look At My Study Information?

You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

17. WHERE CAN I FIND ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY OR THE RESEARCH RESULTS?

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. It may be many years; however, before research results are posted.

18. GETTING ANSWERS TO YOUR QUESTIONS OR CONCERNS ABOUT THE STUDY

You can ask questions about this consent form or the study (before you decide to start the study, at any time during the study, or after completion of the study). Questions may include:

- Who to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a study subject;
- Eligibility to participate in the research;
- The study doctor's or study site's decision to exclude you from participation;
- Results of tests and/or procedures;
- Other questions, concerns, or complaints.

Contact the study doctor or study staff listed on the first page of this form with any questions, concerns or complaints.

19. GETTING ANSWERS TO YOUR QUESTIONS ABOUT YOUR RIGHTS AS A RESEARCH SUBJECT

This study has been reviewed by an Institutional Review Board (IRB). This Committee reviewed this study to help ensure that your rights and welfare are protected and that this study is carried out in an ethical manner.

For questions about your rights as a research subject, contact:

- By mail:
  Study Subject Adviser
  Chesapeake IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@chesapeakeirb.com

Please reference the following number when contacting the Study Subject Adviser: Pro00021652.

An IRB is a group of people who review research studies to protect the rights and welfare of research participants.

20. SIGNATURES:

I have read the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to take part in this study. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I do not give up any of my legal rights by signing this consent document.

I have been told that I will receive a signed and dated copy of this document.

_____
Printed name of Study Participant

_____ _____ _____
Signature of Study Participant Date of signature Time

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____ _____
Signature of the Person Conducting the Consent Discussion † Date of signature Time

†The Investigator, or a suitably qualified and trained person designated by the Investigator to conduct the informed consent process, must sign and date the consent document during the same interview when the subject signs the consent document.

21. WOMEN OF CHILDBEARING POTENTIAL ADDENDUM

If you are a female of childbearing potential, by signing this form you agree to use adequate contraception during and for 1 month following completion of the study.

You must have a negative serum 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 one month 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, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double-barrier method (for example, condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

_____
Printed name of Study participant

_____ _____ _____
Signature of Study participant Date of signature Time

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____ _____
Signature of the Person Conducting the Consent Discussion † Date of signature Time

†The investigator, or a suitably qualified and trained person designated by the investigator to conduct the informed consent addendum process, must sign and date the consent document during the same interview when the subject signs the consent document.

CONSENT TO TAKE PART IN A RESEARCH STUDY AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Name of Research Study:	**Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo**
Protocol Number:	**115**
Name of Company Sponsoring the Research Study:	**Neurana Pharmaceuticals, Inc.**
Principal Investigator: (Study Doctor)	**David P. Walling, Ph.D.**
Telephone:	**(866) 787-4257** **(714) 910-9247 (24 Hours)**
Address:	**Collaborative Neuroscience Network** **2600 Redondo Avenue, Suite 500** **Long Beach, CA 90806**

You have been asked to take part in a research study. First, we want you to know that taking part in a research study is entirely voluntary. Second, you need to know that there are important differences between being cared for in a research study and being cared for by your doctor outside of a research study. Participating in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information. Being in this study does not replace your regular medical care. Therefore, it is important that you understand the difference between the regular care you get from your doctor and what is involved in this research study.

This consent document gives you important information about the research study. Please read this information carefully before deciding to take part. No one can make you take part and you can stop at any time. If you choose to take part in this research study, you will need to sign and date this consent document and you will receive a copy of this signed and dated document for your records.

This research study is being conducted for Neurana Pharmaceuticals, Inc. Neurana Pharmaceuticals, Inc. is sponsoring the study and will be paying the study doctor and the study site to conduct the study.

The following sections describe the research study. Before you decide to take part, please take as much time as you need to ask questions with the study team, with family and friends, or with your personal physician or other healthcare professionals. The study team will fully answer any questions you have before you make a decision.

1. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this research study is to compare how certain drugs affect how you feel, how you perform on a simulated driving task, and your cognitive functioning after taking the drug. This research study will compare the effects of the following study drugs: tolperisone, cyclobenzaprine, and placebo.

During the study, subjects will receive oral doses of 450 mg tolperisone (150 mg administered three times daily), 30 mg cyclobenzaprine (10 mg administered three times daily), and placebo. Subjects will receive each study treatment for the 3 days, with only 1 dose being administered on the 3rd day.

