16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

16.1.9.2 MiniSim Drive Summary Measures

16.1.9.1 Statistical Analysis Plan

The Statistical Analysis Plan dated 13 October 2017 is attached.

STATISTICAL ANALYSIS PLAN

PROTOCOL: 115

Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo

SPONSOR: Neurana Pharmaceuticals, Inc.
3525 Del Mar Heights Rd, #609
San Diego, CA 92130

PRODUCT: Tolperisone hydrochloride, NR100

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DATE: October 13, 2017

STATUS: Final Version 1.0

Statistical Analysis Plan

Protocol: 115

Final Version: 1.0 Date: 13-Oct-2017

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1 LIST OF ABBREVIATIONS

AE(s)	Adverse event(s)
BAC	Blood Alcohol Content
BMI	Body mass index
CRCDS-MiniSim	Cognitive Research Corporation Driving Simulator-MiniSim
CRF	Case report form
CVDA	Country Vigilance-Divided Attention
DA	Divided attention
ECG	Electrocardiogram
EOS	End of study
ESS	Epworth Sleepiness Scale
HIV	Human immunodeficiency virus
ITT	Intent-to-Treat
KSS	Karolinska Sleepiness Scale
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
N	Number
NI	Non-inferiority
PK	Pharmacokinetic
PT	Preferred term
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
TEAE	Treatment Emergent Adverse Event
TID	Three times a day
VAS	Visual analog scale

2 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the study entitled “Driving Simulation Cross-Over Study of Sedative Effects of Tolperisone Compared to Cyclobenzaprine and Placebo” finalized 28 April 2017.

3 STUDY OBJECTIVE

3.1 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).

3.2 SECONDARY OBJECTIVE

The secondary objective of this study is:

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

4 STUDY DESIGN

4.1 DURATION OF STUDY

The total duration of study participation will be approximately 4 weeks (range 4-8 weeks), including Screening and Follow-up. Subject participation will be approximately 3 weeks as outpatients with 3 days each week as overnight clinic participants.

4.2 NUMBER OF SUBJECTS (STUDY POPULATION)

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.

4.3 DESIGN AND TREATMENTS

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 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.

A schematic of the study design is presented in Table 1.

Table 1 Schematic of Design

Hour	Day -1	Day 1	Day 2	Day 3	Days 4-7
6:00	**(WASHOUT)**	Breakfast	Breakfast	Breakfast	
7:00			Driving Simulation		WASHOUT
8:00		AM Dosing	AM Dosing	AM Dosing	
9:00				Driving Simulation	
10:00					
11:30		Lunch	Lunch	Lunch	
12:00					
13:00					
14:00		PM Dosing	PM Dosing	Discharge	
15:00		Driving Simulation			
16:00	**Check-in**				
17:00	Dinner	Dinner	Dinner		
18:00					
19:00					
20:00	Practice Cog & Driving Simulation				
21:00					
22:00	Bedtime	HS Dosing/Bedtime	HS Dosing/Bedtime		

4.4 TREATMENTS

4.4.1 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.

4.4.2 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.

4.5 RANDOMIZATION

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.

4.5.1 SCHEDULE OF EVENTS AND ASSESSMENTS

The schedule of study events and assessments are presented in Table 2.

Table 2 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	

	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)**
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

5 OUTCOME VARIABLE DEFINITIONS

5.1 SCREENING AND BASELINE ASSESSMENT

Screening:
Demographic characteristics of age, sex, race, ethnicity, height, weight, and body mass index (BMI), informed consent, substance use (social history), inclusion criteria, exclusion criteria, medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), laboratory results, urine drug screen, alcohol screen, pregnancy test, Epworth Sleepiness Scale (ESS), CogScreen Training and practice, driving simulator training and practice, simulator sickness questionnaire, prior medications, and concomitant medications will be collected at Screening.

Baseline Assessment:
Eligibility, vital signs, urine drug screen, alcohol screen, pregnancy test, pharmacokinetic sampling, CogScreen practice, driving simulator practice, adverse events, and concomitant medications will be collected at Baseline.

5.2 PHARMACODYNAMIC ASSESSMENTS

5.2.1 CVDA DRIVING SCENARIO ON THE CRCDS-MiniSim

The present study employs the Cognitive Research Corporation Driving Simulator (CRCDS) Country Vigilance-Divided Attention (CVDA) driving scenario, a 62.1 mile (100 km), monotonous, two-lane highway driving task that includes a secondary visual vigilance task (Divided Attention DA). The monotonous Country Vigilance scenario has been demonstrated to be sensitive to detect the effects of fatigue or sleepiness on driving performance [CRCDS]. 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 [Siemen, 2015].

Subjects will perform the driving simulator test at the times specified in Table 2. Data will be captured in electronic format. Details are provided in the Cognitive Research Corporation CRCDS Testing Operations Manual.

5.2.2 KAROLINSKA SLEEPINESS SCALE (KSS)

The Karolinska Sleepiness Scale (KSS) (Akerstedt 1990) 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 (Kaida 2006). It is a 9-point categorical Likert scale:

(1) extremely alert
(2)
(3) alert
(4)
(5) neither sleepy nor alert
(6)
(7) sleepy - but no difficulty remaining awake
(8)
(9) extremely sleepy-fighting sleep

5.2.3 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?"). Subject will answer "yes" or "no".

5.2.4 COGSCREEN SYMBOL DIGIT CODING (SDC)

The CogScreen Symbol Digit Coding (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 digit symbol substitution task found in the WAIS-R Digit Symbol subtest and the Symbol Digit Modalities Test (Wechsler 1981).

SDC will be administered by trained study site personnel. 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.

5.2.5 VISUAL ANALOG SCALE (VAS) TO ASSESS 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 (VAS). 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 case report form (CRF).

