IV TRAMADOL

PROTOCOL AVE-901-104

Tramadol Infusion - Postoperative Pain Safety Study

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

Sponsor:

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New York, NY 10014

IND #: 108124

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30-Aug-18

Lucy Lu, MD — Date

CEO, Avenue Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for Tramadol Infusion. I confirm that I have read this protocol. I understand it, and I will work according to the protocol and moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of ICH guidelines for GCP and according to applicable local regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1. Emergency Contact Information (Study AVE-901-104)

Role in Study	Name	Contact Information
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CRO Responsible Physician	Jon Ruckle, MD	Principal, Pacific Pharma Group, LLC 1402 S. Brookside Terrace Tacoma, WA 98465-1210 Office: 253-448-8690 Mobile: 808-349-9812 Secondary: 1-877-508-8727
24-Hour Emergency Contact	Jon Ruckle, MD	1-877-508-8727 (reference: SAE during the contact)

1. SYNOPSIS

Name of Sponsor/Company: Avenue Therapeutics, Inc.	
Name of Investigational Product: AVE-901 (Tramadol)	
Name of Active Ingredient: Tramadol for intravenous infusion	
Title of Study: A Phase 3, Multi center, Single-Arm, Open-Label Study to Evaluate the Safety of Tramadol Infusion (AVE-901) in the Management of Postoperative Pain Following Surgery	
Study center: Up to approximately 10 centers in the United States	
Studied period: Estimated date first patient enrolls: Q4 2017 Estimated date last patient enrolls: Q2 2019 Estimated date primary analysis: Q2 2019	**Phase of development:** 3

Objectives:

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 events (classified by the MedDRA System Organ Class (SOC) and preferred term).
- Clinical laboratory, vital sign, and ECG changes
- Local tolerability of the infusion site via pain, swelling, tenderness, and erythema.

Throughout the protocol, AVE-901 will be used to indicate the treatment.

Study Design:

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 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 should always tie back 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

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allowed to use non-opioid-based analgesics per treating physician's discretion, if additional pain relief is required.

Study Periods and Methodology

There are 5 periods in this study:

- Screening
- Preoperative
- Surgery
- Treatment Period/Post Surgery
- Follow-up.

Procedures for each study period are described below.

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, demographics, height and weight, BMI, vital signs (heart rate, systolic blood pressure, and diastolic blood pressure, respiratory rate, temperature, pulse oximetry), ASA Physical Status, 12-lead electrocardiogram (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, ALT, AST and hemoglobin.

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, physical exam, 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.

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Surgery: Surgery will occur on Day 0. Sites will follow their standard operating procedures. ***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 (SpO_2), temperature, and blood pressure as per the schedule of events. A Patient Global Assessment (PGA – Appendix 1) of efficacy will be obtained at Hour 24 and End of Treatment. If the patient continues treatment beyond Hour 24, PGA will be conducted at Hour 24 and End of Treatment (total of 2 PGAs). If the patient ends treatment prior to Hour 24, PGA will be conducted as part of the End of Treatment visit (total of 1 PGA). At the End of Treatment assessment, patients will undergo a brief physical examination, vital signs measurements, ECG, PGA and clinical laboratory evaluations for safety. AEs and concomitant medication use will be recorded. ***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. ***Concomitant Medication:*** Medications deemed necessary for the patient's welfare are permitted. The following drugs are EXCLUDED from use: • Moderate or strong inhibitors of CYP3A4 or CYP2D, inducers of CYP3A4, drugs which may increase serotonergic tone including SSRIs, SNRIs, tricyclic antidepressants, trazodone, cyclobenzaprine triptans, 5-HT3 antagonists including ondansetron, and amphetamines; and drugs which may lower seizure threshold. • Any opioid based analgesic (post dosing). Postoperative adverse events (AEs) such as nausea, vomiting and pruritus should be managed using standard of care, excluding medications specifically noted in the study protocol.
Number of patients (planned): A total of approximately 250 patients in United States (US) who meet all of the inclusion and none of the exclusion criteria are planned to be enrolled. Every patient treated will receive AVE-901.

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Diagnosis and main criteria for Eligibility

This study intends to enroll patients undergoing elective surgery who are willing to be confined in a healthcare facility and receive AVE-901 for at least 24 hours as their primary treatment for post-surgical pain.

Inclusion Criteria:

1. The patient is male or female 18-75 years of age
2. The patient or legal representative has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent.
3. Female patients must be of non-childbearing potential (surgically sterile or post-menopausal for at least 1 year) or be practicing a highly effective contraception method from consent to at least 7 days after the last dose of study medication. Surgically sterile is defined as status post hysterectomy, bilateral oophorectomy or bilateral tubal ligation. Highly effective contraception methods include: abstinence, vasectomized partner (at least 6 months prior to dosing); double barrier (diaphragm with spermicide; condoms with spermicide); intrauterine device; implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration; oral, patch, or injected contraceptives in use for at least 3 consecutive months prior to study dosing.
4. Female patients of childbearing potential have a negative pregnancy test (serum human chorionic gonadotropin [HCG]) during screening and a negative pregnancy test (urine) ≤ 24 hours prior to surgery, and are not lactating.
5. Patient is undergoing elective surgery and, in the opinion of the investigator, is an appropriate candidate for IV Tramadol for pain management post-operatively.
6. The study patient is willing to be housed in a healthcare facility capable of administering parenteral analgesia for at least 24 hours after surgery. Treatment may extend through Hour 168 if deemed appropriate.
7. The patient meets definition of American Society of Anesthesiologists (ASA) Physical Class 1 or 2.
8. The patient is willing and able to understand the study procedures to communicate meaningfully with the study personnel, and to comply with the study protocol.

Exclusion Criteria:

1. The patient has current or historical evidence of any clinically significant disease or condition that might place the patient at unacceptable risk due to receiving the study medication, in the opinion of the investigator.
2. The patient has allergy or hypersensitivity (or is intolerant) to opioids or tramadol.

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3. The patient has used chronic opioid therapy, defined as >= 20 MEQs of morphine per day >=3 days out of 7 days over the past 4 weeks.
4. The patient has a recent (within 2 years) and/or current history of alcohol, opiate or tranquilizer abuse or dependence.
5. The patient is taking herbal or dietary supplements or medications that are moderate or strong inhibitors of CYP2D6 or CYP3A4 (e.g., fluoxetine, paroxetine, amitriptyline, quinidine, ketoconazole, erythromycin, grapefruit juice) or inducers of CYP3A4 (e.g., carbamazepine, rifampin, St. John's Wort) and cannot go through a minimum washout period of 7 days prior to surgery.
6. The patient has a history of epilepsy, is susceptible to seizures.
7. The patient cannot be withdrawn from medications (at least 7 days prior to surgery) that may lower the seizure threshold (e.g. anti-psychotic agents, MAOI inhibitors) or which increase serotonergic tone (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, triptans, amphetamines).
8. The patient has had a recent (within 6 months) cardiovascular event or clinically significant abnormal ECG finding at screening.
9. The patient has a history of Long QT Syndrome or a relative with this condition.
10. The patient has expressed suicidal ideation within the past 3 months or is considered to be at risk of suicide.
11. The patient is morbidly obese (body mass index [BMI] $\geq$ 40 kg/m2) or has documented sleep apnea requiring CPAP or other treatment.
12. Female patient is pregnant and/or undergoing a pregnancy-related surgery, or breastfeeding.
13. The patient has a history of cardiopulmonary, neurological or psychiatric condition that may confound the assessments of efficacy or safety.
14. The patient has cirrhosis, moderate or severe hepatic impairment or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value > 3X upper limit of normal (ULN) at Screening.
15. The patient has severe renal impairment or a serum creatinine value of > 2x upper limit of normal (ULN) at Screening.
16. The patient has potassium, sodium, calcium or magnesium levels outside of the normal range at Screening.
17. The patient has a hemoglobin level at screening which, in the judgment of the Investigator, is not suitable for participation in this study.

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18. The patient was administered an investigational drug product within 30 days prior to Screening.
19. The patient has previously participated in a clinical study with AVE-901.