Tolperisone is marketed in multiple countries in Europe, and Asia, for muscle spasticity (tightness or stiffness) and muscle spasms. It will be studied in the United States to determine its safety and efficacy (how well it works).

Cyclobenzaprine has been approved by the Food and Drug Administration in the USA as Flexiril®. It is available by prescription to relax muscles. The 10 mg dose three times per day represents the highest dose typically administered for adults with muscle spasms.

Researchers use a placebo (sugar pill) to see if the study drug works better or is safer than not taking any drug.

Because this is a research study, the study drugs will be given to you only during this study and not after the study is over.

2. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY?

There will be about 30 male and female participants between the ages of 21-55 years enrolled in this study. The study is being conducted at 1 or 2 different research sites in the USA. About 15-30 people will be enrolled at this site.

3. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

If you decide to participate, you will be in this study for at least 3 weeks but no longer than 7 weeks. You will need to visit the research site 5 times during the study, including 3 visits with 3 overnight stays.

4. WHAT WILL HAPPEN BEFORE THE RESEARCH STUDY BEGINS?

If you decide to take part in this study, we will ask you to sign this consent document before we conduct any study-related activities.

5. WHAT WILL HAPPEN DURING THE RESEARCH STUDY?

Screening Visit (Visit 1)
After signing and dating this consent document, you will begin in the study with a screening visit. The purpose of the screening visit is to find out if you meet all of the requirements to take part in this research study.

During the screening visit, you will be asked to have the following tests and activities or assessments:

- Provide a social and medical history;
- An electrocardiogram (ECG, a recording of the heart's rhythm) will be performed;
- You will also be asked about any medications and treatments you are currently taking. It is important to tell the study site staff if you are taking any "over the counter" medications, herbal or natural remedies or dietary supplements;
- Physical examination and vital signs (includes an examination of major body systems, height, weight, blood pressure while lying down and standing, pulse [heartrate], oral temperature, and respiratory [breathing] rate);
- You will provide a urine sample and be given a breathalyzer test. The urine sample will be used for safety laboratory assessments (urinalysis) and to detect drugs and alcohol that are not allowed in this study, including illegal drugs (such as: amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opiates). Your urine sample must test negative for all of these drugs, and your breathalyzer must test negative for alcohol to participate in the study;
- You will be required to complete a questionnaire regarding your sleep habits;
- Collection of about 2 teaspoons of blood. This blood sample will be used to determine if you have HIV (Human Immunodeficiency Virus) or hepatitis (liver problem), and will also measure blood counts (hematology) and organ function (blood chemistry). For females who could become pregnant, the sample will also be used to help confirm if you are pregnant. If the HIV or hepatitis result is positive, the physician in charge of the study or designee will personally inform you and at that moment he or she will indicate the procedure to follow. Note that a positive result for HIV, hepatitis B, or hepatitis C must be reported to the public health department as required by law. If you have any questions about what information is required to be reported, please ask the Study Doctor or study staff.

  All blood collections for this study will be taken by individual needle sticks into one of the veins in your arm.

The following assessments may also be done while you are at the site for your screening visit or the study staff may ask that you come back to the site within the next 4 weeks to complete them. If you return within 4 weeks to complete the following assessments, this will be an extra study visit (so you will have 6 visits in total).

- You will learn more about driving simulators and practice for about 20 minutes. A driving simulator is an open booth with a steering wheel and computer screens. You will then complete a questionnaire that asks you how you feel after driving the simulator. Once you have completed the questionnaire you will complete another drive in the simulator for about 20 minutes.
- You will complete a practice test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The practice test will be completed on a computer.

By the end of the screening period, the study doctor will determine if you are eligible to continue into the study. If you will not be able to continue in the study, the study doctor will explain why.

Study Treatment Period 1

Visit 2 (Day -1 to Day 3)

Day -1

You will return to the site for your next visit (visit 2) in the evening (4:00 PM) before the first drug administration.