5.3 PHARMACODYNAMIC ENDPOINTS

5.3.1 PRIMARY ENDPOINT

The primary endpoint for this study is simulated driving performance as measured by standard deviation of lateral position (SDLP) using the CRCDS-MiniSim.

5.3.2 SECONDARY ENDPOINTS

The secondary endpoints for this study are:

- SDLP
- KSS
- Self-reported readiness to drive (“Right now do you feel safe to drive?)
- VAS for motivation
- VAS for self-appraisal of driving performance
- SDC:
    - Number of correct responses
    - Accuracy
    - Standard deviation of reaction time
- Other Driving Performance Endpoints
    - Lane exceedance; including number, maximum, and duration
    - Average speed, speed deviation, excessive speeding count, speeding ratio
    - Excessive Ay (cornering speed threshold exceeded)
    - Total collisions
    - DA measures: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Time
- Plasma drug levels and driving performance

5.4 SAFETY ASSESSMENTS

5.4.1 SECONDARY SAFETY ENDPOINTS

The secondary safety endpoints for this study are:

- Adverse events (AEs)
- Laboratory safety tests (blood chemistry, hematology, urinalysis, serum and urine pregnancy tests for women of childbearing potential)
- Physical examinations
- Vital signs

- Orthostatic effects
- 12-lead electrocardiograms (ECGs)

5.4.2 ADVERSE EVENTS

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.

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

5.4.3 CLINICAL LABORATORY EVALUATIONS

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[c] Red blood cells White blood cells with differential (absolute)
Chemistry	Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Blood urea nitrogen Creatinine Gamma glutamyltransferase Glucose Potassium Sodium Total and direct bilirubin Thyroid stimulating hormone[c]
Urinalysis	Bilirubin Erythrocytes Glucose Ketones Leukocytes Nitrite

Category	Test Name
	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).	

5.4.4 PHYSICAL EXAMINATION

A physical examination will be performed at Screening and End of Study (Day 17).

5.4.5 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.

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.

5.4.6 12-LEAD ELECTROCARDIOGRAM

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

5.5 CONCOMITANT MEDICATIONS

The use of any concomitant medication taken during the study, including any medication taken for the treatment of AEs, will be recorded in the case report form (CRF). Recording of a concomitant medication will include the medication name, indication, dose, route, frequency, date started and date stopped.

5.6 SCREENING ASSESSMENTS

5.6.1 EPWORTH SLEEPINESS SCALE

The Epworth Sleepiness Scale (ESS) will be used to exclude subjects who demonstrated excessive sleepiness prior to randomization.

The ESS is an 8-item self-administered questionnaire to measure general level of daytime sleepiness. The Scale is based on questions referring to situations that vary in their likelihood to induce a person 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 Likert scale that ranges from “0 = Would never doze” to “3 = High chance of dozing.” The total score on the Scale is the sum of the responses to each of the 8 items; therefore, the range of possible scores for each responder is 0 to 24. A total score of <10 indicates that the patient is not suffering from excessive daytime sleepiness. Individual items are not analyzed and have no independent, valid interpretations.

Subjects will complete the ESS at Screening.

6 STATISTICAL ANALYSES

All programming and analyses will be performed using SAS software v9.4.

6.1 STATISTICAL METHODOLOGY

6.1.1 DETERMINATION OF SAMPLE SIZE

This study is designed to test non-inferiority (NI) 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 NI margin is proposed to be 4.4 cm, which is the effect seen with 0.05% of blood alcohol content (BAC) with this driving simulator scenario. Under these assumptions, a sample of 30 subjects would provide in excess of 90% power to establish NI 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.

6.1.2 ANALYSIS POPULATIONS

6.1.2.1 SAFETY POPULATION

The Safety Population includes all subjects who received at least 1 dose of study drug, according to the treatment received in any given treatment period.

6.1.2.2 INTENT-TO-TREAT (ITT) POPULATION

The Intent-to-Treat (ITT) Population includes all randomized subjects who receive at least 1 dose of study drug, according to the planned treatment 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.

6.1.2.3 PHARMACOKINETIC (PK) POPULATION

The Pharmacokinetic (PK) Population includes all subjects with evaluable plasma concentration data.

6.1.3 STATISTICAL ANALYSES – GENERAL CONSIDERATIONS

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.

Formal statistical tests (where performed) will be two-sided and testing at the alpha=0.05 level of significance.

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

6.1.4 MULTIPLE COMPARISONS

There are a number of comparisons of interest from which conclusions with respect to the NI of tolperisone vs. placebo will result. Initially, the statistical significance of the cyclobenzaprine vs. placebo ($p<0.05$) comparison is necessary to validate the experiment as having the ability to detect effects (i.e., assay sensitivity).

Subsequently, the NI of tolperisone to placebo (for initial dose, next day residual, and steady-state dose comparisons) will result in a conclusion of NI of tolperisone relative to placebo. For NI conclusions, the alternative hypothesis (of NI) will be considered established if the upper 95% confidence limit for tolperisone vs placebo difference is less than the pre-specified NI margin of 4.4 cm.

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.

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 NI.

6.1.5 PROCEDURES FOR HANDLING MISSING DATA

Subjects who discontinue, will only contribute to the pair-wise comparisons for which they have data.

For subjects that have incomplete data within an assessment, data will be listed but not summarized and/or analyzed for that assessment.

6.2 SCREENING AND BASELINE CHARACTERISTICS

Summary tables will be constructed for the following screening or baseline data: demographic characteristics of age, sex, ethnic origin, height, weight and BMI for the safety population (Table 14.1.3), reason for screen failures (Table 14.1.4), medical history (Table 14.1.7), prior medications (Table 14.3.8.1), laboratory examinations (Tables 14.3.3.1-14.3.5.2), vital signs (Tables 14.3.6.1-14.3.6.5.3), and physical examination abnormalities (Table 14.3.8.1).