POST SURGICAL EXCLUSION CRITERIA

The patient is to be evaluated post-operatively prior to the initial treatment with the study drug and will be withdrawn prior to treatment with the study drug if any of the following exclusion criteria are met:

1. Patients who, in the opinion of the investigator, are not likely to tolerate the protocol's allowed analgesic regimen (tramadol plus non-opioid adjuvants).
2. Patients who have been admitted to the ICU post-surgery or have experienced complications during the surgical procedure that would put them at increased risk from receipt of the investigational product in the opinion of the investigator.
3. The patient is not clinically stable and not able to answer questions and follow commands.
4. The patient has evidence of respiratory insufficiency, such as a respiratory rate that is less than 8 breaths per minute or arterial oxygen saturation by pulse oximetry of less than 90% with supplemental oxygen.
5. Use of 5-HT3 antagonists (e.g. ondansetron, granisetron, palonosetron) preoperatively, intraoperatively, or postoperatively

Investigational product, dosage and mode of administration:

AVE-901, 50 mg. Assigned study treatment (51 mL) doses will be administered IV over 15 minutes (+/- 4 minutes) via infusion pump. A trained health care professional will flush the line with normal saline at the end of each infusion.

Duration of treatment:

Study drug will be administered for up to 7 days following initiation of the first dose.

Total patient participation in this study, from initial screening through the final assessment, is expected to be between 1 and 7 weeks.

Reference therapy, dosage and mode of administration:

None.

Criteria for evaluation:

This study is designed to assess the safety profile of IV Tramadol post-surgery for patients having elective surgery. Therefore, the primary evaluations will be based on safety outcomes. Efficacy is considered a secondary outcome.

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Safety:

- Treatment-Emergent 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, pulse oximetry and blood pressure,
- Physical examination pre-treatment and discharge
- 12-lead ECG at protocol specified time points
- Concomitant treatments

Efficacy:

- Patient Global Assessment at 24 hours and/or end of treatment

Statistical methods:

Sample Size

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%).

General Statistical Methods

This is an open-label study in which the objective is to assess the safety of Tramadol for post-surgical pain in patients having elective surgery. The statistical methods utilized will be consistent with this objective.

Outcomes will be tabulated utilizing descriptive methods only (e.g., mean, standard deviation, median, min, max for continuous variables, and number and percent for categorical variables).

The baseline for all variables will be the last measurement obtained prior to the patient receiving the first dose of study drug.

Patient disposition (including the number and percent of patients who are enrolled, who receive treatment, who prematurely discontinue and reasons for discontinuation, and who complete the study) will be tabulated. The number (%) of patients by exposure (number of doses given, total dose given, time from first dose to last dose) will be tabulated.

Study Populations

The Safety Population is defined as all patients who receive at least one dose of study medication. This will be the primary population for which conclusions will be drawn.

Alpha Levels

No inferential testing is planned for this safety-based study. If inferential statistics are used, they will only be applied to allow for better understanding of any treatment effects, but will not be used for hypothesis testing.

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Subgroups

Incidences of treatment-emergent AEs, serious AEs, and discontinuations for AEs, will be provided by the following subgroups:

- Surgery type
- Gender
- Race
- Age (using the median age of the treated population)

Safety

All AEs will be classified with respect to the MedDRA System Organ Class (SOC) and preferred term. The number and percent of patients who report treatment-emergent adverse events (TEAEs) will be summarized. Additional summaries by severity, relationship, and subgroup will be presented. Serious AEs (SAEs) will be summarized similarly.

For purposes of analysis, TEAEs will be defined as any AE with a start time 'on or after the start of the first IV infusion'. Thus, the start day AND start time of AEs will be collected. Adverse events occurring prior to the start of the first treatment infusion will be classified as Medical History for the purposes of the analysis. Events occurring > 168 hours (7 days) after the END of the last infusion will be classified as Post-Treatment AEs.

As the infusions are given intermittently according to the dosing instructions, an assessment of onset of TEAEs within 1 hour after the start of any infusion will be tabulated separately. The incidence of TEAEs will also be tabulated by infusion number (e.g., Infusion 1, Infusion 2, etc.) to explore the safety profile over multiple doses. Summaries of the time to onset of TEAEs will also be included.

Exploratory analyses of use of anti-emetics may be performed.

Clinical laboratory, and vital sign data will be summarized descriptively by time point. Local tolerability of the infusion site will be assessed via AE's.

Other safety data presentations will be descriptive in nature, with no formal inferential testing planned.

Efficacy

Patient Global Assessment at 24 hours, and/or end of treatment

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2 Abbreviations and Specialist Terms (Study AVE 901-104)

Abbreviation or special term	Explanation
°C	Degrees Celsius
°F	Degrees Fahrenheit
µM	Micromolar
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-tlast}}$	Area under the concentration-time curve from time 0 to the last measurable concentration; calculated using linear trapezoid rule
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}24}$	Area under the plasma concentration vs. time curve from time 0 to 24 hours
BLQ	Below the Lower Limit of Quantitation
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{12}	Plasma concentration at 12 hours after oral drug administration
C_{24}	Plasma concentration at 24 hours after oral drug administration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CL/F	Oral clearance
CNS	Central nervous system
Conmed	Concomitant Medication
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CV	Coefficient of variance
dL	Deciliter(s)
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
EDTA	Ethylenediaminetetraacetic Acid
FOB	Functional Observational Battery
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
Hct	Hematocrit
Hgb	Hemoglobin
HPBL	Human Peripheral Blood Lymphocytes
hr(s)	Hour(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
kg	Kilogram
L	Liter
LDL	Low Density Lipoprotein
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
min(s)	Minute(s)
mg	Milligram
mL	Milliter
mm	Millimeter
msec	Millisecond
N/A	Not Applicable
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
pH	Hydrogen Ion Concentration
PHI	Personal Health Information
PI	Protease inhibitor
PIS	Patient Information Sheet(s)
PK	Pharmacokinetic
PR	Pulse Rate
QTc	The QTc interval is the corrected QT interval, adjusted for heart rate

Abbreviation or special term	**Explanation**
RBC	Red Blood Cell
rpm	Revolutions Per Minute
RR	Respiratory Rate
RTV	Ritonavir
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Document Verification
$t_{1/2}$	Plasma elimination half-life
t_{lag}	Time to the first measurable plasma concentration
t_{max}	Time to reach peak plasma concentration
ULN	Upper limit of normal
V_{ss}	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

4. INTRODUCTION

Effective postoperative pain control is a critical need as most patients undergoing surgical procedures experience pain immediately following the procedure, and require treatment for several days. For instance, patients undergoing total knee arthroplasty (TKA) or bunionectomy typically demonstrate a need for short-term analgesia, which is critical for earlier mobilization and rehabilitation. In this setting, reducing pain intensity without providing extensive medical oversight required for some methods of treatment (such as neuraxial anesthesia) and prevention of effects such as opiate-induced respiratory depression and dependency would be highly beneficial (Sinatra 2002).

Several options are available for postoperative pain management (Singelyn 1998; Sinatra 2002). Options include intermittent "on-demand" analgesia, including oral and via patient controlled analgesia (PCA) or by nurse-administered bolus injections of systemic opioids such as morphine. Second, continuous epidural analgesia with opioids and/or local anesthetics is effective, although this requires continued presence of the epidural catheter and oversight by an anesthesiologist. A third alternative is to provide a combination of nerve blocks with long-acting local anesthetics and/or opioids initiated intra-operatively and continued into the immediate postoperative period.

4.1. Tramadol Infusion

Tramadol is a centrally acting synthetic analgesic with a dual mechanism of action, comprised of μ-opioid activity and monoamine (serotonin and noradrenalin) reuptake inhibition. Tramadol is an analog of the phenanthrene group of opium alkaloids, which includes morphine and codeine, and is structurally related to these opioids (Grond 2004). Like codeine, there is a substitution of the methyl group on the phenol ring that imparts a relatively weak affinity for opioid receptors.

Tramadol was originally developed by the German pharmaceutical company Grünenthal GmbH in the late 1970s and is marketed globally under the trade names TRAMAL® and others outside of the United States (US). The approved doses of tramadol are 50 mg or 100 mg administered as a slow injection every 4-6 hours (Tramadol Core Product Label, 2008).

In the US, tramadol is approved by the Food and Drug Administration (FDA) and marketed as an oral tablet (the only available formulation) for moderate to moderately severe pain in adults. Tramadol was first approved in the US in April 1995 under the trade name ULTRAM® (Ortho-McNeil-Janssen Pharmaceuticals, Inc). Tramadol is also an active agent in an extended release (ER) product, Ultram® ER, and as a combination product with acetaminophen, ULTRACET®. In the US, tramadol is only available as immediate release tablets or extended release tablets.

