STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO EVALUATE THE SAFETY OF TRAMADOL INFUSION (AVE-901) IN THE MANAGEMENT OF POSTOPERATIVE PAIN FOLLOWING SURGERY

PROTOCOL AVE-901-104

Protocol Version 1.0 (11DEC2017)

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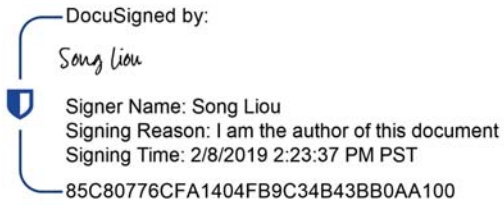

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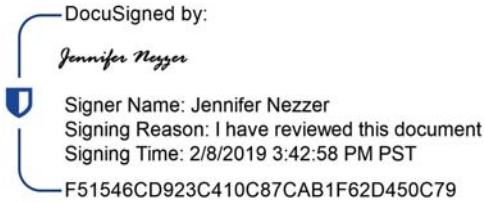

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LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CDER	Center for Drug Evaluation and Research
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
EOT	End of Treatment
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potential Clinically Significant
PE	Physical Exam
PGA	Patient Global Assessment
PT	Preferred Term
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SDTM	Standard Data Table Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number AVE-901-104 Amendment 1.0 (29AUG2018) from Avenue Therapeutics, Inc. The SAP will be signed off before the final database lock. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline and the Guidance for Industry: Structure and Content of Clinical Study and the most recent FDA draft Guidance for Industry - Analgesic Indications: Developing Drug and Biological Products, dated February 2014.

This SAP describes the data sets that will be analyzed and the patient characteristics, safety, and efficacy assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are performed after database lock to supplement the planned analyses described in this SAP, they will be completed and will be clearly identified as post-hoc in the CSR.

2. PROTOCOL SUMMARY

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the safety of intravenous (IV) tramadol (AVE-901) 50 mg for the management of postoperative pain.

Safety endpoints will include

- Adverse event (classified by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term (PT)).
- Clinical laboratory, vital sign, and electrocardiogram (ECG) changes.
- Local tolerability of the infusion site via pain, swelling, tenderness, and erythema.

2.2. Overall Study Design and Plan

This study is a Phase 3, multicenter, single-arm, open-label, repeat-dose trial to assess the safety of AVE-901 in the management of postoperative pain. Eligible patients will be patients that are undergoing elective surgery and are willing to be confined in a healthcare facility and receive AVE-901 for the treatment of post-surgical pain for at least 24 hours. Approximately 250 patients will be enrolled into the study. Each patient will undergo the Screening Visit (Day -28 to Day -1), the Pre-operative assessment (within 24 hours prior to surgery), the Surgery (Day 0), the Primary treatment period (hour 0 through hour 168), end of treatment (EOT) visit, and the Follow-up Visit (Day 14).

Screening will occur up to 28 days prior to surgery. Following the pre-operative assessments, after the patient has met eligibility criteria, patients will be enrolled into the study.

Surgery will occur on Day 0. There are no restrictions on the agents to be used for induction, neuromuscular blockade, maintenance of anesthesia, or on hypnotics, sedatives, analgesics (including narcotics) or anxiolytics.

Following surgery, each patient will receive their study medication infusion at T0, T2, T4, and then every 4 hours for up to 168 hours after the first study drug administration (a total of up to 43 doses per patient). The dosing time point will always be defined relative to T0 for all doses. The latest (last) dose that is allowed is at Hour 164. Patients will be confined at an appropriate healthcare or research facility for as long as they are still using AVE-901. Following the first dose of study drug, the patients will be allowed to use non-opioid-based analgesics per treating physician’s discretion, if additional pain relief is required.

2.3. Description of Study Periods

There are 5 periods in this study: Screening, Preoperative, Surgery, Treatment Period/Post Surgery, and Follow-up. Procedures for each study period are described below.

2.3.1. Screening

Screening will occur from Day -28 through Day -1 and will be conducted as a clinic visit. Patients will have the purpose and procedures of the study explained to them and, those who elect to participate in the study, will provide written informed consent and be screened for participation according to the eligibility criteria. Screening will include eligibility assessment, medical history, physical examination (PE), demographics, height and weight, body mass index (BMI), vital signs (heart rate, systolic blood pressure (BP), and diastolic BP, respiratory rate, temperature, pulse oximetry), American Society of Anesthesiologists (ASA) Physical Status, 12-lead ECG, hematology panel, chemistry panel, urinalysis, serum pregnancy test (in females of childbearing potential), and prior/current treatments. All screening laboratory evaluations must be within acceptable limits as determined by the investigator prior to enrollment. For patients that screen within 5 days of surgery, central laboratory values may not be available to assess eligibility. For these patients it is acceptable for sites to draw local labs to assess eligibility in addition to the central lab which will still be used as the baseline in the study. The local laboratory listed on the FDA 1572 Form must be used for all local blood draws. At a minimum the following analytes must be reviewed from the local laboratory prior to dosing; magnesium, calcium, potassium, sodium, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hemoglobin.

