STATISTICAL ANALYSIS PLAN

Neurana Pharmaceuticals, Inc.

Protocol: 201

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1 STATISTICAL ANALYSIS PLAN APPROVAL

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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	Alanine Aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BUN	Blood Urea Nitrogen
CGI-C	Clinician's Global Impression of Change of pain
CGI-S	Clinician's Global Impression of Severity of pain
CI	confidence interval
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOT	End of Treatment
ET	Early Termination
FFD	Fingers to floor distance
GGT	Gamma glutamyltransferase
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
IWRS	interactive web response system
LOCF	last observation carried forward
LSM	least-square mean
LSMD	least-square mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
PGI-C	Patient's Global Impression of Change of pain
PGI-S	Patient's Global Impression of Severity of pain
PP	Per-Protocol
PT	Prothrombin time
Q1	25^{th} percentile
Q3	75^{th} percentile
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	Système International
SRMH	Subject Rating of Medication Helpfulness
TEAE	treatment-emergent adverse event
TID	three times a day
TSH	Thyroid stimulating hormone
WHODDE	World Health Organization Drug Dictionary Enhanced
VAS	Visual Analogue Scale

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Neurana Pharmaceuticals, Inc. Protocol 201 (Dose Ranging Study of Tolperisone in Acute Muscle Spasm of the Back "STAR Study"). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and before treatment unblinding and database lock to provide full details to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR.

5 STUDY OBJECTIVES

5.1 Primary Study Objective

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

5.2 Secondary Study Objective

The secondary objectives of this study are to:

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

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a double-blind, randomized, placebo-controlled, parallel group study of the efficacy and safety of tolperisone or placebo administered as multiple doses three times a day (TID) in approximately 400 male and female subjects experiencing back pain due to or associated with muscle spasm. This study will be conducted at approximately 45 clinical sites in the USA.

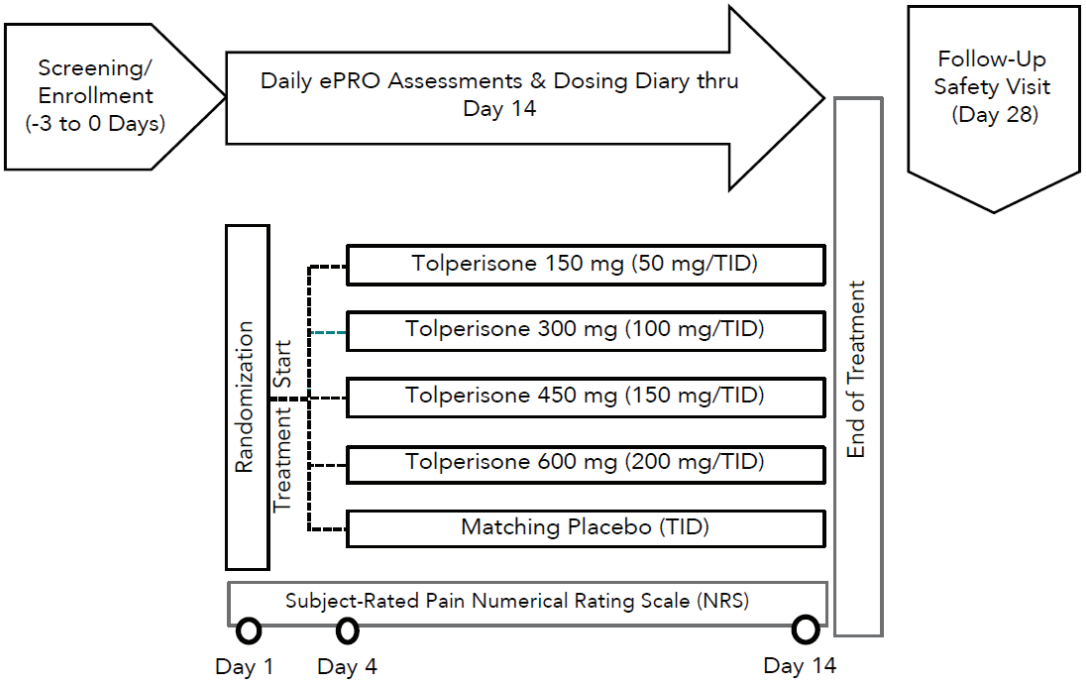
The tolperisone groups consist of dose levels of 150, 300, 450, and 600 mg administered TID in doses of 50, 100, 150, or 200 mg for 14 days, with a visit at 28 days as follow-up. Subjects

randomized to the placebo group will receive matching placebo tablets TID for 14 days with a follow-up visit at Day 28. Subject participation will be approximately 4 weeks.