Tramadol injection (IV/IM/SC) is approved and used for the management of moderate to severe acute postoperative pain in several regions, including Europe, India and Australia/New Zealand; however, this dosage form is not available in the US. Tramadol ampoules or vials for parenteral (intravenous [IV], intramuscular [IM] and subcutaneous [SC]) administration and preservative-free solutions for injection by the various spinal routes (epidural, intrathecal, caudal, etc.) are available forms in these regions. Other tramadol formulations approved in several countries include tablets, capsules, effervescent powders, and suppositories (Grond 2004; Rosenberg 2009).

There is extensive data demonstrating that tramadol use is not associated with the classic-opioid side effects seen with more potent opioids. There are numerous reports of the safety and efficacy of tramadol in this setting (Scott 2000; Grond 2004).

4.2. Nonclinical Summary

Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. Tramadol is extensively metabolized following administration, which results in a number of enantiomeric metabolites that display different opioid-receptor binding properties, and monoaminergic reuptake inhibition (Grond 2004).

Both enantiomers of tramadol and (+)-M1 are responsible for the analgesic effect. The primary metabolite [(+)-M1 or (+)-O-desmethyltramadol] of tramadol confers significant μ-opioid activity; (+)-tramadol confers weak μ-opioid activity and significant serotonin reuptake inhibition; and (−)-tramadol is responsible for the inhibition of noradrenaline re-uptake (Gillen 2000; Raffa 2008). Nonclinical studies have shown that antinociception induced by tramadol is only partially antagonized by the opiate antagonist, naloxone, indicating that non-opioid mechanisms are also involved in its pharmacodynamic action (Collart 1992).

Consistent with the known clinical effects of opioids, non-clinical safety pharmacology studies have shown that tramadol at high doses affects the central nervous system (CNS), producing sedation, impaired mobility, vomiting (dogs), decreased activity, and convulsions (Matthiesen et al., 1998). Also consistent with clinical effects, changes in blood pressure have been observed in cardiovascular studies in rats at high doses (Raimundo 2006).

The toxicity of tramadol has been summarized by Matthiesen (Matthiesen 1998). The single dose toxicity of tramadol was similar in all species tested, independent of the route of administration. Notable acute findings included restlessness, unsteady gait, reduced spontaneous activity, exophthalmus, mydriasis, salivation, vomiting (dog), tremor, convulsions, slight cyanosis and dyspnea. The principle findings in repeat-dose toxicity studies in rats and dogs were behavioral/clinical signs and convulsions at doses of ≥25 mg/kg/day. The kidney and liver were identified as potential target organs in rats, with mild effects (minimal tubular vacuolization and perivenular hydropic degeneration, respectively) following repeat intraperitoneal dosing at high doses of tramadol.

There was no evidence of genotoxic potential for tramadol in standard in vitro and in vivo studies (Matthiesen 1998). Carcinogenicity bioassays in mice and rats showed no evidence of carcinogenic potential. An extensive reproductive and teratology program revealed no safety concerns with respect to fertility or teratogenic effects after oral administration (Matthiesen; Yamamoto 1972). Toxicity to offspring only occurred at doses associated with maternal toxicity.

In conclusion, none of the results in non-clinical toxicity studies indicated a safety concern regarding administration of AVE-901 at the intended clinical dose.

4.3. Pharmacokinetic Profile

Following oral administration, tramadol is rapidly and almost completely absorbed. The pharmacokinetics (PK) of tramadol were evaluated in healthy male volunteers (n=10) in a crossover design using 100 mg (PO) or IV doses (Lintz 1986). Peak serum concentrations (Tmax) were reached approximately 2 hours after oral dosing and the peak serum concentration

(Cmax) for PO tramadol was 280±49 ng/mL. The terminal half-life was 5.1 hours for PO and 5.2 hours for IV administration. The area under the serum tramadol concentration-time curve (AUC) was 2488±774 ng·h/mL for PO and 3709±977 ng·h/mL for IV administration. Total clearance was 467±124 mL/min for PO and 710±174 mL/min for IV administration. The absolute bioavailability of the oral dose was 68±13%, based on comparison of the AUC values, while the estimated absorption of the oral dose was 86-88%. The difference between absorption and bioavailability was attributed to first pass metabolism, which was estimated to be ~20%. However, the absolute bioavailability approaches 90-100% with continuous dosing, probably due to saturation of first pass metabolism (Liao et al., 1992). Other studies have corroborated these findings (Grond 2004).

Tramadol undergoes hepatic metabolism and both the parent drug and the active metabolite are excreted by the kidneys. The only known active metabolite, M1 (O desmethyltramadol), is produced by the action of cytochrome P450 CYP2D6 isozyme of the cytochrome P450 enzyme system. It has a half-life of approximately 6.7 hours after oral administration (single dose of 100 mg), compared to a half-life of 5.6 hours for tramadol. Hepatic impairment results in decreased metabolism of both the parent compound and the active metabolite. Elimination half-life increases approximately 2-fold in patients with renal or hepatic impairment. Patients who metabolize drugs poorly via CYP2D6 (Caucasian population prevalence ~ 8%) may obtain reduced benefit from tramadol due to reduced formation of M1 (Ultram® Prescribing Information, Ortho McNeil-Janssen, 2009).

A Phase 1 study was performed to determine a treatment regimen of IV tramadol that would be comparable to the approved 100 mg dose of oral tramadol at steady state [Study title: "A Phase 1, Open-Label, Single Center, Three-Period, Multi-dose Crossover Study to Evaluate the Pharmacokinetics of Two Different AVE-901 (Tramadol Infusion) Regimens versus Oral Tramadol Tablets" (Study AVE-901-101)].

The two different IV regimens were evaluated and compared to the oral regimen. A total of 18 patients, ages 24 to 55 years (inclusive) were enrolled (3 patients to each of the 6 sequences). The study included 11 males and 7 females. 17 patients completed all 3 treatment sequences.

The treatment regimens evaluated were:

1. 75 mg IV REGIMEN: IV tramadol 75 mg administered at Hour 0, followed by 75 mg at Hour 3 and Hour 6, and 75 mg every 6 hours thereafter through Hour 42
2. 50 mg IV REGIMEN: IV tramadol 50 mg administered at Hour 0, followed by 50 mg at Hour 2, 50 mg at Hour 4, and 50 mg every 4 hours thereafter through Hour 44
3. ORAL REGIMEN: Oral tramadol 100 mg (50 mg tablets x 2) at Hour 0, 6, and every 6 hours thereafter through Hour 42

Examination of the parent (tramadol) as well as the primary metabolite, M1 (O-desmethyltramadol), was performed over the 48-hour treatment period. A focus of the analysis was on assessment of C_{max} values (to ensure the C_{max} for the IV formulation was similar to that of the oral formulation) as well as on early concentrations during the first doses (to ensure adequate medication would be provided during the initial 6 to 12 hours of treatment as the drugs reached steady-state concentrations). Overall exposure to tramadol was estimated primarily from average trough plasma concentrations.

Figure 1 provides the mean plasma tramadol time-concentration profiles for the 100 mg oral, 50 mg IV, and 75 mg IV regimens from Study AVE 901-101. Mean plasma tramadol concentrations were higher after the 75 mg IV regimen compared to the 50 mg IV regimen and 100 mg PO q6h. As evidenced from the trough/pre-dose samples between 24 and 42 h, the mean tramadol trough concentrations were very similar for the 50 mg IV regimen and 100 mg PO q6h but somewhat lower for the 75 mg IV regimen.

Tramadol peak and trough concentrations for the 50 mg IV and the 100 mg PO q6h regimens were very similar at the end of the pharmacokinetic sampling period, between approximately 44 and 48 h.