2.3.2. Preoperative

Preoperative assessments to confirm the patient's eligibility will be performed within 24 hours of scheduled surgery start time. This visit will include reassessment of eligibility criteria, interim medical history, vital signs, PE, ASA Physical Status, urine pregnancy test (in females of childbearing potential), and concomitant treatments.

Note: If the patient's scheduled surgery has time considerations, patients may have Screening and Preoperative Visits combined into one visit if required (at the time of pre-op). The procedures associated with the Screening Visit will be acceptable for both visits. Both central and local labs should be drawn for eligibility

2.3.3. Surgery

Surgery will occur on Day 0. Sites will follow their standard operating procedures.

2.3.4. Treatment Period/ Post Surgery

Patients will receive their first dose of study medication (T0) within 8 hours of meeting the postsurgical eligibility criteria. Patients will be dosed at Hour T0, T2, T4, and then every 4 hours thereafter, for a total of up to 43 doses administered over the 168-hour treatment period (with the last possible dose at Hour 164). Treatment is anticipated to occur from Hours 0 to 48 and may extend through to Hour 168.

Safety will be assessed by recording vital signs including: ECG's, respiratory rate, heart rate, pulse oximetry (SpO2), temperature, and BP as per the schedule of events.

A PGA will be obtained at Hour 24 and EOT. If the patient continues treatment beyond Hour 24,

PGA will be conducted at Hour 24 and EOT (total of 2 PGAs). If the patient ends treatment prior to Hour 24, PGA will be conducted as part of the EOT visit (total of 1 PGA).

At the EOT assessment, patients will undergo a brief PE, vital signs measurements, ECG, PGA and clinical laboratory evaluations for safety. AEs and concomitant medication use will be recorded.

2.3.5. Follow up:

A final safety assessment will be conducted on Day 14 (± 2 days) from the first dose via a telephone call to check on general well-being, including spontaneous reports of adverse events and concomitant medications.

The protocol-defined visits are presented in Table 1.

Table 1: Protocol-Specified Visits and Visit Windows (Study AVE-901-104)

Study Phase	*Visit Time*
Screening	From days -28 to -1
Pre-Operative	0 - 24 Hours prior to surgery
Surgery	Day 0
Treatment Period /Post Surgery	Hours 0 up to Hour 168 after infusion of first study drug administration
Follow-up	Day 14 (approximately Day 14±2 days)

2.4. Study Population

Approximately 250 patients in United States (US) who meet all the inclusion and none of the exclusion criteria (Described in Sections 7.1, 7.2 and 7.2.1 of Protocol) are planned to be enrolled. Every patient treated will receive AVE-901.

2.5. Treatment Regimens

2.5.1. Study Material

AVE-901, 50 mg. Assigned study treatment (51 mL) doses will be administered IV over 15 minutes (+/- 4 minutes) via infusion pump.

All patients will receive tramadol infusion per the treatment dosing regimen. A trained health care professional will flush the line with normal saline at the end of each infusion. Throughout the SAP, AVE-901 will be used to indicate the study treatment.

2.5.2. Comparator Group

NA as this is a single arm study.

2.6. Treatment Assignment and Randomization

No randomization will be utilized in this study.

2.7. Sample Size Determination

A sample size of approximately 250 patients will be enrolled. This sample size of 250 patients will provide approximately 90% power to detect at least one incidence of uncommon adverse events (those events with a true underlying incidence of 1%).

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies are provided in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by time point (as applicable) using the descriptive statistics n, mean, SD, median, and range (minimum, and maximum). All of the categorical study assessments will be summarized by time point (as applicable) using frequency counts and rates of occurrence (%).

The treatment group will be labeled as '**Tramadol 50 mg**' for all outputs. All study data will be listed by study center, patient, and time point (as applicable).

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the raw data. Standard deviations will be presented with two more decimal places than the precision of the raw data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

All analyses will be performed using the SAS System® version 9.3 or higher. The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the SAS programs that generate the report-ready tables, figures and listings. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries.

The following conventions will be used throughout the study analysis:

- Time T0 is the time of start of the first study drug administration.
- Study Day is defined as (Date of Assessment minus Date of First Dose of Study Medication). The first day of dosing is Study Day 0. The day immediately prior to first dose is Study Day -1. Study Day will be calculated for every record in the database and presented alongside the date fields in the data listings, where applicable. For instance, the start *date* of each TEAE will also have the Start *Day* presented in the listings.
- Assessment and visit times are defined relative to time T0.
- Baseline value is defined as the last valid measurement prior to the first treatment administration.
- Change from baseline is defined as post-baseline value minus baseline value.
- Unscheduled visits and measurements will be included in subject listings but will not be used in analyses.

- If duplicate values are obtained at a given visit (e.g., lab assay is repeated on a sample resulting in two results, or vital sign repeated during a visit), the last reported value will be used unless it is noted that the measurement was in error for that value.
- Values that compromise interpretation will not be used in summaries (e.g., values that were obtained post-dose will not be summarized as pre-dose values).