Subjects will be screened for eligibility for participation in the study at the Screening/Baseline Visit 1 (Day 1) after reviewing and signing the informed consent form. Subjects meeting all inclusion/exclusion criteria will then be randomized into the study (Day 1) and begin dosing this same day.

After completing all screening and baseline assessments by Day 1, subjects will receive all study drug and rescue medication (acetaminophen 500 mg) and will be instructed to begin taking their study drug that same day. Depending on the time of their clinic visit, they should be instructed to begin dosing with either the midday dose (12-2 pm) or the evening dose (6-8 pm). Subjects will be instructed to continue taking study drug TID through Day 14 and complete dosing dairy and daily electronic Patient-Reported Outcomes (ePRO) assessments. Subjects will return to the clinic to complete the procedures listed in the Schedule of Procedures on Day 4 (±1 day; Visit 2) and Day 14 (+1 day, End of Treatment [EOT] visit, Visit 3). Subjects must also return to the clinic for a follow-up visit on Day 28 (+3 days, 2-week follow-up visit, Visit 4).

Figure 1 Study Design



6.2 Schedule of Assessments

Table 2 Schedule of Assessments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Treatment

6.3.1 Treatment Administered

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

6.3.2 Method of Assigning Subjects to Treatment Groups

The study will be double-blinded. No treatment assignment information will be disclosed to any staff member (site, sponsor, or contract research organization) working on the trial, with the exception of the unblinded statistician and the pharmacovigilance representative in the event of emergency unblinding (only to be done when knowledge of treatment assignment is considered critical for patient care).

Subjects will be randomized to treatment group (150mg/day, 300 mg/day, 450 mg/day, 600mg/day or Placebo) in a 1:1:1:1:1 ratio and stratified by site. Upon confirmation that all study eligibility criteria have been met at Baseline (Day 0), unique randomization numbers will be assigned to subjects using an interactive web response system (IWRS) and the Investigator will

dispense a single bottle of tolperisone/placebo to the eligible patient. The assigned bottle number will be captured on the electronic case report form (eCRF).

6.4 Efficacy and Safety Variables

6.4.1 Efficacy Variable

6.4.1.1 Primary Efficacy Variable

The primary efficacy endpoint is subject-rated pain "right now" due to acute back spasm using a Numerical Rating Scale (NRS; a scale of 0-10 where 0 = no pain and 10 = worst possible pain) on Day 14.

6.4.1.2 Secondary Efficacy Variables

Secondary efficacy endpoints include assessments administered on a study-provisioned tablet at the clinical site on Day 1 (baseline), Day 4, and Day 14 or captured by the subject with smartphone/trial application daily at home from Day 1 to Day 14 (See Table 2)

- Subject-rated pain due to acute back spasm "right now" using NRS on Day 4
- Subject-rated average pain due to acute back spasm over past 12 hours using NRS on Days 1 to 14, measured in morning and evening.
- Subject-rated average pain due to acute back spasm over past 1 hour using NRS on Days 1 to 14, measured in morning and evening
- Subject-rated average pain at rest due to acute back spasm using NRS on Days 1 to 14, measured in evening
- Subject-rated average pain on movement due to acute back spasm using NRS on Days 1 to 14, measured in evening
- Subject rating of medication helpfulness (SRMH) using a scale of 1-5 on Days 4 and 14, where 1=poor, 2=fair, 3=good, 4=very good, and 5=excellent.
- Time to relief of pain due to acute back spasm (days) from baseline using subject-rated NRS of pain over past 12 hours. The first NRS score of 2 or lower will be used to define relief.
- Clinician's Global Impression of Severity (CGI-S) using 1–5 scale at baseline (Day 1), where 1=no pain, 2=mild pain, 3=moderate pain, 4=severe pain, and 5=worst possible pain
- Clinician's Global Impression of Change (CGI-C) using a scale of 1-7 on Days 4 and 14, where 1=Very Much Worse, 2=Much Worse, 3=Minimally Worse, 4=No Change, 5=Minimally Improved, 6=Much Improved, and 7=Very Much Improved

- Patient's Global Impression of Severity (PGI-S) using a scale of 1–5 scale at baseline (Day 1), where 1=no pain, 2=mild pain, 3=moderate pain, 4=severe pain, and 5=worst possible pain

- Patient's Global Impression of Change (PGI-C) based on subject's global assessment using a scale of 1-7 on Days 4 and 14, where 1=Very Much Worse, 2=Much Worse, 3=Minimally Worse, 4=No Change, 5=Minimally Improved, 6=Much Improved, and 7=Very Much Improved).

- Fingers to floor distance (FFD) measured at Baseline (Day 1), Day 4, and Day 14

  FFD is an index of mobility of the spinal cord and is measured as distance in cm when standing with the spinal cord flexed with complete extension of knee joint, on Days 4 and 14 compared to baseline (Day 1) (assessments should be conducted at the same time of day for all three time points).