Figure 1: Mean Plasma Tramadol Time-Concentration Profiles for 100 mg oral, 50 mg IV, and 75 mg IV Regimens (Study AVE-901-101)

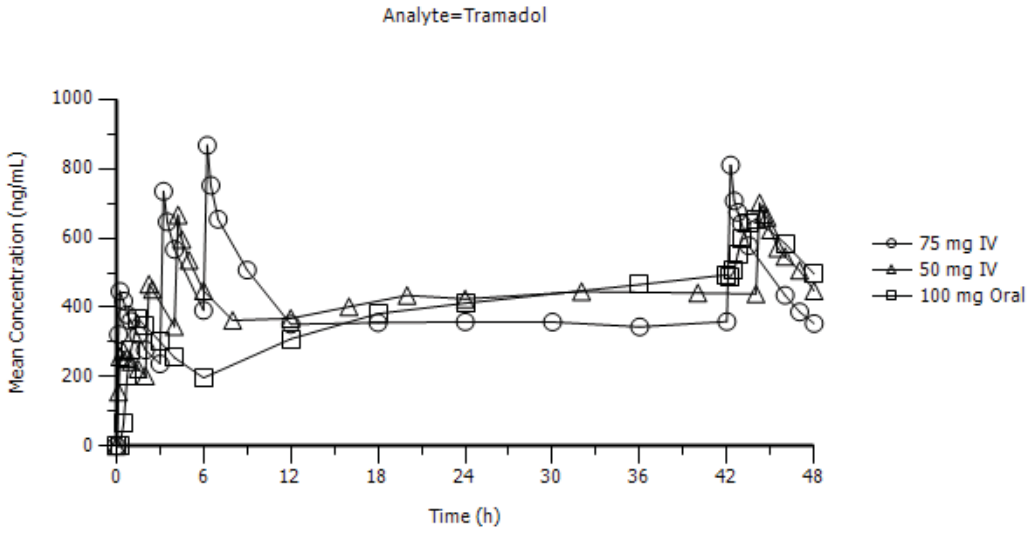
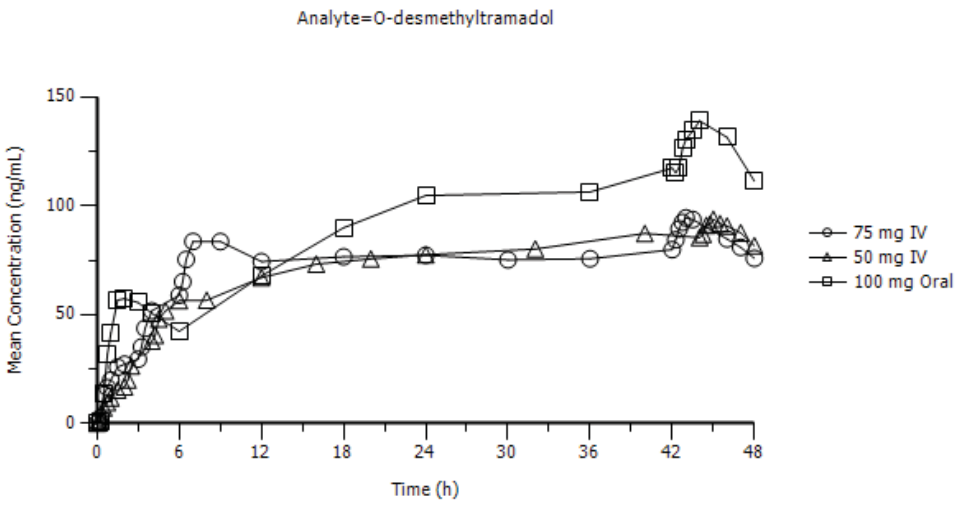


Figure 2 provides the mean plasma O-desmethyltramadol time-concentration profiles for the 100 mg oral, 50 mg IV, and 75 mg IV regimens from Study AVE 901-101. The mean plasma O-desmethyltramadol concentrations were higher for the 75 mg IV regimen following the 3rd dose at 6 h, but there was appreciable overlap of the trough concentrations for the 75 mg IV and 50 mg IV regimens between 24 and 42 h. The pre-dose concentrations as well as the concentrations after the last dose at 42 h were higher for 100 mg PO q6h compared to both IV arms, presumably due to first pass metabolism which results in a higher fraction of the active metabolite in systemic circulation after oral administration.

Figure 2: Mean Plasma O-desmethyltramadol Time-Concentration Profiles for 100 mg oral, 50 mg IV, and 75 mg IV Regimens (Study AVE-901-101)



Select pharmacokinetic parameters (overall C_{max}, C_{max} at steady state, trough at steady state, AUC over the last dosing interval for each regimen, i.e., $AUC_{tau\ n}$) for tramadol are summarized in Table 3.

Table 3: Additional Plasma Pharmacokinetic Parameters of Tramadol (Study AVE-901-101)

Parameter	75 mg IV				50 mg IV				100 mg Oral			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
C_{max} (ng/mL)	14	932	199	21.30	14	736	152	20.60	17	701	178	25.44
$C_{max(42-48)}$ (ng/mL)	14	827	234	28.24	-	-	-	-	17	701	178	25.44
$C_{max(44-48)}$ (ng/mL)	-	-	-	-	14	711	152	21.40	-	-	-	-
T_{48} (ng/mL)	14	354	85.9	24.31	14	448	131	29.36	17	497	144	29.09
Css (ng/mL)	14	506	101	20.03	14	557	131	23.60	17	579	150	25.96

The 50 mg IV regimen provided favorable C_{max} and AUC values over the full 48 hour treatment period. Specifically:

- Overall C_{max} was comparable between the 50 mg IV and 100 mg PO regimens
- Exposure to tramadol at steady state (or near steady state, in the case of the oral regimen), based on C_{max} and AUC, was also comparable between the 50 mg IV regimen and 100 mg PO q6h.
- The 50 mg IV regimen, as compared to the 75 mg IV regimen, resulted in less peak to trough fluctuation with lower C_{max}. This regimen also provided a pharmacokinetic profile very similar to the 100 mg oral dose regimen

- Exposure to O-desmethyltramadol was higher after 100 mg PO q6h compared to either IV treatment, 50 mg IV or 75 mg IV regimens, based on AUC and C_{max} values

Based on these findings, the 50 mg IV regimen will be studied in this current protocol.

4.4. Rationale for this Study

This open-label safety study will be conducted in parallel with two efficacy Phase 3 studies, one in an orthopedic model (AVE-901-102) and the other in a soft tissue model (AVE-901-103). Data from this current study will be combined with data from those two efficacy studies into an overall safety database for tramadol infusion.

A brief summary of the two double-blind studies follows.

- Protocol AVE-901-102: Orthopedic surgery study in a Phase 3, multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group trial to evaluate the safety, tolerability and efficacy of 2 doses (50 mg and 25 mg) of IV Tramadol hydrochloride injection (AVE-901) versus placebo in the management of postoperative pain in consenting patients undergoing an orthopedic surgery (bunionectomy). The primary objective of this study is to evaluate the analgesic efficacy of intravenous (IV) Tramadol (AVE-901) in the management of postoperative pain following orthopedic surgery. The Sum of Pain Intensity Differences (SPID) through 48 hours post first dose (SPID48) at rest will be used as the primary measure of efficacy. Up to approximately 405 patients will be randomized. This study has commenced and expected to be completed second quarter 2018
- Protocol AVE-901-103: Soft tissue surgery study is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group trial to evaluate the safety, tolerability and efficacy of IV Tramadol (AVE-901) versus placebo in the management of postoperative pain in consenting patients undergoing elective abdominoplasty. The primary objective of this study is to evaluate the analgesic efficacy of intravenous (IV) Tramadol (AVE-901) in the management of postoperative pain following soft tissue surgery. The Sum of Pain Intensity Differences (SPID) through 24 hours post first dose (SPID24) at rest will be used as the primary measure of efficacy. Up to approximately 360 patients will be randomized. A smaller morphine comparator arm will be included in the study.

5. TRIAL OBJECTIVES AND PURPOSE

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 events (classified by the MedDRA System Organ Class (SOC) and preferred term).
- Clinical laboratory, vital sign, and ECG changes
- Local tolerability of the infusion site via pain, swelling, tenderness, and erythema.

Throughout the protocol, AVE-901 will be used to indicate the treatment.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This study is a Phase 3, multicenter, single-arm, open-label, uncontrolled, 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 deemed appropriate to receive IV AVE-901 for the treatment of post-surgical pain. 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 visit, and the Follow-up Visit (Day 14).

Note: Patients may have Screening and Preoperative visits combined into one visit if required to accommodate timelines for scheduled surgeries. The procedures associated with the Screening Visit should be completed.

Screening will occur up to 28 days prior to surgery. Eligible patients will be made aware of the use of additional pain medication, and of the various post-treatment safety measures. These patient training procedures may be conducted on different days as appropriate during Screening.

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, 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 latest (last) dose that is allowed is at Hour 164. Patients will be confined at the healthcare 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 pain medication per the treating physician's discretion, if additional pain relief is required.

6.2. Number of Patients

A total of approximately 250 patients in United States (US) at approximately 8-10 study sites who meet all inclusion and none of the exclusion criteria are planned to be enrolled. Every patient treated will receive AVE-901. Patients who withdraw from the trial are not planned to be replaced.