4. PATIENT SUMMARIES

4.1. Analysis Populations

Three population are identified for purposes of the statistical analysis:

- Screened Population, defined as all screened patients.
- Screened Not Treated, defined as the subset of patients who are screened but not treated due to not moving forward to surgery or not meeting post-surgical dosing criteria.
- The Safety Population is defined as all patients who receive study medication. Patients will be analyzed according to the actual treatment they receive.

In general, data listings will include only subjects who receive study treatment (Safety population).

4.2. Disposition of Patients

Disposition of all patients screened will be tabulated. The Inclusion/Exclusion criteria failed for screen failures will be presented. The denominator will be based on all screened patients.

Patient completion status (completer, screen failure, or post-op failure) and reasons for study completion will be tabulated descriptively in a patient disposition summary table. Reasons for study completion include:

- Dosing Completed (patient discharged and did not stop dosing for the other items listed below)
- Adverse Event
- Lost to Follow-Up
- Death
- Protocol Violation
- Subject Non-compliance or uncooperativeness
- Withdrawal of Consent
- Other

The number of days in the study will also be summarized. The number of days is computed as: [Date of study completion (i.e., date of discharge) or withdrawal minus the date of first treatment administration (Day 1)] + 1.

All patient disposition data will be presented in listings.

4.3. Protocol Deviations

Protocol deviations will be documented in the electronic case report from (eCRF), categorized according to type of deviation (e.g., out of window, etc.) and classified as major or minor by the Sponsor's medical monitor. Protocol deviations, both minor and major, will be presented in a

data listing and major violations will be summarized by category of deviation and classification. A listing describing patients excluded from the Per Protocol Population will be provided.

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Demographic variables include age, sex, race, and ethnicity. Baseline characteristics include American Society of Anesthesiologists (ASA) physical status, previous opioid history (Y/N), height, weight (kg) and BMI (kg/m^2). Demographics and baseline characteristics will be presented in by-patient listings and summarized.

5.2. Medical History

Medical history, as collected at screening and prior to surgery, will be presented in a by-patient listing and summarized by body system.

5.3. Prior and Concomitant Medications

Prior and concomitant medications are collected at screening and updated throughout the study as needed. Prior and concomitant medications will be coded using WHODDE (C Format) version 01SEP2017. The number and percentage of patients who take concomitant medications will be summarized by drug class (Anatomical Therapeutic Chemical (ATC) Level 3) and PT for the safety population and presented in a by-patient listing.

Prior medications, including medications given during surgery, and non-medical therapies will appear in a data listing but will not be summarized.

Medications will be classified as follows:

- Prior medications. Prior medications/therapies are those that have a start date/time and end date/time prior to the start of the first treatment administration. Prior medications will not be tabulated but will be included in the data listings.
- Concomitant medications. Medications will be considered as concomitant if the medication is taken on or after the date/time of first intake of treatment product and has a start date/time that is no later than 1 day (24 hours) after the start of the last administration of study medication.
- New-onset concomitant medications are defined as those medications starting between the start of the first dose of study medication and 1 day (24 hours) after the start of the last dose of study medication. Medications with no start time but starting on the day of study medication will be assumed to be new-onset.
- Post-treatment medications. Post-treatment medications are defined as a medication with a start date/time at least 24 hours (1 day) after the start of the last dose of study medication.

If a missing medication start date cannot be definitively determined as having started after first dose, the medication will be considered as started prior to first dose; similarly, if a missing medication stop date/time cannot be determined as having stopped prior to first dose, the medication will be considered concomitant (taken after first dose). Imputation of missing start

and stop date/times will be performed in the same manner as described for AEs in Table 2. Medications with entirely missing start and stop dates will be listed but not included in the tabulations.

6. MEASUREMENTS OF TREATMENT EXPOSURE

Patient dosing data will be listed and the number of doses per subject and total exposure (mg) per subject will be tabulated. If less than the complete volume of study medication is infused, total exposure will be calculated as the intended dosage (50mg) times the proportion of total saline volume infused (xx mL / 50 mL).

- The duration of exposure will be defined in hours, in which the time from the start of the first dose to start of the last dose, plus 4 hours (i.e., exposure is assumed to be 4 hours for each dose), will be tabulated.
- The number (%) of patients by number of doses received will be presented. The maximum total number of doses is 43.
- The total exposure (mg) will be summarized through 24, 48, 72, 96, 120, 144 and 164 hours, respectively. Maximum exposure is 2150 mg (given at Hours 0, 2, 4, and then 4 hours up to 164).
- If infusion end time is not available, the end time will be imputed as 15 minutes after the infusion start time for use in calculations dependent upon the end time.

In addition, cumulative percent of subjects (%) versus total study drug exposure will be provided graphically.

7. OVERVIEW OF ANALYSIS ISSUES

No inferential testing is planned for this safety-based single arm study.

7.1. Handling of Dropouts or Missing Data

No study outcomes will be imputed.

7.2. Assessment Time Windows

Summaries will be based on the nominal protocol-specified visits as appropriate.