- Oswestry Pain and Disability (ODI) assessment at baseline (Day 1), Day 4, and Day 14

  The ODI questionnaire contains 10 questions with one answer each for pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life [if applicable], social life, and traveling). Scores are assigned for each section from 0 to 5 (5 being the worst case).

  ODI scores are derived based on the methods described in Mehra et.al. (2008). The method is equivalent to an ODI score calculated as (total score × 2) / (number of sections answered / 10), rounded to the nearest integer. The total score is the sum of the individual section scores.

- Use of study-provided rescue medication [acetaminophen tablets (500 mg)] measured daily and assessed as number of rescue tablets administered by the subject and recorded via smartphone/use of trial application.

- Quality of sleep as rated by subjects daily from Day 1 to Day 14. The rating scale is 1-5, where 1 = not at all to 5 = slept all night. Assessments are collected via smartphone/use of trial application.

- Visual Analogue Scale (VAS) for subject-reported sleepiness as measured in the clinic on at Day 4 via tablet ePRO. Scale is from 0 to 10, where 0 = alert, wide awake to 10 = very sleepy, difficulty remaining awake.

6.4.2 Description of Safety Variables

Safety variables include:

- Adverse events and serious adverse events

- Clinical evaluations including vital signs (blood pressure, heart rate, respiratory rate, body temperature), orthostatic effects on blood pressure, physical examinations, and 12-lead electrocardiogram (ECG)

- Laboratory tests including blood chemistry, hematology, and urinalysis

6.4.2.1 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. 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 occurring after the initiation of the study drug treatment are referred to as treatment-emergent adverse events (TEAEs).

See Section 15.1 of the study Protocol for further details regarding the definition of AEs.

6.4.2.2 Serious Adverse Events

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

- Results in death,

- Is life-threatening,

- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),

- Is a congenital anomaly or birth defect,

- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the Principal Investigator).

See Section 15.3 of the study Protocol for further details regarding SAEs and reporting.

6.4.2.3 Laboratory Parameters

A central laboratory will perform all laboratory testing. Table 3 lists all planned clinical laboratory tests to be performed.

Table 3 Clinical Laboratory Assessments

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

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

a Screening only.

b Day 1 (Screening/Baseline), Day 4, and Day 14 (End of Treatment).

c Includes testing for amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates – ethanol will be determined by breathalyzer.

d Urine pregnancy test at Days 1, 14, and 28 for females of childbearing potential.

6.4.2.4 Other Safety Variables

6.4.2.4.1 Vital Signs

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

6.4.2.4.2 12-Lead Electrocardiogram

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

6.4.2.4.3 Physical and Neurological Examination

A complete physical examination will be performed at Screening/Baseline (Day 1). Physical examinations may be abbreviated (i.e. disease-specific and symptom directed) on Days 4, 14, 28.

A neurological examination will be performed at Screening/Baseline (Day 1), Day 4 and 14. Overall status (improved, stable, or deteriorated) will be collected.

6.4.2.4.4 Prior and Concomitant Medications

Concomitant use of medications, including rescue analgesia other than study-provided acetaminophen taken for acute back spasms, used during the study will be recorded as concomitant medications on the eCRF (see Section 13 of the study protocol for allowed and disallowed medications during the study) and will be analyzed at the time of report following dosing of study drug through Visit 4 (Day 28).

6.4.3 Population Pharmacokinetics (PK)

Blood samples for the determination of plasma tolperisone concentrations will be drawn on Day 4 (Visit 2) after completion of all study assessments for a subset of subjects.

6.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

Tables and figures will be summarized by tolperisone dose group/placebo. Tables summarizing demographics, baseline characteristics and all safety endpoints will also include a column for all tolperisone treated subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by treatment group, site, subject number, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

Unless otherwise specified, 95% confidence intervals will be calculated for point estimates and statistical significance testing will be two-sided and performed using α=0.05. P-values will be reported for all statistical tests, rounded to four decimal places. P-values less than 0.0001 will be

displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999". Tests of interaction terms, if applicable, will be two-sided and performed using α=0.10.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit from the eCRF or tablet. Analysis visits will be labelled as Baseline or Day 1, Day 4, Day 14, and Day 28 in all table summaries.

Data collected for the last subject treatment visit completed will be summarized separately for:

- The scheduled Day 14 (End of Treatment) visit for those subjects who complete the scheduled end of study visit, per protocol. This summary will be labeled as "Day 14" in the analysis.

- The last visit completed on-study, combining data collected for subjects who complete the Day 14 (End of Treatment) visit as well as the early termination (ET) visit for those subjects who discontinue the study early. This summary will be labeled as "Day 14/ET" in the analysis.