Data listings will be provided for the following screening and baseline data: screen failures (Listing 16.2.2.3), inclusion/exclusion criteria (Listing 16.2.3.2.1), inclusion/exclusion criteria violations (Listing 16.2.3.2.2), characteristics of age, sex, race, ethnicity (Listing 16.2.4.1), substance use (Listing 16.2.4.2, medical history (Listing 16.2.4.3), simulator sickness questionnaire (Listing 16.2.4.4), ESS (Listing 16.2.4.5), pharmacokinetic sampling (Listing 16.2.5.2), driving simulator (Listings 16.2.6.1.1-16.2.6.1.X), AEs (Listing 16.2.7.1) laboratory collections (Listing 16.2.8.1-16.2.8.3, urine drug screen, alcohol screen, and pregnancy test (Listing 16.2.8.4), prior medication (Listing 16.2.8.6.1), physical examination (Listing 16.2.8.7), 12-lead ECG (Listings 16.2.8.8.1 and 16.2.8.8.2), and vital signs, height, weight, and BMI (Listing 16.2.8.9).

6.3 SUBJECT DISPOSITION

The number of subjects in each study population group will be presented by sequence (Table 14.1.1). The number of subjects randomized, completing each visit, discontinuing at each visit, and completing the study will be presented by

sequence (Table 14.1.2). A listing for study populations will be presented by subject (Listing 16.2.2.1).

For subjects discontinuing, individual subject information will be listed (Listing 16.2.1 respectively).

An important protocol deviation listing will be provided by subject (Listing 16.2.2.2). Deviations will be summarized category of deviation (Table 14.1.6).

Subjects excluded from the pharmacodynamics analyses will be listed (Listing 16.2.3.1).

6.4 STUDY MEDICATION ADMINISTRATION

Study drug administration data will be listed by subject (Listing 16.2.5.1). The number of days exposed for each of the three treatment populations will be summarized (Table 14.1.5).

6.5 PHARMACODYNAMIC ANALYSES

6.5.1 PRIMARY ANALYSIS

The primary endpoint, SDLP, will be analyzed using a mixed model repeated measures with fixed effects for sequence, period, and treatment, with repeated observations for subjects. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a variance components covariance structure will be assumed.

In addition to assessments of treatment effect, p-values for significance testing of period and sequence effects will be provided.

Pair-wise comparisons (hypothesis tests) of differences in least squares means, and 95% confidence intervals on differences will be provided (Table 14.2.1.1) 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. Pair-wise, within subject differences in SDLP will also be tested for symmetry about zero (Laska 2012) using the maximally selected McNemar test (Table 14.2.1.2.1-14.2.1.2.9).

Summary statistics for raw values and change from baseline will be provided (mean, SD, median, minimum, maximum) for SDLP for each time point and treatment group. Figures will be provided for the within subject difference scores by treatment and day as both a histogram and scatter plot.

Data listings for driving simulator data will be provided (Listing 16.2.6.1.1-16.2.6.1.X).

6.5.2 SECONDARY ANALYSES

Secondary endpoints of VAS, SDC, and driving performance endpoints will be evaluated and presented similarly, however Lane Exceedance will be log transformed (more specifically ln(x+1)) prior to analyses.

Tables will be presented in the same format as the primary output:

- VAS for motivation (Table 14.2.2.1)
- VAS for self-appraisal of driving performance (Table 14.2.2.2)
- Symbol Digit Coding:
  - Number of correct responses (Table 14.2.3.1)
  - Accuracy (Table 14.2.3.2)
  - Standard deviation of reaction time (Table 14.2.3.3)
- Other Driving Performance Endpoints
  - Lane exceedance; including number, maximum, and duration (Tables 14.2.4.1-14.2.4.3)
  - Average speed, speed deviation, excessive speeding count, speeding ratio (Tables 14.2.5.1-14.2.5.4)
  - Excessive Ay and Total Collisions(cornering speed threshold exceeded) (Table 14.2.6)

- Divided Attention (DA): Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Time (Tables 14.2.8.1-14.2.8.5)
- KSS (Table 14.2.9)

A data listing for KSS will be provided (Listing 16.2.6.2). A data listing for SDC will be provided (Listing 16.2.6.3). A data listing for the two VAS results will be provided (Listing 16.2.6.4).

Additional Secondary Analyses:

Total Collisions:
Summary statistics will be provided (mean, SD, median, minimum, maximum) for total number of collisions for each time point and treatment group (Table 14.2.7). Additionally, differences in number of collisions for each pair-wise comparison will be provided with their corresponding Wilcoxon Signed Rank p-value. A bar chart will be provided pooling total number of collisions by 0, 1, 2, or >=3 for all 3 treatment groups.

Self-reported readiness
Pair-wise comparisons for readiness to drive will be analyzed using McNemar's test (Table 14.2.10).

Plasma drug levels
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. The relationship between initial dose effect, next day residual dose effect, and steady-state dose effect plasma drug levels and driving performance (i.e. the primary endpoint of SDLP) will be assessed by correlation. Both the Spearman and Pearson correlations will be reported (Tables 14.2.11.2-14.2.11.22).

6.6 SAFETY ANALYSES

Safety analysis will be based on the safety population. Safety measures will be summarized using descriptive statistics and listed for each subject.

MedDRA thesaurus will be used to map AEs verbatim to preferred terms and body systems. WHOdrug thesaurus (Sep 1, 2016) will be used to map prior medication and concomitant medication verbatim to preferred terms and ATC Class.

6.6.1 ADVERSE EVENTS (AE)

AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 20.0) coding system. Frequency tables will be presented by dose group summarizing:

- all treatment emergent AEs (Table 14.3.1.1),
- all treatment emergent treatment-related (defined as possibly or definitely related) AEs (Table 14.3.1.2),
- all serious treatment emergent AEs (Table 14.3.2.1)
- all AEs leading to discontinuation (Table 14.3.2.2).