8. EFFICACY EVALUATION

The primary objective of this study is to evaluate the safety of AVE-901. Efficacy is considered a secondary, exploratory, given that this is an uncontrolled study in patients with various surgery types. Efficacy will be assessed by patient global assessments (PGAs) using a 5-point scale.

8.1. Efficacy Outcome

Patient Global Assessment of efficacy will be collected at 24 hours post first dose and EOT. The question to be posed is "How would you rate the study medication in terms of its effectiveness in controlling your pain?" (0=poor; 1=fair; 2=good; 3=very good; 4=excellent). If the patient continues treatment beyond Hour 24, PGA will be conducted at Hour 24 and EOT (total of 2 PGAs). If the patient ends treatment prior to Hour 24, PGA will be conducted as part of the EOT visit (total of 1 PGA).

The PGA results will be presented in a summary table by time point. The number (%) of subjects answering in each category will also be presented by time point.

Individual PGA scores will be listed

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

The safety analysis will be descriptive in nature. All safety data will be listed, and data will be tabulated where the data warrant. Safety data include:

- AEs, including assessment of infusion site local reactions (skin and vein)
- Clinical laboratory tests (hematology panel, chemistry panel and urinalysis) pre-treatment and discharge
- Vital signs including: respiratory rate, heart rate, oral temperature, pulse oximetry (SpO2) and BP, as per the schedule of events
- PE at pre-treatment and discharge
- 12-lead ECG at protocol specified time points
- Concomitant treatments

Anti-emetic usage data will be included with the concomitant treatments. Exploratory analyses of use of anti-emetics may be performed if warranted. Other safety data presentations will be descriptive in nature and no formal statistical tests will be performed.

ECG results will be analyzed on an ongoing basis by a central ECG reader on an individual patient level.

9.2. Adverse Events

Any events starting before the first dose of treatment will be reported as Medical History. Verbatim terms used by investigators to identify AEs in the CRFs will be mapped to the appropriate PT and SOC using a standardized coding dictionary (MedDRA Version 20.1). All coding will be reviewed prior to database lock. All recorded AEs will be listed; adverse events starting on or after the first dose of treatment are considered treatment-emergent adverse events as per the protocol, but the definition of treatment emergent will be further categorized for summaries as follows:

- Adverse events occurring on or after the first dose of study medication, and within 1 day (up to 24 hours) after the start of the last dose of study medication. For simplicity, these will be referred to as Treatment Emergent AEs (TEAEs) in the summaries.
- Events occurring after that will be presented as Post-Treatment AEs.

Separate tabulations will be presented for TEAEs and for Post-Treatment AEs.

For evaluation of causal relatedness to treatment, the categories are definite, probable, possible, remote or definitely not. For categorization in the summary tables, AEs designated as definite, probable, or possible will be considered to be related.

For the evaluation of event severity, the criteria are based on National Cancer Institute Common

Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03:

CTC Grade	CTCAE Grade Description
Grade 1: Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1].
Grade 3: Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
Grade 4: Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5: Death	Death related to the AE.

[1] ADL = Activities of Daily Living. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Local tolerability at the infusion site will be assessed for pain, swelling, tenderness, and erythema. Any such AEs related to tolerability at the infusion site will be identified by the sponsor and medical monitor for listing and possible summarization.

In addition to a listing of all TEAEs, treatment related TEAEs, serious TEAEs, TEAEs leading to premature discontinuation from the study, and TEAEs related to local tolerability at the infusion site will be provided.

An overall summary will be prepared including both the number of TEAEs, and the number of patients with TEAEs, as well as SAEs, treatment related TEAEs, TEAEs by severity and TEAEs leading to premature discontinuation from study.

Incidence of TEAEs will be summarized by SOC and PT sorted in descending frequency by SOC, and then by PT within SOC. These summaries will be given in separate tables for each of the following TEAE event sets:

- All events (Post-Treatment AEs will be tabulated separately)
- Treatment related events (defined by a relationship to study drug of possible, probable, or definite). (Post-Treatment AEs will be tabulated separately)
- Events leading to premature discontinuation from study
- Events related to local tolerability at the infusion site
- Events by maximum severity

If a given patient experiences a TEAE that maps to the same PT more than once, the patient will be counted once for the PT at its greatest severity (i.e., mild, moderate, or severe) and causality

(i.e., attribution to study material).

TEAEs occurring within 1 hour of any infusion will be summarized.

The number/ percentages of subjects with any TEAE will also be presented by Infusion #. Each AE will be matched to an Infusion # by the start date/time of the AE (after all imputation for missing dates). E.g., An AE with start date/time on or after the start date/time of Infusion #3 and prior to start date/time of Infusion #4, will be counted under Infusion #3. Percentages will be calculated from the number of subjects receiving the referenced injection (i.e., Subjects receiving 4 injections will be counted in the denominator for Infusion #1, #2, #3 and #4, and will not be included in the denominator for other Infusions).