For assessments collected daily on the smartphone/trial application, visits will be summarized based on the study day relative to the date of treatment start for all data. However, statistical analyses will be conducted using Day 1 through 14 observations only.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Baseline Value

For analyses listed in this SAP, the baseline value is defined as the last measurement reported prior to the first dose of study drug, unless otherwise noted.

7.1.4 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

If duplicate post-baseline subject reported outcomes are present for a study day and/or time point, the earlier of the duplicates recorded will be used for analysis. Duplicate data that is not used in table summaries for efficacy endpoints will be flagged with an asterisk in their respective listings.

7.1.5 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and

- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:

    - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study drug; or

    - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.

- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value.

7.2 Analysis Populations

The analysis populations are defined as follows:

- Intent-to-Treat (ITT) Population: All randomized subjects who receive any amount of study drug. This population will be used as the primary analysis population for all efficacy endpoints. Subjects will be included in this population based on their randomized treatment assignment.

- Safety Population: All subjects who receive any amount of study drug. This population will be used for all summaries of safety data. Subjects will be included in this population based on the highest dose level received.

- Per-Protocol (PP) Population: All randomized subjects who complete the study treatment period with a minimum of 12 days of treatment and have no significant protocol violations that would affect the efficacy analyses. The PP Population will be determined prior to database lock and will be used for sensitivity analyses on the primary and select secondary endpoints. Subjects with major protocol deviations will be excluded from the efficacy analyses. See section 7.3.2 for further details on protocol deviations.

Data summaries to be presented on both the Safety Population and the ITT Population will only be produced on both analysis sets if there is a difference in the population groups.

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all randomized subjects by tolperisone dose group/placebo and total tolperisone treated subjects combined. Summaries will include the number and percentage of subjects in each analysis population, subjects completing a minimum of 12 days of treatment, subjects completing the study, and those discontinuing the study early by the primary reason for discontinuation. Subject disposition will also be summarized separately for each study site.

A data listing of study disposition will be presented by treatment group, site, and subject.

7.3.2 Protocol Deviations

Major protocol deviations will be summarized by tolperisone dose group/placebo and for total tolperisone treated subjects combined for the ITT Population. Major protocol deviations are protocol deviations captured on-study that are deemed by the Sponsor to potentially impact the efficacy or safety conclusions of the study. Subjects with major protocol deviations will be excluded from the PP Population for analysis.

All major protocol deviations will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any major protocol violations as well as the number and percentage of subjects with violations within each category will presented. Anticipated protocol deviation categories include inclusion/exclusion criteria, investigation product, prohibited concomitant medications, visit schedule, procedures/tests, SAEs not reported/reported late, and other.

A data listing of patients with all protocol deviations will be presented by treatment group, site, subject, and date of deviation. In addition to protocol violations, a data listing of informed consent and eligibility criteria will be presented.

7.3.3 Enrollment

A data listing of the randomization scheme and treatment codes will be presented.

7.4 Efficacy Evaluation

7.4.1 Datasets Analyzed

All efficacy summaries will be based on the ITT Population; select efficacy summaries will also be produced on the PP Population. A data listing of subjects excluded from the ITT or PP Population, to include the reason for exclusion, will be presented.

7.4.2 Demographic and Other Baseline Characteristics

Demographic variables including age, sex, ethnicity and race will be summarized by tolperisone dose group/placebo and for total tolperisone treated subjects combined for the Safety, ITT, and PP Populations. Age will be summarized using descriptive statistics. Frequency counts and percentages of subjects by age category, sex, ethnicity, and race categories will be summarized.

Baseline characteristics including CYP450 2D6 polymorphism, smoking history, height, weight, and body mass index (BMI) will be summarized by tolperisone dose group/placebo and for total tolperisone treated subjects combined for the Safety, ITT, and PP Populations.

Height, weight, and BMI at baseline will be summarized using descriptive statistics. Genotype and smoking history will be summarized with frequency counts and percentages.

Genotype results will also be presented in a by-subject data listing.

7.4.3 Measurements of Treatment Compliance

Compliance to the study treatment regimen will be determined as the total number of doses received divided by the expected number of doses received, multiplied by 100.

The total number of doses received will be determined based on the number of protocol-required doses (i.e. 42 doses) minus the number of tablets returned as reported in the eCRF.

Subjects are not expected to receive all three doses on the first (Day 1) and last (EOT/ET) day of dosing. The expected number of doses will be derived as outlined in Table 4.