When you arrive, the following tests, activities or assessments will be performed:

- Review of any changes to your health;
- You will be asked how you are feeling and if there have been any changes in your medications since the last visit. It is important to tell your study doctor if you are taking any “over the counter” medication, herbal or natural remedies or dietary supplements, including multi-vitamins;
- You will provide a urine sample. The urine sample will be used to determine if you are pregnant (if you are a female who can become pregnant) and to test for certain drugs that are not allowed in this study, including illegal drugs. Your urine sample must test negative for all of these drugs to participate in the study;
- You will take a breathalyzer test;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff;
- You will complete a practice test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The practice test will be completed on a computer;
- You will be required to complete a 20-minute practice drive in the driving simulator;

- You will be served dinner.

After completing the assessments, the Study Doctor will determine if you are eligible to continue in the study. If you are not eligible, the Study Doctor will explain why. If you are eligible for the study, you will stay at the clinical site overnight and continue with the visit 2 procedures (Day 1). If you enroll in the study, you will receive each of the study drugs (tolperisone, cyclobenzaprine, and placebo) for 3 days, but at different study visits.

Day 1

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast at 6:00 AM;
- You will be asked how you are feeling and if there have been any changes in your medications since yesterday. It is important to tell your study doctor if you are taking any "over the counter" medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- About one teaspoon of blood will be collected prior to study drug administration to compare how much study drug is in your system later;
- You will be randomly assigned (by chance) and administered a study drug. This is a double-blind study, which means neither you nor the study team will know to which study drug you are assigned at each study visit. This is done to make sure the results of the study cannot be unfairly influenced by anyone. In case of urgent need, the study team can get this information quickly. At each visit, you will be blindfolded while you take your study drug and will not know what study drug you took.
- You will be fed lunch;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your afternoon dose;
- You will receive your afternoon dose of study drug;
- You will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;

- You will be fed dinner;
- You will receive your evening dose of study drug at about 10:00 PM;
- You will spend the night at the clinical site and will go to bed immediately after taking your evening dose of study drug.

Day 2

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast at 6:00 AM;
- You will be asked how you are feeling and if there have been any changes in your medications since the previous day. It is important to tell your study doctor if you are taking any "over the counter" medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- You will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much drug is in your system;
- You will receive your morning dose of study drug at about 8:00 AM;
- You will be fed lunch at about 11:30 AM;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your afternoon dose;
- You will receive your afternoon dose of study drug;
- You will be fed dinner at about 5:00 PM;
- You will receive your evening dose of study drug at about 10:00 PM;
- You will spend the night at the clinical site and will go to bed immediately after taking your evening dose of study drug.

Day 3

The next day, upon awakening, the following tests, activities or assessments will be performed:

- You will be served breakfast at 6:00 AM;

- You will be asked how you are feeling and if there have been any changes in your medications since the previous day. It is important to tell your study doctor if you are taking any “over the counter” medication, herbal or natural remedies or dietary supplements;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff prior to your morning dose;
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;
- You will receive your morning dose of study drug at about 8:00 AM;
- About 30 minutes after your morning dose, you will be asked whether you feel safe to drive;
- You will complete some pen and paper questions about how sleepy you are;
- You will complete a test that measures how your brain performs with regard to memory, attention, perception, action, problem solving and mental imagery capacity. The test will be completed on a computer;
- You will take a 60-minute drive on the driving simulator. You will be videotaped during this drive.
- You will then complete a pen and paper test as to your own performance on the driving simulator and how ready and motivated you felt to drive at your best on the driving simulator.
- About one teaspoon of blood will be drawn to use to compare how much study drug is in your system;
- You will be fed lunch at about 11:30 AM;
- Blood pressure while lying down and standing, pulse, oral temperature, and respiratory rate (breathing rate) will be obtained by the study staff at about 1:55 PM;

When all assessments in Study Treatment 1 have been completed, a study staff member will schedule your next visit, which will occur in about 4 days. You will leave the clinical site at approximately 2:00 PM and can go home. However, you will be advised to stay at the clinical site, if the study doctor in charge feels it is necessary, for safety reasons. You will not be allowed to drive yourself home. You must arrange for someone to take you home.

Study Treatment Periods 2 and 3

Study Treatment Periods 2 and 3 will be exactly the same as Study Treatment Period 1. In between each visit (Study Treatment Period), you will not take any study drug while you are at home.