Duration of a TEAE will be computed in days as the stop date of the event minus the start date plus 1. If reported as ongoing at the time of database lock, the duration of the AE will be calculated using the date/time of the last visit or the last date of any adverse event for the patient in the database, whichever is later. If a TEAE is considered resolved, but the stop date is missing, the last day of the month will be imputed if the month and year are available. If only the year is available, and the year is the same as the year of the last visit, the stop date will be imputed as the latest of the last visit date or latest event for the patient in the database. If the year of the event is prior to the year of the last treatment, the end day and month will be imputed as 31 December.

For missing or partial start dates, they will be imputed as temporally related to the first dose of study medication. Table 2 demonstrates the rules to be used to impute any missing AE start dates.

Table 2: Table of Imputation Rules for Missing AE Start Date Times (Study AVE-901-104)

Missing Start Date Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	Month and Year < Month and Year of first treatment: Start Day = 1 Stop Day = last day of the month	*Month and Year = Month and Year of first treatment:* Start Day = Day of first treatment Stop Day= last day of the month	*Month and Year > Month and Year of First Treatment:* Start Day = 1 Stop Day= last day of the month
Day and Month Define Day as above, then:	*Year < Year of first treatment:* Start Month = July Stop Month = Dec	*Year = Year of first treatment:* Start Month = Month of first treatment Stop Month = Dec	*Year > Year of first treatment:* Month = January Stop Month = Dec
Day, Month, and Year	To be conservative, completely missing start dates will be set to the date of first treatment, completely missing end dates will be set to the date of last contact.		
Time	Missing start times will be imputed as 00:01 (or the start time of the first dose administration if AE occurred on the date of first dose administration) Missing stop times will be imputed as 23:59		

After following these imputation rules, if the start date/time is imputed as a date after the end date/time, the start date/time will be set to the end date/time to provide a positive duration for the event incidence.

Missing assessments for AE study medication relationship or severity will be analyzed as related or severe respectively. No other imputation is planned for safety data.

9.2.1. Subgroups

Descriptive analysis of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and discontinuations due to AEs, will be provided by the following subgroups:

- Gender (male versus female)
- Race (White versus non-White)
- Age (using the study median age: less or equal to (≤) median age group versus greater than (>) median age group)
- Age (<65 vs >=65 years)
- BMI (> versus <= median value)
- Surgery Type (Orthopedic versus soft tissue)

9.3. Deaths and Serious Adverse Events

A serious adverse event is an AE occurring during the study that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Serious adverse events and deaths will be listed and summarized separately for the safety population.

9.4. Clinical Laboratory Evaluation

Clinical laboratory test results (blood chemistry, hematology and urinalysis) will be listed for individual patients. Baseline for clinical laboratory parameters will be defined as the last evaluation before dosing with study treatment. For each individual lab test value, results and change from baseline will be summarized by time point (baseline and at discharge).

The number and percent of patients with potentially clinically significant (PCS) values will be summarized. Only new-onset PCS values, i.e., patients with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment. The criteria used to identify potentially clinically significant laboratory values are listed in Table 3.

Table 3: List of Potentially Clinically Significant Ranges for Clinical Laboratory Parameters (Study AVE-901-104)

Variable Name (Normal Range)	Low	High
Hematology		
White Blood Cells (NR: 3.7 - 11.0x K/cu /mm)	≤2.8 x 10^3 /mm^3	≥16 x 10^3 /mm^3
Neutrophils (NR: 46 - 72%)	≤ 15%	NA
Lymphocytes (NR: 14 - 46%)	NA	≥75%
Monocytes (NR: 0 - 11%)	NA	≥15%
Eosinophils (NR: 0 - 7%)	NA	≥10%
Basophils (NR: 0 - 3%)	NA	≥10%
Red Blood Cells		
Female: (NR: 3.8 - 5.1 x 10^6 /mm^3)	≤3 x 10^6 /mm^3	≥6 x 10^6 /mm^3
Male: (NR: 4.1 - 5.6 x 10^6 /mm^3)	≤3.5 x 10^6 /mm^3	≥6.5 x 10^6 /mm^3
Hematocrit		
Female: (NR: 36.4 – 48.9%)	≤32%	NA
Male: (NR: 41.6 – 54.1%)	≤37%	NA
Hemoglobin		
Female: (NR: 11.5 – 16.0 g/dL)	≤9.5 g/dL	NA
Male: (NR: 13.0 – 17.5 g/dL)	≤11.5 g/dL	NA
Platelets (NR: 125 - 375 K/cu /mm)	≤75 x 10^3 /mm^3	≥700 x 10^3 /mm^3
Serum Chemistry		
Total protein (NR: 6.0 - 8.0 g/dL)	≤4.0 g/dL	≥10 g/dL
Albumin (NR: 3.5 - 5.5 g/dL)	≤2.0 g/dL	NA
Creatinine (NR: 0.7 - 1.4 mg/dL)	NA	≥2 mg/dL
BUN (NR: 5 - 20 mg/dL)	NA	≥30 mg/dL
Uric Acid: (NR: 2.0 - 6.0 mg/dL	NA	≥9.0 mg/dL
Bilirubin total (NR: 0.1 – 1.1 mg/dL)	NA	≥2.5 mg/dL
Bilirubin direct (NR: 0 - 0.4 mg/dL)	NA	≥0.6 mg/dL
Alkaline phosphatase (NR: 30 - 115 U/L)	NA	≥390 IU/L
AST/SGOT	NA	□150 U/L
ALT/SGPT	NA	□165 U/L
CPK (NR: 24 - 169 U/L)	NA	≥702 IU/L
Glucose random (NR: 60 - 115 mg/dL)	≤40 mg/dL	≥250 mg/dL
Calcium (NR: 8.5 - 10.5 mg/dL)	≤8.0 mg/dL	≥12 mg/dL