Table 4 Expected Number of Doses

Row	First Dose Time	Doses expected Day 1	Last Dose Time	Doses expected *EOS/ET*	Doses *expected* Day 1 & EOS/ET	Doses *not expected* Day 1 & EOS/ET
1	12am-12pm	3	12am-12pm	1	4	2
2	12am-12pm	3	12pm-6pm	2	5	1
3	12am-12pm	3	6pm-12am	3	6	0
4	12pm-6pm	2	12am-12pm	1	3	3
5	12pm-6pm	2	12pm-6pm	2	4	2
6	12pm-6pm	2	6pm-12am	3	5	1
7	6pm-12am	1	12am-12pm	1	2	4
8	6pm-12am	1	12pm-6pm	2	3	3
9	6pm-12am	1	6pm-12am	3	4	2

Complete 14 day TID dosing

If the first dose of study drug occurs in the morning (between 12am and 12pm) and the last dose occurs in the evening (between 6pm and 12am) then the expected number of doses should be calculated as 3 × (date of last dose – the date of first dose + 1) (Table 4: Row 3).

Partial dosing on First and Last Day of Dosing

If the first dose occurs in the afternoon (between 12pm and 6pm) and last dose occurs in the morning (between 12am and 12pm), the expected number of doses should be calculated as 3 × (date of last dose – the date of first dose + 1) – (3 [doses not expected on first & last days]) to account for the fewer number of expected doses on the first and last days of treatment (Table 4: Row 4).

For subjects with non-missing date of last dose, but missing time of last dose on the CRF, if the date of last dose on the CRF is equivalent to the last date of entry on the subject eDiary, the corresponding eDiary time point (AM, MID, PM) will be used for compliance calculations. Otherwise, if the last dose date on the CRF and date of latest entry on the eDiary are not equivalent, subjects will be imputed to have received 1 dose on the given CRF date of last dose.

Dosing compliance will be summarized using descriptive statistics, by treatment group, based on the Safety Population. The number and percentages of subjects who are < 80% compliant and ≥ 80% compliant within each treatment group will be summarized. A data listing of subject compliance will also be presented.

7.4.4 Primary Efficacy Endpoint Analysis Methods

The primary efficacy endpoint is NRS subject-rated pain "right now" due to acute back spasm on Day 14 for all subjects in the ITT population. This analysis will be performed using a linear test of trend across all tolperisone doses.

The null and alternate hypotheses to be tested are:

H_0: There is no significant trend in NRS rating of pain "right now" across dose groups

H_1: There is significant trend in NRS rating of pain "right now" across dose groups

The linear test of trend will be performed using a mixed effect model for repeated measures (MMRM) using an unstructured covariance matrix to model within-patient errors. However, if the computational algorithm fails to converge, other covariance structures will be evaluated (e.g., compound symmetry). The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. Based on this model, the hypothesis test described above will be tested using a two-sided test at the alpha=0.05 level of significance.

The response variable will be the observed NRS rating of pain "right now". The observed value on Day 14 is the primary time point of interest. The model will include factors for treatment group (5 levels: placebo, 150 mg/day, 300 mg/day, 450 mg/day and 600 mg/day) and visit (three levels: Day 1/Baseline, Day 4, and Day 14) as fixed effects, the treatment by visit interaction, and the baseline NRS rating as a covariate. The primary analysis will be based on all available data without imputation. Day 14 will reflect subjects that have the completed the scheduled Day 14 (Visit 3). Subjects discontinuing the study may be analyzed as part of the sensitivity analysis using data imputation methods (LOCF and Multiple Imputation) to address missing data.

The observed NRS rating and change from baseline values will be presented using descriptive statistics for each treatment group by visit. The p-value for the overall test of trend on Day 14 will be presented. The pairwise least-square mean (LSM) estimates and least-square mean differences (LSMD) for each tolperisone dose level versus placebo will also be presented with 95% confidence intervals of the LSMD and associated p-values for the Day 14 visit observed values.

A plot of NRS subject rating of pain right now across study days will be presented.

7.4.5 Secondary Endpoint Analysis Methods

7.4.5.1 NRS Rating of pain "right now" on Day 4

Analysis performed for the primary endpoint will be repeated for the NRS at Day 4 using the same MMRM model. Contrast and estimate statements will be used in the primary model to analyze the Day 4 values.

7.4.5.2 NRS Rating of pain over past 1 hour and 12 hours on Days 1 through 14

NRS subject rating of pain over past 1 hour and 12 hours is collected daily as AM and PM assessments. The AM, PM and average of AM/PM values will be summarized descriptively by study day for each treatment group. Summaries for the 1 hour assessment and 12 hours assessment will be presented separately.

An MMRM model using a linear test of trend will be performed similar to the primary endpoint. The model will include response as the average of the AM and PM NRS rating over past 1 hour or 12 hours and factors for treatment group (5 levels: placebo, 150 mg/day, 300 mg/day, 450 mg/day and 600 mg/day) and visit (14 levels: Day 1 to Day 14) as fixed effects and the treatment by visit interaction.