At the end of the Study Treatment Period 3, after you have completed all study procedures and prior to discharge, the following tests, activities or assessments will be performed:

- An ECG will be performed;

- You will be asked how you are feeling and if there have been any changes in your medications since the last visit. It is important to tell your study doctor if you have taken any "over the counter" medication, herbal or natural remedies or dietary supplements, including multi-vitamins;
- Physical examination and vital signs (includes an examination of major body systems, weight, blood pressure while lying down and standing, pulse [heart rate], oral temperature, and respiratory [breathing] rate);
- About 2 teaspoons of blood will be collected. This blood sample will be used to measure blood counts (hematology) and organ function (blood chemistry).
- You will provide a urine sample. The urine sample will be used for safety laboratory assessments (urinalysis).

Follow-Up

Approximately 1 week after discharge from the clinical site after Study Treatment Period 3, site staff will conduct a follow-up safety phone call. The site staff will ask you subject about your health and any medications you have taken since being discharged from the clinical site. Following this phone call, your participation in the study will be complete.

6. HOW WILL I RECEIVE THE STUDY DRUG?

This study involves 3 different study treatments (tolperisone, cyclobenzaprine, and placebo). You will receive a different study treatment during each of the 3 Study Treatment Periods. You will receive study drug 3 times on Day 1, 3 times on Day 2, and 1 time on Day 3 of each Study Treatment Period. Prior to receiving study drug, you will be blindfolded so that you will not see which study drug you are taking. Each dose of study drug will consist of 1 tablet. You will take each dose of study drug with water. You must swallow the study tablet whole, without chewing the tablet.

7. WHAT HAPPENS WHEN I FINISH TAKING THE STUDY DRUG?

About 1 week after you have taken the last dose of study drug and completed the Study Treatment Period 3 assessments, you will receive a follow-up safety phone call from the clinical site staff. Following this phone call, your participation in the study will be complete.

8. WHAT ARE THE RISKS AND POSSIBLE DISCOMFORTS OF BEING IN THIS RESEARCH STUDY?

Any clinical research may have some risks, which may include things that could make you sick, make you feel uncomfortable, or harm you. You might experience negative effects related to the study drug while participating in the study. All research participants taking part in the study will be watched carefully for any negative effects; however, the study team does not know all the effects that the study drug may have on you. The study team may give you medicines to help reduce negative effects. These effects may be mild or serious. In some cases, these effects might be long lasting, or permanent, and may even be life threatening.

The negative events that are the most likely to happen to you if you take part in this study are listed below.

For tolperisone:

Common Side Effects:

- Muscle weakness
- Headache
- Dizziness
- Somnolence (drowsiness)
- Vertigo (loss of balance)
- Low blood pressure
- Nausea
- Vomiting
- Abdominal (stomach) discomfort
- Indigestion
- Dry mouth

For cyclobenzaprine:

Common Side Effects:

- Drowsiness
- Somnolence ("sleepiness" or "drowsiness" – a state of strong desire for sleep, or sleeping for unusually long periods)
- Dry mouth
- Fatigue (tiredness)
- Headache
- Dizziness
- Abdominal pain
- Acid reflux
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Irritability
- Decreased mental sharpness
- Nervousness
- Upper respiratory infection
- Pharyngitis (sore throat)
- Asthenia (weakness or lack of energy)
- Indigestion
- Unpleasant taste
- Blurred vision

Placebo Risk:
Taking a placebo may be similar to not taking any medication.

Risks and possible discomforts you might experience from the study procedures include:

Other Risks

Since the use of the study drug is investigational when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening. You should get medical help and contact the Study Doctor right away if you think you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck. Other allergic reactions may include rash, hives, or blisters.

If you experience the symptoms of an allergic reaction while outside the clinic, please go to the nearest hospital emergency department. If you experience these symptoms while inside the clinic, please tell the study staff.

It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the study drug. The phone numbers for the study team are on the first page of this document.

Blood draws: A blood draw may cause faintness, swelling of the vein, pain, redness, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

Simulator Sickness: You may feel sick after driving the simulator. This is a feeling similar to motion sickness.

HIV/Hepatitis Testing: Some of your blood will be tested for HIV, hepatitis B, and hepatitis C. The study doctor may be required by law to report the result of these tests to the local health authority.

Pregnancy Related Risks / Use of Birth Control

Women who are pregnant or nursing a child may not participate in this study. To participate in the study, you must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant during the study or for at least one month after you complete the study. If there is any possibility that you may become pregnant during the study, you will not be able to participate in the study. If you suspect that you have become pregnant during the study, you must notify the study doctor immediately. You will not be able to participate in the study if you become pregnant.