Listings will be presented to provide:

- all AEs (Listing 16.2.7.1)
- all treatment related AEs (terms including definitely and probably related) (Listing 16.2.7.2).

6.6.2 CLINICAL LABORATORY EVALUATIONS

Each laboratory examination observed value and change from baseline (when appropriate) will be summarized for hematology, blood chemistry, and urinalysis for each treatment at screening and end of study (Tables 14.3.2.1, 14.3.3.1, and 14.3.4.1). Shift tables will be constructed for hematology, blood chemistry, and urinalysis (Tables 14.3.2.2, 14.3.3.2, and 14.3.4.2).

Subject laboratory examination data listings will be provided (Listings 16.2.8.1-16.2.8.4). 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 (Listing 16.2.8.5).

6.6.3 PHYSICAL EXAMINATION

A listing of physical examination data will be provided by subject (Listing 16.2.8.7.1). Subjects with any changes in the physical examination evaluation from Screening/Visit 1 to EOS/Day 17 will be listed (Listing 16.2.8.7.2).

6.6.4 VITAL SIGNS

Summary statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for the raw values and change from baseline (defined as pre-dose Day 1 Period 1) values at each time point for all vital signs (including orthostatic vital signs) (Tables 14.3.6.1-14.3.6.5.3).

A data listing of vital sign data will be provided by treatment and subject (Listing 16.2.8.9).

6.6.5 12-LEAD ELECTROCARDIOGRAM

Each ECG parameter observed value and change from screening will be summarized (Table 14.3.7.1). The ECG results will be categorized as normal, clinically significant abnormal, and not clinically significant abnormal. A shift table for ECG abnormalities will be provided (Table 14.3.7.2).

A data listing of ECG results for each parameter will be provided by subject (Listing 16.2.8.8.1). A data listing of ECG normality will be provided by subject (Listing 16.2.8.8.2).

6.7 CONCOMITANT MEDICATIONS

Concomitant medications will be summarized (n and %) by ATC class and preferred term (Table 14.3.8.2).

Concomitant medications will be listed by subject (Listing 16.2.8.6.2).

6.8 CONCENTRATION DATA

Concentration data will be summarized (n and %) by treatment (Table 14.2.11).

Concentration data will be listed by treatment and subject (Listing 16.2.5.2).

6.9 ADDITIONAL COLLECTED DATA

General comments will be listed by subject (Listing 16.2.8.10).

7 REFERENCES

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8 TABLES, LISTINGS, AND FIGURES

Tables, listings, and figures numbering and titles will be finalized by the Sponsor at a later date.

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Table 14.1.1
Study Populations

Study Population	Placebo (N=xx) n (%)	Tolperisone 450 mg (N=xx) n (%)	Cyclobenzaprine 30 mg (N=xx) n (%)	Overall (N=xx) n (%)
Screening Failures				xx
Safety Population*	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
ITT Population**	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)	xx (xx.xx)
PK Population ***				

* The Safety Population includes all subjects who received at least 1 dose of study drug
** The Intent-to-Treat (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.
*** The Pharmacokinetic (PK) Population includes all subjects with evaluable plasma concentration data.
SAS Program Name: Date: Source Data: Listing 16.2.2.1

Table 14.1.2
Subject Disposition
(Safety Population)

	Placebo		Tolperisone 450 mg		Cyclobenzaprine 30 mg		Overall	
	(N=xx)		(N=xx)		(N=xx)		(N=xx)	
Study Population	n	(%)	n	(%)	n	(%)	n	(%)
Completed Study	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
Withdrew From Study	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
XXXXXXX	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
YYYYYYY	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x

SAS Program Name: Date: Source Data: Listing 16.2.2.1

Table 14.1.3
Demographics and Baseline Characteristics
(Safety Population)

Characteristic		Placebo (N=xx)	Tolperisone 450 mg (N=xx)	Cyclobenzaprine 30 mg (N=xx)	Overall (N=xx)
Age					
N		xx	xx	xx	xx
Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median		xx.x	xx.x	xx.x	xx.x
Minimum, Maximum		xx.x , xx.x	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
Sex		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race					
Caucasian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hispanic	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)					
N		xx	xx	xx	xx
Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median		xx.x	xx.x	xx.x	xx.x
Minimum, Maximum		xx.x , xx.x	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
Weight (kg)					

N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
BMI (kg/m^2)				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x

SAS Program Name: Date: Source Data: Listing 16.2.4.1 and Listing 16.2.8.9

Table 14.1.4
Reason for Screening Failures

	Overall (N=xx) n (%)
Reason #1	xx xx.x
etc	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x
	xx xx.x

Table 14.1.5
Drug Exposure
(Safety Population)

Characteristic	Placebo (N=xx)	Tolperisone 450 mg (N=xx)	Cyclobenzaprine 30 mg (N=xx)	Overall (N=xx)
Days				
N	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Minimum, Maximum	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x

SAS Program Name: Date: Source Data: Listing 16.2.5.1

Table 14.1.6
Protocol Deviations
(Safety Population)

Deviation Category	Overall (N=xx) n (%)
xxxx	xx (xx.xx)
yyyy	xx (xx.xx)

SAS Program Name: Date: Source Data: Listing 16.2.2.2

Table 14.1.7
Medical History
(Safety Population)

Category	Overall (N=xx) n	%
HEENT	xx	(xx.x)
etc	xx	(xx.x)

Subjects with more than one occurrence in a category are only counted once.