The pairwise least square mean (LSM) estimates and least-square mean differences (LSMD) for each tolperisone dose level versus placebo will be presented with 95% confidence intervals of the LSMD and associated p-values for the Day 14 visit. The p-value for the overall test of trend on Day 14 will also be presented.

Plots of NRS subject rating of pain due to back spasm over past 12 hours and past 1 hour will be plotted with the average of the AM and PM assessments on the y-axis and study day on x-axis.

7.4.5.3 NRS Rating of pain at rest and on movement on Days 1 through 14

NRS subject rating of pain at rest and with movement collected once daily in the evening for the 14 day treatment period. The observed values will be summarized descriptively by study day for each treatment group. Summaries for the at rest assessment and with movement assessment will be presented separately.

An MMRM model using a linear test of trend will be performed similar to the primary endpoint. Plots of NRS subject rating of pain at rest and with movement across study days will be presented.

7.4.5.4 Subject Rating of Medication Helpfulness

SRMH values will be summarized categorically by treatment group for Days 4 and 14 for the ITT Population. The frequency and percentage of subjects in each response category will be presented. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 values and p-values presented.

7.4.5.5 Fingers to Floor Distance

Fingers to floor distance will be assessed at Baseline, Day 4, and Day 14 and will be analyzed using a linear test of trend similar to the primary endpoint on Day 14. Pairwise estimates of the observed value will be presented.

7.4.5.6 Global Symptom assessments (CGI and PGI)

Global symptom assessments will be summarized by treatment group for the ITT population. CGI-S and PGI-S will be assessed at the baseline visit only. CGI-C and PGI-C will be assessed at Day 4 and Day 14. The frequency and percentage of subjects in each response category at Baseline, Day 4 and Day 14 will be presented. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 values and p-values presented.

7.4.5.7 Quality of Sleep

Quality of sleep will be analyzed using the same methods described for the global symptom assessments in section 7.4.5.6. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 observed values.

7.4.5.8 Time to Pain Relief

Time to pain relief (days) will assessed using the NRS assessment of subject rating of pain over the past 12 hours. NRS assessments on or after Day 2 will be considered for time to relief. The first post-baseline occurrence of an AM or PM 12-hour NRS score equal to 2 or lower (0 = no pain, 10 = worst possible pain) will be used as the criterion for relief.

Subjects who withdraw from the study prior to the end of treatment visit or who complete the treatment period without having met the criteria for relief will be censored at the time of their last NRS assessment. Time to relief will be presented in days as (date of relief/censoring – date of first dose + 1).

The number of subjects with relief and those censored will be summarized by treatment group for the ITT population. Estimates of the median times will be presented along with their associated 95% confidence intervals. Treatment group comparisons will be summarized with hazard ratios and their associated 95% CI from a Cox Proportional Hazards regression model with treatment as the main effect and p-values from a generalized Wilcoxon test.

The Kaplan Meier plots of time to pain relief by treatment group will be presented and display the subjects with relief and those censored at each study day.

A by subject listing of derived time to relief estimates will also be presented.

7.4.5.9 Rescue Medication Use

The use of study provisioned medication will be summarized using frequency counts and percentages for the number of tablets consumed by treatment group for the ITT population. Descriptive statistics will also be presented by treatment group. The number of days of medication use, average daily use (caplets/day of medication use) and total use will be tabulated using descriptive statistics. The frequency and percentage of subjects with rescue medication entry will be presented.

The Shapiro-Wilk test will be used to examine the assumption of normality for total rescue medication use across all dose groups. If this test is statistically significant (i.e., $p \leq 0.05$) then the assumption of normality is violated and the total rescue medication consumption will be analyzed using a Wilcoxon Rank Sum test.

However, if the assumption of normality holds (i.e., Shapiro-Wilk p-value > 0.05), then the total rescue medication consumption will be analyzed using an analysis of variance (ANOVA) model with randomized treatment as the main effect. The LSM and LSMD will be presented with associated 95% CI and p-values comparing each treatment group to placebo.

A data listing of rescue medication use will be presented and include the average number of tablets consumed and total number of tablets rescue medication consumed for each subject.

7.4.5.10 Oswestry Disability Index

ODI score (%) will be calculated as (total score × 2) / (number of sections answered / 10), rounded to the nearest integer, where the total score is the sum of the individual section scores.

Observed ODI score and change from baseline will be summarized descriptively for each treatment group for the ITT population. Each dose group will be compared to placebo using an ANCOVA model with observed value as the response, main effects for treatment group and a covariate adjusted for the baseline ODI score. The LSM, LSMD, 95% CI and p-values will be presented at Day 14.

Individual section scores will be summarized separately for the ITT population by treatment group. The frequency and percentage of subjects in each response category at Baseline, Day 4 and Day 14 will be presented. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 values and p-values presented.

7.4.5.11 Visual Analogue Scale of Sleepiness

The Day 4 VAS ratings of sleepiness will be summarized descriptively by treatment group for the ITT population. Each dose group will be compared to placebo using an ANOVA model with the observed values as the response and main effects for treatment group. The LSM, LSMD, 95% CI and p-values will be presented.

7.4.5.12 Daily Activities

Daily activity scores will be summarized categorically for Days 1 to 14 by treatment group for the ITT population. The frequency and percentage of subjects in each response category will be presented. The comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 values and p-values presented.

7.4.6 Statistical/Analytical Issues

7.4.6.1 Adjustments for Covariates

The MMRM model to test for linear trend for the primary endpoint will include a covariate adjustment for the baseline value. Secondary endpoints utilizing an MMRM will be analyzed similarly when a baseline value is captured.

7.4.6.2 Handling of Dropouts or Missing Data

Primary and secondary endpoints including all NRS assessments (right now, past 12 hours, past 1 hour, at rest, on movement), Fingers to floor Distance, Clinician's Global Impression, and Oswestry Disability Index assessments will be analyzed using both observed data and data imputed using last observation carried forward (LOCF), if the dropout rate is ≥ 5% (20/400 subjects). In the LOCF method, the most recent non-missing value for the endpoint is carried forward to replace a missing value at a post-baseline visit within a subject. Baseline values will not be carried forward.

Methods for multiple imputation (MI) for missing data may be explored for endpoints if the dropout rate is ≥ 15% (60/400 subjects).

7.4.6.3 Interim Analyses and Data Monitoring

There are no interim analyses planned, nor is there a plan to establish a data monitoring committee for this study.

7.4.6.4 Multicenter Studies

This is a multicenter study, with approximately 45 sites expected to participate. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

7.4.6.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. All of the above analyses will be conducted using two-sided tests at the alpha = 0.05 level of significance.

7.4.6.6 Use of an "Efficacy Subset" of Subjects

The primary efficacy analysis will be performed on the ITT population; the PP population will be utilized as a sensitivity analysis for the primary endpoint and secondary endpoints, including NRS (right now, past 12 hours, past 1 hour, at rest, on movement), Subject Rating of Medication Helpfulness, Fingers to Floor Distance, Clinician's Global Impression assessments, and Oswestry Disability Index. The PP population will exclude subjects with major protocol violations.

7.4.6.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

7.4.6.8 Examination of Subgroups

There are no planned analyses to assess efficacy results by subgroups.

7.4.7 Plasma Concentrations

Plasma concentration measurements will be summarized in a separate report and is outside the scope of this SAP.

7.4.8 Pharmacokinetic Analysis

Pharmacokinetic analysis will be summarized in a separate report and is outside the scope of this SAP.

7.5 Safety Evaluation

Safety analysis will be carried out for the Safety Population, which will include all subjects who receive at least one dose of study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first study drug administration. All analyses will be presented by treatment group.

7.5.1 Extent of Exposure

Extent of exposure to study treatment will be summarized for the Safety Population by treatment group. The date of first and last dose is collected on the eCRF. If missing, subjects' dosing eDiary data will be used to determine dates of first and last doses. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Duration of exposure, average dose received, and total dose received (mg) will be summarized using descriptive statistics.

Total dose received will be derived based on the number of tablets returned at the end of treatment visit and the actual dose (mg) received. Average dose will be calculated as the total

dose divided by the duration of exposure. The planned number of doses for each subject is 42 (14 days of TID dosing).

7.5.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those adverse events (AEs) with onset on or after the first dose of study drug through 24 hours after the last dose of study drug. Existing events that worsened during this period will also be considered treatment emergent. If start time is not available, AEs with onset between the date of the first dose through the day after the date of last dose (+1 day) will be considered treatment-emergent.

Adverse events with onset greater than 24 hours (or >1 day) after the date of the last dose of study drug through the date of the follow-up visit (Visit 4/Day 28) will be considered after-treatment events.

Treatment-emergent and after-treatment AEs will be summarized by treatment group. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent serious adverse events (SAEs) and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs by MedDRA preferred term;
- Subject incidence of TEAEs by severity grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term;
- Subject incidence of SAEs by MedDRA system organ class and preferred term;
- Subject incidence of TEAEs Leading to Study Drug Discontinuation by MedDRA system organ class and preferred term; and
- Subject incidence of TEAEs by CYP450 2D6 Genotype, MedDRA system organ class and preferred term.

- Subject incidence of After-treatment Adverse Events by MedDRA preferred term.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one AE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug. Related events include those reported as "Possibly Related" or "Definitely Related" to study drug; events considered not related are those reported as "Unrelated" to study drug.

Adverse event data will be presented in data listings by patient, treatment group, and event. The study phase (e.g., treatment-emergent, after-treatment) will also be presented in the listing. Serious AEs and AEs leading to discontinuation, interruption or dose reduction, interruption of the study drug will be presented in separate data listings.

7.5.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs and other significant AEs, including those that led to discontinuation, interruption or dose reduction of the study drug, will be provided in separate subject data listings.

7.5.4 Clinical Laboratory Evaluation

7.5.4.1 Hematology and Chemistry

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit.

Serum chemistry and hematology clinical laboratory measurements will be summarized by treatment group and for total tolperisone treated subjects at Baseline, Day 14,and at Day 14/ET. Descriptive statistics will be presented for observed values and changes from baseline at each visit.

7.5.4.2 Urinalysis

Urinalysis and microscopic urinalysis results will be summarized in by-subject data listings.

7.5.4.3 Pregnancy Test

Pregnancy test results will be presented in a by-subject data listing

7.5.4.4 Alcohol Breathalyzer Test

Alcohol breathalyzer test results will be presented in a by-subject data listing

7.5.4.5 Urine Drug Screen

Urine drug screen results will be presented in a by-subject data listing

7.5.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.5.5.1 Vital Signs

Vital sign parameters including blood pressure (standing, supine, orthostatic), heart rate, respiratory rate and body temperature will be summarized by treatment group and for total tolperisone treated subjects. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

Orthostatic blood pressure will be calculated as the standing minus supine measurement for both systolic and diastolic blood pressure.

Weight will be converted from lbs to kg using a conversion factor of 0.4536.

7.5.5.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters will be summarized categorically as normal, clinically significant abnormal, and not clinically significant abnormal by treatment group and for total tolperisone treated subjects at each scheduled visit.

7.5.5.3 Neurological Examination

Results of the neurological examination will be summarized categorically as improved, stable, and deteriorated by treatment group and for total tolperisone treated subjects at each scheduled visit.

7.5.5.4 Physical Examination

Results of the physical examination will be presented in subject data listings by subject and study visit.

7.5.5.5 Concomitant and After-Treatment Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE), version B3 March 1, 2018. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Concomitant and after-treatment medications will be summarized separately for the Safety Population. The study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medications is defined as any

medication administered on or after the date of the first dose of study drug through 24 hours after the date of last dose of study drug. If medication time is not available, any medication administered on or after the date of first dose through the day after the date of last dose (+1 day) will be considered concomitant. An after-treatment medication is defined as any medication administered greater than 24 hours (or >1 day) after the date of the last dose of study drug through the date of the follow-up visit (Visit 4/Day 28).

A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For both concomitant, and after-treatment medications summaries, the number and percentage of subjects receiving any medication will be summarized by treatment group and for total tolperisone treated subjects, as will the number and percentage receiving any medication by ATC drug class and generic drug name.

Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

A summary of concomitant analgesic medications received, outside of the study-provided medication, will also be presented. These medications will be identified from list of generic drug names and indications as determined by the sponsor prior to data base closure. Analgesic medications taken on Day 1 will not be considered as concomitant as use was allowed per protocol on Day 1 of treatment.

All medications will be presented in a data listing by subject and medication name. The study phase during which each medication was received (e.g., prior, concomitant, or after-treatment) and whether the medication is a rescue medication will be presented on the listing.

7.6 Determination of Sample Size

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

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

7.7 Changes in the Conduct of the Study or Planned Analyses

7.7.1 Changes in Planned Analyses

VAS ratings of sleepiness will be analyzed using an ANOVA in place of an ANCOVA model since no baseline values are collected to be used as a covariate. Daily activity scores and Subject Rating of Medication Helpfulness will be summarized categorically and the comparison of each group to placebo will be conducted using a Wilcoxon Rank Sum test for the Day 14 values instead of an MMRM or ANCOVA model.

7.7.2 Other Changes

An independent audit of Site 21 (Mariano), conducted May 12 and May 15, 2019, described substantial evidence of clinical trial misconduct during the execution of the trial. Based on the inspection findings report (signed May 17, 2019), Site 21 subject data will be excluded from all analyses described in this SAP.

8 REFERENCE LIST

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[3] Data Standards: Position on Use of SI Units for Lab Tests. U.S Food and Drug Administration; 25 October 2013. Available from: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

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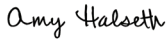
Amy Halseth ahalseth@neuranapharma.com Precision for Medicine - Part 11 Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: B3209FE6-E358-4D91-8B87-D8E13F8B4E73 Using IP Address: 98.153.177.58 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 8/6/2019 9:34:11 AM Viewed: 8/6/2019 12:10:22 PM Signed: 8/6/2019 12:12:09 PM
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