Acceptable methods of birth control must be used for 14 days before taking the study drug and for 30 days after the end of the study. Acceptable methods of birth control include oral, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double-barrier method (for example, condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

Pregnancy Follow Up

If you become pregnant during the study or within 1 month after your last dose of study drug, please tell the Study Doctor immediately. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this study. The Study Doctor will ask if your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you agree, this information will be provided to the study sponsor for safety monitoring follow-up.

9. ARE THERE ANY SPECIAL INSTRUCTIONS TO FOLLOW WHILE PARTICIPATING IN THIS STUDY?

During this study, it is important that you:

- Do not travel across time zones or work on a rotating shift during the study;
- Do not work a night shift for one week before each study visit;
- Do not consume alcohol for 48 hours prior to any study visit;
- Do not consume caffeine or caffeinated products (medicines, supplements, foods, beverages or confections) from 1:00 PM on the day of each study visit until you return home after the visit;
- Nicotine-containing products may not be used while at the research site;
- Do not practice vigorous physical activity for 24 hours prior to any study visit;
- The study doctor will tell you what medications are not allowed during the study. They include:
    - Do not use any sleep aids [for example, diphenhydramine hydrochloride (Benadryl, Unisom SleepGels, Tylenol PM, Nyquil ZZZ, Advil PM, others), doxylamine succinate (Unisom SleepTabs, Kirkland, others), melatonin, and valerian];
    - Do not use any cold or allergy products containing an antihistamine (for example, Dimetapp® Cold and Allergy Elixir, Chlor-Trimeton®, Dramamine®, Benadryl® Allergy, Nytol®, Sominex®, Vicks NyQuil®, Alka-Seltzer® Plus Night-Time Cold Medicine);
- Go to bed between 9:00 pm and 12:00 am on the night before every study visit.
- Do not have your cellphone turned on during any of the cognitive procedures (for example, driving, CogScreen, forms) and from the time you receive the study drug until you complete the cognitive tests during each treatment period.

10. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

This research study is for research purposes only. The only alternative is to not take part in this study.

11. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

This study is for research purposes only. There is no direct benefit to you from your participation in the study. Information learned from the study may help other people in the future.

12. WHAT HAPPENS IF I AM INJURED AS A RESULT OF TAKING PART IN THIS RESEARCH STUDY?

If you become ill or are hurt while you are in the study, get the medical care that you need right away. You must notify the study doctor immediately of any injury. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact the study doctor using the contact information on the first page of this form.

If you experience a research injury, the study doctor or study site will provide or arrange for medical treatment at no cost to you. Neurana Pharmaceuticals, Inc. will cover the costs of this treatment. A research injury is any physical injury or illness caused by your taking part in this study. If you are injured by a medical treatment or procedure that you would have received even if you were not in this study, that is not a research injury. To help avoid injury, it is very important to follow all study directions. The sponsor has no plans for other financial compensation.

To pay these medical expenses, the sponsor will need to know some information about you like your name, date of birth, and social security number or Medicare Health Insurance Claim Number. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

You still have the right to make a claim through the legal system even if you sign this form, accept medical care, or accept payment for medical expenses.

13. IS BEING IN THE STUDY VOLUNTARY?

Yes. Taking part in this research study is up to you. You may choose not to take part, or you can change your mind and withdraw (drop out) later. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could change your mind about taking part or continuing in this research study. If you want to drop out, you should tell us.

We will make sure you can end the study in the safest way. We will also talk to you about follow-up care, if needed.

The study doctor or the study sponsor may decide to take you out of the study without your agreement if:

- You do not follow the directions of the study team;
- The study doctor decides that the study is not in your best interest;
- The study is stopped by the study sponsor, the institutional review board (IRB) (a group of people who review the research to protect your rights), or by a regulatory agency;
- You become pregnant, intend to become pregnant or are nursing a child during this study.

If you withdraw or are removed from the study, biological samples (for example, blood or urine samples) that have been collected from you (but not yet fully analyzed) can be destroyed by making a request to the study doctor in person or at the telephone number listed on the first page of this form. However, any data already generated from your samples will be kept to preserve the value of the study.

14. WHAT WILL I HAVE TO PAY FOR IF I TAKE PART IN THIS RESEARCH STUDY?

There will be no charge to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

The study drugs (tolperisone, cyclobenzaprine, and placebo) and all other study procedures will be provided at no charge while you are participating in this study.

Will I Be Paid For Taking Part In This Study?

You will be compensated according to the following payment schedule.

Screening, Day 3, Day 10, and Day 17: $75.00

Day -1, Day 1, Day 2, Day 7, Day 8, Day 9, Day 14, Day 15, and Day 16: $200.00

Day 24 Phone Call: $38.00

If you do not complete the study, you will only be compensated for the visits that you have completed. You will be compensated for completed visits at least quarterly with final payment within 30 days of the end of your participation the study.

If you test positive for illicit drugs during the screening process, you will not be paid for that visit. If you are participating in this or any other study at more than one site, you will not be paid for any visits.

If you enroll in this study in more than one site please be aware that you will be terminated from the study as this is prohibited.

Neurana Pharmaceuticals, Inc. may use information from your sample(s) to develop products or processes from which they may make a profit. There are no plans to pay you or provide you with any products developed from this research. Neurana Pharmaceuticals, Inc. will own all products or processes that are developed using information from your sample(s).

15. CONFIDENTIALITY

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location. Please understand that representatives of the Food and Drug Administration (FDA), the sponsor of this study, and any other entities included in the section below, may review your study data for the purposes of verifying research data, and will see personal identifiers.

16. IF I TAKE PART IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

A federal regulation, known as the Privacy Rule, gives you certain rights concerning the privacy of your health information. The Privacy Rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. However, if you do not, you will not be able to take part in the study.

Who Will Use and Disclose My Health Information?

The study team may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication.

What Health Information will be Used and Disclosed?

During the study, the study team will use, collect, and record health information about you (your "records"). Your records will include any information about you that the study team needs to do the study, including information from the procedures described above. Your records may include other health information about you and will include identifying information such as your name and address. The study team will record some of this information on "study forms" provided by the study sponsor. Your name or address will not appear on the study forms. Instead, you will be assigned a participant identification number.

The study team will send the completed study forms to the study sponsor and may share this information with others, as described below.

Representatives from the groups identified below may also need to look at your records (which identify you) to make sure that the information on the study forms is correct or that the study was conducted properly. Reviews like that will take place at the research site or where the records are stored and can take place after the study is over.

Who Will Receive My Health Information?

Your study information may be shared with the following people or groups:

- The study sponsor (Neurana Pharmaceuticals, Inc.) or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other research sites
- The Institutional Review Board (ethics committee) that approved this study and any other committees responsible for overseeing the research
- Government health agencies (such as the Food and Drug Administration) in the US or other countries
- Your study doctor may inform your primary physician about your participation in the study if you have a primary physician and you agree to the primary physician being informed.

Will My Information Be Protected by the Privacy Rule After it is Disclosed to Others?

The study site is required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. However, the study sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the study sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs or diseases or to help design better studies in the future. When using your information in these ways, the study sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services. This could result in transfer of your information outside the United States. **However, your name will never appear in any study sponsor reports or publications, or in any future disclosures by the study sponsor.**

What Happens if I Leave the Study Early?

If you stop participating in the study early for any reason, the study team will tell the study sponsor why. If the study team asks you to come to any more study visits and if you agree, the study team will send the study sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire?

This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over. The review of your medical records (described above) may also take place after the study is over.

May I Take Back My Authorization?

You have the right to take back (revoke) your Authorization at any time by writing to the study doctor at the address listed on the first page of this form.

If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already collected information if that is necessary for the reliability (the scientific value) of the study. The study sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

In California and any other state that requires an expiration date, the Authorization will expire 50 years after you sign this authorization document.

_____ ____/____/____
Signature of Research Subject Date

_____
Printed Name of Research Subject

May I Look At My Study Information?

You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

17. WHERE CAN I FIND ADDITIONAL INFORMATION ABOUT THIS RESEARCH STUDY OR THE RESEARCH RESULTS?

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. It may be many years; however, before research results are posted.

18. GETTING ANSWERS TO YOUR QUESTIONS OR CONCERNS ABOUT THE STUDY

You can ask questions about this consent form or the study (before you decide to start the study, at any time during the study, or after completion of the study). Questions may include:

- Who to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a study subject;
- Eligibility to participate in the research;
- The study doctor's or study site's decision to exclude you from participation;
- Results of tests and/or procedures;
- Other questions, concerns, or complaints.

Contact the study doctor or study staff listed on the first page of this form with any questions, concerns or complaints.

19. GETTING ANSWERS TO YOUR QUESTIONS ABOUT YOUR RIGHTS AS A RESEARCH SUBJECT

This study has been reviewed by an Institutional Review Board (IRB). This Committee reviewed this study to help ensure that your rights and welfare are protected and that this study is carried out in an ethical manner.

For questions about your rights as a research subject, contact:

- By mail:
  Study Subject Adviser
  Chesapeake IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@chesapeakeirb.com

Please reference the following number when contacting the Study Subject Adviser: Pro00021652.

An IRB is a group of people who review research studies to protect the rights and welfare of research participants.

20. SIGNATURES:

I have read the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to take part in this study. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I do not give up any of my legal rights by signing this consent document.

I have been told that I will receive a signed and dated copy of this document.

_____
Printed name of Study Participant

_____ _____ _____
Signature of Study Participant Date of signature Time

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____ _____
Signature of the Person Conducting the Consent Discussion † Date of signature Time

†The Investigator, or a suitably qualified and trained person designated by the Investigator to conduct the informed consent process, must sign and date the consent document during the same interview when the subject signs the consent document.

21. WOMEN OF CHILDBEARING POTENTIAL ADDENDUM

If you are a female of childbearing potential, by signing this form you agree to use adequate contraception during and for 1 month following completion of the study.

You must have a negative serum 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 one month 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, injected, vaginal or patch contraceptives, IUD (copper intrauterine device), or double-barrier method (for example, condom, diaphragm or cervical cap with spermicidal foam, cream, gel or suppository).

_____
Printed name of Study participant

_____ _____ _____
Signature of Study participant Date of signature Time

PERSON OBTAINING CONSENT

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____ _____
Signature of the Person Conducting the Consent Discussion † Date of signature Time

†The investigator, or a suitably qualified and trained person designated by the investigator to conduct the informed consent addendum process, must sign and date the consent document during the same interview when the subject signs the consent document.

Chesapeake IRB Membership Roster

OHRP/FDA IRB Registration Number: IRB#00000790

Member's Name	Profession	Status	GP*Mo-5	GP*Tu-1	GP*W-2	GP*Th-4	GP*F-3	Affiliated Y/N
Willard Abe Andes, M.D.	Oncologist - Hematology/Oncology	Physician Scientist	Alternate	Alternate	Alternate	Member	Alternate	N
Sarah Altier, Ed.D.	Educator	Non-Scientist	Member	Alternate	Alternate	Alternate	Alternate	N
Joy Cavagnaro, Ph.D., DABT, RAC	Toxicologist/Regulatory Affairs Consultant	Other Scientist	Alternate	Member**	Alternate	Alternate	Alternate	N
George Cianciolo, Ph.D.	Immunologist	Other Scientist	Alternate	Alternate	Alternate	Member	Member	N
Laura Clark, M.D.	Physician –Anesthesiologist	Physician Scientist	Alternate	Alternate	Alternate	Member	Alternate	N
Thomas H. Closson, B.S., RPh, CIP	Pharmacist	Other Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	Y
Walter Durkin, M.D.	Physician – Oncologist	Physician Scientist	Member	Alternate	Alternate	Alternate	Alternate	N
Daniel Fernicola, M.D., FACC	Physician-Cardiologist	Physician Scientist	Alternate	Member	Alternate	Alternate	Alternate	N
Janelle Flowers, M.Ed.	Guidance Counselor	Non-Scientist	Member	Alternate	Alternate	Alternate	Member	N
Robert Frenck, Jr. M.D.	Physician - Pediatrics, Infectious Disease	Physician Scientist	Alternate	Alternate	Alternate	Member	Alternate	
Paul Goebel Jr., B.S., CIP	Human Subject Protection Consultant	Non Scientist	Alternate	Member	Alternate	Member	Alternate	N
C. Vernon Gray, Ph.D.	County Government Administrator	Non Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
Melinda Group, B.S., R.Ph.	Hospital and Research Pharmacist	Other Scientist	Member	Alternate	Alternate	Alternate	Member	N
G. Levering Keely, B.S.N., M.P.A.	Nurse, Device specialist	Other Scientist	Alternate	Alternate	Alternate	Member	Alternate	N
Janet Keyser, B.S.	Clinical Development & Compliance Consultant	Other Scientist	Alternate	Alternate	Alternate	Alternate	Member	N
Peter LaCount, MHS, M.Ed.	Compliance Director	Non Scientist	Alternate	Member	Alternate	Alternate	Alternate	N
Kelley Letter, B.B.A.	Regulatory Affairs, IRB specialist	Non Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	y
Joseph Markoff, M.D., Ph.D.	Ophthalmologist, Neuroscientist	Physician Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N
Joseph McPhillips, Ph.D.	Clinical Research Consultant	Other Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
David C. Miller, M.D., MBA, FAAFP	Physician-Family Practice	Physician Scientist	Alternate	Alternate	Alternate	Alternate	Member	N
Tiffani Moss, BA, MS, CIP	Regulatory Affairs, IRB specialist	Non Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	Y
Karen Near, M.D., M.S.	Physician – Internal Med., Infectious Diseases	Physician Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
Kyle Patrick, D.O.	Physician - Medical Research	Physician Scientist	Alternate	Alternate	Alternate	Member	Alternate	N
Gail Povar, M.D., M.P.H., FACP	Physician-Internal Medicine	Physician Scientist	Alternate	Member	Alternate	Alternate	Alternate	N
Troy Priest, B.A., J.D.	Attorney	Non Scientist	Alternate	Alternate	Alternate	Member**	Member**	N
Albert Razzetti, M.D.	Physician – Internal Medicine / Pulmonologist	Physician Scientist	Member	Alternate	Alternate	Alternate	Alternate	N
Mitchell Reddish, Ph.D.	University Professor, Religious Studies, Ethicist	Non-Scientist	Member**	Alternate	Alternate	Alternate	Alternate	N
Aixa Rey, Pharm.D.	Clinical Pharmacist	Other Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
Deborah Reynolds, R.N., OCN	Oncology Nurse	Other Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N
Carol Sadorra, Ph.D.	Research Consultant	Non Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N
Clifford Selsky, M.D. Ph.D.	Phsician – Pediatrics, Hematology Oncology	Physician Scientist	Member	Alternate	Alternate	Alternate	Alternate	N
John Sever, M.D., Ph.D.	Physician-Pediatrics, Infectious Diseases	Physician Scientist	Alternate	Member	Alternate	Alternate	Member	N
Cheri Smith, B.BA., LCSW-C	Social Work, Subject Advocate	Non Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
Karen Gabel Speroni, Ph.D., R.N.	Nursing Research Director/Consultant	Other Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N
Neil W. Steinhorn, J.D.	Attorney, Prisoner Representative	Non Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N

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Member's Name	Profession	Status	GP*Mo-5	GP*Tu-1	GP*W-2	GP*Th-4	GP*F-3	Affiliated Y/N
Amy Strahl, CIP	Regulatory Affairs, IRB specialist	Non Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	Y
Anita Tarzian, Ph.D., R.N.	Ethics and Research Consultant / Ethicist	Other Scientist	Alternate	Alternate	Member**	Alternate	Alternate	N
Marc Teitelbaum, M.D., M.S.	Physician – OB/Gyn, Clinical Safety Director	Physician Scientist	Member	Member	Alternate	Alternate	Alternate	N
Katherine Tkaczuk, M.D.	Physician-Oncologist/Hematologist	Physician Scientist	Alternate	Alternate	Member	Alternate	Alternate	N
Susan Trimbo, Ph.D.	Scientific Affairs Consultant – Nutrition	Other Scientist	Alternate	Alternate	Alternate	Alternate	Alternate	N

*General Panel (GP), **Chair

Chesapeake IRB is organized and operates in compliance with FDA regulations as described in 21 CFR Parts 50 and 56, DHHS regulations as described in 45 CFR 46, guidelines resulting from the International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and potentially The Common Rule as appropriate. In addition, the IRB operates in compliance with the portions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA Privacy Rule) that apply to research, as described in 45 CFR Parts 160 and 164.

Chesapeake IRB has been awarded Full Accreditation from the Association for the Accreditation of Human Research Protection Programs®, Inc. (AAHRPP).