SAS Program Name: Date: Source Data: Listing 16.2.4.3

Table 14.2.1.1
Standard Deviation of Lateral Position (SDLP)
(ITT Population)

Day		Placebo (N=xx)	Tolperisone 450 mg (N=xx)	Cyclobenzaprine 30 mg (N=xx)	
Day X	N	xx	xx	xx	
	Mean (SD)	xx.xxxx (xx.xx)	xx.xxxx (xx.xx)	xx.xxxx (xx.xx)	
	Median	xx.x	xx.x	xx.x	
	Min, Max	xx.xxxx , xx.xxxx	xx.xxxx , xx.xxxx	xx.xxxx , xx.xxxx	
		Model Fixed Effects of Interest	Tolperisone 450 mg vs PBO	Cyclobenzaprine vs PBO	Tolperisone 450 mg vs Cyclobenzaprine
	Diff in LSMean		xx.xxxx	xx.xxxx	xx.xxxx
	95%CI*		(xx.xx , xx.xx)	(xx.xx , xx.xx)	(xx.xx , xx.xx)
	p-value Treatment*		0.xxxx	0.xxxx	0.xxxx
	p-value Sequence*	0.xxxx			
	p-value Period*	0.xxxx			

Repeat table for VAS, SDC, KSS, and other driving performance measures (see SAP for proposed table list).
Mixed model repeated measures with fixed effects for sequence, period, and treatment, repeated assessments for subjects, unstructured covariance structure, and Kenward-Roger degrees of freedom.
SAS Program Name: Date: Source Data: Listing 16.2.6.1.X

Table 14.2.1.2.1
Standard Deviation of Lateral Position (SDLP) Analysis of Symmetry about Zero
(ITT Population – Cyclobenzaprine 30 mg versus Placebo)

Threshold	Sign	Low	Neutral	High	McNemar	Nominal P-value
x.xxxx	-/+	xx	xx	xx	x.xxxx	0.xxxxx
x.xxxx	-/+	xx	xx	xx	x.xxxx	0.xxxxx

Repeat for each comparison

SAS Program Name: Date: Source Data: Listing 16.2.6.1.X

Table 14.2.7
Driving Performance Total Collisions
(ITT Population)

Day	Statistic	Placebo (N=xx)	Tolperisone 450 mg (N=xx)	Cyclobenzaprine 30 mg (N=xx)	
Day 1	N	xx	xx	xx	
	Mean	x.x	x.x	x.x	
	SD	x.xx	x.xx	x.xx	
	Median	x.x	x.x	x.x	
	Min, Max	xx, xx	xx, xx	xx, xx	
	Diff in # of Collisions		Tolperisone 450 vs PBO	Cyclobenzaprine 30 mg	Tolperisone vs Cyclobenzaprine
	N		xx	xx	xx
	Mean		x.x	x.x	x.x
	SD		x.xx	x.xx	x.xx
	Median		x.x	x.x	x.x
	Min, Max		xx, xx	xx, xx	xx, xx
etc	p-value*		0.xxxx	0.xxxx	0.xxxx

*Wilcoxon Signed Ranks test.

SAS Program Name: Date: Source Data: Listing 16.2.6.1.X

Table 14.2.12
Self-Reported Readiness
(ITT Population)

Day	Comparison	First Treatment	Second Treatment	N(%)	p-value*
Day 1	xxxxxxxxxxxxx	No	No	xx (xxx.x%)	0.xxxx
		Yes	No	xx (xxx.x%)	0.xxxx
		No	Yes	xx (xxx.x%)	0.xxxx
		Yes	Yes	xx (xxx.x%)	0.xxxx

*McNemar's test.

SAS Program Name: Date: Source Data: Listing 16.2.6.X

Table 14.2.11.1
Plasma Concentration
(PK Population)

Timepoint		Tolperisone 450 mg (N=xx)
XXXX	N	xx
	Mean (SD)	xx.xxxx (xx.xx)
	Median	xx.x
	Geometric Mean	xx.xxxx
	Min, Max	xx.xxxx , xx.xxxx

SAS Program Name: Date: Source Data: Listing 16.2.5.2

Table 14.2.11.2
Correlation of ln(Plasma Drug Levels) to SDLP
(ITT Population)

Day		Tolperisone 450 mg (N=xx)
Day X	Pearson Correlation	x.xxxx
	Spearman Correlation	x.xxxx

SAS Program Name: Date: Source Data: Listings 16.2.5.2 and 16.2.6.1.1

Table 14.3.1.1
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
(Safety population)

Primary System Organ Class\ Preferred Term\ Severity	Placebo (N=xx) n(%)	Tolperisone 450 mg (N=xx) n(%)	Cyclobenzaprine 30 mg (N=xx) n(%)	Overall (N=xx) n(%)
Total Number of Adverse Events	xxx	xxx	xxx	xxx
Any primary system organ class	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Mild	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Moderate	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Severe	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
SOC 1	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Mild	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Moderate	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Severe	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Preferred Term 1	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Mild	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Moderate	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
Severe	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)

Etc

NOTE FOR PROGRAMMING: repeat table for treatment related (with footnote defining related) 14.3.1.2
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.
Subjects with more than one occurrence in a category are only counted once.
SAS Program Name: Date: Source Data: Listing 16.2.7.1

Table 14.3.2.1
Serious Adverse Events
(Safety Population)

Treatment:

Subject No./ Age/ Sex	Subject No.	AE Seq	AE Number	AE Term/ Preferred Term/ SOC Class	Start Date/ Start Time	End Date/ End Time	Frequency	Maximum Severity	Serious?	Relationship to Study Drug	Action Taken Due to AE	Outcome	Sequelae
xx-xxx/ xx /X	xx-xxx	XXX	xx	xxxxxxxxxx xxxxxxxxxx xxxxxxxxxx	YYYYMMDD hh:mm	YYYYMMDD hh:mm	Single Episode/ Intermittent/Continuous	Mild/ Moderate/ Severe	Yes	Unrelated/ Possibly Related/ Definitely Related	No Action/ etc	Resolved without Sequelae/ etc	xxxxxxxxxx