6.3. Treatment Assignment and Randomization

No randomization will be utilized in this study; all patients will receive tramadol infusion per the treatment dosing regimen.

6.4. Criteria for Study Termination

If the Investigator, Study Medical Monitor, or Avenue Therapeutics discovers conditions arising during the study, which indicate that the clinical investigation should be halted, the study must be terminated after appropriate consultation between Avenue Therapeutics, Study Medical Monitor, and the Investigators. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study,
- Failure of the Investigator to enter patients at an acceptable rate,
- Insufficient adherence to protocol requirements and good clinical practices, or;
- A decision on the part of the Avenue Therapeutics to suspend or discontinue development of the drug.

6.4.1. Individual Patient Stopping Rules

If a patient experiences a serious or severe adverse event assessed as possibly, probably or definitely related to study drug, the Investigator will review the patient's medical record, consult with the Medical Monitor if necessary and determine whether the patient should have study treatment either temporarily interrupted or permanently discontinued.

6.5. Schedule of Events

Table 4 provides the schedule of events. Note that patients who discontinue treatment at any time after receiving their first dose of study drug (T0) will have all End of Treatment assessments performed.

Table 4. Schedule of Assessments for each Study Period (Study AVE 901-104)

Assessments	Screening Day -28 to Day -1[4]	Pre-op Day -1/0[4]	Surgery Day 0	Treatment Hours Post Start of First Infusion Hour 0 to Hour 164 (assessments ± 10 minute window)							End of Treatment (completed prior to discharge)	Phone Call Day 14±2
				0	0.5	1	2	3	4	Every 4 hours	EoT	
Informed Consent	X											
Medical History	X	X										
Demographic Data	X											
Height and Weight (BMI)	X											
Physical Examination	X	X									X	
ASA Physical Status	X	X										
Vital Signs (and SpO2)[1]	X	X		X	X	X	X	X	X	X	X	
Pregnancy Test[2]	X	X									X	
Hem/Chem/Urinalysis[3]	X										X	
12-Lead ECG	X		X[5]	X (Done 20 to 30 minutes after start of each dose for first 24 hours)							X	
Eligibility Criteria	X	X		X[4]								
Surgery			X									
Study Drug Admin				X			X		X	X		
PGA										X (24 hours only)	X	
Adverse Events		X (ongoing)										
Prior/Conmeds	X (ongoing)											

[1] Post 48 hour treatment, vitals drawn only every 8 hours
[2] Screening and End of Treatment Pregnancy test (serum) by central laboratory, Pre-op pregnancy test (urine) conducted locally for female patients of childbearing potential.
[3] Hematology, Chemistry, Urinalysis sent to central laboratory for analysis. Patients screened and not receiving results from central labs prior to surgery may have local lab done to assess eligibility.
[4] If necessary, Screening and Pre-Op procedures may be combined into one visit assessment for time considerations associated with scheduled surgeries. Screening Visit procedures should take precedent.
[5] ECG should be taken post-surgery, prior to dosing at T0

6.6. Description of Visits

There are 5 distinct periods in this study:

- Screening (Days -28 to -1)
- Pre-operative (within 24 hours of scheduled surgery)
- Surgery (Day 0)
- Treatment Period/Post Surgery (Hours 0 up to Hour 168)
- Follow–up (approximately Day 14)

Procedures for each study period are described below.

6.6.1. 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. Patients will undergo protocol specific education including but not limited to the various post-treatment efficacy and safety measures. The following information and procedures will be performed and documented as part of the screening assessment:

- Demographics, including gender, race and ethnic origin, date of birth, height, weight and calculated BMI. (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm)
- Inclusion/exclusion eligibility criteria
- Physical examination
- ASA Physical Status
- Medical history
- Prior and ongoing medications (taken in previous 30 days)
- Vital signs: blood pressure, heart rate, respiratory rate, and oral temperature (after seated or supine for 5 minutes) and SpO2
- 12-lead ECG (after supine for 5 minutes)
- Blood samples for hematology and clinical chemistry
- Pregnancy test (serum) for women of child-bearing potential
- Urine samples for urinalysis

Compliance with inclusion criteria and exclusion criteria will be verified against information collected and documented in the source documents and the eCRF.

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 lab to assess eligibility, in addition to the central lab, which will still be used as the baseline in the study. If local labs are used to access eligibility at screening, at a minimum the following analytes must be reviewed from the local laboratory prior to dosing; magnesium, calcium, potassium, sodium, serum creatinine, ALT, AST, hemoglobin. The local laboratory listed on the FDA 1572 Form must be used for all local blood draws.

Central labs supersede local labs for eligibility. If during the screening process the central labs are received prior to the subject being dosed/treated, even though local labs were drawn, the central lab values will be used to indicate eligibility. If central labs show exclusionary lab values discrepant from the local labs and the subject has not yet been treated, subject will be deemed a screen failure and will not be treated. If the subject is treated based on local lab values and the central lab values show exclusionary labs after subject is dosed, the PI will inform the Medical Monitor and discuss patient safety and suitability to continue treatment.

6.6.2. 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:

- Inclusion/exclusion eligibility criteria
- Physical examination
- ASA Physical Status
- Medical history within 2 years
- Prior and ongoing medications (taken in previous 30 days)
- Vital signs: blood pressure, heart rate, respiratory rate, and oral temperature (after seated or supine for 5 minutes) and SpO2
- Urine pregnancy test for women of child-bearing potential

6.6.3. Surgery

Surgery will occur on Day 0. Standard of care procedures should be followed.

6.6.4. Treatment Period/Post Surgery

Patients will receive their first dose of study medication (T0) within 8 hours of meeting the postsurgical eligibility. Treatment is anticipated to occur from Hours 0 up to Hour 168. The latest (last dose) that is allowed is at Hour 164. 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. Assessments will have a $\pm$ 10 minute window.

Antiemetic treatments (with the exception of Zofran or other 5-HT3 antagonists) are allowed.

Treatment period assessments include:

- Recording vital signs including: respiratory rate, heart rate, pulse oximetry (SpO2), temperature, and blood pressure at 0, 0.5, 1, 2, 3, 4, and then every 4 hours thereafter during the first 48 hours. After 48 hours patients continuing treatment should have vitals taken every 8 hours.
- ECGs will be assessed at screening, post-surgery prior to dosing (T0), and at 20 to 30 minutes after the start of each infusion for the first 24 hours. With the 10-minute window allowed per assessments, the on-treatment ECGs need to be done between 10 to 40 minutes after the start of each dosing infusion.
- Patient Global Assessment at 24 hours
- Adverse events and concomitant medications will be collected as appropriate.
- Following the first dose of study drug, the patient will be allowed to use non-opioid analgesics if additional pain relief is required. These medications will be captured on the concomitant medications page
- Concomitant medication use

6.6.5. End of Treatment

At the End of Treatment patients will undergo:

- A brief symptom driven physical examination
- Vital signs: blood pressure, heart rate, respiratory rate, and oral temperature (after seated or supine for 5 minutes) and SpO2
- 12-lead ECG (after supine for 5 minutes)
- Blood samples for hematology, clinical chemistry, urinalysis, and pregnancy test
- Patient Global Assessment
- AEs
- Concomitant medication use

End of Treatment assessments do not follow a +/- 10 minute window, but just need to be completed prior to discharge

6.6.6. 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.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

The following are patient inclusion criteria for this study; each patient must meet all inclusion criteria in order to be enrolled into this study.

1. The patient is male or female 18-75 years of age
2. The patient or legal representative has voluntarily signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent.
3. Female patients must be of non-childbearing potential (surgically sterile or post-menopausal for at least 1 year) or be practicing a highly effective contraception method from consent to at least 7 days after the last dose of study medication. Surgically sterile is defined as status post hysterectomy, bilateral oophorectomy or bilateral tubal ligation. Highly effective contraception methods include: abstinence, vasectomized partner (at least 6 months prior to dosing); double barrier (diaphragm with spermicide; condoms with spermicide); intrauterine device; implanted or intrauterine hormonal contraceptives in use for at least 6 consecutive months prior to study dosing and throughout the study duration; oral, patch, or injected contraceptives in use for at least 3 consecutive months prior to study dosing.
4. Female patients of childbearing potential have a negative pregnancy test (serum human chorionic gonadotropin [HCG]) during screening and a negative pregnancy test (urine) ≤ 24 hours prior to surgery, and are not lactating.
5. Patient is undergoing elective surgery and, in the opinion of the investigator, is an appropriate candidate for IV Tramadol for pain management post-operatively.
6. The study patient is willing to be housed in a healthcare facility capable of administering parenteral analgesia for at least 24 after surgery. Treatment may extend through Hour 168 if deemed appropriate.
7. The patient meets definition of American Society of Anesthesiologists (ASA) Physical Class 1 or 2.
8. The patient is willing and able to understand the study procedures to communicate meaningfully with the study personnel, and to comply with the study protocol.

7.2. Patient Exclusion Criteria

The following are patient exclusion criteria for this study; each patient must **not** meet any of these exclusion criteria in order to be enrolled into this study.

1. The patient has current or historical evidence of any clinically significant disease or condition that might place the patient at unacceptable risk due to receiving the study medication, in the opinion of the investigator.
2. The patient has allergy or hypersensitivity (or is intolerant) to opioids or tramadol.

3. The patient has used chronic opioid therapy, defined as >= 20 MEQs of morphine per day >=3 days out of 7 days over the past 4 weeks.
4. The patient has a recent (within 2 years) and/or current history of alcohol, opiate or tranquilizer abuse or dependence.
5. The patient is taking herbal or dietary supplements or medications that are moderate or strong inhibitors of CYP2D6 or CYP3A4 (e.g., fluoxetine, paroxetine, amitriptyline, quinidine, ketoconazole, erythromycin, grapefruit juice) or inducers of CYP3A4 (e.g., carbamazepine, rifampin, St. John's Wort) and cannot go through a minimum washout period of 7 days prior to surgery.
6. The patient has a history of epilepsy, is susceptible to seizures.
7. The patient cannot be withdrawn from medications (at least 7 days prior to surgery) that may lower the seizure threshold (e.g. anti-psychotic agents, MAOI inhibitors) or which increase serotonergic tone (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, triptans, amphetamines).
8. The patient has had a recent (within 6 months) cardiovascular event or clinically significant abnormal ECG finding at screening.
9. The patient has a history of Long QT Syndrome or a relative with this condition
10. The patient has expressed suicidal ideation within the past 3 months or is considered to be at risk of suicide.
11. The patient is morbidly obese (body mass index [BMI] ≥ 40 kg/m2) or has documented sleep apnea requiring CPAP or other treatment.
12. Female patient is pregnant and/or undergoing a pregnancy-related surgery, or breastfeeding.
13. The patient has a history of cardiopulmonary, neurological or psychiatric condition that may confound the assessments of efficacy or safety.
14. The patient has cirrhosis, moderate or severe hepatic impairment or an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value > 3X upper limit of normal (ULN) at Screening.
15. The patient has severe renal impairment or a serum creatinine value of > 2x upper limit of normal (ULN) at Screening.
16. The patient has potassium, sodium, calcium or magnesium levels outside of the normal range at Screening
17. The patient has a hemoglobin level at screening which, in the judgment of the Investigator, is not suitable for participation in this study.
18. The patient was administered an investigational drug product within 30 days prior to Screening.
19. The patient has previously participated in a clinical study with AVE-901.

7.2.1. Post-Surgical Additional Exclusion Criteria

The patient is to be evaluated post-operatively prior to the initial treatment with the study drug and will be withdrawn prior to treatment with the study drug if any of the following exclusion criteria are met:

1. Patients who, in the opinion of the investigator, are not likely to tolerate the protocol's allowed analgesic regimen (tramadol plus non-opioid adjuvants).
2. Patients who have been admitted to the ICU post-surgery or have experienced complications during the surgical procedure that would put them at increased risk from receipt of the investigational product in the opinion of the investigator.
3. The patient is not clinically stable and not able to answer questions and follow commands.
4. The patient has evidence of respiratory insufficiency, such as a respiratory rate that is less than 8 breaths per minute or arterial oxygen saturation by pulse oximetry of less than 90% with supplemental oxygen.
5. Use of 5-HT3 antagonists (e.g. ondansetron, granisetron, palonosetron) preoperatively, intraoperatively, or postoperatively

7.3. Patient Withdrawal Criteria

If a patient is discontinued from the study prematurely, the Investigator must select the primary reason for discontinuation on the End of Study eCRF. In addition, every effort should be made to complete the assessments listed under the End of Treatment/Discharge from Clinic column on the Schedule of Assessments.

Patients withdrawn from the study will be considered evaluable for statistical assessment.

A patient may be removed from the study for the following medical or administrative reasons:

- Adverse Event: If a patient experiences an adverse event that the patient finds unacceptable or that, in the judgment of the Investigator or the Medical Monitor presents an unacceptable consequence or risk to the patient, the patient may be discontinued from further participation in the study. If doses are missed due to an Adverse Event and the event resolves, the patient can resume their scheduled treatment at the discretion of the Investigator. Missed doses should be recorded in the eCRF.
- Administrative Discontinuation: After consultation with the Investigator or Medical Monitor, a patient may be discontinued from the study for failure to comply with protocol requirements. All instances of noncompliance must be documented in the eCRF.
- Refusal of Assessments: If for any reason, following dosing, the patient refuses further assessment during the study, the patient shall be discontinued from the study and the reasons for refusal documented. Reasonable efforts shall be made to monitor the patient for adverse events following such discontinuation. Such efforts shall be documented.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drug

Investigational product will be packaged in identical ampoules containing 1ml of AVE-901. Each ampoule of AVE-901 contains 50 mg of tramadol hydrochloride and sodium acetate trihydrate as buffering agent diluted in water. Ampoules will be packaged in bulk cartons.

Study drugs will be distributed to the clinic using a designated distribution center. The Sponsor will provide the investigator with adequate quantities of investigational product and supplies to conduct the study. Specific details regarding investigational product supplies, dose preparation, and accountability will be described in a pharmacy manual at the clinic.

Table 5 provides a summary description of the drug products, including the dosage form, the unit dose, and a physical description of the product.

Table 5: Investigational Product (Study AVE-901-104)

	Investigational Product
Product Name:	Tramadol for infusion 50 mg
Dosage Form:	Liquid
Unit Dose:	50 mg/1mL ampoule
Route of Administration:	Intravenous infusion
Physical Description:	Clear solution
Manufacturer:	Siegfried Hameln

8.2. Concomitant Medications

Medications deemed necessary for the patient's welfare are permitted. The following drugs are EXCLUDED from use:

- Moderate or strong inhibitors of CYP3A4 or CYP2D, inducers of CYP3A4, drugs which may increase serotonergic tone including SSRIs, SNRIs, tricyclic antidepressants, trazodone, cyclobenzaprine triptans, 5-HT3 antagonists including ondansetron, and amphetamines; and drugs which may lower seizure threshold.
- Any opioid based analgesic (post dosing)

Adverse events (AEs) such as nausea, vomiting and pruritus should be managed using standard of care, excluding medications specifically noted in the study protocol.

8.3. Treatment Compliance

Treatment compliance with study medication during the treatment periods is expected to be high, as patients will be dosed directly in the clinic under well-controlled conditions. The date and time of study drug administration will be recorded on the eCRF.

8.4. Overdose

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a cause of drug-related deaths. Acute over dosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death. Serious potential consequences of over dosage with tramadol are CNS depression, respiratory depression and death. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs, while others were associated with abuse of tramadol. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids (Ultram® Prescribing Information, 2009).

Of note, while naloxone will reverse some, but not all, symptoms caused by over dosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period (Ultram® Prescribing Information, 2009).

Additional details may be found in the Investigator's Brochure.

8.5. Randomization, Blinding and Unblinding

This is an open-label study in which all patients will receive the same treatment. Thus, there is no randomization or blinding applied in this study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

Study drug will be provided to the investigational centers.

9.1. Study Drug Packaging and Labeling

Single-use, glass ampoules with labels and an outer fiberboard carton with a single panel label will have the following information:

1. Protocol #: AVE-901-104
2. Each 1ml ampoule contains 50mg of IV Tramadol (C-IV)
3. Intravenous injection administration only. Use as directed per protocol.
4. Store at 20°C to 25°C (68°F to 77°F). Store away from heat sources and direct sunlight.
5. Caution: New Drug – Limited by Federal (United States) Law to Investigational Use.
6. Sponsor: Avenue Therapeutics, New York, NY 10019
7. Manufactured by: Siegfried Hameln
8. Lot number: _____

The clinical trial supply label will be in accordance with ICH GCP and local requirements for investigational product labelling.

9.2. Packaging, Labeling, and Storage of Clinical Supplies

Investigational products are for investigational use only and the study drug supplied for this study is intended for use only within the context of this study. The study drug supplied for this study should be stored in a secure place and maintained under adequate security until dispensed for patient use or returned to the Sponsor. Tramadol is classified as a Schedule IV controlled drug and security requirements as per 21CFR 1301.71-77 are to be followed at the clinic.

Investigational products should be stored at room temperature (20-25°C or 68-77°F). Investigational products should be stored away from heat sources and direct sunlight.

The Investigator, pharmacist, or their designee, will verify that study drug supplies are received intact and in the correct amounts by signing and dating the investigational product receipt log. The person receiving the supplies must verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable drug in a given shipment will be documented in the study files. The Investigator must notify the Sponsor or designee of any damaged or unusable investigational product supplied to the Investigator's site.

The site will maintain a Drug Inventory Log (includes, but not limited to, the following: lot number, number of units received and number of ampoules dispensed). The site will also maintain patient-specific drug dispensing logs.

An overall accountability of investigational product will be performed and verified throughout the study and at the site closeout visit. Upon completion of the study, copies of the investigational product accountability records will be returned to the Sponsor. All used and unused study drug supplies will be inventoried, accounted, and returned to the Sponsor at the end of the study. By signing the Investigator Agreement page of this protocol, the investigator or

named sub-investigator agrees not to supply study drug to any person(s) not enrolled in the study.

9.3. Study Drug Preparation and Administration

Study drug will be dispensed by the qualified, licensed study personnel and administered to the patient by a licensed designated staff member. The designated personnel will prepare the treatments for administration and maintain accountability records.

AVE-901 will be provided in ampoules containing 1 mL of IV Tramadol. Directions for preparation of study medication will be recorded in the pharmacy manual prior to initiation of the study. The pharmacy manual will provide procedures for preparation (and destruction) that correspond to the dose of study medication used in this study.

9.4. Study Drug Accountability

Patients will be treated at the investigational center and therefore the Pharmacist or other investigational staff via documentation of receipt of the study drug and dosing/treatment given will perform drug accountability.

9.5. Study Drug Handling and Disposal

Records of receipt, dispensing records and inventory forms, as applicable, will be examined and reconciled during and at the end of the study. Both the investigational drug that is used during the course of the study, as well as any remaining unused investigational drug, must be accounted for on a drug accountability record provided to the PI by the Sponsor or its designee. Drug destruction will be completed following the clinical sites SOP on destruction and a destruction certificate will be maintained at the clinic.

If directed and if drug is not destroyed on site, at the end of the study, all unused investigational drug, accompanied by a packing slip will be shipped to designee provided by the sponsor.

In addition, a copy of all completed drug accountability records must be retained in the Investigators' Study Files, with a copy sent to the Sponsor or its designee.

The products are to be stored in a safe place (locked facility) at the appropriate temperature and without exposure to freezing.

10. PHARMACOKINETIC ASSESSMENTS

There are no pharmacokinetic assessments being performed in this study.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety assessments will include collection of adverse events. In addition, safety assessments include clinical laboratory tests, vital signs, physical examination, concomitant medications, and 12-lead ECGs.

11.1.1. Demographic/Medical History

Demographic information and medical history will be collected at Screening for determination of eligibility. Demographic information will include the following: age, gender, race and ethnic origin. Significant medical history within the past two years should be recorded on the eCRF.

11.1.2. Vital Signs

Vital sign assessments include blood pressure, pulse, temperature, respiratory rate, and SpO2, and are collected at varied times as per the Schedule of Events. Vital signs will be performed after the patient has rested sitting or supine for 5 minutes.

11.1.3. Weight and Height

Height and weight will be captured as per the Schedule of Events. BMI will be calculated using the NIH website BMI calculator.
https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

11.1.4. Electrocardiogram (ECG)

All scheduled ECGs will be performed after the patient has rested supine for approximately 5 minutes as per the schedule of events.

11.1.5. Physical Examination

A physical examination will be conducted and abnormalities will be described. After the initial full physical exam only symptom-driven examinations will be performed.

11.1.6. Laboratory Assessments

All laboratory assessments will be collected as per the schedule of events and as described in the study laboratory manual.

11.1.6.1. Hematology and Blood Chemistry

Clinical Laboratories (Hematology and Serum Chemistry) will be performed as per the schedule of events and will be described in the study laboratory manual.

11.1.6.2. Urinalysis

Urinalysis will be performed as per the schedule of events and will be described in the study laboratory manual.

Instruct patient to obtain a "clean-catch" urine sample, collected in midstream.

11.1.6.3. Pregnancy Screen

Pregnancy screening will be performed for all females of childbearing potential in accordance with the schedule of events.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Adverse events may include safety findings considered to be clinically significant by the Investigator. An adverse drug event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is related to the medicinal product. Reporting an adverse event does not necessarily reflect a conclusion by the Investigator that the event is causally related to the drug.

All adverse events should be captured and documented along with any supporting documentation. Adverse events should be spontaneously reported or elicited by non-suggestive probing. Signs or symptoms associated with a worsening in either severity or frequency as compared to a baseline condition should be evaluated by the Investigator for clinical significance and adverse event reporting.

Each adverse event in this study will be assessed for Grade, where Grade of an AE refers to the severity of the AE. Grade will be assessed according to CTCAE Version 4.03 or higher. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE that are based on this general guideline. Table 6 provides the CTCAE grades and grade descriptions to be used in this study.

Table 6: CTCAE Grade (Study AVE 901-104)

CTCAE 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.

Activities of Daily Living (ADL)
[1] 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.
National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 will be used for AE grading. A complete CTCAE list can be downloaded at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

11.2.1.2. Serious Adverse Event (SAE)

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

Reporting serious adverse events requires additional detailed reports and follow-up, depending upon the Investigator's estimate of a causal relationship between the test agent and the adverse event(s), and whether the adverse event(s) is identified in nature, severity, and frequency in the Investigator's Brochure or other risk information supplied to the Investigator.

All serious adverse events (SAEs) should be submitted promptly to the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The investigator must make an effort to obtain all hospital medical records including discharge summary confirming final diagnosis. The death of a patient must be immediately (within 24 hours) reported to the IRB. All serious and non-

serious adverse events should be thoroughly documented and followed out by the Investigator until the event resolves or until the termination visit. The event may be followed longer, if deemed necessary. For any death occurring during the trial, the medical condition that led to the death should also be noted. The "outcome" status should be noted as "death" in these cases of SAEs that resulted in death. In addition, all SAEs that occur from treatment through the follow-up phone call should be recorded and reported as noted previously.

11.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. For purposes of the definitions below, "temporal sequence" is defined as an association between administration of a drug and the observed reaction or event such that the drug was present prior to the reaction or event.

DEFINITE - The adverse event:

- follows a reasonable temporal sequence from drug administration,
- abates upon discontinuation of the drug (dechallenge), AND
- is confirmed by reappearance of the reaction on repeat exposure (rechallenge).

PROBABLE - The adverse event:

- follows a reasonable temporal sequence from drug administration,
- abates upon discontinuation of the drug (dechallenge), and
- cannot be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLE - The adverse event:

- follows a reasonable temporal sequence from drug administration, and;
- could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.

REMOTE

- There is another more likely explanation for the adverse event, such as a concomitant therapy or procedure. The known pharmacology of the drug is not consistent with the event and the temporal relationship to study drug is unknown or may be consistent with the drug being present at the time of event.

DEFINITELY NOT – The adverse event:

- is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient. The temporal relationship indicates that the drug was not present at the time of the event.

11.4. Recording Adverse Events

Adverse events spontaneously reported by the patient/caregiver and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious, outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on a pregnancy reporting form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Adverse Events

Information about AEs and SAEs will be collected from treatment (i.e. from time of first dose) through the follow-up phone call. AEs or SAEs occurring prior to first dose of study treatment will be considered Medical History. AEs or SAEs occurring during or after the first dose of study treatment will be treatment-emergent (S)AE. Any SAEs considered at least possibly related to the investigational product and discovered by the Investigator at any time after the study should be reported. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents.

Additional follow-up information, if required or available, should all be communicated within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12. STATISTICS

This is an open-label treatment study in which all patients will be treated with the study medication. The primary objective of this study is to assess safety. The statistical methods to be used in the analysis are consistent with both the study design and the study objectives.

12.1. Sample Size Considerations

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%).

12.2. General Statistical Methods

Data will be tabulated using descriptive statistics where specified. A comprehensive statistical analysis plan (SAP) will be written and approved prior to completion of the final analysis. This SAP will detail how missing values, windows for study visits, and other analysis considerations will be addressed.

12.3. Analysis Populations

There is one populations identified for purposes of the statistical analysis.

- Safety Population: All patients treated with the study treatment will be included in the Safety Population.

12.4. Handling of Missing Data

Missing data will not be replaced.

12.5. Baseline Characteristics

Baseline characteristics will be tabulated descriptively (eg, number and percent of patients for each category for categorical parameters, and the number, mean, standard deviation, and range for continuous parameters).

12.6. Patient Disposition

Patient completion status and reasons for end of treatment will be tabulated descriptively.

12.7. Exposure

Exposure to AVE-901 will be tabulated via the number of infusions given, the total amount of drug given over the course of treatment, and the duration of treatment.

12.8. Alpha Levels

This is a safety study with only one treatment arm and therefore inferential testing will not be performed.

12.9. Subgroups

Analysis of the primary and key secondary endpoints, as well as treatment-emergent AE and serious AE incidence, will be provided by the following subgroups:

- Surgery type
- Gender
- Race
- Age (using the study median age)

12.10. Safety

The safety analysis will be descriptive in nature. All safety data will be listed, and data will be tabulated where the data warrant. An assessment of the association between AE incidence and exposure will be explored.

Safety data include:

- AEs, including assessment of infusion site local reactions (skin and vein)
- Clinical laboratory tests pre-treatment and discharge
- Vital signs including: respiratory rate, heart rate, pulse oximetry temperature and blood pressure.
- Physical examination pre-treatment and discharge
- 12-lead ECG at protocol specified time points
- Concomitant treatments

Exploratory analyses of use of anti-emetics may be performed. Other safety data presentations will be descriptive in nature and no formal statistical tests will be performed.

12.10.1. Adverse Events

Adverse events will be coded using the MedDRA coding dictionary; patient incidence of each system organ class and unique term will be tabulated. AE incidence will also be tabulated according to relationship to study medication and severity. Serious AEs and AEs resulting in premature discontinuation will be tabulated.

Adverse events starting before the first dose of treatment will be recorded as Medical History. Adverse events starting after the first dose of treatment will be considered treatment-emergent adverse events.

Local tolerability of the infusion site will be assessed for pain, swelling, tenderness, and erythema via AE's.

12.10.2. Prior and Concomitant Medications

Prior and concomitant medications will be reviewed and coded using the WHO Drug Dictionary, and tabulated by treatment. Concomitant medications will be reported in a fashion similar to that of AEs.

12.10.3. Clinical Laboratories

Clinical laboratory observed values and changes from pre-treatment to on-treatment time points may be tabulated for continuous parameters, as warranted.

12.10.4. Vital Signs

Vital sign parameter outcomes (including SpO2) will be assessed for clinical significance; observed values and changes from pre-treatment to on-treatment time points may be tabulated for continuous parameters, as warranted.

12.10.5. Physical Examination

Physical examination outcomes will be listed in data listings.

12.11. Efficacy Analyses

PGA (Appendix 1) will be measured at Hour 24 and at the End of Treatment and summarized descriptively. If the patient continues treatment beyond Hour 24, PGA will be conducted at Hour 24 and End of Treatment (total of 2 PGAs). If the patient ends treatment prior to Hour 24, PGA will be conducted as part of the End of Treatment visit (total of 1 PGA).

13. STUDY MONITORING, AUDITS, IRB, AND QUALITY

13.1. Study Monitoring

Before an investigational site can enter a patient into the study, a Sponsor representative will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor (or its delegate) and the investigator.

During the study, a monitor or Sponsor representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original (or faxed/copied, if requested) records for each patient (e.g. clinic charts) which may include access to medical records for purposes of remote (i.e. not on-site at the Investigator's clinic) source data verification
- Record and report any protocol deviations not previously sent to the Sponsor (or its delegate)
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sponsor (or its delegate) and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, its delegate, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The

investigator should contact the Sponsor or its delegate immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board/ Independent Ethics Committee

The Investigator must obtain appropriate IRB approval prior to study initiation. A copy of the written approval from the IRB and a copy of the approved ICF should be sent to the Sponsor or its delegate. It is also necessary to submit a list of the IRB members (including their Institution affiliations, gender makeup, and occupations) or supply a statement from the IRB specifying that the membership comply with applicable regulations.

The study protocol, patient information and consent form, the Investigator Brochure, available safety information, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to the patients and documentation evidencing the Investigator's qualifications should be submitted to the IRB/Ethics Committee for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

13.4. Quality Control and Quality Assurance

The investigator is responsible for all quality control and quality assurance for the performance of the study.

14. ETHICS

14.1. Ethics Review

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

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

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

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

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor or its delegate's policy on Bioethics.

14.3. Written Informed Consent

The Investigator(s) will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated ICF and assent if applicable must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

The Sponsor or its delegate will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor, its delegate, or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15.3. Data Capture and Processing

Data will be captured on source documents and will be entered into an electronic data capture system via electronic case report forms (eCRFs) and will be processed according to a data management plan. The database will be cleaned and 'locked' according to that data management plan prior to the final statistical analysis being performed.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data entered in each patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. Any outstanding entries must be entered immediately after the final examination. An explanation should be given for all missing data.

16. PUBLICATION POLICY

All information concerning the product, as well as any matter concerning the operation of the Sponsor or its delegate, such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by the Sponsor or its delegate and are unpublished, are confidential and must remain the sole property of the Sponsor or its delegate. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor or its delegate is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

All publications and presentations of the results of the Study are governed by the applicable provisions of the Clinical Trial Agreement between the Sponsor (or its delegate) and the institution. By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor or its delegate. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the Sponsor or its delegate. Additionally, the Sponsor or its delegate may, for any reason, withhold approval for publication or presentation. Such manuscript or materials should be provided for Sponsor/delegate review only after the final database, which has been approved by Quality Assurance, is available.

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18. APPENDIX

Patient Global Assessment (PGA)

***Instructions to Study Subject*:** Please respond to the question below. When completed, please initial at the bottom of the assessment.

How would you rate the study medication in terms of its effectiveness in controlling your pain?

(Please mark an 'X' in one box)

☐ **Poor (0)**

☐ **Fair (1)**

☐ **Good (2)**

☐ **Very Good (3)**

☐ **Excellent (4)**

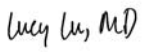
Subject Initials: _____

Certificate Of Completion

Envelope Id: 8E82A4FD917243C8A2C76BB840869E46
Status: Completed
Subject: Please DocuSign: AVE-901-104_Protocol_Final_2.0_29Aug2018.docx
Source Envelope:
Document Pages: 55
Signatures: 1
Envelope Originator:
Certificate Pages: 3
Initials: 0
Jeffrey O'Hagan
AutoNav: Enabled
100 W California Blvd., Unit 25
EnvelopeId Stamping: Enabled
Pasadena, CA 91105
Time Zone: (UTC-08:00) Pacific Time (US & Canada)
johagan@lotuscr.com
IP Address: 108.243.103.187

Record Tracking

Status: Original
8/30/2018 10:10:07 AM
Holder: Jeffrey O'Hagan
johagan@lotuscr.com
Location: DocuSign

Signer Events	Signature	Timestamp
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: 107.77.234.194 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 8/30/2018 10:14:45 AM Viewed: 8/30/2018 10:16:46 AM Signed: 8/30/2018 10:19:02 AM

Electronic Record and Signature Disclosure:
Accepted: 8/30/2018 10:16:46 AM
ID: 05ce6aa5-5056-4b8a-92ae-68a9bd870f99

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/30/2018 10:14:45 AM
Certified Delivered	Security Checked	8/30/2018 10:16:46 AM
Signing Complete	Security Checked	8/30/2018 10:19:02 AM
Completed	Security Checked	8/30/2018 10:19:02 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

Please read the information below carefully and thoroughly. By checking the "I agree to use Electronic Records and Signatures" box in the DocuSign system, you confirm you can access this information electronically to your satisfaction and agree to these terms and conditions below.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after signing session. If you wish for us to send you paper copies of any such documents from our office to you, please contact your Lotus Lead Project Manager.

Withdrawing your consent

If you decide to receive documents from us electronically, you may at any time change your mind and tell us thereafter that you want to receive documents only in paper format. If you want to withdraw your consent and receive future documents in paper format, please contact your Lotus Lead Project Manager.

Consequences of changing your mind

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Screen Resolution:	800 x 600 minimum
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