Variable Name (Normal Range)	Low	High
Phosphorous (NR: 2.5 - 4.5 mg/dL)	≤1.7 mg/dL	NA
Sodium (NR: 133 - 145 mEq/L)	≤126 mEq/L	≥156 mEq/L
Potassium (NR: 3.5 - 5.0 mEq/L)	≤3 mEq/	≥6 mEq/L
Chloride (NR: 95 - 110 mEq/L)	≤90 mEq/L	≥118 mEq/L
Bicarbonate (CO_2) (NR: 21 - 33 mEq/L)	≤19 mEq/L	≥35 mEq/L
Urinalysis		
Specific gravity (NR: 1.002 - 1.035)	≤1.001	NA
pH (NR: 5.0 – 8.0)	≤4	≥9
UA Ketones (Normal = negative) mg/dL	NA	≥2+
UA Protein (Normal = negative) mg/dL	NA	≥2+
UA Blood (Normal = negative)	NA	≥3+
UA Leukocyte Esterase	NA	≥3+
Nitrates	NA	≥2

Each clinical laboratory test will be defined to be “Low”, “Normal”, or “High”, according to the normal reference range from the clinical laboratory. The number and percentage of patients who have a shift from within to outside the normal reference range from baseline (and vice versa) to each follow-up visit will be summarized by time point.

9.5. Vital Signs

Vital signs results including BP (systolic and diastolic), heart rate, respiration rate, pulse oximetry, and temperature will be listed for individual patients. Baseline for vital signs measurements will be defined as the last evaluation before dosing with study medication. Vital signs and changes from baseline will be summarized by time point.

Vital sign parameter outcomes will be assessed for potential clinical significance; observed values and changes from pre-treatment to on-treatment time points will be tabulated for continuous parameters, as warranted.

The number and percent of patients with potentially clinically significant (PCS) values during the treatment phase will be summarized. A focus will be on new-onset PCS values, i.e., patients with pre-existing PCS values at pre-treatment will not be considered to have new-onset values on-treatment. The criteria for identifying potentially clinically significant vital signs values are provided in Table 4.

Table 4: List of Potentially Clinically Significant Ranges for Vital Sign Parameters (Study AVE-901-104)

Variable Name	LOW	HIGH

Systolic BP	<86 mm Hg OR a decrease of ≥25 mm Hg from baseline	>200 mm Hg OR an increase of ≥25 mm Hg from baseline
Diastolic BP	<48 mm Hg OR a decrease of ≥20 mm Hg from baseline	>110 mm Hg OR an increase of ≥20 mm Hg from baseline
Heart rate [1]	1) <45 bpm OR a decrease of ≥25 bpm from baseline	1) >105 bpm and increase ≥25 bpm from baseline OR >125 bpm

[1] bpm: beats per minute

9.6. Physical Examination

Physical examination results will be listed for individual patients.

9.7. ECG Examinations

ECG examination interpretation results and heart rate and interval duration results will be listed for individual patients. Baseline for ECG continuous measurements will be defined as the last evaluation before dosing with study medication. Continuous ECG values and changes from baseline will be summarized by time point. The proportion of subjects with Normal, Abnormal: Not Clinically Significant, and Abnormal: Clinically Significant will be summarized by time point.

The ECG analysis will include a careful review of QTcF values. As part of this review, a summary of the number (percent) of patients with QTcF values in the following ranges will be provided: ≤450 msec, >450 to ≤480 msec, >480 to ≤500 msec, and >500 msec. This will be performed by visit as well as at ANY time during the treatment period (where the highest QTcF value will be used for that assessment).

The incidence of PCS values will be presented, with a focus on new-onset PCS values. The criteria for identifying potentially clinically significant ECG values are provided in Table 5.

Table 5: List of Potentially Clinically Significant Ranges for ECG Parameters (Study AVE-901-104)

PR Interval
High: >200 msec OR Increase ≥ 20 msec from baseline
QRS Interval
High: >100 msec OR Increase ≥ 10 msec from baseline
QT Interval
High: >500 msec OR Increase ≥ 60 msec from baseline
QTcF Interval

High: > 450 msec (Males); >470 msec (Females) OR Increase ≥ 50 msec from baseline
Heart Rate
Low: <45 bpm OR a decrease of ≥25 bpm from baseline
High: >105 bpm and increase ≥25 bpm from baseline OR >125 bpm

10. PHARMACOKINETIC EVALUATION

There are no pharmacokinetic assessments being performed in this study.