Repeat for AE leading to discontinuation Table 14.3.2.2
A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: screening, placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Table 14.3.3.1
Hematology Change From Screening
(Safety population)

Labtest (Units)		Overall (N=xx)
Screening		
Observed	n	xx
	Mean (SD)	xx.xxx (xx.xxx)
	Median	xx.xxx
	Min, Max	xx.x , xx.x
End of Study	n	xx
Observed	Mean (SD)	xx.xxx (xx.xxx)
	Median	xx.xxx
	Min, Max	xx.x , xx.x
End of Study	n	xx
Change from		xx.xxx (xx.xxx)
Screening	Mean (SD)	
	Median	xx.xxx
	Min, Max	xx.x , xx.x

[repeat for each lab/parameter]
NOTE FOR PROGRAMMING: Repeat for blood chemistry (Table 14.3.4.1), urinalysis (Table 14.3.5.1), and ECG (Table 14.3.7.1)
Change N reflects number of subjects with both screening and end of study evaluation.
SAS Program Name: Date: Source Data: Listing 16.2.8.1

Table 14.3.3.2
Hematology Shift Table
(Safety Population)

Laboratory Examination	Shift Category	Overall (N=xx) n (%)
xxxxxxxxxx	LOW TO LOW	xx (xx.x)
	LOW TO NORMAL	xx (xx.x)

[repeat for each lab]
NOTE FOR PROGRAMMING: Repeat for blood chemistry (Table 14.3.4.2), urinalysis (Table 14.3.5.2), and ECG (Table 14.3.7.2).

SAS Program Name: Date: Source Data: Listing 16.2.8.1

Table 14.3.6.3.1
Vital Signs Change From Baseline – Supine Heart Rate
(Safety population)

Heart Rate (bpm)		Overall (N=xx)	Placebo (N=xx)	Tolperisone 450 mg (N=xx)	Cyclobenzaprine 30 mg (N=xx)
Screening					
Observed	n	xx			
	Mean (SD)	xx.x (xx.xx)			
	Min, Max	xx.x , xx.x			
Day 1 Pre-dose					
Observed	n		xx	xx	xx
	Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Min, Max		xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
etc					
Observed	n		xx	xx	xx
	Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Min, Max		xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
etc					
Change	n		xx	xx	xx
	Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Min, Max		xx.x , xx.x	xx.x , xx.x	xx.x , xx.x

[repeat for all post dose measurements]

NOTE FOR PROGRAMMING: Repeat for all vitals tables
Note for programming trt columns populated for visits after baseline visit. Orthostatic tables need footnote defining standing-supine.
Baseline defined as pre-dose Day 1.
Note: Change N reflects number of subjects with both baseline and at least one post-dose assessment.
SAS Program Name: Date: Source Data: Listing 16.2.8.9

Table 14.3.8.1
Prior Medications
(Safety population)

ATC Class/Preferred Term	Overall (N=xx) n	%
Any ATC Class with medication	xx	xx.x
ATC Therapeutic Class 1		
-Total	xx	xx.x
Ingredient 1	xx	xx.x
Ingredient 2	xx	xx.x
Ingredient 3	xx	xx.x
ATC Therapeutic Class 2	xx	xx.x
-Total	xx	xx.x
Ingredient 1	xx	xx.x
Ingredient 2	xx	xx.x
etc.		
[repeat for all ingredients and ATC classes/ingredients]		

ATC classes are presented alphabetically; preferred terms are sorted within ATC class alphabetically.
Subjects with more than one occurrence in a category are only counted once.
SAS Program Name: Date: Source Data: Listing 16.2.8.6.1

Table 14.3.8.2
Concomitant Medications
(Safety population)

ATC Class/Preferred Term	Overall (N=xx) n	%
Any ATC Class with medication/surgery	xx	xx.x
ATC Therapeutic Class 1		
-Total	xx	xx.x
Ingredient 1	xx	xx.x
Ingredient 2	xx	xx.x
Ingredient 3	xx	xx.x
ATC Therapeutic Class 2	xx	xx.x
-Total	xx	xx.x
Ingredient 1	xx	xx.x
Ingredient 2	xx	xx.x
etc.		
[repeat for all ingredients and ATC classes/ingredients]		

ATC classes are presented alphabetically; preferred terms are sorted within ATC class alphabetically.
Subjects with more than one occurrence in a category are only counted once.
SAS Program Name: Date: Source Data: Listing 16.2.8.6.2

Listing 16.2.1
Subject Disposition
(Safety Population)

Subject No.	Sequence	Visit Date	Completed / Premature Withdrawal	Date	Reason for Withdrawal
xx-xxx	XXX	YYYYMMDD	Completed / Withdrew	YYYYMMDD	Adverse Event etc

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.2.1
Study Population

Subject No.	Sequence	Safety*	ITT**	PK***
xx-xxx	XXX	Yes/no	Yes/no	Yes/no
xx-xxx	XXX	Yes/no	Yes/no	Yes/no

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
* The Safety Population includes all subjects who received at least 1 dose of study drug
** The Intent-to-Treat (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.
*** The Pharmacokinetic (PK) Population includes all subjects with evaluable plasma concentration data.