11. INTERIM ANALYSES AND DATA MONITORING

There are no planned interim analyses for this study.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

This SAP analysis is consistent with that described in the study protocol, with clarifications and minor modifications to ensure a robust and scientifically valid analysis.

13. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

Guidance for Industry (2014) Analgesic Indications: Developing Drug and Biological Products - Draft Guidance. Department of Health and Human Services: Food and Drug Administration. Center for Drug Evaluation and Research (CDER) February 2014 Clinical/Medical.

14. APPENDICES

14.1. Tables, Figures and Listings for Final Study Report

14.1.1. Tables

Table Number	Table Title	Analysis Populations	Subgroups	Topline	Unique or Repeat
Table 14.1.1	Summary of Subject Disposition	All Screened Subjects			Unique
Table 14.1.2	Summary of Subjects by Study Center	Safety Population			Unique
Table 14.1.3	Summary of Major Protocol Deviations	FAS Population			Repeat
Table 14.1.4	Summary of Demographic and Baseline Characteristics	FAS Population		Yes	Unique
Table 14.1.5	Summary of Medical/ Surgical History by Body System	Safety Population			Unique
Table 14.1.6.1	Summary of Concomitant Medications by ATC Class and Preferred Term	Safety Population			Unique
Table 14.1.6.2	Summary of New-Onset Concomitant Medications by ATC Class and Preferred Term	Safety Population			Repeat
Table 14.1.7	Summary of Study Medication Exposure	Safety Population		Yes	Unique
Table 14.2	Summary of Patient Global Assessment (PGA)	Safety Population			Unique
Table 14.3.1	Overall Incidence of Treatment-Emergent Adverse Events	Safety Population		Yes	Unique
Table 14.3.1.1	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population		Yes	Unique
Table 14.3.1.1.1	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Surgery Type	Safety Population	Surgery Type		Unique
Table 14.3.1.1.2	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Gender	Safety Population	Gender		Repeat
Table 14.3.1.1.3	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Race	Safety Population	Race		Repeat

Table 14.3.1.1.4.1	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age Group (Median)	Safety Population	Age (<=, > Median)		Repeat
Table 14.3.1.1.4.2	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Age Group (65 Years Old)	Safety Population	Age (<65, >= 65 years old)		Repeat
Table 14.3.1.1.5	Incidence of Treatment-Emergent Adverse Events and Treatment Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and BMI	Safety Population	BMI		Repeat
Table 14.3.1.2	Incidence of Post-Treatment Adverse Events and Treatment Related Post-Treatment Adverse Events by System Organ Class and Preferred Term	Safety Population			Repeat
Table 14.3.1.3	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class and Preferred Term	Safety Population			Repeat
Table 14.3.1.3.1	Incidence of Treatment-Emergent Adverse Events Leading to Completion from Study by System Organ Class, Preferred Term and Surgery Type	Safety Population	Surgery Type		Repeat
Table 14.3.1.3.2	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class, Preferred Term and Race	Safety Population	Gender		Repeat
Table 14.3.1.3.3	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class, Preferred Term and Race	Safety Population	Race		Repeat
Table 14.3.1.3.4.1	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class, Preferred Term and Age Group (Median)	Safety Population	Age (<=, > Median)		Repeat
Table 14.3.1.3.4.2	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class, Preferred Term and Age Group (65 Years Old)	Safety Population	Age (<65, >= 65 years old)		Repeat

Table 14.3.1.3.5	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation from Study by System Organ Class, Preferred Term and BMI	Safety Population	BMI		Repeat
Table 14.3.1.4	Incidence of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety Population			Repeat
Table 14.3.1.5	Incidence of Treatment-Emergent Adverse Events Related to Local Tolerability at the Infusion Site by Preferred Term	Safety Population			Repeat
Table 14.3.1.6	Incidence of Treatment Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population			Unique
Table 14.3.1.7.1	Incidence of Treatment-Emergent Adverse Events and Treatment Related Adverse Events by Infusion Number	Safety Population			Unique
Table 14.3.1.7.2	Incidence of Treatment Adverse Events and Treatment Related Adverse Events within One Hour of Any Infusion by System Organ Class and Preferred Term	Safety Population			Repeat
Table 14.3.1.8	Incidence of Serious Adverse Events by System Organ Class and Preferred Term	Safety Population		Yes	Repeat
Table 14.3.1.8.1	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and Surgery Type	Safety Population	Surgery Type		Repeat
Table 14.3.1.8.2	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and Gender	Safety Population	Gender		Repeat
Table 14.3.1.8.3	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and Race	Safety Population	Race		Repeat
Table 14.3.1.8.4.1	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and Age Group (Median)	Safety Population	Age (<=, > Median)		Repeat
Table 14.3.1.8.4.2	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and Age Group (65 Years Old)	Safety Population	Age (<65, >= 65 years old)		Repeat
Table 14.3.1.8.5	Incidence of Serious Adverse Events by System Organ Class, Preferred Term and BMI	Safety Population	BMI		Repeat

Table 14.3.2.1.1	Chemistry Laboratory Parameters: Results and Change from Baseline to End of Treatment	Safety Population			Unique
Table 14.3.2.1.2	Shift from Baseline to End of Treatment in Serum Chemistry Parameters	Safety Population			Repeat
Table 14.3.2.1.3	Potentially Clinically Significant Results in Chemistry values	Safety Population			Unique
Table 14.3.2.2.1	Hematology Laboratory Parameters: Results and Change from Baseline to End of Treatment	Safety Population			Repeat
Table 14.3.2.2.2	Shift from Baseline to End of Treatment in Hematology Parameters	Safety Population			Repeat
Table 14.3.2.2.3	Potentially Clinically Significant Results in Hematology values	Safety Population			Unique
Table 14.3.2.3.1	Urinalysis Parameters: Continuous Results and Change from Baseline to End of Treatment	Safety Population			Repeat
Table 14.3.2.3.2	Urinalysis Parameters: Categorical Results	Safety Population			Repeat
Table 14.3.2.3.3	Shift from Baseline to End of Treatment in Urinalysis Parameters	Safety Population			Repeat
Table 14.3.2.3.4	Potentially Clinically Significant Results in Urinalysis values	Safety Population			Unique
Table 14.3.3.1	Vital Signs: Results and Change from Baseline	Safety Population			Repeat
Table 14.3.3.2	Potentially Clinically Significant Results in Vital Signs	Safety Population			Unique
Table 14.3.4.1	12-Lead ECG Exam: Results and Change from Baseline	Safety Population			Repeat
Table 14.3.4.2	ECG Interpretation in 12-Lead ECG Exam	Safety Population			Repeat
Table 14.3.4.3	Potentially Clinically Significant Results in 12-Lead ECG Exam	Safety Population			Repeat

14.1.2. Figures

Figure Number	Figure Title	Study Population
Figure 14.2.1	Cumulative Proportion of Subjects (%) Versus Total Exposure (mg)	Safety Population

14.1.3. Listings

Listing Number	Listing Title	Study Population
Listing 16.2.1	Screening, Informed Consent and Study Population	All Screened Subjects
Listing 16.2.2.1	List of Inclusion/Exclusion Eligibility Criteria	
Listing 16.2.2.2	Subjects not Meeting I/E or Pre-Operative Criteria	Safety Population
Listing 16.2.3	Local Laboratory Tests for Eligibility checking	Safety Population
Listing 16.2.4	Protocol Deviations	Safety Population
Listing 16.2.5	Subject Completion/Early Termination	Safety Population
Listing 16.2.6	Demographics and Baseline Characteristics	Safety Population
Listing 16.2.7	Medical/Surgical History	Safety Population
Listing 16.2.8	Opioid History	Safety Population
Listing 16.2.9	Pregnancy Test	Safety Population
Listing 16.2.10	ASA Physical Status	Safety Population
Listing 16.2.11	Surgery Information	Safety Population
Listing 16.2.12	Prior and Concomitant Medications	Safety Population
Listing 16.2.13	Non-Medication Therapy	Safety Population
Listing 16.2.14	Study Drug Administration	Safety Population
Listing 16.2.15	Summary of Study Drug Exposure	Safety Population
Listing 16.2.16	Patient Global Assessment (PGA)	Safety Population
Listing 16.2.17	Adverse Events	Safety Population
Listing 16.2.18	Serious Adverse Events	Safety Population
Listing 16.2.19	At Least Possibly Related Treatment Emergent Adverse Events	Safety Population
Listing 16.2.20	Adverse Events Leading to Study Discontinuation	Safety Population
Listing 16.2.21	Adverse Events Leading to Death	Safety Population
Listing 16.2.22	Adverse Events Related to Local Tolerability at The Infusion Site	Safety Population
Listing 16.2.23.1	Chemistry Laboratory Results	Safety Population
Listing 16.2.23.2	Hematology Laboratory Results	Safety Population
Listing 16.2.23.3	Urinalysis Laboratory Results	Safety Population
Listing 16.2.24	Vital Signs	Safety Population
Listing 16.2.25	Physical Examination	Safety Population
Listing 16.2.26	12-Lead ECG Exam Assessments	Safety Population

15. DOCUMENT HISTORY

Version #	Summary of Changes	Section Changed	Date
1.0	• Initial Version	NA	07FEB2019

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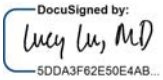
Lucy Lu, MD llu@avenuetx.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 5DDA3F62-E50E-4ABB-BCEE-9D8284AEA67B Using IP Address: 108.29.13.105 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/11/2019 5:36:49 PM Viewed: 2/11/2019 6:47:45 PM Signed: 2/11/2019 6:48:37 PM
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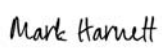
Mark Harnett markharnett@comcast.net Avenue Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 0D9F4DA5-2C0A-4BDD-8A63-BE5F1FE45B64 Using IP Address: 73.249.51.37 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 2/11/2019 6:48:39 PM Viewed: 2/12/2019 4:19:37 AM Signed: 2/12/2019 4:20:06 AM

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