SAS Program Name: Date:

Listing 16.2.2.2
Important Protocol Deviations
(Safety Population)

Subject No.	Sequence	Deviation Category	Description of Deviation
xx-xxx	XXX	xxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.2.3
Screen Failures

Investigator No.	Screening Number	Visit Date	Date of Birth	Date of Informed Consent	Age	Sex	Race	Race Other	Ethnicity	Reason for Screen Failure
xx	xxx	YYYYMMDD	YYYYMMDD	YYYYMMDD	xxx	Female	xxxxxx	xxxxxxxx	xxxxxxxx	xxxxxxxx

SAS Program Name: Date:

Listing 16.2.3.1
Subjects Who Were Excluded From ITT Population
(Safety Population)

Subject No.	Sequence	Reason for Exclusion
xx-xxx	XXX	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.3.2.1
Inclusion, Exclusion, and Eligibility Criteria Legend

To be populated

Listing 16.2.3.2.2
Inclusion and Exclusion Criteria Violations
(Safety Population)

Subject No.	Sequence	Visit	Category	Question Number	Inclusion/Exclusion Question	Result
xx-xxx	XXX	XXXX	XXXXXXXXX	XXXXXXX	XXXXXXXXXXXXXXXX	X

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.4.1
Demographics and Baseline Characteristics
(Safety Population)

Subject No.	Sequence	Visit Date	Date of Birth	Date of Informed Consent	Age	Sex	Race	Race Other	Ethnicity
xx-x	XXX	YYYYMMDD	YYYYMMDD	YYYYMMDD	xxx	Female	xxxxxx	xxxxxx	xxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.4.2
Substance Use
(Safety Population)

Subject No.	Sequence	Status	Substance	Quantity	Frequency	Start Date	End Date
xx-xxx	XXX	XXXXXXXXXXXXX	xx	xx	xx	YYYYMMDD	YYYYMMDD

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.4.3
Medical History
(Safety Population)

Subject No.	Sequence	Date of Visit	System	Condition	Date of Diagnosis	Status
xx-xxx	XXX	YYYYMMDD	xxxxxx	xxxxxxxxxxxxxxxxxx	YYYYMMDD	Resolved, Stable, Unstable

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.4.4
Simulator Sickness Questionnaire
(Safety Population)

Subject No.	Sequence	Date of Visit	Was the Simulator Sickness Questionnaire Completed?
xx-xxx	XXX	YYYYMMDD	Yes/No

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.4.5
Epworth Sleepiness Scale (ESS)
(Safety Population)

Subject No.	Sequence	Date of Visit	Situation	Result
xx-xxx	XXX	YYYYMMDD	xxxxxxxxxxxxxxxx	0-3

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.5.1
Study Drug Administration
(Safety Population)

Treatment:

Subject Number	Sequence	Visit Date	Visit	Date of Randomization	Randomization Number	Date of Administration	Time of Administration
xx-xxx	XXX	YYYYMMDD	xxxxx	YYYYMMDD	xxx	YYYYMMDD	hh:mm

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.5.2
Plasma Concentration
(Safety Population)

Treatment:

Subject No.	Sequence	Visit Date	Visit	Time Point	Not Done	Date of Draw	Time of Draw	Concentration
xx-xxx	XXX	YYYYMMDD	xxxxxxxxx	xxxxx	xxxx	YYYYMMDD	hh:mm	xxxxx.xx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.6.1.1
Driving Simulator Part 1 of X
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Test	Not Done	Start Date	Start Time	Feel Safe to Drive?	Columns TBD
xx-xxx	XXX	xxxx	xxxxxxxxxxxxxxx	xxx	YYYYMMDD	hh:mm	Yes/No	xx.xx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.6.1.X
Driving Simulator Part X of X
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Visit Date	Feel Safe to Drive?	Columns TBD
xx-xxx	XXX	xxxx	YYYYMMDD	Yes/No	xx.xx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.6.2
Karolinska Sleepiness Scale (KSS)
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Visit Date	Test	Not Done	Start Date	Start Time	Score (1-9)
xx-xxx	XXX	xxxxxxxx	YYYYMMDD	Pre-Dose/ Post-Dose	xxxx	YYYYMMDD	hh:mm	x

NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.6.3
Cogscreen Symbol Digit Coding (SDC)
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Not Done	Start Date	Start Time	Test	Total Number of Correct Responses	Accuracy	Speed Variability
xx-xxx	XXX	xxxxx	Yes/no	YYYYMMDD	xx.xx	xxxxxxxxxx	xx	xxx.xx	x.xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.6.4
Self-Rating of Driving Simulator Performance Visual Analog Scale (VAS)
(Safety Population)

Subject No.	Sequence	Visit	Visit Date	Not Done	How Well do You Think You Drove For The Last 60 Minutes?	How Motivated Did You Feel To Drive At Your Best During Your Last 60 Minutes of Driving?
xx-xxx	XXX	xxxxxx	YYYYMMDD	Yes/blank	xxx	Yes/mm

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine

SAS Program Name: Date:

Listing 16.2.7.1
Adverse Events
(Safety Population)

Treatment:

Subject No./ Age/ Sex	Subject No.	AE Seq	AE Number	AE Term/ Preferred Term/ SOC Class	Start Date/ Start Time	End Date/ End Time	Frequency	Maximum Severity	Serious?	Relationship to Study Drug	Action Taken Due to AE	Outcome	Sequelae
xx-xxx/ xx /X	xx-xxx	XXX	xx	xxxxxxxxxx xxxxxxxxxx xxxxxxxxxx	YYYYMMDD hh:mm	YYYYMMDD hh:mm	Single Episode/ Intermittent/Continuous	Mild/ Moderate/ Severe	Yes/no	Unrelated/ Possibly Related/ Definitely Related	No Action/ etc	Resolved without Sequelae/ etc	xxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: screening, placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.7.2
Treatment-Related, Treatment-Emergent Adverse Events
(Safety Population)

Treatment:

Subject No./ Age/ Sex	Seq	AE Number	AE Term/ Preferred Term/ SOC Class	Start Date/ Start Time	End Date/ End Time	Frequency	Maximum Severity	Serious?	Relationship to Study Drug	Action Taken with Study Medication	Action Taken to Treat AE	Outcome	Sequelae
xx-xxx/XXX xx /X		xx	xxxxxxxxxxx xxxxxxxxxx xxxxxxxxxx	YYYYMMDD hh:mm	YYYYMMDD hh:mm	Single Episode/ Intermittent/Continuous	Mild/ Moderate/ Severe	Yes/no	Unrelated/ Possibly Related/ Probably Related	None/ Dosage Increased/ Dose Reduced/ Dose Interrupted/ Dose Permanently Discontinued/ Not applicable	No Action/ Subject Withdrawn from Study/ Treatment Given/ Other	Resolved without Sequelae/ Resolved with Sequelae/ Resolved with Death: Event Contributed to Death/ Resolved with Death: Event did not Contribute to Death/ Ongoing/ Lost to Follow-Up	xxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.1
Hematology - Laboratory Collections
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Date Sample Collected	Time Sample Collected	Accession Number	Test	Result	Units	Normal Range Low	Normal Range High	Flag
xx-xxx	XXX	xxxxxxxxxx	YYYYMMDD	hh:mm	xxxxxx	xxxxxx	Xxxx	xxxx	xxxx	xxxx	xxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.2
Blood Chemistry - Laboratory Collections
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Date Sample Collected	Time Sample Collected	Accession Number	Test	Result	Units	Normal Range Low	Normal Range High	Flag
xx-xxx	XXX	xxxxxxxxxx	YYYYMMDD	hh:mm	xxxxxx	xxxxxx	Xxxx	xxxx	xxxx	xxxx	xxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.3
Urinalysis - Laboratory Collections
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Date Sample Collected	Time Sample Collected	Accession Number	Test	Result	Units	Normal Range Low	Normal Range High	Flag
xx-xxx	XXX	xxxxxxxxxx	YYYYMMDD	hh:mm	xxxxxx	xxxxxx	Xxxx	xxxx	xxxx	xxxx	xxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.4
Drug Screen, Alcohol Screen, Pregnancy, Test Results
(Safety Population)

Treatment:

Subject No.	Sequence	Visit Date	Visit	Test	Results
xx-xxx	XXX	YYYYMMDD	xxxxxxxxx	xxxxxxxx	xxxxxxxxxxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.5
Laboratory Values Outside of Normal Range
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Date Sample Collected	Time Sample Collected	Category	Test	Result	Units	Normal Range Low	Normal Range High	Flag
xx-xxx	XXX	xxxxxxxxxx	YYYYMMDD	hh:mm	xxxxxx	xxxxxx	Xxxx	xxxx	xxxx	xxxx	xxxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.6.1
Prior Medications
(Safety Population)

Subject No.	Sequence	Visit Date	Medication/ Preferred Term/ ATC Class	Indication	Dose	Units	Freq	Route	Date Started	Date Stopped
xx-xxx	XXX	YYYYMMDD	xxxxxxxxx/ xxxxxxxx/ xxxxxxxx	xxxxx	xxxx	xxxx	xxxxxxx	xxxxxxx	YYYYMMDD	YYYYMMDD

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.8.6.2
Concomitant Medications
(Safety Population)

Subject No.	Sequence	Medication/ Preferred Term/ ATC Class	Indication	Dose	Units	Frequency	Route	Date Started	Date Stopped	Ongoing	Med Taken Due to AE?
xx-xxx	XXX	xxxxxxxxx/ xxxxxxxx/ xxxxxxxx	xxx	xxxx	xxxx	xxxx	xxxxxxx	YYYYMMDD	YYYYMMDD	xxx	xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.8.7.1
Physical Examination
(Safety Population)

Subject No.	Sequence	Visit Date	Visit	Site	Other specification	Physical examination result	Abnormal Finding
xx-xxx	XXX	YYYYMMDD	xxxxxxxx	xxxxxxxxxxx	xxxxxx	Normal/abnormal/not done	xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.8.7.2
Shift in Physical Examination
(Safety Population)

Subject No.	Sequence	Visit Date	Visit	Site	Other specification	Physical examination result	Abnormal Finding
xx-xxx	XXX	YYYYMMDD	xxxxxxxx	xxxxxxxxxxx	xxxxxx	Normal/abnormal/not done	xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:

Listing 16.2.8.8.1
12-Lead Electrocardiogram Results
(Safety Population)

Treatment:

Subject No.	Sequence	Date of Assessment	Time of Assessment	Not Done	Visit	Ventricular Heart Rate (beats/min)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTcF Interval (msec)
xx-xxx	XXX	YYYYMMDD	hh:mm	xx	xxxxxx	xxx	xxx	xxx	xxx	xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.8.2
12-Lead Electrocardiogram Assessment
(Safety Population)

Treatment:

Subject No.	Sequence	Visit	Date of ECG	Time of ECG	Clinical Evaluation	Abnormality	Clinical Significance*
xx-xxx	XXX	xxxxxxxxxx	YYYYMMDD	hh:mm	Normal/ Abnormal NCS/ Abnormal CS	xxxxxxxxxx	NCS/CS

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
*NCS=not clinically significant, CS=clinically significant.
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.9
Vital Signs
(Safety Population)

Treatment:

Subject No.	Sequence	Date of Assessment	Time of Assessment	Not Done	Visit	Time Point	Position	Height (cm)	Weight (kg)	BMI (kg/m^2)	Temperature (C)	Heart Rate (bpm)	Blood Pressure (mm Hg)	Respiration Rate (breaths/min)
xx-xxx	XXX	YYYYMMDD	hh:mm	xx	xxxxxx	xxxx	xxxxxxx	xx	xx	xx.x	xx	xxx	xxx/xxx	xx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine
SAS Program Name: Date:
NOTE TO PROGRAMMER: placebo, 450 mg tolperisone, 30 mg cyclobenzaprine

Listing 16.2.8.10
General Comments
(Safety Population)

Subject No.	Sequence	CRF page	SDTM Domain	Comments
xx-xxx	XXX	xx	xx	xxx

A=placebo, B=450 mg tolperisone, C=30 mg cyclobenzaprine

SAS Program Name: Date: