FDA Briefing Document

NDA# 213231

Drug name: Tramadol Hydrochloride 50 mg/mL injection (tramadol IV)

Applicant: Avenue Therapeutics, Inc.

Combined Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and Drug Safety and Risk Management Advisory Committee (DsARM)

February 15, 2022

Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/Office of Neuroscience

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of time to onset of action and risks related to delayed onset of action for tramadol IV to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
AC	Advisory Committee
AE	adverse event
APAP	acetaminophen
AUC	area under the concentration-time curve
C_{max}	maximum plasma concentration
CSA	Controlled Substances Act
CYP	cytochrome P450
DAAP	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DEA	Drug Enforcement Administration
DsARM	Drug Safety and Risk Management Advisory Committee
ECG	electrocardiogram
FAS	full analysis set
FDA	Food and Drug Administration
FDRR	formal dispute resolution request
HHS	Department of Health and Human Services
IV	intravenous
PID	pain intensity difference
PGA	patient global assessment
PGA24	patient global assessment at 24 hours
QT	QT interval
M1	O-desmethyltramadol
M5	N, O-desmethyltramadol
NDA	new drug application
NPRS	numeric pain rating scale
NSAID	nonsteroidal anti-inflammatory drugs
OUD	opioid use disorder
SPID	summed pain intensity difference
SPID24	time-weighted summed pain intensity difference from baseline over 24 hours
SPID48	time-weighted summed pain intensity difference from baseline over 48 hours

TEAE	treatment-emergent adverse events
U.S.	United States

1. Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee (AC) Meeting

The food and Drug Administration (FDA) is convening this Advisory Committee meeting to discuss the clinical implications of time to onset of action and potential risks related to delayed onset of action for tramadol intravenous (IV), an opioid analgesic proposed for the management of acute pain. Time to onset of analgesia and the safety concern of potential additive opioid-related adverse effects with use of tramadol IV are important factors in the benefit-risk assessment of tramadol IV.

1.2 Context for Issues to be Discussed at the AC

Pain is a subjective experience that is affected by biological, psychological, and social factors. Acute pain is a normal response to tissue injury. It is usually sudden in onset, short-term, and self-limiting. Acute pain is a serious medical condition that, if left untreated, has a significant impact on quality of life and may progress to chronic pain.

Most patients who undergo surgical procedures experience post-operative pain. Severe pain after surgery is associated with decreased patient satisfaction and increased morbidity and mortality (Meissner et al. 2018).

Multiple drugs are approved for IV administration to treat acute pain including drugs from different analgesic classes, such as APAP, NSAIDs, and opioids. Tramadol is approved only for oral administration in the United States. If approved, tramadol IV would be the first injection formulation of tramadol hydrochloride available in the United States.

Tramadol is a μ-opioid agonist and a norepinephrine and serotonin reuptake inhibitor. It is in Schedule IV under the federal Controlled Substances Act (CSA). Tramadol is metabolized by the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to O-desmethyltramadol (M1) and N, O-desmethyltramadol (M5) in the liver. M1 has stronger affinity for mu-opioid receptors than the parent compound. Therefore, tramadol exerts much of its analgesic effect through its major metabolite, M1. When tramadol is administered intravenously, first pass metabolism in the liver is bypassed resulting in delayed M1 formation. Delayed M1 formation appears to contribute to the delay in tramadol IV's onset of effects.

Avenue Therapeutics, Inc. (Applicant) has developed an IV formulation of tramadol hydrochloride (HCl) with the proposed indication, "for the management of moderate to moderately severe pain in adults in a medically supervised health care setting", which is not a typical indication for an immediate-release opioid analgesic.

The typical indication for an immediate-release opioid analgesic is "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate." The Applicant's proposal to use tramadol IV for moderate to moderately severe pain suggests broader use than the typical immediate-release opioid indication. First, opioid analgesics are typically reserved for treatment of opioid-level pain. Second, opioid analgesics are typically reserved for treatment of pain when all other treatment options have failed or been excluded. These differences between tramadol IV's proposed

indication and the typical immediate-release opioid indication are significant given the known safety concerns of respiratory depression, misuse, abuse, addiction, and death associated with opioid use.

The proposed dosing regimen is tramadol 50 mg IV infusion over 15 minutes for the first dose, repeated at 2 and 4 hours, then every 4 hours thereafter. The Applicant contends that tramadol IV will fill a gap in the current postoperative analgesic armamentarium by serving as a potential alternative to conventional opioids.

1.3 Brief Description of Issues for Discussion at the AC

First Review Cycle

In December 2019, Avenue Therapeutics, Inc. submitted a 505(b)(2) new drug application (NDA) that relied in part on FDA's findings of safety and efficacy for Ultram® (tramadol hydrochloride).

The original proposed indication was:

> Management of moderate to moderately severe pain in adults in a medically supervised health care setting.

The Applicant conducted two adequate and well-controlled Phase 3 trials (Studies 102 and 103) in support of the efficacy of tramadol IV. The results of both studies showed a statistically significant difference between tramadol IV 50 mg and placebo for the prespecified primary and secondary endpoints.

DAAP's analyses of pain intensity difference (PID) at early time points (Hours 0-2) and of time to meaningful pain relief, using the two-stopwatch method, demonstrated that tramadol IV had a delayed onset of analgesia, likely beyond 2 hours. This finding was expected given the known metabolism of tramadol via the IV route which bypasses first pass metabolism resulting in delayed formation of tramadol's major metabolite, M1, a more potent opioid agonist than the parent compound.

The Applicant submitted data from Studies 102 and 103, and data from one open-label uncontrolled Phase 3 trial (Study 104) to support the safety of tramadol IV. The overall safety profile of tramadol IV was generally consistent with the safety profile of Ultram® and other available opioid products.

The Division concluded that tramadol IV was efficacious for the acute pain indication; however, the finding of delayed onset of analgesia raised a safety concern. The Division asserted that patients whose pain is not adequately controlled with the first dose of tramadol IV will likely require another analgesic as rescue, which will likely be another immediate-release opioid. This will result in opioid stacking and increase the potential for opioid-related adverse events (AEs), such as oversedation and respiratory depression.

The Division did not engage in any indication or labeling negotiations with the Applicant because the application received a Complete Response.

First Complete Response Letter

In October 2020, the Division issued a Complete Response Letter to the Applicant. The Complete Response Letter included one clinical deficiency and one product quality deficiency. The Division had the following safety concern about tramadol IV:

Safety issue Tramadol IV's delayed onset of analgesia combined with its inability to be titrated to effect leads to a theoretical, yet serious safety concern of additive opioid-related adverse effects from use of opioids in succession, also known as opioid stacking.

The Division asked the Applicant to identify a population for which tramadol IV is both safe and effective for the acute pain indication.

First Post-Action Meeting

During the first post-action meeting in November 2020, the Applicant agreed with the Division about tramadol IV's delayed onset of analgesia but disagreed with the Division about the need for an immediate-release opioid as rescue analgesia. The Applicant stated that patients in need of rescue analgesia can be adequately managed with another non-opioid analgesic. The Applicant also disagreed with the Division about the safety concern of opioid stacking. The Applicant asserted that use of multiple opioids is standard practice in the hospital setting. The Applicant stated that communication in labeling should be an effective way to address the Division's concerns. The Division agreed to review the Applicant's proposed labeling revisions once submitted.

Second Review Cycle

In February 2021, Avenue Therapeutics, Inc. submitted a resubmission in response to the Agency's Complete Response Letter. The resubmission adequately addressed the product quality deficiency. No new clinical data were included in the resubmission. The Applicant proposed a revised indication as well as revised language in the Limitations of Use, Dosage and Administration, and Clinical Studies sections of the label to address the clinical deficiency.

The revised proposed indication was:

> Management of moderate to moderately severe pain in adults in a medically supervised setting, alone or in combination with other analgesics.

The Applicant proposed including language that recommended use of a non-opioid analgesic in patients who experience delayed onset of pain relief with tramadol IV. The Applicant asserted that data from the NDA demonstrated that patients in need of rescue analgesia were adequately managed with another non-opioid analgesic.

The Division considered the Applicant's labeling revisions and the Applicant's argument about using a non-opioid medication rather than an opioid medication as rescue analgesia. The Division concluded that the Applicant's proposed labeling did not adequately address tramadol IV's clinical deficiency.

Again, the Division did not engage in any indication or labeling negotiations with the Applicant because the application received a second Complete Response.

Second Complete Response Letter

The Division issued a second Complete Response Letter to the Applicant in June 2021. The Division restated the initial safety concern about tramadol IV:

Safety issue Tramadol IV's delayed onset of analgesia combined with its inability to be titrated to effect leads to a theoretical, yet serious safety concern of additive opioid-related adverse events from use of opioids in succession, also known as opioid stacking.

The Division stated that intravenous opioid products are intended to be used in the management of pain that is not controlled by analgesics in other drug classes; therefore, therapy with an opioid for a painful condition that could be managed with a non-opioid is not consistent with the intended use of IV opioids.

The Division also stated that the studies in the NDA submission were not designed to evaluate the analgesic effect of tramadol IV combined with another analgesic. The studies were designed to evaluate the analgesic effect of tramadol IV as monotherapy. Consequently, there was insufficient information to support the conclusion that tramadol IV in combination with other analgesics is safe and effective for the intended patient population.

Second Post-Action Meeting

During the second post-action meeting in July 2021, the Applicant expressed dissatisfaction with the second Complete Response Letter. The Applicant stated that the totality of the data from the NDA, looking at endpoints other than time to meaningful pain relief, demonstrated that tramadol IV can be successfully used in a multimodal analgesic approach in the postoperative pain setting. The Applicant also stated that opioid stacking was not a safety concern identified in the NDA nor has it been a concern in countries outside the United States where tramadol IV is utilized.

First Formal Dispute Resolution Request

In July 2021, the Applicant submitted a formal dispute resolution request (FDRR) to the Office of Neuroscience. The Applicant provided rationale in support of appealing the Complete Response decision made by DAAP. The Applicant also asserted that approval of tramadol IV would have a public health benefit because tramadol is a Schedule IV drug that has less abuse potential than schedule II opioids generally used for management of postoperative pain. The FDRR was delegated to the Deputy Director of the Office of Neuroscience, Dr. Eric Bastings. He reviewed the FDRR and issued a Dispute Appeal Denied Letter in August 2021. Dr. Bastings expressed agreement with DAAP's position that tramadol IV's delayed onset of effect raises a safety concern about a risk of opioid stacking, with potentially serious opioid-related adverse reactions, that has not been adequately addressed in the NDA.

Second Formal Dispute Resolution Request

In September 2021, the Applicant submitted a FDRR to the Office of New Drugs. The Applicant provided their arguments for appealing the Complete Response decision made by DAAP and the August 2021 FDRR denial decision made by the Office of Neuroscience. The FDRR was delegated to the Deputy Director of the Office of New Drugs, Dr. Mary Thanh Hai. She reviewed the FDRR and issued a Dispute Appeal Interim Response in October 2021. Dr. Thanh Hai concluded that additional input from an advisory committee was needed to reach a decision regarding the appeal.

1.4 Draft Points for Consideration

As you review the AC Background materials, we ask that you consider the following points in advance of the meeting:

- The importance of time to onset of action and risks related to delayed onset of action for tramadol IV proposed for the management of moderate to severe acute pain in the inpatient setting such as post-operative or acute severe injury setting.
- The benefits and risks of tramadol IV for acute pain management in the inpatient setting considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.

- The relevance of tramadol's Schedule IV status in the context of the proposed use for the management of acute pain in an inpatient setting with consideration on the following issues:
    - Any impact on risk of abuse, misuse, or addiction in the outpatient setting
    - Any comparative advantage over currently available Schedule II opioids approved for the management of acute pain in an inpatient setting

2. Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (International Association for the Study of Pain 2020). Pain is a subjective experience that is affected by biological, psychological, and social factors. Though pain usually serves an adaptive role, it may have adverse effects on function as well as social and psychological well-being.

Pain is the most common reason people seek medical care (Fishman 2007). Pain impairs sleep, impairs activities of daily living, and lowers work productivity. Untreated pain has a significant impact on quality of life with physical, psychological, social, and economic ramifications. Untreated or inappropriately managed acute pain can also alter neural pathways making future pain worse and leading to the development of chronic pain (Stephens et al. 2003).

Acute pain is a normal response to tissue injury. It is usually sudden in onset, short-term, and self-limiting. An individual in acute pain may experience sharp, throbbing, burning, or stabbing sensations or may experience weakness, numbness, and tingling. Acute pain gradually resolves with healing of the underlying cause. Examples of acute pain include muscular or ligamentous sprains and strains, burns, bone fractures, and the post-surgical experience.

Most patients who undergo surgical procedures experience post-operative pain and 80 percent of those with post-operative pain report the severity as moderate or severe (Apfelbaum et al. 2003). Severe pain after surgery is associated with decreased patient satisfaction, delayed ambulation, increased incidence of cardiac and pulmonary complications, and increased morbidity and mortality (Meissner et al. 2018).

A variety of drugs are currently available for the management of acute pain. Some products are FDA approved for the pain indication and other products are used off-label. For use in the inpatient setting, examples of drugs with an FDA approved pain indication include injectable and oral formulations of APAP, opioids and NSAIDs as well as local anesthetics administered epidurally, spinally, or as nerve blocks. Gabapentinoids, on the other hand, are used off-label in conjunction with other analgesics in the peri-operative setting. Drug options for the outpatient setting are typically limited to oral formulations of APAP, opioids, and NSAIDs as well as some suppository analgesic formulations.

Notable safety concerns with the above listed drug products are as follows:

- Hepatotoxicity in the setting of overdose with APAP. The Agency addressed this safety concern in January 2011 by asking drug manufacturers to limit the amount of APAP in prescription products to 325 mg per tablet, capsule, or other dosage unit.
- Cardiovascular, gastrointestinal, and renal toxicity with NSAIDs.

- Risk of misuse, abuse, addiction, and fatal overdose due to respiratory depression with opioids as well as common opioid-related adverse effects of sedation, somnolence, respiratory depression, and constipation.
- Somnolence, sedation, and dizziness with gabapentinoids. Risk of respiratory depression and death when gabapentinoids are used concomitantly with central nervous system depressants.

The Applicant is seeking FDA approval of tramadol IV for the management of moderate to moderately severe pain in adults in a medically supervised health care setting. The Applicant states that tramadol IV will fill a gap in the current postoperative pain medication armamentarium by providing clinicians with a Schedule IV intravenous analgesic that has less risk for misuse and abuse than Schedule II intravenous analgesics. If approved, tramadol IV would be the first injection formulation of tramadol hydrochloride available in the United States.

2.2 Pertinent Drug Development and Regulatory History

Tramadol IV is a parenteral formulation of the opioid, tramadol hydrochloride. It is a clear, colorless solution containing tramadol hydrochloride, sodium acetate, and water for injection in a 2 mL glass ampule. The drug substance, tramadol hydrochloride, is a centrally acting synthetic analgesic with a mechanism of action that is not completely understood. The analgesic effect of tramadol is believed to be due to binding at μ-opioid receptors and weak inhibition of norepinephrine and serotonin reuptake.

Tramadol is metabolized in the liver by the CYP enzymes, CYP2D6 and CYP3A4, to M1 and M5. The parent compound has weak affinity for μ-opioid receptors while the major metabolite, M1, has stronger affinity for μ-opioid receptors. Therefore, tramadol exerts much of its opioid-related analgesic effect through M1. With IV administration of tramadol, first pass metabolism is bypassed and there is delayed formation of M1. Delayed M1 formation appears to contribute to the delay in tramadol IV's onset of effects.

There are wide interindividual variabilities in tramadol metabolism due to CYP2D6 polymorphisms. Some individuals are rapid metabolizers, some are extensive metabolizers, some are normal metabolizers, and some are slow metabolizers. These interindividual variabilities in tramadol metabolism lead to some unpredictability with respect to tramadol's efficacy, safety, and abuse potential.

Avenue Therapeutics, Inc. developed tramadol IV for the proposed indication of management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The proposed dose is 50 mg IV. The proposed fixed dosing regimen is 50 mg IV for the first dose, repeated after 2 hours and 4 hours, then every 4 hours thereafter.

The Applicant submitted a 505(b)(2) new drug application that relies in part on FDA's findings of safety and efficacy for Ultram® (tramadol hydrochloride). Tramadol hydrochloride was initially approved on March 3, 1995 under the brand name Ultram (NDA 020281). Ultram® is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Ultram® is supplied as 50 mg tablets for oral administration. The labeled dosage is as below:

For patients not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: Start ULTRAM at 25 mg/day and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four

times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg/day.

The Applicant submitted data from two pharmacokinetic studies (Studies RVG-10-018 and AVE-901-101) and two controlled Phase 3 clinical studies (Studies 102 and 103) to support the efficacy of tramadol IV. The Applicant submitted data from Studies 102 and 103, one Phase 3 open-label clinical study (Study 104), and a literature review to support the safety of short-term use of tramadol IV. The Applicant submitted an epidemiology review in the United States and outside of the United States and an assessment of abuse-related AEs in the clinical trials conducted during drug development to evaluate the abuse potential of oral and IV formulations of tramadol.

Table 1. Summary of Relevant Regulatory History

Drug Development Stage	FDA Communication	Date	Comments
IND 108124	Advice Letter	November 2010	Agency comments: Phase 3 study must have primary efficacy outcome based on pain intensity score; SPID48 is an acceptable primary endpoint. Recommended secondary endpoints – Time to onset of analgesia (two-stopwatch method) Time to re-medication Time course of pain intensity difference Pain intensity at rest and with movement SPID24 and SPID48 at rest and with movement Pain relief scores Total pain relief at 24 and 48 hours
IND 108124	Written Response	June 2015	Agency comments: It is your choice to select either SPID24 or SPID48 as the primary endpoint; however, the summation scores must be supported by clinically significant pain curve (using time-specific pain measurements) separation between your product and placebo.
IND 108124	End-of-Phase 2 Meeting Minutes	July 2016	Agency comments: It will be important to understand how a new treatment option for acute pain (IV tramadol) compares to the standard treatments with respect to efficacy and tolerability in order to define its place in the analgesic armamentarium for this setting. At least two, adequate and well-controlled trials in at least two pain models appears sufficient to support a general acute pain indication. We strongly recommend inclusion of an active control in the Phase 3 studies. Lack of an active control could make it difficult to interpret the study results. Add time-specific pain intensity difference as a key secondary endpoint.
IND 108124	Pre-NDA Meeting	September 2019	Agency comments added as post-meeting minutes to pre-NDA meeting: As a parenteral analgesic for acute pain, expect your product's onset of action will be within an hour of dosing or less. If not the case, then determine how pain will be managed until the onset of action occurs. Onset of action measured using two-stopwatch method where first stopwatch is stopped by patient when they feel the first perceptible pain relief and the second

Drug Development Stage	FDA Communication	Date	Comments
			stopwatch is stopped when they feel onset of meaningful pain relief. Median time to meaningful pain relief is the time of onset. Duration of effect measured using time to request for either rescue medication or a second dose of study medication. Expect median time to rescue will be consistent with the proposed dosing interval. This advice is in place throughout your development program, even if not repeated in each interaction with the Agency, unless there is a specific agreement, based on data for some alternative approach to time to onset and time to rescue.
IND 108124	Teleconference Minutes	October 2019	The Applicant requested a teleconference to discuss the post-meeting note included in the pre-NDA meeting minutes regarding the onset of action for a parenteral analgesic for acute pain. Agency comments: An IV analgesic drug product should have quick effective pain relief. The measure of time to onset for an acute pain indication is important and meaningful to evaluate a patient's pain relief and efficacy of the product. Similar endpoints are necessary for acute pain drug products regardless of drug substance and route.
NDA 213231 submitted to FDA December 2019			

Abbreviations: FDA, Food and Drug Administration; IND, investigational new drug application; IV, intravenous; NDA, new drug application; SPID24, time-weighted summed pain intensity difference from baseline over 24 hours; SPID48, time-weighted summed pain intensity difference from baseline over 48 hours

3. Summary of Issues for the AC

3.1 Efficacy Issues

The Division reviewed the efficacy data in support of tramadol IV and concluded that tramadol IV was statistically significantly superior to placebo for the acute pain indication. Although the Division had no concerns with tramadol IV's treatment effect, tramadol IV's delayed time to onset is an aspect of its efficacy profile that has safety implications for treatment of moderate to severe acute pain.

Key Efficacy Findings

The efficacy of tramadol IV was evaluated in two placebo-controlled Phase 3 studies in post-surgical adult patients with acute pain. One study was conducted in patients following bunionectomy (Study 102) and the other study was conducted in patients following abdominoplasty (Study 103). The studies were adequate and well-controlled and provided evidence of the efficacy of tramadol IV 50 mg based on the prespecified primary endpoint of time-weighted summed pain intensity difference from baseline over 48 hours (SPID48) for Study 102 and time-weighted summed pain intensity difference from baseline over 24 hours (SPID24) for Study 103. Study 103 also demonstrated the efficacy of tramadol IV 50 mg based on its prespecified secondary endpoints of SPID48, total rescue medication consumption, and patient global assessment at 24 hours (PGA24).

However, analyses of PID at early time points (Hours 0-2) for Study 103 and of time to meaningful pain relief for both Studies 102 and 103, using the two-stopwatch method, demonstrated that tramadol IV has a delayed onset of analgesia, likely beyond two hours. These findings are consistent with the known metabolism of tramadol. Specifically, IV administration of tramadol bypasses first pass hepatic metabolism resulting in delayed formation of the active metabolite, M1. Delayed formation of M1 appears to contribute to a delayed analgesic effect for tramadol IV.

3.1.1 Sources of Data for Efficacy

Pharmacokinetic Studies

Avenue Therapeutics, Inc. submitted data from two pharmacokinetic studies, RVG-10-018 and AVE-901-101, in support of the 505(b)(2) NDA. The studies included tramadol and metabolite M1 exposure information for the Applicant's tramadol IV injection and Ultram® tablet, the listed drug. Study AVE-901-101 provided pharmacokinetic information using the label-proposed tramadol IV dosing regimen of 50 mg administered at Hours 0, 2, 4, and every 4 hours thereafter. Study RVG-10-018 utilized a 6-hour dosing regimen for both tramadol IV and Ultram® tablet.

Study RVG-10-018

RVG-10-018 was a Phase 1, open-label, parallel treatment, randomized, steady-state study conducted to compare the bioavailability of tramadol hydrochloride IV 50 mg and 100 mg versus tramadol oral 50 mg and 100 mg administered every 6 hours in healthy subjects. The primary objective of this study was to establish the comparative bioavailability of tramadol IV at steady-state relative to tramadol oral administration. The every 6 hour dosing regimen for tramadol IV used in this study was not the same as the Applicant's proposed dosing regimen for tramadol IV in the NDA, which is tramadol 50 mg IV at Hour 0, Hour 2, Hour 4, then every 4 hours thereafter. For the reference oral tramadol product

(Ultram®), the highest approved dosage is 100 mg. The clinical pharmacology review team focused on the pharmacokinetic comparison between tramadol IV 50 mg and tramadol oral 100 mg.

Pharmacokinetic data were obtained from predose sampling (samples were obtained within 15 minutes prior to study drug administration for each of the 9 doses). The mean predose tramadol and M1 plasma concentration-time profiles demonstrated that steady state was reached by Dose 9. The mean pharmacokinetic parameters for tramadol and M1 after Dose 9 demonstrated the following:

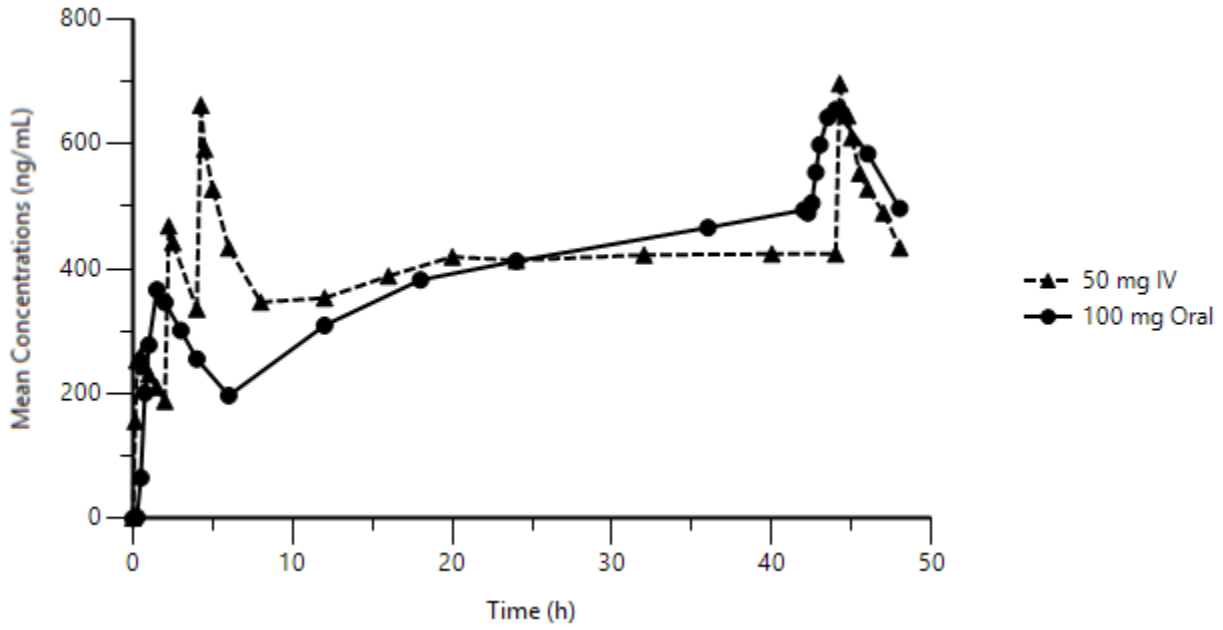
- At steady state (Dose 9), tramadol mean maximum plasma concentration (C_{max}) and area under the concentration-time curve $(AUC)_{6hr}$ (dosing interval comparison at steady state) values following tramadol IV 50 mg administration were less than tramadol mean C_{max} and AUC_{6hr} values following tramadol oral 100 mg administration.
- At steady state, M1 mean C_{max} and AUC_{6hr} (dosing interval comparison at steady state) values following tramadol IV 50 mg administration were less than M1 mean C_{max} and AUC_{6hr} values following tramadol oral 100 mg administration.
- At steady state, the mean metabolite-to-parent ratio (calculated using AUC_{6hr} values) for tramadol IV 50 mg administered as a 6-hour regimen was approximately 20.1 to 20.9% and the mean metabolite-to-parent ratio for tramadol oral 100 mg administered as a 6-hour regimen was approximately 23.2 to 32.8%.

Study AVE-901-101

AVE-901-101 was a Phase 1, open-label, three-period, three-treatment, multiple-dose crossover study conducted to evaluate the pharmacokinetics of tramadol IV 50 mg and 75 mg (IV infusion over approximately 15 minutes) versus tramadol oral 100 mg (administered as two 50 mg Ultram® tablets) dosing regimens in healthy subjects over 48 hours of treatment. The primary objective of this study was to evaluate the PK properties of the proposed tramadol IV regimen and tramadol oral administration during 48 hours of treatment. Tramadol IV 50 mg was administered at Hour 0, Hour 2, Hour 4, and every 4 hours thereafter as per the label-proposed tramadol IV dosing regimen. However, tramadol IV 75 mg was not administered using the label-proposed tramadol IV dosing regimen. Tramadol IV 75 mg was administered at Hour 0, Hour 3, Hour 6, and every 6 hours thereafter. Tramadol oral 100 mg was administered every 6 hours.

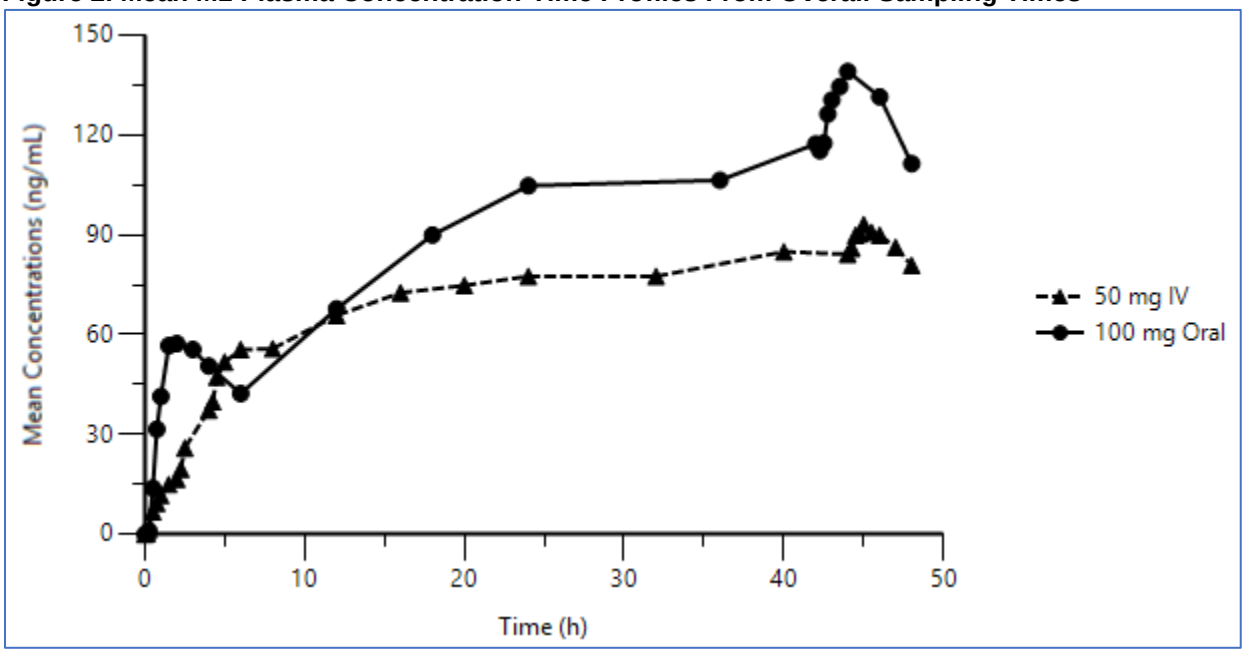
The mean tramadol and M1 plasma concentration-time profiles over the 48 hours of treatment are presented in the figures below (Figure 1 and Figure 2, respectively). The mean M1 plasma concentration-time profile (Figure 2) showed lower mean M1 plasma concentrations in the first three hours for tramadol IV 50 mg and 75 mg as compared to tramadol oral 100 mg. Mean M1 plasma concentrations for tramadol IV 50 mg and 75 mg are comparable to tramadol oral 100 mg by approximately Hour 6.

Figure 1. Mean Tramadol Plasma Concentration-Time Profiles From Overall Sampling Times



Source: m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ave-901-101\ave-901-101.pdf, p.57/544, adapted, and replotted to show only 50 mg IV and 100 mg oral from Dr. David Lee's review, pg. 13.
Abbreviations: h, hour; IV, intravenous

Figure 2. Mean M1 Plasma Concentration-Time Profiles From Overall Sampling Times



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Abbreviations: h, hour; IV, intravenous; M1, O-desmethyltramadol

The pharmacokinetic parameters of tramadol and M1 are summarized from the single dose and overall dosing regimen in Table 2. The dosing intervals for tramadol IV 50 mg, tramadol IV 75 mg, and tramadol oral 100 mg were different; therefore, the AUC values were compared based on the common dosing interval, e.g., 24 or 48 hours. Based on predose drug concentrations, steady state was achieved by approximately 18 to 24 hours. At steady state, mean tramadol exposures for tramadol IV 50 mg administered every 4 hours and tramadol oral 100 mg administered every 6 hours were comparable (see steady-state concentration values, Css). Mean M1 exposure at 1 hour after administration of the first dose was significantly lower for tramadol IV 50 mg (11.8 ng/mL) than for tramadol oral 100 mg (41.4 ng/mL). At steady state, mean M1 exposures for tramadol IV 50 mg were approximately 20% lower (based on $AUC_{0\text{-}48hr}$) than mean M1 exposures for tramadol oral 100 mg. These pharmacokinetic findings confirm that there is delayed formation of M1 as well as decreased overall M1 exposure with IV administration of tramadol. These pharmacokinetic findings are expected with IV administration of tramadol because first pass hepatic metabolism is bypassed and there is decreased production of M1.

Table 2. Tramadol and M1 Pharmacokinetic Parameters After First Dose and Overall in Study AVE-901-101

	50 mg IV N=14		100 mg PO N=17		50 mg IV N=14		100 mg PO N=17	
	Tramadol				M1			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
After the first dose								
C1h[1]	243	45.2	278	77.0	11.8	4.57	41.4	19.7
Cmax(0-2)[2] (ng/mL)	294	68.5	-	-	17.1	6.46	-	-
Cmax(2-4)[3] (ng/mL)	479	77.7	-	-	37.8	15.5	-	-
Cmax(0-6)[4] (ng/mL)	-	-	377	68.9	-	-	60.3	22.7
Tmax(0-2)[2] (h)	0.54	0.22			1.85	0.19		
Tmax(2-4)[3] (h)	2.36	0.13	-	-	3.95	0.00	-	-
Tmax(0-6)[4] (h)	-	-	1.54	0.33	-	-	2.04	0.87
AUC(0-2)[2,^]	428	124	441	97.3	20.4	9.0	69.9	29.7
AUC(0-4)[3,^]	1207	209	1042	185.4	78.2	33.9	179.4	67.2
AUC(0-6)[4,^]	2249	345	1495	281.8	177.1	71.3	272.3	97.5
AUC(0-8)[5,^]	3028	483	1926	397.2	288.4	110.1	365.4	125.4
AUC(0-12)[6,^]	4427	784	3013	734.6	531.6	186.1	602.5	194.6
Overall								
Tmax[*] (h)	44.25	4.25-44.5	44	43-46	45.01	39.95-47	44	41.95-46
Cmax[7] (ng/mL)	736	152	701	178	96.6	24.5	146	37.4
Css(ng/mL)	557	131	579	150	88.9	22.3	128	34.9
AUC0-24[8] (ng•h/mL)	9520	2106	7491	1936	1425	405.4	1655	476.6
AUC24-48 (ng•h/mL)	11020	2852	11650	3387	2002	514.9	2693	750.0
AUC0-48 (ng•h/mL)	20540	4906	19140	5172	3427	889.9	4349	1139

1 C1h Concentration at 1 hour after administration of the first dose;
2 Cmax and AUC for 0-2h, determined directly from individual concentration-time data for first dose of IV Regimen 2 (single dose);
3 Cmax 2-4h and AUC for 0-4h, determined directly from individual concentration-time data for second dose of IV Regimen 2;
4 Cmax and AUC for 0-6h, determined directly from individual concentration-time data for first dose of Oral Regimen (single dose);
5 Cmax and AUC for 0-8h, determined directly from individual concentration-time data for first dose of Oral Regimen (single dose);
6 Cmax and AUC for 0-12h, determined directly from individual concentration-time data for first dose of Oral Regimen (single dose);
7 Cmax Maximum plasma concentration, over 0-48 h;
8 AUC0-24: AUC values from 0-24 hours post dose
^ Additional calculation provided by the reviewer from the study report
*Median (min-max) over 0-48 h
Source: m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ave-901-101\ ave-901-101.pdf, p.67-68/544.
Source: m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\ave-901-101\ ave-901-101.pdf, p.67-68/544 and adapted from Dr. David Lee's review, pg. 14
Abbreviations: Css, steady state plasma concentration; IV, intravenous; M1, O-desmethyltramadol; N, number of subjects; PO, by mouth; SD, standard deviation

Studies 102 and 103

Avenue Therapeutics, Inc. conducted two clinical studies to evaluate the efficacy of tramadol IV 50 mg for the treatment of acute pain (Table 3). AVE-901-102 will be referred to as Study 102 and AVE-901-103 will be referred to as Study 103.

Table 3. Summary of the Phase 3 Clinical Studies Evaluating the Efficacy of Tramadol IV 50 mg

Study Sites	NCT No.	Surgical Model Duration/Follow Up	Dose/ Number of Patients Regimen	Rescue Medication
AVE-901-102 **5 sites**	03290378	Adults (18-75 y/o) undergoing unilateral primary first metatarsal bunionectomy 48 hours/14 (± 2) days	Tramadol IV 25 mg /139 Tramadol IV 50 mg /134 Placebo/136 Hour 0, 2, 4, then every 4 hours	Ibuprofen 400 mg, every 4 hours, maximum 2400 mg/day
AVE-901-103 **3 sites**	03774836	Adults (18-75 y/o) undergoing abdominoplasty 48 hours/14 (± 2) days	Tramadol IV 50 mg /141 Morphine IV 4 mg /93 Placebo/136 Hour 0, 2, 4, then every 4 hours	Ibuprofen 400 mg, every 4 hours, maximum 2400 mg/day

Source: NDA 213231 Primary Combined Review, pp.29-30
Abbreviations: IV, intravenous; NCT, national clinical trial; NDA, new drug application; y/o, years old

Studies 102 and 103 had some similarities. Both were multicenter, randomized, double-blind, three-arm studies designed to compare tramadol 50 mg IV infusion to placebo. Rescue medication was ibuprofen 400 mg every 4 hours (maximum 2400 mg/day) for both studies. SPID24 and SPID48 were planned for comparison in both studies; however, SPID48 was the primary efficacy endpoint in Study 102 and SPID24 was the primary efficacy endpoint in Study 103 (Table 4).

Table 4. Efficacy Endpoints for Studies 102 and 103

Study	AVE-901-102	AVE-901-103
Primary endpoint*	SPID48	SPID24
Secondary* endpoints	SPID24	SPID48
	Total rescue consumption	
	PGA at 24 and 48 hours	
Tertiary Endpoints	Time to perceptible pain relief[#]	
	Time to meaningful pain relief[#]	
	Time specific PID	

Source: CDTL reviewer, Dr. Ning Hu
*Prespecified efficacy endpoints
[#]Two-stopwatch method, where the first stopwatch is stopped by the patient when they feel the first perceptible pain relief, and the second when they feel the onset of meaningful pain relief
Abbreviations: CDTL, Cross-Discipline Team Leader; PGA, patient global assessment; PID, pain intensity difference; SPID24, time-weighted summed pain intensity difference from baseline over 24 hours; SPID48, time-weighted summed pain intensity difference from baseline over 48 hours

Study 102 was conducted before Study 103. Study 102 was a dose-finding study and included a lower dose of tramadol (25 mg). The higher dose of tramadol (50 mg) was selected for further evaluation in Study 103. Study 103 included a morphine IV 4 mg arm, in addition to tramadol IV 50 mg. The inclusion of a morphine IV arm allowed for descriptive comparison of tramadol IV's efficacy and safety profile to current standard treatment for acute pain. Based on the statistical analysis plan for each study, there were no planned comparisons between the two tramadol doses in Study 102 or between the morphine 4 mg arm and the tramadol 50 mg arm in Study 103.

Evaluation of Efficacy

Eligible subjects were adults, ages 18 to 75 years, scheduled for the protocol-specific surgical procedure. Presurgical screening determined enrollment eligibility. Randomization was done before surgery after all eligibility criteria were met. Following surgery, subjects were screened for minimum pain scores prior to

receiving study treatment. Eligible subjects had study drug administered via 15-minute IV infusion at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.

The full analysis set (FAS) was defined as all randomized patients who received at least one dose of study medication. Subjects were analyzed according to the treatment group to which they were randomized. Between 3% and 6% of randomized subjects did not receive study medication because they did not reach the minimum postsurgical pain score required for dosing.

The FAS dataset was designated as the primary analysis population for efficacy endpoints. Pain intensity was recorded on an 11-point, 0 to 10, numeric pain rating scale (NPRS) at baseline (time 0; prior to first dose) then at 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, and every 2 through 48 hours after first dose. Pain intensity was also recorded prior to any use of rescue medication.

The primary efficacy endpoint was the Summed Pain Intensity Difference (SPID) calculated as the weighted average of the difference in pain intensity score at each timepoint, weighted by the length of the time interval. Negative SPID scores indicated a subject's pain decreased over time, with lower SPID values indicating greater reduction in pain intensity.

Pain assessments were adjusted for use of rescue. The NPRS score obtained before rescue medication was used to replace the NPRS score obtained within 4 hours after rescue medication. All other missing NPRS were imputed using multiple imputation method with a pattern mixture approach.

Patient global assessment (PGA) was recorded at 24 and 48 hours after first dose of study drug using a 5-point Likert scale assessed as: 0=poor; 1=fair; 2=good; 3=very good; or 4=excellent.

Total consumption of rescue medication was calculated as the total amount of rescue analgesia (mg) given to the subject between first dose of study drug through 48 hours post first dose (4 hours after the start of the last dose of study drug).

Time-specific pain intensity difference, time to perceptible pain relief, and time to meaningful pain relief were planned as tertiary endpoints. Time to perceptible and meaningful pain relief were calculated using the two-stopwatch method. The two-stopwatch method entailed starting two stopwatches at the start of the first dose of study drug. Subjects were then instructed to stop the first stopwatch when pain relief was first perceptible and the second stopwatch when pain relief was considered meaningful.

Study 102: Efficacy Results

Study 102 demonstrated that tramadol IV 50 mg was statistically significantly superior to placebo, but tramadol IV 25 mg was not, for the prespecified primary endpoint of SPID48. According to the statistical analysis plan, all testing of the key secondary endpoints should have stopped because of the non-significant test result for the primary efficacy analysis in the tramadol IV 25 mg arm. As such, key secondary endpoints summarized in the table below (Table 5) should be interpreted with caution.

Table 5. Efficacy Analysis Results for Study 102 Bunionectomy

All Treated (FAS)		Tramadol 25 mg N=134	Tramadol 50 mg N=139	Placebo N=136
Primary: SPID48	LS Mean (SE)	-111 (6.5)	-123 (6.3)	-98 (6.5)
	Diff vs. placebo	-13	-25	
	(95% CI)	(-31, 5)	(-42, -8)	
	p-value	0.145	0.005	
Secondary: SPID24	LS Mean (SE)	-34 (3.3)	-44 (3.2)	-26 (3.3)
	Diff vs. placebo	-8	-18	
	(95% CI)	(-17, 1)	(-27, -9)	
	p-value	NA	<0.001	
Secondary: Total Rescue Medication Consumption 48 hrs (mg)	Mean (SD)	1337 (1112)	1027 (952)	1371 (960)
	Wilcoxon Rank Sum Mean	213	180	223
	Diff vs. placebo	-6	-30	
	p-value	NA	0.002	
Secondary: Patient Global Assessment at 24 Hours	LS Mean (SE)	1.9 (0.1)	2.3 (01)	1.5 (0.1)
	Diff vs. placebo	0.4	0.8	
	(95% CI)	(0.2, 0.7)	(0.5, 1.1)	
	p-value	NA	<0.001	
Secondary: Patient Global Assessment at 48 Hours	LS Mean (SE)	2.3 (0.1)	2.6 (0.1)	1.8 (0.1)
	Diff vs. placebo	0.5	0.8	
	(95% CI)	(0.2, 0.8)	(0.5, 1.1)	
	p-value	NA	<0.001	
Tertiary: Time to Perceptible Pain Relief (mins)	Had event (%)	57 (43%)	70 (50%)	46 (34%)
	Censored (%)	77 (57%)	69 (50%)	90 (66%)
	Median (95% CI)	-- (181, --)	167 (16, --)	-- (--, --)
	p-value vs. placebo	NA	0.009	
Tertiary: Time to Meaningful Pain Relief (mins)	Had event (%)	57 (43%)	70 (50%)	46 (34%)
	Censored (%)	77 (57%)	69 (50%)	90 (66%)
	Median (95% CI)	-- (238, --)	321 (84, --)	-- (--, --)
	p-value vs. placebo	NA	0.009	

Source:CSR Tables 15-18 and 22

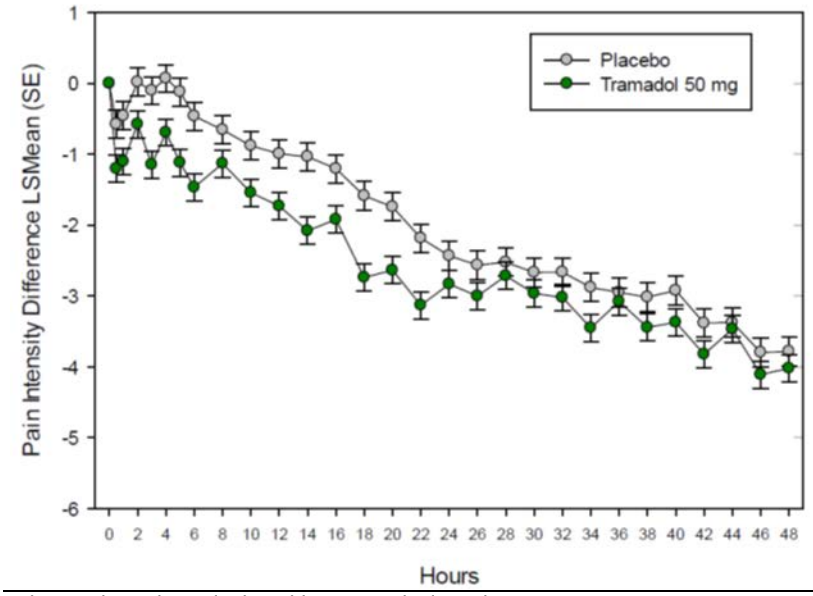
Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; N, number of subjects; SD, standard deviation; SE, standard error; SPID24, time-weighted summed pain intensity difference from baseline over 24 hours; SPID48, time-weighted summed pain intensity difference from baseline over 48 hours

Study 102: Additional Efficacy Analyses

The clinical and statistical review teams conducted further analyses to evaluate tramadol IV 50 mg's onset of analgesia and sustainability of analgesic efficacy in Study 102. These analyses were performed to better understand the complete efficacy profile of tramadol IV 50 mg in the acute pain setting.

Time-specific PID curves showed statistically significant separation of the tramadol IV 50 mg and placebo arms from 30 minutes through 23 hours after first dose of study drug. At 24 hours and beyond, however, the curves merged and appeared to suggest that there was no apparent meaningful difference between tramadol IV 50 mg and placebo (Figure 3).

Figure 3. Least Square Mean (Standard Error) Pain Intensity Differences by Timepoint for Tramadol IV 50 mg and Placebo in Study 102 Bunionectomy

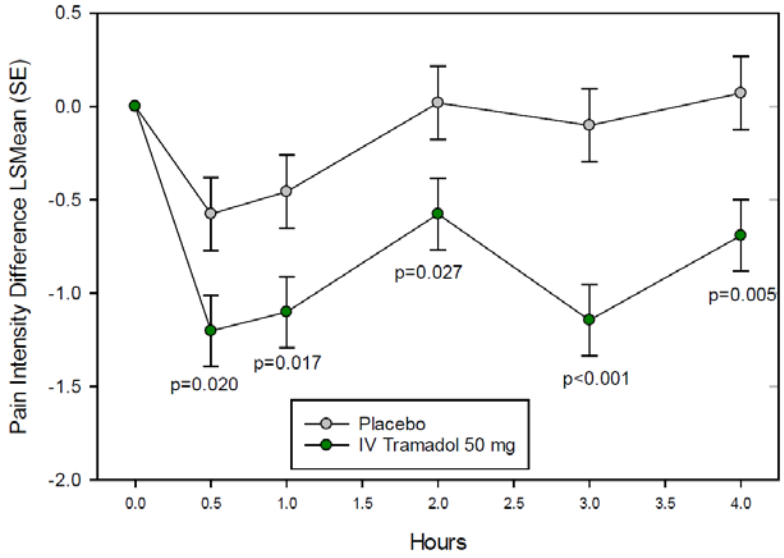


Time (hour)	LS Mean PID (Tramadol 50 mg)	p-value[1]
22	-0.9	<.001
24	-0.4	0.145
26	-0.4	0.113
28	-0.2	0.484
30	-0.3	0.281
32	-0.4	0.194
34	-0.6	0.037
36	-0.1	0.638
38	-0.4	0.12
40	-0.4	0.103
42	-0.4	0.109
44	-0.1	0.74
46	-0.3	0.258
48	-0.2	0.387

1The p-values shown in the table are nominal p-values.
Source: CDTL reviewer, Dr. Ning Hu; Left side figure: adapted from submission SCE page 50; right side table: Clinical reviewer, Dr. Lisa Wiltrout
Abbreviations: CDTL, Cross-Discipline Team Leader; LS, least squares; PID, pain intensity difference; SE, standard error

Figure 4 below focuses on the time-specific PID curves at early time points, Hours 0 through 4 after first dose of study drug. Again, the time-specific PID curves had a statistically significant separation starting at 30 minutes after first dose of study drug.

Figure 4. Least Square Mean (Standard Error) Pain Intensity Differences at Early Timepoints for Tramadol IV 50 mg and Placebo in Study 102 Bunionectomy



Source: Summary of Clinical Efficacy, Figure 12, p. 116/151.
Abbreviations: IV, intravenous; LS, least squares; SE, standard error

The clinical and statistical review teams closely reviewed the data generated from the two-stopwatch method to better understand subjects' perception of analgesia in Study 102. Approximately 50% of patients (60/139) administered tramadol IV 50 mg did not report meaningful pain relief in 6 hours; therefore, their outcomes were censored. The reported median time to meaningful pain relief value of 321 minutes was difficult to interpret because of the high amount of censored measures (Table 6).

Table 6. Time to Onset of Pain Relief in Study 102 Bunionectomy

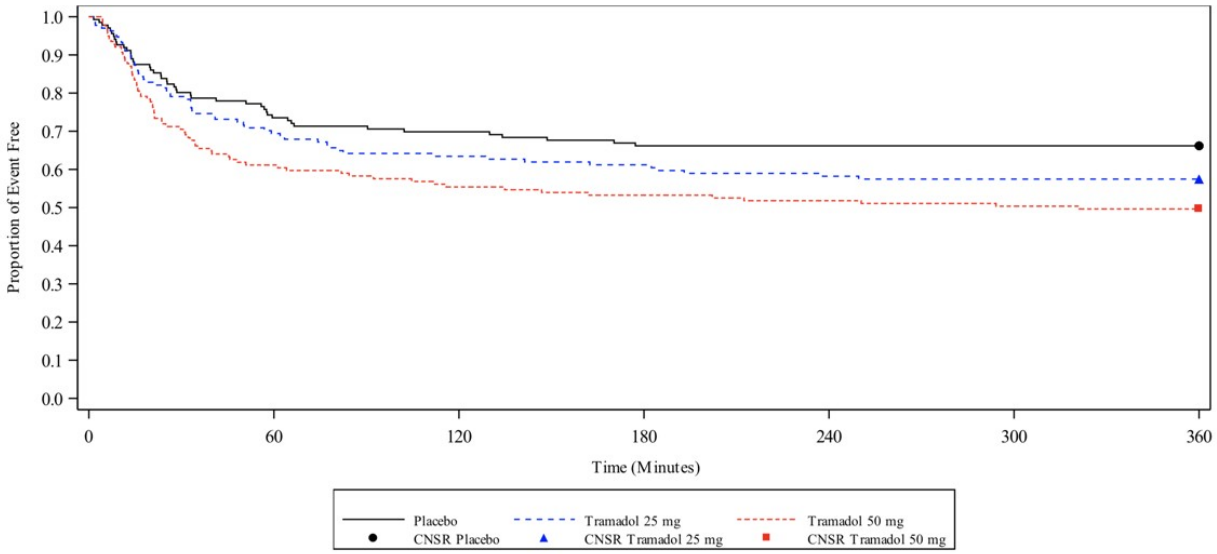
Parameters	Placebo (N=136)	Tramadol 25 mg (N=134)	Tramadol 50 mg (N=139)
Number (%) of subjects with meaningful pain relief	46 (34)	57 (43)	70 (50)
Number (%) of subjects censored	90 (66)	77 (57)	69 (50)
Time (minutes) to meaningful pain relief			
Median (95% CI)	NE (-, -)	NE (237.9, -)	321 (84.4, -)
p-value vs. placebo		0.228	0.009

Source: Adapted from submission SCE Table 36 on page 113.
Abbreviations: CI, confidence interval; N, number of subjects; NE, not estimated

The Applicant's explanation for the high amount of censoring was that subjects may have been asleep or inattentive to using the stopwatches rather than experiencing pain. The statistical review team conducted an exploratory analysis in which subjects were divided into subgroups according to whether the time to pain relief outcome was censored. Pain intensity scores and rescue medication use were evaluated by subgroup. In this exploratory analysis, it was found that subjects who were censored were more likely to use rescue medication and had higher (worse) pain scores than subjects who recorded meaningful pain relief using the two stopwatches. The descriptive statistics seemed to suggest that the incidence of censoring might be related to inadequate pain relief. The high rate of censoring might be related to lack of treatment efficacy. See the Statistical Review and Evaluation of Dr. Katherine Meaker (pp. 13-14) for details of this analysis.

The data in the Kaplan-Meier plot below (Figure 5) demonstrated that almost 60% of subjects had not achieved meaningful pain relief (did not stop the second stopwatch) at 60 minutes after start of study drug. This value remained at approximately 50% through at least 6 hours after start of study drug. On the other hand, the data also demonstrated that approximately 40% of subjects (54/139) experienced onset of analgesia within 60 minutes of tramadol IV initiation.

Figure 5. Kaplan-Meier Plot of Time to First Meaningful Pain Relief (FAS Population) in Study 102



Source: CSR Study 102, Figure 14.2.11.b, page 72/810
Notes: Time to pain relief was measured using the two-stopwatch approach. Time to pain relief was calculated as minutes from first dose or censored at discontinuation or at 6 hours, whichever was earlier.
Abbreviation: CNSR, censored; FAS, Full Analysis Set

Study 103: Efficacy Results

Study 103 demonstrated that tramadol IV 50 mg was statistically significantly superior to placebo for the prespecified primary endpoint of SPID24. According to the statistical analysis plan, the hierarchical testing for the secondary efficacy endpoints was planned as follows: PGA24; SPID48; total rescue consumption through 24 hours. Study 103 also demonstrated that tramadol IV 50 mg was statistically significantly superior to placebo for the prespecified secondary endpoints of PGA24, SPID48, and total rescue medication consumption through 24 hours (Table 7).

Table 7. Efficacy Analysis Results for Study 103 Abdominoplasty

All Treated (FAS)		Tramadol 50 mg N=141	Placebo N=136	Morphine 4 mg N=93
Primary: SPID24	LS Mean (SE)	-79 (3.4)	-48 (3.9)	-82 (4.5)
	Diff vs. placebo	-31		
	(95% CI)	(-41, -22)		
	p-value	<0.001		
Secondary: SPID48	LS Mean (SE)	-181 (8.2)	-121 (8.2)	-179 (9.6)
	Diff vs. placebo	-60		
	(95% CI)	(-79, -40)		
	p-value	<0.001		
Secondary: Total Rescue Medication Consumption 24 hrs (mg)	Mean (SD)	312 (409)	659 (571)	189 (261)
	Wilcoxon Rank Sum Mean	167	235	141
	Diff vs. placebo	-51		
	p-value	<0.001		
Secondary: Patient Global Assessment at 24 Hours	LS Mean (SE)	3.0 (0.1)	2.2 (01)	3.1 (0.1)
	Diff vs. placebo	0.9		
	(95% CI)	(0.6, 1.1)		
	p-value	<0.001		
Tertiary: Time to Perceptible Pain Relief (mins)	Had event (%)	92 (65%)	75 (55%)	69 (74%)
	Censored (%)	49 (35%)	61 (45%)	24 (26%)
	Median (95% CI)	27 (14, 73)	69 (29, --)	5 (4, 7)
	p-value vs. placebo	0.21	0.009	
Tertiary: Time to Meaningful Pain Relief (mins)	Had event (%)	93 (66%)	77 (57%)	69 (74%)
	Censored (%)	48 (34%)	59 (43%)	24 (26%)
	Median (95% CI)	106 (54, 153)	145 (67, --)	42 (17, 96)
	p-value vs. placebo	0.28		

Source: CSR Tables 17-20 and 22

Abbreviations: CI, confidence interval; LS, least squares; FAS, full analysis set: N, number of subjects; SD, standard deviation; SE, standard error; SPID24, time-weighted summed pain intensity difference from baseline over 24 hours; SPID48, time-weighted summed pain intensity difference from baseline over 48 hours

Study 103 included a morphine 4 mg IV treatment arm. Morphine IV is widely used to manage moderate to severe postoperative pain. In clinical practice, morphine IV is typically administered as needed every 2 to 4 hours and titrated to effect.

The prescribing information for morphine sulfate injection states the following in the Dosage and Administration and Clinical Pharmacology sections:

> 2.2 Initial Dosage
>
> Direct Intravenous Injection
>
> The usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed to manage pain. Administer the injection slowly.
>
> Intramuscular Injection
>
> The initial IM dose is 10 mg every 4 hours as needed to manage pain (based on a 70 kg adult).
>
> 2.3 Titration and Maintenance of Therapy

Individually titrate Morphine Sulfate Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Morphine Sulfate Injection to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addition, abuse, or misuse *[see Warnings and Precautions (5.1)]*.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

12.2 Pharmacodynamics

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance. *[see Dosage and Administration (2.1, 2.3)]*

Onset of analgesia occurs within 5-20 minutes following intramuscular administration of morphine, rising to peak analgesia sixty minutes after a single intramuscular injection. The duration of analgesia after a single injection is usually three to four hours.

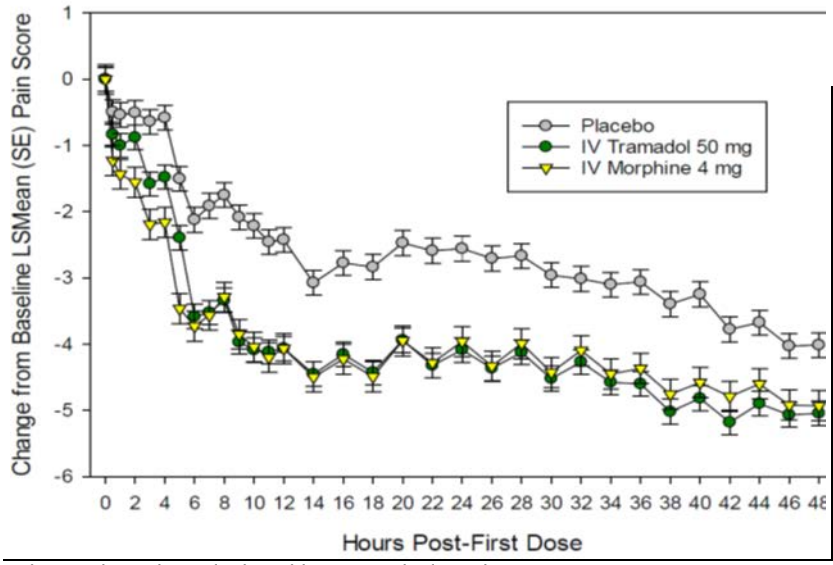
The proposed dosing schedule for tramadol IV as studied in Study 103 was a fixed dosing schedule that did not allow for titration. Therefore, morphine 4 mg IV push was administered at Hour 0, Hour 2, and Hour 4, then every 4 hours using the same fixed dosing schedule as tramadol IV. Morphine IV is considered a reasonable comparator to tramadol IV and a standard treatment in the postoperative setting.

Study 103: Additional Efficacy Analyses

The clinical and statistical review teams conducted further analyses to evaluate tramadol IV 50 mg's onset of analgesia and sustainability of analgesic efficacy in Study 103. These analyses were performed to better understand the complete efficacy profile of tramadol IV 50 mg in the acute pain setting.

Time-specific PID curves showed statistically significant separation of the tramadol IV 50 mg and placebo arms from 3 hours through 48 hours after first dose of study drug. From Hours 0 to 3, however, the time-specific PID curves did not demonstrate a clear separation between tramadol IV 50 mg and placebo (Figure 6). Although comparisons between tramadol IV 50 mg and morphine IV 4 mg were not planned in Study 103, the Least Square Mean PID of tramadol IV was 50% lower than the Least Square Mean PID of morphine IV during the first 2 hours after study drug start.

Figure 6. Least Square Mean (Standard Error) Pain Intensity Differences by Timepoint for Tramadol IV 50 mg and Placebo in Study 103 Abdominoplasty

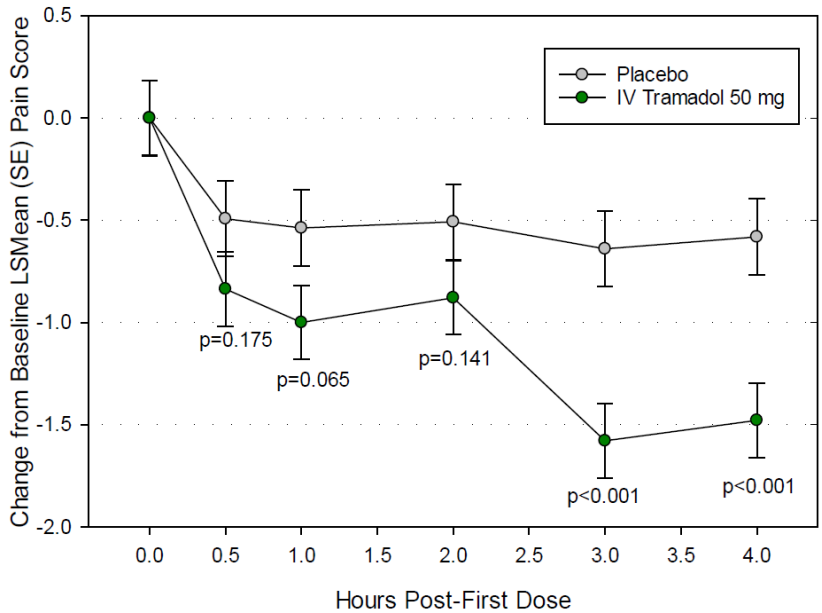


Time	LS Mean PID (p-value[1]) (Tramadol 50 mg)	LS Mean PID (p-value[1]) (Morphine 4 mg)
0.5	-0.3 (0.175)	-0.6 (0.021)
1	-0.4 (0.065)	-0.8 (0.004)
2	-0.4 (0.141)	-0.9 (<.001)
3	-0.9 (<.001)	-1.4 (<.001)
4	-0.9 (<.001)	-1.5 (<.001)

1The p-values shown in the table are nominal p-values.
Source: CDTL reviewer, Dr. Ning Hu; Left side figure: adapted from SCE, p.50; right side table: Clinical reviewer, Dr. Lisa Wiltrout
Abbreviations: CDTL, Cross-Discipline Team Leader; IV, intravenous; LS, least squares; PID, pain intensity difference; SE, standard error

Figure 7 below focuses on the time-specific PID curves at early time points, Hours 0 through 4 after first dose of study drug. The time-specific PID curves did not have a clear separation until 3 hours after first dose of study drug.

Figure 7. Least Square Mean (Standard Error) Pain Intensity Differences at Early Timepoints for Tramadol IV 50 mg and Placebo in Study 103 Abdominoplasty



Source: Applicant's Response to Clinical Information Request dated June 4, 2020, Figure 1, p.2/3
Abbreviations: IV, intravenous; LS, least squares; SE, standard error

The clinical and statistical review teams further evaluated whether tramadol IV provided adequate analgesia over the dose interval by analyzing the number of patients who used first rescue medication within two hours of initiating study drug. As shown in the table below (Table 8), more patients in the tramadol IV 50 mg arm (42.6%) than in the morphine IV 4 mg arm (28%) used first rescue medication within two hours of initiating study drug. The clinical review team concluded that this difference in use of rescue medication between the tramadol and morphine arms within the first two hours after initiating study drug may be related to tramadol IV's delayed onset of analgesia.

Table 8. Number (%) of Patients With First Rescue Medication Use Within Two Hours of Initiating the First Dose in Study 103 Abdominoplasty

Planned Treatment	Within 30 minutes	Within 1 hour	Within 2 hours
Morphine IV 4 mg	5(5.4%)	16(17.2%)	26(28.0%)
Placebo	15(11.0%)	36(26.5%)	69(50.7%)
Tramadol IV 50 mg	10(7.1%)	25(17.7%)	60(42.6%)

Source: Statistical team, Dr. Jinglin Zhong
Abbreviations: IV, intravenous

The clinical and statistical review teams closely reviewed the data generated from the two-stopwatch method to better understand subjects' perception of analgesia in Study 103. Approximately 34% of subjects (48/141) did not report meaningful pain relief in 6 hours; therefore, their outcomes were censored. The median time to meaningful pain relief was 106 minutes for tramadol IV 50 mg compared to 42 minutes for morphine IV 4 mg (Table 9).

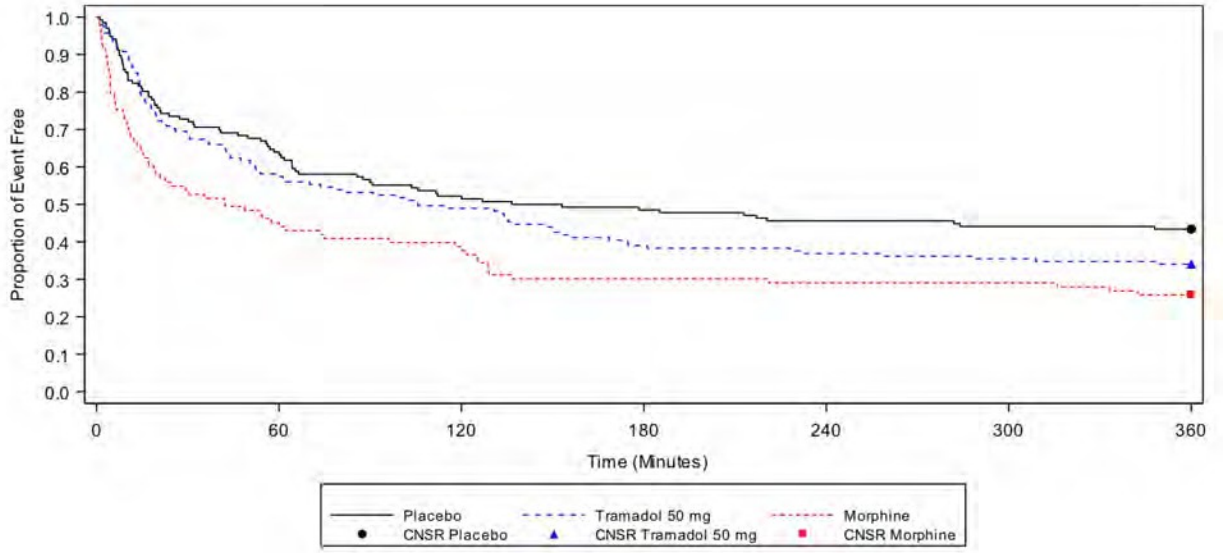
Table 9. Time to Onset of Pain Relief in Study 103 Abdominoplasty

Parameters	Placebo (N=136)	Tramadol 50 mg (N=141)	Morphine 4 mg (N=93)
Number (%) of subjects with meaningful pain relief	77 (57)	93 (68)	69 (74)
Number (%) of subjects censored	59 (43)	48 (34)	24 (26)
Time (minutes) to meaningful pain relief			
Median (95% CI)	145 (66.5, -)	106 (53.9, 152.9)	42 (17.2, 96.2)
p-value vs. placebo		0.287	0.003

Source: Adapted from submission SCE table 37 on page 50
Abbreviations: CI, confidence interval; N, number of subjects

The data in the Kaplan-Meier plot below (Figure 8) demonstrated a separation between the tramadol IV 50 mg arm and the morphine IV 4 mg arm over the first 60 minutes after study drug start. At 60 minutes, approximately 60% of subjects in the tramadol IV 50 mg arm had not experienced meaningful pain relief compared to approximately 45% of subjects in the morphine IV 4 mg arm. On the other hand, the data also demonstrated that approximately 40% of subjects experienced onset of analgesia within 60 minutes of tramadol IV initiation.

Figure 8. Kaplan-Meier Plot of Time to First Meaningful Pain Relief (FAS Population) in Study 103



Source: CSR Study 103, Figure 14.2.5.b, page 77/1050.
Notes: Time to pain relief was measured using the two-stopwatch approach. Time to pain relief was calculated as minutes from first dose or censored at discontinuation or at 6 hours, whichever was earlier.
Abbreviations: CNSR, censored; FAS, Full Analysis Set

3.1.2 Efficacy Summary

The Applicant conducted two adequate and well-controlled Phase 3 studies in support of the proposed acute pain indication. The first was a placebo-controlled, dose-finding study in a bunionectomy pain model. The second was a placebo-controlled study in an abdominoplasty pain model with morphine 4 mg IV push used as the active comparator. The only allowed rescue medication was oral ibuprofen 400 mg every 4 hours as needed for pain. The two clinical studies demonstrated statistically significant differences between tramadol IV 50 mg and placebo based on the prespecified primary endpoint for Study 102 and primary and secondary endpoints for Study 103. However, data needed to support a timely onset of action for an analgesic, specifically, PID at early time points and time to meaningful pain relief, demonstrated a delayed onset of analgesia for tramadol IV. Tramadol IV's delayed onset of efficacy may have been expected given that tramadol bypasses first pass metabolism after IV administration, leading to less M1 production at earlier time points and a delayed onset of effect.

A morphine treatment arm was included in Study 103 for comparison of tramadol IV to standard opioid treatment in a postoperative setting. Evidence from multiple endpoints demonstrated that morphine IV 4 mg had quicker onset of analgesia than tramadol IV 50 mg over the first 2 hours of treatment.

3.1.3 Efficacy Issues in Detail

Although there are no concerns with tramadol IV's treatment effect as demonstrated in Studies 102 and 103, tramadol IV's delayed onset of analgesia is an aspect of the product's efficacy profile that has safety implications.

3.2 Safety Issues

- **Opioid Stacking:** Tramadol IV's delayed onset of analgesia, combined with its inability to be titrated to effect leads to a theoretical, yet reasonable and serious safety concern of additive opioid-related AEs. Patients whose pain is not adequately controlled with the first dose of

tramadol IV will likely receive another immediate-release opioid as rescue analgesia. The use of multiple opioids in succession is also known as opioid stacking. Opioid stacking will increase the potential for opioid-related AEs, such as respiratory depression and sedation.

- **Abuse Liability Considerations:** The Applicant has claimed that there is a safety advantage for tramadol IV, controlled in Schedule IV under the CSA, versus other currently used parenteral opioid analgesics, controlled in Schedule II (e.g., morphine).

3.2.1 Sources of Data for Safety

The Applicant's submission included safety data from six completed clinical studies: three Phase 1 studies, two controlled Phase 3 studies, and one Phase 3 open-label study (Table 10). Safety data from each of the Phase 1 studies were analyzed separately. Safety data from the Phase 3 controlled studies (Studies 102 and 103) was pooled. Safety data from the Phase 3 uncontrolled study (Study 104) was also analyzed separately.

Table 10. Listing of Clinical Trials Relevant to NDA 213231 Tramadol IV

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
AVE-901-102 (Study 102)	03290378	Phase 3, MC, R, DB, 3-arm treatment	IV infusion given at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44: IV tramadol 50 mg IV tramadol 25 mg IV PBO	Primary: SPID48 (at rest) Secondary: SPID24 (at rest) Total consumption of rescue PGA at 24 and 48 hours Additional: Time-specific pain intensity profile over time; Time to perceptible and meaningful pain relief after first dose	48 hours/ 14 (± 2) days	Randomized: 434 (total) Treated: 139 (T 50) 134 (T 25) 136 (PBO)	Adults undergoing unilateral primary first metatarsal bunionectomy surgery	5 study centers in U.S.
AVE-901-103 (Study 103)	03774836	Phase 3, MC, R, DB, 3-arm treatment	IV infusion given at Hours 0, 2, 4, 8, 12, 16, 20, 24, 24, 28, 32, 36, 40, and 44: IV tramadol 50 mg IV PBO IV morphine 4 mg	Primary: SPID24 (at rest) Secondary: PGA at 24 hours SPID48 (at rest) Total consumption of rescue through 24 hours post dosing Tertiary: Time-specific pain intensity profile over time Time to perceptible and meaningful pain relief Safety: Respiratory impairment and GI events with tramadol IV vs. morphine IV	48 hours/ 7 (± 2) days	Randomized: 380 (total) Treated: 141 (T 50) 136 (PBO) 93 (Morphine)	Adults undergoing abdominal surgery	3 study centers in U.S.

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
AVE-901-104 (Study 104)	03395808	Phase 3, MC, OL, single-arm treatment	IV tramadol 50 mg infusion given at Hours 0, 2, 4, and every 4 hours for up to 168 hours (last dose allowed at Hour 164)	Safety: VSs, PEs, AEs, laboratory tests, ECG changes, local tolerability at infusion site Efficacy: PGA at 24 hours and end of treatment	Up to 7 days/ 14 (± 2) days	Treated: 251	Adults undergoing elective surgery and appropriate to receive IV tramadol	2 study centers in U.S.
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
RVG-12-001	N/A	R, DB, single-dose, positive- and PC, 3-way crossover (QT study)	Tramadol: 1 x 200 mg IV PBO: 1 x 200 mg IV Moxifloxacin: 1 x 400 mg tablet po concurrent with PBO IV	PK profile of tramadol and o-desmethyltramadol after each treatment Safety: VSs, PEs, ECGs, EEGs, AEs, laboratory, tests, and continuous Holter monitoring	3 single-dose treatments with 7-day washout between doses	60	Healthy adult subjects	1 study center in U.S.
RVG-10-018	N/A	OL, multidose, R, parallel treatment	Treatment groups q6 hours for total of 9 doses: IV tramadol 50 mg Ultram 50 mg tablet po IV tramadol (2x50 mg) 100 mg Ultram (2x50 mg) 100 mg po	PK profile of tramadol and o-desmethyltramadol after each treatment Safety: VSs, PEs, AEs, and laboratory tests	3 48-hour treatments in a single period	32	Healthy adult subjects	1 study center in U.S.

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
AVE-901-101	N/A	OL, multidose, 3-treatment, 3-period crossover	IV tramadol 75 mg at Hour 0, Hour 3, and Hour 6, then every 6 hours through Hour 42 IV tramadol 50 mg at Hour 0, Hour 2, and Hour 4, then every 4 hours through Hour 44 Oral tramadol 100 mg (50 mg tablets x 2) at Hour 0 and Hour 6, then every 6 hours through Hour 42	PK profile of tramadol and o-desmethyltramadol after each treatment Safety: VSs, PEs, ECGs, AEs, and laboratory tests	3 48-hour treatment periods with 3-day washout between periods	18	Healthy adult subjects	1 study center in U.S.

Source: Clinical Overview/NDA 213231, Table 1, pp. 8-11.
Abbreviations: AE, adverse event; DB, double-blind; ECG, electrocardiogram; EEG, electroencephalography; GI, gastrointestinal; IV, intravenous; MC, multicenter; N/A, not applicable; NCT, national clinical trial; NDA, new drug application; OL, open-label; PBO, placebo; PC, placebo-controlled; PE, physical examination; PGA, patient global assessment; PK, pharmacokinetic; QT, QT interval; R, randomized; SPID24, time-weighted summed pain intensity difference from baseline over 24 hours; SPID48, time-weighted summed pain intensity difference from baseline over 48 hours; T, tramadol; VS, vital signs.

3.2.2 Safety Summary

The Division's safety review of tramadol IV was based primarily on data from the two controlled Phase 3 studies (Studies 102 and 103) and one Phase 3 open-label study (Study 104) in patients with postoperative pain.

The Applicant's safety database of approximately 500 patients treated with multiple doses of tramadol IV 50 mg for a mean duration of approximately 45 hours was adequate to evaluate the safety of tramadol IV 50 mg for the proposed acute pain indication. A total of 1,140 subjects were included in the tramadol IV clinical development program with 110 healthy subjects in the Phase 1 studies and 1,030 patients in the Phase 3 studies. A total of 756 subjects were exposed to at least one dose of tramadol IV during the clinical development program.

In the Phase 1 studies, 90 healthy subjects received at least one dose of tramadol IV, either 50 mg, 75 mg, 100 mg, or 200 mg.

In the Phase 3 program, 666 patients received tramadol IV (25 mg or 50 mg), 271 patients received placebo, and 93 patients received morphine IV. Of the 666 patients who received tramadol IV, 533 patients received tramadol IV 50 mg and 133 patients received tramadol IV 25 mg. In the Phase 3 controlled studies, a total of 282 patients received tramadol 50 mg IV - 140 patients in Study 102 and 142 patients in Study 103. In the Phase 3 uncontrolled study (Study 104), 251 patients received tramadol 50 mg IV (Table 11).

Table 11. Exposure to Tramadol IV in Phase 3 Controlled and Uncontrolled Studies

	Number of Patients Treated by Treatment and Dose Received				Total Patients Treated by Study
Study Number	Placebo	IV Tramadol 25 mg	IV Tramadol 50 mg	Morphine	
AVE-901-102	136	133	140	0	409
AVE-901-103	135	0	142	93	370
AVE-901-104	0	0	251	0	251
Total patients by treatment and dose received	271	133	533	93	1030

Source: ISS/NDA 213231, Table 9, p. 38.
Abbreviations ISS, integrated summary of safety; IV, intravenous; NDA, new drug application

Demographics

There were no significant differences between treatment groups in demographic or baseline characteristics in the controlled studies. In Studies 102 and 103, most patients were under age 65 years and female with a mean age of 42.8 years and a mean body mass index of 27.3 kg/m^2. In Study 104, patients had a mean age of 45.6 years and a mean body mass index of 27.2 kg/m^2. Twenty percent of patients were ≥ 65 years of age with approximately 40% of patients being male and 60% female.

Clinical Safety Assessments

The Applicant's approach to clinical safety (including opioid-related adverse effects), laboratory and electrocardiogram (ECG) assessments was similar to Phase 3 studies in other therapeutic programs for management of acute pain.

Deaths

No deaths occurred in any of the clinical studies during the tramadol IV development program.

Serious Adverse Events

A total of six serious AEs were reported in the clinical studies: one in Study 102, two in Study 103, and two in Study 104. There were no serious AEs reported in the placebo groups. Review of the serious AEs did not raise any new safety concerns about tramadol IV. None of the serious AEs were opioid-complication related.

Adverse Events Leading to Discontinuation

A total of 23 AEs leading to discontinuation were reported in the clinical studies: three in study 102, 20 in Study 103, and 11 in Study 104. Review of the AEs leading to discontinuation yielded no new safety concerns about tramadol IV. In Study 103, the most common treatment-emergent adverse events (TEAEs) leading to discontinuation across all treatment arms were in the gastrointestinal disorders system organ class and the respiratory, thoracic and mediastinal disorders system organ class.

Treatment-Emergent Adverse Events

The overall safety profile of tramadol IV 50 mg was consistent with the safety profile of Ultram and the typical safety profile of other available opioid products. The most common AEs reported in Studies 102 and 103 were nausea, vomiting, dizziness, headache, somnolence, constipation, and hypoxia (Table 12).

Table 12. Incidence of All TEAEs in at Least 2% of Patients in Either Treatment Group by SOC and Preferred Term (Studies 102 and 103 Combined)

MedDRA System organ class Preferred term	Number of patients (%)	
	Placebo (N=271) n (%)	Tramadol 50 mg (N=282) n (%)
Total patients with at least 1 TEAE	137 (50.6)	215 (76.2)
Gastrointestinal Disorders		
Nausea	61 (22.5)	144 (51.1)
Vomiting	14 (5.2)	83 (29.4)
Constipation	6 (2.2)	15 (5.3)
Nervous System Disorders		
Headache	33 (12.2)	34 (12.1)
Dizziness	13 (4.8)	39 (13.8)
Somnolence	5 (1.8)	19 (6.7)
General disorders and administration site conditions		
Infusion site pain	16 (5.9)	12 (4.3)
Respiratory, thoracic and mediastinal disorders		
Hypoxia	1 (0.4)	14 (5.0)
Respiratory disorder	0	9 (3.2)
Oropharyngeal pain	5 (1.8)	6 (2.1)
Skin and subcutaneous tissue disorders		
Pruritus generalized	4 (1.5)	11 (3.9)
TEAE = treatment-emergent adverse event. Reference: ISS Table 14.3.1.1.1		

Source: ISS, Table 41, p. 83

Abbreviations: ISS, integrated summary of safety; MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in group; SOC, system organ class; TEAE, treatment-emergent adverse event

In Studies 102 and 103, the majority of TEAEs were either Grade 1 or Grade 2 (mild or moderate) in severity. In Study 102, four patients in the tramadol IV 50 mg arm had Grade 3 (severe) vomiting and one patient in the tramadol IV 50 mg arm had Grade 3 hypotension. In Study 103, one patient in the tramadol IV 50 mg arm had a Grade 3 post-procedural hematoma. No Grade 4 or 5 TEAEs occurred in either of the two studies.

A dose-dependent increase in AEs was demonstrated in Study 102.

The safety profile of tramadol IV 50 mg was generally comparable to morphine IV 4 mg in Study 103. The incidence of nausea, vomiting, headache, and dizziness was higher in the morphine arm than in the tramadol arm. The incidence of constipation, hypoxia, and respiratory disorder was higher in the tramadol arm than in the morphine arm. The incidence of somnolence, pruritus, and pruritus generalized was comparable between the tramadol and morphine arms (Table 13).

Table 13. Incidence of TEAEs by Preferred Term in Study 103

MedDRA Preferred Term	Placebo (N=135) n (%)	Tramadol 50 mg (N=142) n (%)	Morphine (N=93) n (%)	Total (N=370) n (%)
Nausea	50 (37.0)	99 (69.7)	73 (78.5)	222 (60.0)
Vomiting	9 (6.7)	55 (38.7)	42 (45.2)	106 (28.6)
Headache	20 (14.8)	26 (18.3)	22 (23.7)	68 (18.4)
Dizziness	9 (6.7)	18 (12.7)	17 (18.3)	44 (11.9)
Constipation	3 (2.2)	7 (4.9)	3 (3.2)	13 (3.5)
Hypoxia	0	9 (6.3)	4 (4.3)	13 (3.5)
Respiratory disorder	0	9 (6.3)	4 (4.3)	13 (3.5)
Oropharyngeal pain	5 (3.7)	6 (4.2)	2 (2.2)	13 (3.5)
Pruritus generalized	3 (2.2)	7 (4.9)	3 (3.2)	13 (3.5)
Pruritus	1 (0.7)	4 (2.8)	5 (5.4)	10 (2.7)
Infusion site pain	6 (4.4)	1 (0.7)	1 (1.1)	8 (2.2)
Back pain	3 (2.2)	2 (1.4)	3 (3.2)	8 (2.2)
Somnolence	2 (1.5)	3 (2.1)	2 (2.2)	7 (1.9)
Flatulence	2 (1.5)	3 (2.1)	2 (2.2)	7 (1.9)
Hypotension	2 (1.5)	3 (2.1)	2 (2.2)	7 (1.9)
Tachycardia	2 (1.5)	3 (2.1)	1 (1.1)	6 (1.6)
Dizziness postural	1 (0.7)	2 (1.4)	3 (3.2)	6 (1.6)
Infusion site erythema	1 (0.7)	1 (0.7)	2 (2.2)	4 (1.1)
Abdominal distension	1 (0.7)	1 (0.7)	2 (2.2)	4 (1.1)
Dyspepsia	0	2 (1.4)	2 (2.2)	4 (1.1)
Hot flush	1 (0.7)	3 (2.1)	0	4 (1.1)
Infusion site pruritus	0	0	3 (3.2)	3 (0.8)

Source: CSR/Study AVE-901-103, Table 35, p. 100.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in subgroup; TEAE, treatment-emergent adverse event

In Study 104, the safety profile of tramadol IV 50 mg was similar to the safety profile of tramadol IV in Studies 102 and 103. The most commonly reported AEs were nausea, vomiting, hypoxia, blood creatine phosphokinase increased, constipation, and infusion site pain. Most patients reported TEAEs that were either Grade 1 or Grade 2 in severity. Two patients had Grade 3 post-procedural hematomas and one patient had Grade 3 T-wave inversion documented on the ECG.

Nausea, Vomiting, and Anti-Emetic Usage

A review of the safety data in the Phase 3 program revealed more gastrointestinal events and more anti-emetic usage in the tramadol IV 50 mg arm than in the placebo arm and fewer gastrointestinal events and less anti-emetic usage in the tramadol IV 50 mg arm than in the morphine IV 4 mg arm.

TEAEs Related to Respiratory Impairment

A review of the respiratory-related safety data in the Phase 3 program revealed that tramadol IV 50 mg was associated with more respiratory impairment events than either morphine IV or placebo. The increased incidence of respiratory impairment with tramadol IV administration was of clinical concern because these AEs, if not treated promptly, can lead to brain injury and death. Overall, from a respiratory safety perspective, tramadol IV appeared no better and, with dosing regimens studied, potentially worse than morphine IV.

In Study 102, the Applicant collected safety data on any respiratory-related TEAEs across all three treatment arms but did not pre-specify a safety assessment of TEAEs related to respiratory impairment. The clinical review team analyzed the AE dataset looking for any AEs associated with respiratory impairment. We identified five AEs of hypoxia (defined as oxygen saturation < 92%) in the tramadol IV 50 mg arm; one AE of dyspnea in the tramadol IV 25 mg arm; and one AE of hypoxia and one AE of dyspnea in the placebo arm (Table 14). We did not identify any AEs of bradypnea or sedation. We identified AEs of somnolence, but none occurred in conjunction with an AE of hypoxia; therefore, we concluded that AEs of somnolence did not result in respiratory impairment. Overall, tramadol IV 50 mg had a higher incidence of TEAEs related to respiratory impairment than tramadol IV 25 mg or placebo.

Table 14. Incidence of TEAEs Related to Respiratory Impairment by PT in Study 102 Bunionectomy

Adverse Event by Preferred Term	Placebo N=136 n (%)	Tramadol 25 mg N=133 n (%)	Tramadol 50 mg N=140 n (%)
Hypoxia	1 (0.7)	0	5 (3.6%)
Dyspnea	1 (0.7)	1 (0.8)	0

Source: CSR/Study AVE-901-102, AE Analysis Dataset.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

The clinical review team also analyzed the vital signs dataset for Study 102 looking for oxygen saturation measurements ≤ 92% and respiratory rates < 12 breaths per minute. A review of the vital signs dataset demonstrated that use of tramadol IV 50 mg was associated with more oxygen desaturation events and larger decreases in oxygen saturation measurements than use of tramadol IV 25 mg and placebo.

In Study 103, the Applicant pre-specified a safety assessment of TEAEs related to respiratory impairment in order to allow for a comparison of the respiratory safety and tolerability of tramadol IV and morphine IV. The Applicant prospectively defined respiratory impairment as a clinically relevant worsening in respiratory status based on the safety parameters of respiratory rate, oxygen saturation, and somnolence/sedation. A respiratory impairment event was documented as an AE with the preferred term of respiratory disorder. An AE of hypoxia, defined as an oxygen saturation < 92%, was also considered an AE of respiratory disorder. Any associated events (i.e., bradypnea, sedation, somnolence) that led to the respiratory impairment event were also recorded as AEs. Therefore, multiple AEs were included in the database for patients who had respiratory impairment.

Thirteen patients (3.5%) had at least one respiratory impairment event in Study 103. The incidence of respiratory impairment events was higher in the tramadol IV 50 mg arm (n=9; 6.3%) compared to the morphine IV 4 mg arm (n=4; 4.3%). For the nine patients in the tramadol IV 50 mg arm who experienced respiratory impairment, all had AEs of hypoxia and respiratory disorder, two had AEs of sedation, one had an AE of bradypnea, and four discontinued study participation due to the event. For the four patients in the morphine IV arm who experienced respiratory impairment, all had AEs of hypoxia and respiratory disorder, one had an AE of sedation, and three discontinued study participation due to the event (Table 15). In summary, tramadol IV 50 mg had a higher incidence of respiratory impairment than morphine 4 mg IV.

Table 15. Incidence of Respiratory Impairment Events in Study 103 Abdominoplasty

Respiratory Impairment Events	Placebo N=135 n (%)	Tramadol 50 mg N=142 n (%)	Morphine N=93 n (%)	Total N=370 n (%)
Number of patients with at least one respiratory impairment event	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Hypoxia	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Respiratory disorder	0	9 (6.3%)	4 (4.3%)	13 (3.5%)
Sedation	0	2 (1.4%)	1 (1.1%)	3 (0.8%)
Bradypnea	0	1 (0.7%)	0	1 (0.3%)
Number of patients who discontinued due to a respiratory impairment event	0	4 (2.8%)	3 (3.2%)	7 (1.9%)

Source: ISS/NDA 213231, Table 35
Abbreviations: N, number of subjects; n, number of subjects in subgroup

The clinical review team analyzed the vital signs dataset for Study 103 looking for oxygen saturation measurements ≤ 92% and respiratory rates < 12 breaths per minute. A review of the vital signs dataset demonstrated that use of tramadol IV 50 mg was associated with more oxygen desaturation events and larger decreases in oxygen saturation measurements than morphine IV 4 mg.

In Study 104, AEs of hypoxia were documented. Seventeen patients experienced hypoxia with 16 patients having undergone hernia procedures and one patient having undergone breast augmentation (Table 16). As Study 104 was an open-label, uncontrolled study, conclusions on safety are limited.

Table 16. Incidence of TEAEs by Preferred Term in Study 104

MedDRA Preferred Term	Tramadol 50 mg (N=251) n (%)
Nausea	72 (28.7)
Vomiting	49 (19.5)
Hypoxia	17 (6.8)
Blood creatine phosphokinase increased	16 (6.4)
Constipation	14 (5.6)
Infusion site pain	13 (5.2)
Dizziness	10 (4.0)
Headache	6 (2.4)
Infusion site phlebitis	5 (2.0)

Source: CSR/Study AVE-901-104, Table 19, p. 58.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in subgroup; TEAE, treatment-emergent adverse event

Laboratory Findings

A review of laboratory findings, including hematology, serum chemistry, and urinalysis values, did not reveal any significant laboratory-related AEs in Studies 102 and 103.

A review of laboratory findings in Study 104 revealed 16 TEAEs of increased creatinine kinase reported in 16 patients. Twelve of the 16 patients had undergone total hip replacements, two had undergone total knee replacements, and two had undergone colon surgeries. Review of the demographics for these patients was unremarkable. Only two patients in Studies 102 and 103 had similar findings of increased creatinine kinase at end of study. The clinical review team concluded that the increased incidence of high creatinine kinase in Study 104 was likely related to the surgical procedure and not related to tramadol IV administration.

Vital Signs

A review of the vital signs data collected did not reveal any specific trend that would suggest a new safety concern with tramadol IV. In Study 103, tramadol IV 50 mg was associated with a higher incidence of hypoxia than morphine IV 4 mg.

Electrocardiograms

No clinically relevant trends in the measured ECG parameters were observed in Studies 102 and 103. However, TEAEs related to ECG findings were observed in Study 104. Four patients had six TEAEs related to ECG findings. Three of the four patients had AEs of prolonged QT interval (QT) on ECG. The identified cases of QT prolongation do not raise any new concerns beyond what is currently described in the Postmarketing Experience section of the Ultram prescribing information.

QT

The QT interdisciplinary review team concluded that no significant corrected QT prolongation effect was observed following intravenous administration of tramadol at the doses studied.

Safety Analyses by Time Point

The collective data on TEAEs by time to onset demonstrate that nausea, dizziness, and somnolence tend to occur early (0 to 4 hours) after tramadol IV administration, vomiting tends to occur throughout the first 24 hours after tramadol IV administration, headache tends to occur from 8 through 48 hours after tramadol IV administration, and hypoxia and constipation tend to occur later (> 8 hours to 24 hours and > 24 hours to 48 hours, respectively) after tramadol IV administration.

Safety Analyses by Demographic Subgroups

There were no median age-based differences in the incidence of TEAEs in the Phase 3 program. No conclusions were made about gender-based differences in the incidence of TEAEs because of the discrepancy in sample size between genders in the Phase 3 controlled studies. Additionally, no conclusions were made about race-based and geriatric age-based differences in incidence of TEAEs because of the discrepancy in sample size between the race and geriatric age subgroups in the Phase 3 program.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The potential for overdose, abuse, and withdrawal exists with all opioids. No formal evaluation of the abuse potential of IV tramadol was performed for this submission.

The Applicant identified the following AEs related to potential risk of substance abuse in the clinical development program: dizziness, dizziness postural, somnolence, sedation, euphoria/euphoric mood, dysphoria, and disturbance in attention. The Applicant identified no other AEs related to potential risk of substance abuse, such as feeling drunk, feeling of relaxation, thinking abnormal, hallucination, inappropriate affect, or mood disorders.

For Studies 102 and 103, a review of the safety data on potential risk of substance abuse demonstrated that tramadol IV was associated with more TEAEs related to potential risk of substance abuse than placebo and less TEAEs related to potential risk of substance abuse than morphine IV. Only two AEs of euphoria were reported in six clinical trials. This finding was anticipated because IV administration of tramadol bypasses first-pass hepatic metabolism leading to less M1 production and, subsequently, delayed onset of analgesia and lack of subjective reinforcing effects.

In Study 102, the incidence of TEAEs related to potential risk of substance abuse was highest in the tramadol IV 50 mg arm and lowest in the placebo arm. The clinical review team identified two additional AEs that may be related to potential risk of substance abuse – an AE of anxiety reported in one patient treated with tramadol IV 50 mg and an AE of agitation reported in one patient treated with placebo (Table 17).

Table 17. Incidence of TEAEs Related to Potential Risk of Substance Abuse by PT in Study 102 Bunionectomy

Adverse Event by Preferred Term	Placebo N=136 n (%)	Tramadol 25 mg N=133 n (%)	Tramadol 50 mg N=140 n (%)
Dizziness	4 (2.9)	7 (5.3)	21 (15.0)
Somnolence/Drowsiness	3 (2.2)	6 (4.5)	16 (11.4)
Euphoria	0	0	1 (0.7)
Anxiety	0	0	1 (0.7)
Agitation	1 (0.7)	0	0

Source: CSR/Study AVE-901-102, AE Analysis Dataset.
Abbreviations: N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

In Study 103, no TEAEs of euphoria were identified. The incidence of TEAEs related to potential risk of substance abuse was highest in the morphine IV 4 mg arm (23%), followed by the tramadol IV 50 mg arm (16%), and, lastly, the placebo arm (8%) (Table 18).

Table 18. Incidence of TEAEs Related to Potential Risk of Substance Abuse by PT in Study 103 Abdominoplasty

MedDRA System Organ Class Preferred Term	Placebo (N=135) n (%)	Tramadol 50 mg (N=142) n (%)	Morphine (N=93) n (%)	Total (N=370) n (%)
Number of patients with at least one TEAE related to substance abuse	11 (8.1)	23 (16.2)	21 (22.6)	55 (14.9)
Dizziness	9 (6.7)	18 (12.7)	17 (18.3)	44 (11.9)
Somnolence	2 (1.5)	3 (2.1)	2 (2.2)	7 (1.9)
Dizziness postural	1 (0.7)	2 (1.4)	3 (3.2)	6 (1.6)
Sedation	0	2 (1.4)	1 (1.1)	3 (0.8)
Disturbance in attention	1 (0.7)	0	0	1 (0.3)
Dysphoria	0	0	1 (1.1)	1 (0.3)

Source: CSR/Study AVE-901-103, Table 38, p. 104.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Authorities; N, number of subjects; n, number of subjects in subgroup; PT, preferred term; TEAE, treatment-emergent adverse event

Safety Concerns Identified Through the Postmarket Experience

Tramadol HCl for injection has been marketed outside of the United States for over 25 years. The Applicant conducted a review of the medical literature from 1998 to 2019 to identify AEs associated with use of tramadol HCl for injection. The Applicant reviewed 27 studies (21 randomized, controlled studies and 6 case studies) that evaluated tramadol HCl for injection administered for pain in a variety of surgical settings. The doses of tramadol HCl for injection used were generally higher than the Applicant's proposed tramadol IV dosing. In 14 out of 21 controlled studies, tramadol HCl for injection was administered via patient-controlled analgesia rather than using a fixed dosing schedule as proposed by the Applicant for tramadol IV. Comparator drugs were morphine, fentanyl, codeine, oxycodone, lornoxicam, or meperidine. The Applicant concluded that rates of AEs with use of tramadol HCl injection were comparable with those of opioid comparators and all reported AEs were included in product labeling. The clinical review team agrees with the Applicant's conclusions. No new or unexpected safety findings for tramadol were identified after review of the Applicant's summary of the medical literature.

The Applicant also conducted a descriptive analysis of VigiBase, an international drug monitoring database established by the World Health Organization (WHO). The objective was to summarize the ten most frequently reported AEs as well as three AEs of interest (i.e., seizures, serotonin syndrome, and respiratory depression) for oral and IV tramadol for the ten-year period from January 2009 to June 2019. In total, 59 countries contributed AE reports for oral and IV tramadol to VigiBase. AE reports from these 59 countries constituted the All Regions data. AE reports from 20 countries categorized in the European region by WHO constituted the European Region data. The Applicant separately summarized the results for All Regions and the European Region because the All Regions data were more heavily weighted by reports from Asia. The Applicant hypothesized that practice patterns in Europe would be most similar to practice patterns in the U.S.

The All Regions results showed that there were approximately 53,000 AE reports for oral tramadol versus approximately 41,000 AE reports for IV tramadol. The three most frequently reported AEs were nausea, vomiting, and dizziness for both oral and IV tramadol. The percentage of reports of AEs of interest was low, occurring at 1% or less. For both oral and IV tramadol, seizure was reported most frequently followed by serotonin syndrome and respiratory depression. Specifically looking at the AE of

respiratory depression, there were 109 reports (0.2%) with oral tramadol and 16 reports (0.04%) with IV tramadol.

The European Region results showed that there were approximately 12,600 AE reports for oral tramadol versus 1,000 AE reports for IV tramadol. The two most frequently reported AEs were nausea and vomiting for both oral and IV tramadol. The percentage of reports of AEs of interest was low, occurring at 2.5% or less. For both oral and IV tramadol, seizure was reported most frequently followed by serotonin syndrome and respiratory depression. Specifically looking at the AE of respiratory depression, there were 58 reports (0.5%) with oral tramadol and 10 reports (1.0%) with IV tramadol.

The Applicant also analyzed the number of AE reports in which "co-use of opioids" with oral or IV tramadol was documented. The Applicant defined "co-use of opioids" as any AE reports for oral or IV tramadol that also reported use of another opioid by any route of administration. For All Regions, there were 3907 reports (7%) of "co-use of opioids" with oral tramadol and 1393 reports (3%) of "co-use of opioids" with IV tramadol. For the European Region, there were 1186 reports (9%) of "co-use of opioids" with oral tramadol and 198 reports (20%) of "co-use of opioids" with IV tramadol. The Applicant pointed out the disparity in "co-use of opioids" in Europe - the percentage of "co-use of opioids" with IV tramadol was twice that of oral tramadol. The Applicant provided a potential explanation for the disparity stating that IV tramadol is used during surgical procedures where there is use of anesthesia and use of other opioids. The clinical review team concluded that the Applicant's explanation for the disparity in "co-use of opioids" is plausible. Nevertheless, the fact that "co-use of opioids" was reported twice as often with IV tramadol as compared to oral tramadol highlights the Division's safety concern of opioid stacking and additive opioid-related AEs with use of tramadol via the intravenous route.

The Applicant noted some of the limitations of pharmacovigilance reporting databases. VigiBase is a spontaneous reporting system that may be subject to underreporting and reporting biases. Reporting rates may differ between countries. There may be disproportionate representation of a few countries. This type of database lacks a denominator (e.g., all patients prescribed) and, therefore, one cannot estimate incidence of AEs. Percentages should be considered as percentage of reports and not percentages of patients. Any potential safety signals identified may or may not represent AEs that are truly associated with the drug product of interest. Clinical review of the reports is needed to better understand the data, but there may be missing, inaccurate, or unsubstantiated data in the reports. The clinical review team agrees with the Applicant's summary of the limitations of VigiBase data.

The Applicant concluded that AE reports for IV tramadol were generally comparable to AE reports for oral tramadol both worldwide and in Europe. The clinical review team does not agree. We posit that, even though AE reports of "co-use of opioids" with both oral and IV tramadol were generally low, the disparity in reporting of "co-use of opioids" with IV tramadol versus oral tramadol in Europe supports the Division's safety concern of opioid stacking and potential for additive opioid-related AEs with use of tramadol via the intravenous route.

3.2.3 Safety Issues in Detail

Opioid Stacking

Tramadol IV's delayed onset of analgesia combined with its inability to be titrated to effect leads to a theoretical, yet reasonable and serious safety concern of additive opioid-related AEs. Patients whose

pain is not adequately controlled with the first dose of tramadol IV will likely receive another immediate-release opioid as rescue analgesia. The use of multiple opioids in succession is also known as opioid stacking. Opioid stacking will increase the potential for opioid-related AEs, such as respiratory depression and sedation.

The Applicant asserts that tramadol IV's delayed onset of analgesia did not lead to use of multiple opioids in the "vast majority" of subjects in the Phase 3 program. Therefore, the Applicant maintains that opioid stacking is not a serious safety concern with tramadol IV given that there is no evidence of opioid stacking in the NDA submission.

The clinical review team analyzed the safety data in the Phase 3 program looking for events of opioid stacking. In total, eight subjects were administered tramadol IV and another opioid in the Phase 3 program – one subject in Study 102, six subjects in Study 103, and one subject in Study 104. Three subjects had AEs that were considered possibly related to opioid stacking – two AEs of nausea and one of headache. Two subjects had AEs that were considered unlikely related to opioid stacking – one AE each of hypoxia and nausea and vomiting. Three subjects had no documented AEs related to opioid stacking. The clinical review team concluded that there are insufficient data in the NDA submission to answer whether use of tramadol IV followed by another opioid is safe for the intended patient population particularly in light of the increased risk of respiratory depression seen with tramadol IV 50 mg in the clinical program.

The Applicant is correct in stating that the "vast majority" of subjects in the Phase 3 program did not use multiple opioids. However, it was difficult to evaluate for AEs related to opioid stacking in the Phase 3 program because the studies did not allow use of another opioid as rescue medication. The only allowed rescue medication was ibuprofen in Studies 102 and 103 and non-opioid pain medication per the treating physician's discretion in Study 104. Additionally, in Studies 102 and 103, subjects were asked to wait, if possible, until one hour after study drug start to request rescue medication.

The Division contends that physicians' behaviors in the clinical study setting are not necessarily reflective of real-world clinical practice. Physicians in clinical practice may offer opioids rather than non-opioids as rescue analgesia for patients in moderate to severe pain that has not been adequately managed with tramadol IV. Physicians may also offer rescue opioid analgesia much earlier than one hour after the first dose of tramadol IV. As stated above, this will result in opioid stacking and the potential for additive opioid-related AEs.

The Applicant states that no patients discontinued from Study 104 to receive another opioid. Study 104 was a single-arm, open-label, uncontrolled study designed to evaluate the safety of tramadol IV 50 mg for the management of postoperative pain. No pain intensity scores and no data on time to perceptible and meaningful pain relief were collected during the study. Efficacy was assessed using the Patient Global Assessment at Hour 24 and End-of-Treatment in which patients were asked to rate the study medication in terms of its effectiveness in controlling their pain. Study 104 does not meet evidentiary standards for an adequate and well-controlled study. The study was not blinded and had no placebo arm. While the Division agrees with the Applicant's conclusion that no patients discontinued from Study 104 to receive another opioid, we cannot conclude that patients in Study 104 had clinically meaningful pain relief with use of tramadol IV because the study had no placebo comparator arm and there was no measure of patients' pain intensity scores over time.

The Applicant also asserts that subjects in need of rescue analgesia were adequately managed with ibuprofen in Studies 102 and 103 and other non-opioid analgesics in Study 104. Few subjects discontinued due to lack of efficacy in the Phase 3 program.

The Division contends that if subjects whose pain was not adequately managed with tramadol IV were adequately managed with non-opioid medications, then those subjects may not have had opioid-level pain at the time of rescue treatment. Another potential explanation is that ibuprofen and other non-opioid analgesics may be as effective, if not more effective, than tramadol IV due to its delayed onset of analgesia.

The Division anticipates that an IV analgesic intended to treat acute pain will have a relatively quick onset of pain relief. This statement is particularly true for an IV opioid given the known safety concerns of respiratory depression, misuse, abuse, addiction, and death associated with opioid use.

In conclusion, the Division questions whether the potential risk of additive opioid-related AEs from opioid stacking with use of tramadol IV is worth taking for the minimal benefit from using tramadol IV given its delayed onset of analgesia.

Abuse Liability Considerations

Tramadol and its salts are currently controlled in Schedule IV under the CSA. The Applicant's claimed lower abuse liability of tramadol IV relative to approved Schedule II opioids administered for acute pain post-operatively is one of the key attributes of their tramadol IV formulation that the Applicant is highlighting to support its approval under NDA 213231. For purported advantages of tramadol IV on the basis of abuse potential-related differences between tramadol IV and other currently approved opioid analgesics, the Applicant made the following arguments as part of formal dispute resolution request (amendment to NDA 213231 dated August 31, 2021):

- Epidemiology data confirm that tramadol has less abuse potential than approved Schedule II opioids in the United States (U.S.) and in countries where IV tramadol is available.
- IV tramadol would offer U.S. clinicians and patients a safe and effective alternative that can reduce the use of more abusable opioids for post-operative pain management in a medically supervised setting.
- Post-operative opioid use is ubiquitous among patients who underwent common surgical procedures in the in-patient setting.
- Even short-term exposure to highly abusable opioids can lead to chronic opioid dependence and initial exposure in the hospital setting can put patients on the road to withdrawals and possible addiction

The FDA acknowledges that tramadol is a Schedule IV controlled substance; however, it is important to describe what evidence was reviewed in support of this scheduling and whether the context of use of an opioid for the management of acute pain in an inpatient setting can rely on the evidence supporting scheduling to conclude less abuse potential that achieves a greater public health benefit.

The objective of drug scheduling is generally to mitigate the risks of diversion of a drug or other substance from legitimate channels (e.g., authorized manufacturing, distribution, research, and prescribing for medical use) to illicit channels for abuse purposes. For medically used drugs, placement in Schedule II places the maximum controls on these drugs, where Schedule II substances are defined as

having a high potential for abuse. Schedules III, IV, and V have progressively less stringent controls, reflecting relatively lower abuse potential (i.e., III < II, IV < III, V < IV). For example, Schedule III, IV, and V medications can be prescribed by physicians to permit refills, while Schedule II medications require patient assessment by the prescriber for each prescription.

For purposes of scheduling, rescheduling, or decontrolling a drug or other substance via the CSA's provisions for administrative drug scheduling, data must be collected and evaluated to support the scheduling action. These data are presented and evaluated in the form of a scientific and medical evaluation, also known as an Eight Factor Analysis, which is conducted by the Secretary of Health and Human Services (HHS), or delegated representative, i.e., FDA, and provided through HHS' Office of the Assistant Secretary for Health to the Drug Enforcement Administration (DEA) (21 U.S.C. 811). This evaluation must consider these following eight factors, as provided in statute:

(1) Its [the drug or other substance's] actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history and current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the substance is an immediate precursor of a substance already controlled […]

Specific types of data or studies examined to address these factors include: comparison of chemical structure to known scheduled drugs; physical properties of the drug; receptor binding (e.g., at μ-opioid receptors but also others associated with abuse potential); functional activity and efficacy determination; other preclinical pharmacology, including preclinical behavioral studies (i.e., general behavior, drug discrimination, intravenous self-administration studies, physical dependence studies); clinical human abuse potential studies by one or more routes of administration; clinical pharmacokinetic studies; AEs indicative of abuse (i.e., euphoria), actual abuse, and diversion in clinical development studies; documentation of abuse and diversion; and epidemiological studies of nonmedical use, patterns of abuse, substance use disorder, and documented adverse health consequences, including overdoses and deaths.

The evaluation under the eight factors leads to the HHS findings determinative of a recommended schedule placement of a given substance for DEA to consider and implement through the rulemaking process. This process has opportunity also for public comment on a scheduling action proposed by DEA. The three key findings made by HHS are: (1) the extent to which the drug or other substance has abuse potential; (2) whether the drug or other substance has an accepted medical use (Schedules II through V are generally for drugs with a currently accepted medical use); and (3) the extent to which use of the drug or other substance may lead to psychological or physical dependence. Many opioid analgesics are controlled in Schedule II, which is for drugs with a high potential for abuse, an accepted medical use, and severe drug dependence.

Tramadol was not a controlled substance when it was first approved in 1995 as Ultram. Tramadol was proposed for Schedule IV in the DEA's Notice of Proposed Rulemaking dated November 4, 2013 (78 FR 65923-65932). This proposal for Schedule IV was based on the scientific and medical evaluation conducted by HHS and the scheduling action of DEA for placement in Schedule IV became effective on

August 18, 2014 (79 FR 37623-37630). Most of the public comments were supportive of the proposed Schedule IV placement. As noted in the proposed rule for the Schedule IV placement of tramadol, some of the relevant findings are listed below.

- The abuse potential of tramadol was found to be similar to that of other substances in Schedule IV, such as propoxyphene,[1] of the CSA.
- Unlike many other opioids which have intrinsic μ-opioid activity, tramadol primarily depends upon conversion to an active metabolite (M1 metabolite) in order to produce opioid-like effects.
- The available information regarding reinforcing effects and drug dependence shows that the abuse potential of tramadol is less than that of morphine (Schedule II), oxycodone (Schedule II), or buprenorphine (Schedule III), but similar to that of propoxyphene (Schedule IV).
- The accumulated information demonstrated that individuals were taking tramadol nonmedically and in amounts sufficient to create a hazard to their health. Tramadol was being diverted from legitimate sources and was found to produce effects similar to other CSA-controlled opioids known to have an abuse potential. Epidemiological data supported a finding of abuse potential for tramadol that is similar to substances in Schedule IV of the CSA. As observed from these epidemiological data sources, tramadol was abused mainly by the oral route with limited abuse by the intravenous route.
- The dependence liability of tramadol, evaluated as having a lower physical dependency than propoxyphene, was based on data from animal studies and not on clinical data from chronic exposure or from exposure for acute pain management. However, currently, tramadol products, such as Ultram ER, have similar labeling and warnings about physical dependence (section 9.3 of prescribing information) as other opioid analgesics, e.g., Oxycontin.

Of note, the data and information considered for the Schedule IV placement of tramadol was based largely on post-approval nonmedical use patterns from epidemiological sources and tramadol's known pharmacological effects, including from the μ-opioid activity of tramadol's major metabolite, the M1 metabolite. The 2014 scheduling action did not identify or consider data demonstrating any comparatively lower abuse potential of tramadol from Schedule II opioids in the context of clinical trials investigating tramadol and Schedule II opioid analgesic comparators. However, data from two oral human abuse potential studies conducted in non-dependent recreational opioid users demonstrated that when taken by the oral route, tramadol can produce positive subjective effects (i.e., Drug Liking), and demonstrated that tramadol at the higher doses tested (350 mg-700 mg) produced positive subjective effects significantly above placebo and in the range of effects produced by the positive control, 20 mg oxycodone (Schedule II). These studies also demonstrated a delay in the maximum reinforcing effects of tramadol, which is consistent with the fact that the tramadol opioid like activity requires its metabolism to the active M1 metabolite (Epstein et al. 2006; Babalonis et al. 2013).

Another aspect of this product that raises some uncertainty in the benefit of being a Schedule IV opioid is that Tramadol IV solution is intended for use only within the medically supervised setting for treatment of acute pain. The product is not intended for take-home treatment of pain. Under the highly-

[1] Propoxyphene was a schedule IV opioid used in the treatment of mild to moderate pain, that was available at the time the Assistant Secretary of Health of the Department of Health and Human Service (HHS) transmitted to the Drug Enforcement Administration the HHS's scientific and medical evaluation and scheduling recommendation on September 16, 2010. On November 19, 2010, propoxyphene was withdrawn from the U.S. market because its use was associated with serious cardiotoxicity, even when used at therapeutic doses.

supervised clinical settings with monitoring of opioid intake, actual abuse of the opioid by the patient for rewarding effects, whether tramadol or Schedule II opioids, is highly unlikely.

The Applicant's claimed safety advantage may also be based on the idea that a patient's exposure to an intravenously administered opioid analgesic for post-operative pain could lead to a remembered rewarding effect that might lead the patient to seek opioid substances, either prescription opioid analgesics or illicit opioid substances, for nonmedical use following release from the medical setting. Since tramadol IV is not metabolized rapidly to the MI metabolite, there is likely no potential for a "rush" of rewarding effect from tramadol IV. However, it is also important to point out that when assessing the subjective effects of intravenously administered opioids with intrinsic mu opioid activity, the rate of injection of the drug is directly correlated with the positive responses in humans. The administration of the drug in a short period of time will generate higher plasma levels (i.e., the acute 'high' observed with abuse) than the same amount of the same drug administered over a longer period (Comer et al. 2009) In a medically-supervised setting of acute pain management such as post-operative pain management, the intravenous administration of opioids generally involves slow infusion rates, which will not only control the amount of opioid delivered but also diminishes the likelihood of patients obtaining significant rewarding effects. Furthermore, it is not known to what extent exposure to intraveneously administered opioids in a medically supervised setting, regardless of infusion rate, would result in patients transitioning to some form of opioid use disorder (OUD) after discharge. See also Section 3.3 on this point.

In summary, we agree with the Applicant that tramadol is a Schedule IV controlled substance that has less abuse liability than a Schedule II or III opioid based primarily on oral agent use in the postmarket setting, and not on post-operative short-term intravenous use. Hence, no robust conclusions can be drawn from this program on whether intravenous use post-operatively of tramadol would lead to any difference in risk of post-discharge abuse or OUD. Furthermore, tramadol still has μ-opioid activity through its M1 metabolite for which there are data supporting its potential for abuse and misuse.

The clinical development program for tramadol IV solution consisted of three Phase 1 studies (two pharmacokinetic studies and one cardiotoxicity study) and three Phase 3 efficacy studies in patients recovering from different surgical procedures. In all six studies, tramadol IV was administered as a slow infusion over 15 $\pm$ 4 minutes. With the exception of two reported AEs of "euphoria," one in the cardiotoxicity study and the other in Phase 3 Study AVE-901-102, no other AEs indicative of positive subjective effects were observed following treatments with slow infusion of tramadol intravenous solution in the clinical development program. In addition, no reports of positive subjective reinforcing effects, such as euphoria, were observed following slow infusion of morphine, used as a comparator in Phase 3 Study AVE-901-103.

With regard to the post-discharge phase, studies exist documenting the continued use of opioids over various time intervals following surgical treatment in the inpatient setting. These studies generally provide limited evidence that upon discharge from the hospital and in the outpatient setting there can be a pattern of continued opioid use, which in some cases could include nonmedical use for the purpose of achieving rewarding effects (e.g., euphoria, high, intoxication). See Section 3.3 below for further discussion of published epidemiologic studies on this point. Opioids administered under the supervised medical setting may be different (e.g., active ingredient, dosage form and strength, and dosing regimens) from those that patients are dispensed for outpatient use following discharge. We note that for Study AVE-901-103, the Applicant did not collect or provide information as to post-discharge pain

medications that subjects may have received as take-home medication, such as an oral solid dosage form of tramadol or a Schedule II opioid oral dosage form, or a non-opioid analgesic. Thus, we are unable to determine whether there were notable differences in outcomes with respect to any observed overuse of opioid analgesic medication in the home setting, and whether any such difference in outcomes could be correlated with the opioid active ingredient used in the home setting or with the treatment received by subjects (tramadol IV, morphine, or placebo) in the post-operative hospital setting for Study AVE-901-103. Additionally, no reports of manifestations associated with substance abuse or dependence were documented in any group, as this study did not ascertain any outcomes associated with misuse, abuse, or dependence.

3.3 Epidemiology Studies Relevant to Abuse Liability and Public Health Impact

In the formal dispute resolution request,[2] the Applicant states that the theoretical risk of opioid stacking must be weighed against the public health benefit of IV tramadol used in the postoperative, in-hospital setting, arguing that their product could serve as a safer alternative to Schedule II opioid analgesics currently administered intravenously in the postoperative setting because a Schedule II opioid is more likely to cause psychological or physical dependence even with short-term exposure, as compared to a Schedule IV opioid. This argument draws upon FDA's 2019 draft guidance, Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry (June 2019), noting that the guidance highlights the 'consideration of the abuse liability of opioids as it relates to the misuse and abuse in the benefit-risk determination' and arguing that their product would have a potential public health benefit. We fully agree with the need to consider risks of misuse, abuse, OUD, accidental exposures, and overdose for patients and others as they relate to the approval of a new opioid analgesic product. The draft guidance also highlights the importance of providing pertinent information, such as comparative data, to assess these benefit and risks. Furthermore, it notes that assessment of public health benefit must take into account differences in risk based on method of delivery and setting in which the drug is used.

The Applicant provided epidemiologic data on misuse, abuse, route of abuse, and diversion of tramadol and selected comparator opioid analgesics in the U.S. and selected non-U.S. countries where IV tramadol is approved. These results, primarily reflecting misuse and abuse of oral tramadol (and in the U.S., only oral tramadol) are consistent with tramadol's Schedule IV status, reflecting its lower abuse potential compared to Schedule II and Schedule III opioid analgesics. The limited international data provided suggest that misuse and abuse of tramadol liquid for injection is infrequent, as would be expected given its use primarily in medically supervised settings. As discussed above under Abuse Liability Considerations, CSA scheduling does not necessarily inform questions of comparative safety in a postoperative or otherwise medically supervised setting or on longer-term risk following therapeutic use in these settings.

The Applicant also argues, without providing evidence, that almost all patients who initially use IV tramadol would be managed throughout their entire postoperative period, both inpatient and outpatient, with tramadol, reducing overall exposure to Schedule II opioids and leading to fewer patients developing psychological or physical dependence. To support their argument, they cite five articles to demonstrate that short-term patient exposure to opioids postoperatively is prevalent (Kessler et al. 2013) and can lead to prolonged opioid use and dependence (Brummett et al. 2017; Lee et al.

[2] Formal dispute resolution request, Applicant: Avenue Therapeutics, Inc, NDA 213231, August 31, 2021

2017; Koepke et al. 2018; Mehra 2018). We agree that postoperative opioid use is prevalent and that post-discharge, prolonged opioid use and in some cases abuse- and dependence-related outcomes can follow; however, none of the cited articles directly examined the association between inpatient opioid analgesic use and subsequent opioid-related outcomes. Furthermore, none of the articles examined the association between in-hospital use of different intravenous opioid analgesics and either 1) which opioids were dispensed at discharge or 2) the likelihood of prolonged opioid use or abuse- or dependence-related outcomes, such as OUD.

The first study cited by the applicant (Kessler et al. 2013) examined only the prevalence of in-hospital postoperative use of opioid analgesics. Two of the articles cited consisted of a narrative review (Koepke et al. 2018) and an editorial letter cautioning against liberal use of opioid analgesics postoperatively (Mehra 2018). Two of the citations were retrospective cohort studies of opioid dispensing patterns in opioid-naïve patients who underwent surgery; these studies reported that 5.9-6.5% (Brummett et al. 2017) and 10% (Lee et al. 2017), respectively, of these patients had evidence of new prolonged opioid analgesic use after an initial outpatient opioid analgesic dispensing. The studies also found that the risk of prolonged opioid use was strongly influenced by other factors, such as type of surgery, pre-existing pain conditions, previous substance use, and mental health conditions (Brummett et al. 2017). Neither study examined the risk of prolonged opioid use across different opioid ingredients, formulations, or CSA schedules. Furthermore, by citing these studies the Applicant appears to conflate abuse or dependence outcomes with prolonged opioid use, and neither study cited addresses the question of whether prolonged opioid use in these patients was accompanied by misuse, abuse, dependence, or development of an OUD. Whereas these are well-known risks associated with use of opioid analgesics, none of these articles provide any supporting evidence to suggest that any of these outcomes would be less frequent following intravenous administration of a Schedule IV opioid analgesic as compared to a Schedule II opioid analgesic.

Other published studies not cited by the applicant have investigated differences in prolonged opioid analgesic use after initial outpatient exposure to different oral opioid analgesic drugs, including oral tramadol, (e.g., Shah et al. 2017; Thiels et al. 2019), but they also did not examine in-hospital intravenous administration.

In summary, we agree with the Applicant that broader public health impacts such as misuse, OUD, and related risks such as overdose, are important considerations here, as in all regulatory decisions related to opioid analgesic products; however, based on currently available information, it is not possible to determine whether use of intravenous tramadol in a medically supervised setting would decrease the risk of prolonged opioid use, opioid misuse, abuse, dependence, or OUD compared to other currently available opioid analgesics administered intravenously in the same setting. Patterns of opioid use and misuse and pathways to development of OUD are varied and complex and are influenced by many other individual-, system-, and societal-level factors.

3.4 Risk Mitigation

Labeling

In February 2021, Avenue Therapeutics, Inc. submitted a resubmission in response to the Agency's first Complete Response Letter. No new clinical data were included in the resubmission. The Applicant proposed addressing tramadol IV's delayed onset of analgesia and risk of additive opioid-related AEs

from opioid stacking with revisions to the language in Section 1 INDICATIONS AND USAGE, Section 2 DOSAGE AND ADMINISTRATION, and Section 14 CLINICAL STUDIES of the tramadol IV label.

The Division reviewed the Applicant's proposed labeling revisions and any information included to support the proposed labeling revisions. The Division concluded that the Applicant's proposed labeling revisions were not adequate to manage the safety issue of potential additive opioid-related AEs associated with use of tramadol IV because of its delayed onset of analgesia and administration as a standing dose.

The key labeling revisions proposed by the Applicant and a discussion of the Division's thinking about the key labeling revisions are summarized below.

Key Labeling Revisions:

Section 1. INDICATIONS AND USAGE

Proposed labeling additions are shown in bold text and proposed labeling deletions are shown in strikethrough.

ONPREFA is indicated for the management of moderate to moderately severe pain in adults in a medically supervised ~~health care~~ setting, **alone or in combination with other analgesics**.

Limitations of Use

For use only in a medically supervised setting, such as hospitals, ambulatory surgical centers, and emergency departments.

Because of delayed onset of analgesia in some patients, ONPREFA may be supplemented with a rapid-onset analgesic such as a non-steroidal anti-inflammatory drug *[see Dosage and Administration (2.1)]*.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve ONPREFA for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

Discussion of the proposed labeling revisions for Section 1 INDICATIONS AND USAGE:

The Applicant's proposed indication for tramadol IV is different than the typical indication for an immediate-release opioid analgesic. The typical indication has been:

Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

This wording was carefully selected to convey that opioids should be considered for use after all other treatment options have failed or been excluded. Opioids are considered a last resort for analgesia given the serious risks of respiratory depression, misuse, abuse, addiction, and death. This message about

opioid-related safety concerns is also reflected in the class language under Limitations of Use and in the Boxed Warning for opioid analgesic products.

The Division also considered whether it made clinical sense to bridge an opioid medication with delayed onset of analgesia with a non-opioid medication to provide adequate analgesia. From the clinical perspective, it makes sense to bridge a non-opioid medication with delayed onset of analgesia with an opioid medication. The opioid medication acts quickly and provides analgesia until the non-opioid medication starts working, then the opioid can be stopped and the non-opioid medication can be continued. However, the reverse scenario, with an opioid medication, such as tramadol IV, does not make sense clinically. It does not make sense to bridge an opioid medication with delayed onset of analgesia with a non-opioid medication. If the non-opioid medication acts quickly and provides analgesia, then the non-opioid medication can be continued and the opioid medication can be eliminated altogether.

Section 2 DOSAGE AND ADMINISTRATION

Proposed labeling additions are shown in bold text and proposed labeling deletions are shown in strikethrough.

Section 2.1 Important Dosage and Administration Instructions

- When initiation ONPREFA, monitor patient analgesic response. Because the median time **to meaningful pain relief was two hours or more after ONPREFA administration in clinical studies, an additional analgesic may be needed after the initial dose to more rapidly achieve the desired analgesic effect in some patients. Non-opioid analgesics (e.g. NSAIDs) may be sufficient adjunct based on clinical studies [see Clinical Studies (14)]. If an additional opioid analgesic is required, monitor for potential additive opioid-related adverse effects [see Warnings and Precautions (5.6)].**
- Do not use ONPREFA concomitantly with other tramadol-containing products.
- Do not administer ONPREFA at a dose exceeding 350 mg per day.
- Dosing of ONPREFA should be given at the recommended dosage regimen until analgesia is no longer required. There is limited experience with dosing between 48 hours and 5 days after the initial dose.
- Administer for the shortest duration of treatment consistent with individual patient treatment goals [see Warnings and Precautions (5.1)].
- Monitor patients closely for respiratory depression and discontinue ONPREFA, if necessary [see Warnings and Precautions (5.2)].

Discussion of the proposed labeling revisions for Section 2 DOSAGE AND ADMINISTRATION:

The Applicant's Phase 3 studies (Studies 102 and 103) were designed to evaluate the efficacy and safety of tramadol IV as a monotherapy. The studies were not designed to evaluate the analgesic effect of tramadol IV combined with another analgesic. Therefore, the data from the NDA do not support an indication for tramadol IV alone or in combination with other analgesics for the management of moderate to moderately severe pain.

Section 14 CLINICAL STUDIES

Proposed labeling additions are shown in bold text and proposed labeling deletions are shown in strikethrough.

Onset of Meaningful Pain Relief

The median time to patient-reported meaningful pain relief was 321 minutes in patients treated with ONPREFA and not reached in patients treated with placebo in Study 1 and 106 minutes in patients treated with ONPREFA and 145 minutes in patients treated with placebo in Study 2.

Discussion of the proposed labeling revisions in Section 14 CLINICAL STUDIES:

The Division agreed with the Applicant about inclusion of time to meaningful pain relief data in labeling because this information conveys tramadol IV's delayed onset of analgesia to the clinical provider. However, inclusion of time to meaningful pain relief data does not address or resolve the safety concern of opioid stacking with use of tramadol IV.

4. Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Acute pain is a serious medical condition. • If left untreated, acute pain may progress to chronic pain. • Untreated pain has a significant impact on quality of life with physical, psychological, social, and economic ramifications. • Most patients who undergo surgical procedures experience post-operative pain. • Severe pain after surgery is associated with decreased patient satisfaction, delayed ambulation, increased incidence of cardiac and pulmonary complications, and increased morbidity and mortality	Acute pain is a serious medical condition that, if left untreated, has a significant impact on quality of life with physical, psychological, social, and economic consequences.
Current Treatment Options	• Pharmacologic and nonpharmacologic treatment options are available for pain management. • Non-opioid analgesics, such as acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs), are used for mild to moderate pain. • Opioid analgesics alone or in combination with non-opioid analgesics are used for moderate to severe pain. • Examples of drugs with an FDA approved pain indication for use in the inpatient setting include injectable and oral formulations of APAP, opioids, and NSAIDs, as well as local anesthetics administered epidurally, spinally, or as nerve blocks. • Gabapentinoids, on the other hand, are used off-label in conjunction with other analgesics in the peri-operative setting.	Several classes of medication are available for acute pain management in the inpatient setting. Current FDA approved treatment options include oral and injectable formulations of APAP, opioids, and NSAIDs. Local anesthetics are also FDA approved for epidural and spinal administration and for use in nerve blocks to manage acute pain. Gabapentinoids are used off-label in the peri-operative setting for acute pain management. The primary treatment option currently used for management of moderate to severe acute pain is opioids.
Benefits	• The efficacy of tramadol IV was evaluated in two placebo-controlled Phase 3 studies in postsurgical adult patients with acute pain. • The studies were adequate and well-controlled and provided evidence of the efficacy of tramadol IV 50 mg based on the prespecified primary endpoint of time-weighted summed pain intensity difference from baseline over 48 hours (SPID48) for Study 102 and time-weighted summed pain intensity difference from baseline over 24 hours (SPID 24) for Study 103. • Study 103 also demonstrated the efficacy of tramadol IV 50 mg based on its prespecified secondary endpoints of SPID48, total rescue medication consumption, and patient global assessment at 24 hours (PGA24). • Analyses of pain intensity difference (PID) at early time points (Hours 0-2) for Study 103 and of time to meaningful pain relief for both studies 102 and 103, using the two-stopwatch method, demonstrated that tramadol IV had a delayed onset of analgesia, likely beyond two hours.	The two Phase 3 efficacy studies met the FDA-agreed, prespecified primary endpoints of SPID24 and SPID48 but demonstrated that tramadol IV has delayed onset of analgesia. Tramadol IV's delayed onset of analgesia is consistent with the known metabolism of tramadol when administered intravenously. The Applicant's pharmacokinetic studies confirmed the delayed formation of O-desmethyltramadol (M1) at early time points following the first dose of tramadol IV. **Points to consider:** The importance of time to onset of action and risks related to delayed onset of action for tramadol IV proposed for the management of moderate to severe

	Evidence and Uncertainties	Comments to the Advisory Committee
	• Tramadol IV's delayed onset of analgesia is consistent with the known metabolism of tramadol. • Specifically, IV administration of tramadol bypasses first pass hepatic metabolism resulting in delayed formation of the active metabolite, M1. Delayed formation of M1 leads to a delayed analgesic effect for tramadol IV. • Tramadol IV's pharmacokinetic profile confirms delayed M1 formation at early time points following the first dose of tramadol IV 50 mg.	acute pain in the inpatient setting such as post-operative or acute severe injury setting. • The benefits and risks of tramadol IV for acute pain management in the inpatient setting considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.
Risks and Risk Management	• The overall safety profile of tramadol IV 50 mg was consistent with the safety profile of Ultram and the typical safety profile of other available opioid products. • The most common adverse events (AEs) reported in Studies 102 and 103 were nausea, vomiting, dizziness, headache, somnolence, constipation, and hypoxia. • The safety profile of tramadol IV 50 mg was generally comparable to morphine IV 4 mg in Study 103. – The incidence of nausea, vomiting, headache, and dizziness was higher in the morphine arm than in the tramadol arm. – The incidence of constipation, hypoxia, and respiratory disorder was higher in the tramadol arm than in the morphine arm. – The incidence of somnolence, pruritus, and pruritus generalized was comparable between the tramadol and morphine arms. • There were fewer gastrointestinal events and less anti-emetic usage in the tramadol IV 50 mg arm than in the morphine IV 4 mg arm in Study 103. • Tramadol IV 50 mg was associated with more respiratory impairment events than either morphine IV or placebo in the Phase 3 program. • Tramadol IV was associated with fewer treatment-emergent adverse events (TEAEs) related to potential risk of substance abuse than morphine IV in Study 103. • Tramadol IV's delayed onset of analgesia, combined with its administration as a standing dose that is not titrated to effect, poses a theoretical, yet reasonable and serious safety concern of additive opioid-related AEs. • Patients whose pain is not adequately controlled with the first dose of tramadol IV will likely receive another immediate-release opioid as	Tramadol IV 50 mg had an overall safety profile that was similar to the safety profile of Ultram® and the safety profile of morphine IV 4 mg. Tramadol IV 50 mg was associated with more respiratory impairment and hypoxia events than morphine IV 4 mg. Tramadol IV 50 mg was associated with fewer substance abuse-related events than morphine IV 4 mg. Tramadol IV's delayed onset of analgesia, combined with its inability to be titrated to effect, poses a serious safety concern of opioid stacking and additive opioid-related adverse effects. The safety concern of opioid stacking and additive opioid-related adverse effects cannot be mitigated with labeling.. Tramadol is a Schedule IV controlled substance that has less abuse liability than a Schedule II or III opioid based primarily on oral agent use, and not on post-operative short-term intravenous use or use in a medically supervised setting. No robust conclusions can be drawn from either the Applicant's drug development program or the published literature on whether intravenous use of tramadol in a medically supervised setting would lead to any difference in risk of post-discharge misuse, abuse or OUD compared to other currently available opioid analgesics administered intravenously in the same setting.

	Evidence and Uncertainties	Comments to the Advisory Committee
	rescue analgesia. The use of multiple opioids in succession is also known as opioid stacking. Opioid stacking will increase the potential for opioid-related AEs, such as respiratory depression and sedation. • Tramadol is a Schedule IV controlled substance that has less abuse liability than a Schedule II or III opioid based primarily on oral agent use, and not on post-operative short-term intravenous use or use in a medically supervised setting. • It is not possible to determine from Study 103 whether there were notable differences in outcomes with respect to any observed overuse of opioid analgesic medication in the home setting, and whether any such difference in outcomes could be correlated with the opioid active ingredient used in the home setting or with the treatment received by subjects (tramadol IV, morphine, or placebo) in the post-operative hospital setting. • Based on published epidemiologic studies, it is not possible to determine whether use of intravenous tramadol in a medically supervised setting would decrease the risk of prolonged opioid use, opioid misuse, abuse, dependence, or OUD compared to other currently available opioid analgesics administered intravenously in the same setting.	**Points to consider:** • The relevance of tramadol's Schedule IV status in the context of the proposed use for management of acute pain in an inpatient setting with consideration on the following issues: o Any impact on risk of abuse, misuse, or addiction in the outpatient setting. o Any comparative advantage over currently available Schedule II opioids approved for the management of acute pain in the inpatient setting.

Summary of Benefit-Risk

Acute pain is a serious medical condition that, if left untreated, has a significant impact on quality of life. Most patients who undergo surgery experience acute postoperative pain. Several classes of medication are available for acute pain management in the inpatient setting. FDA approved treatment options include oral and injectable formulations of opioids and non-opioids. Moderate to severe acute pain is typically managed with opioids.

Tramadol IV demonstrated efficacy in two adequate and well-controlled Phase 3 studies. However, analyses of pain intensity difference at early time points and time to meaningful pain relief demonstrated that tramadol IV has a delayed onset of analgesia, likely beyond two hours. Tramadol IV's delayed onset of analgesia is an aspect of the product's efficacy profile that has safety implications.

Tramadol IV's overall safety profile was consistent with the safety profile of Ultram® and the typical safety profile of other available opioid products. The most common adverse events reported in Studies 102 and 103 were nausea, vomiting, dizziness, headache, somnolence, constipation, and hypoxia. Tramadol IV was associated with more respiratory impairment and hypoxia events and fewer substance abuse-related events than morphine IV in Study 103.

Tramadol IV's delayed onset of analgesia, combined with its inability to be titrated to effect, poses a theoretical, yet serious safety concern of additive opioid-related adverse effects. Patients whose pain is not adequately controlled with the first dose of tramadol IV will likely receive another immediate-

	Evidence and Uncertainties	Comments to the Advisory Committee
release opioid as rescue analgesia. The use of multiple opioids in succession, also known as opioid stacking, will increase the potential for opioid-related adverse events, such as respiratory depression and sedation. The safety concern of opioid stacking and additive opioid-related adverse events cannot be mitigated with labeling. Tramadol is a Schedule IV controlled substance that has less abuse liability than a Schedule II or III opioid based primarily on oral agent use, and not on post-operative short-term intravenous use or use in a medically supervised setting. No robust conclusions can be drawn from either the Applicant's drug development program or the published epidemiologic literature on whether intravenous use of tramadol in a medically supervised setting would lead to any difference in risk of post-discharge misuse, abuse or OUD, compared to other currently available opioid analgesics administered intravenously in the same setting. In summary, the Division questions whether the minimal benefit from using tramadol IV, given its delayed onset of analgesia, outweighs the potential risk of sedation and respiratory depression from opioid stacking.		

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6. Appendix

6.1 Statistical Review and Evaluation

6.2 Complete Response Letter #1 (October 9, 2020)

6.3 Complete Response Letter #2 (June 11, 2021)

6.4 Formal Dispute Resolution Appeal Denied Letter

6.5 Formal Dispute Resolution Appeal Interim Response Letter

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	213231
Drug Name:	ONPREFA ™ (tramadol hydrochloride) IV 50 mg/mL Injection
Indication(s):	management of moderate to moderately severe pain in adults in a medically supervised health care setting
Applicant:	Avenue Therapeutics
Date(s):	Submitted: 12/10/2019 Primary Review: 8/28/2020 PDUFA: 10/9/2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Jinglin Zhong, Ph.D. – Team Leader Hsien Ming (Jim) Hung, Ph.D. Division Director DBI
Medical Division:	Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP)
Clinical Team:	Lisa Wiltrout, M.D. – Clinical reviewer Ning Hu, M.D. – Clinical Team Leader
Project Manager:	Selma Kraft, Pharm.D.

Keywords: clinical studies

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

This application includes two studies to support the efficacy of Tramadol 50mg infusion for the indication of post-surgical pain relief. Both were multicenter, randomized, double-blind, parallel-arm studies designed to compare Tramadol 50mg infusion to placebo (saline). Study 102 enrolled patients undergoing unilateral first metatarsal bunionectomy surgery. Study 103 enrolled patients undergoing non-laparoscopic abdominoplasty surgery, a cosmetic surgical procedure to remove excess skin and fat from the abdomen (also known as a tummy tuck). The majority of subjects in both studies were female (85% of bunionectomy subjects; 99% of abdominoplasty subjects).

Subjects were screened for eligibility and enrolled prior to surgery. After surgery, when awake and alert, subjects had to report moderate to severe pain and a score of at least 5 on the 0-10 NPRS pain scale to be eligible to receive study treatment, which was administered via IV. Subjects remained at the medical facility for at least 48 hours after first dose of study treatment. Rescue medication (ibuprofen 400mg, every 4 hours, maximum 2400mg/day) was provided if requested. Pain scores were recorded just prior to rescue.

The planned efficacy endpoints in both studies were the SPID 24 or 48, a weighted average of the change in pain scores at time intervals across the 24 or 48 hour timeframe after start of study treatment. Secondary endpoints were the amount of rescue medication used over 48 hours and a patient global assessment. Hierarchical testing was prespecified.

In both studies the analyses of the planned efficacy endpoints demonstrated statistically significant superiority of Tramadol 50mg versus placebo. These consistent results provide sufficient evidence for efficacy of Tramadol 50mg for treatment of post-surgical pain, based on the clinical development plan and protocols discussed at the End of Phase 2 meeting in 2016.

At the pre-NDA meeting, August 21, 2019, the clinical team raised a concern that in the post-surgical setting it is important to describe the time to onset of action. It was acknowledged that this issue was not identified prior to conducting the studies, but the applicant agreed to address it in the submission. The most relevant assessment is the time to perceptible pain relief and time to meaningful pain relief endpoints, recorded with the double stopwatch method. These were planned as tertiary in the protocols.

The results from these time to event endpoints is not as clear or consistent as the pain score and use of rescue efficacy endpoints. In Study 102 (bunionectomy), at least 50% of the subjects were censored at 6 hours. The median time to perceptible pain relief was 167 minutes for the Tramadol 50mg arm, with only 70 of 139 subjects uncensored. This suggests that half the subjects did not report perceptible pain relief prior to 6 hours, and for those who did, the time to onset of action was approximately almost 3 hours. In Study 103 (abdominoplasty) censoring was not an issue (less than 50% censored in all groups). For the Tramadol 50mg arm, the median time to perceptible pain relief was 27 minutes (95% CI: 14, 73) and the median time to meaningful pain relief was 106 minutes (95% CI: 54, 153). The active-control arm in this study, morphine 4mg IV, showed shorter medians times (5 minutes for perceptible pain; 42 minutes for meaningful pain) but direct

comparison of tramadol 50mg to morphine was not planned. These are descriptive results only and are not intended to provide conclusive decisions. The clinical team will determine whether the onset of action can be adequately characterized from these studies.

2 INTRODUCTION

This application is for tramadol hydrochloride for injection. The applicant is seeking an indication for management of moderate to moderately severe pain for adults in a medically supervised health care setting. The product is intended to be administered intravenously (IV). The clinical studies were conducted in two post-surgical acute pain models: one orthopedic (bunionectomy) and one soft tissue (non-laparoscopic abdominoplasty). This application is being submitted as a 505(b)(2) with reference to Ultram® IR (NDA #20,281)

2.1 Overview

Avenue Therapeutics, Inc. is seeking approval for ONPREFA ™ (tramadol hydrochloride injection; 50mg) for the indication of treatment of acute post-surgical pain. The clinical development program included 2 studies of efficacy and safety, shown in Table 1. I will refer to them as Study 102 and Study 103.

Table 1: Clinical Studies included in Statistical Review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
AVE-901-102	Phase 3 R, DB, MC	48 hours post first dose *	14 days	Tramadol 50mg (n=142) Tramadol 25mg (n=143) Placebo (n=149)	Adults (18-75) undergoing unilateral first metatarsal bunionectomy surgery
AVE-901-103	Phase 3 R, DB, MC	48 hours post first dose *	7 days	Tramadol 50mg (n=141) Morphine 4mg (n=93) Placebo (n=136)	Adults (18-75) undergoing non-laparoscopic abdominoplasty surgery

* First dose was administered via infusion after patient was awake and alert following surgery and was screened for minimum pain entry criteria.

The studies were conducted under IND 108124, opened in September 2010. The study designs and surgical models for the two Phase 3 studies were discussed at the End of Phase 2 meeting (June 21, 2016). Study 102 was completed first, and based on those results, the applicant selected only the 50mg dose to include in planning Study 103.

At the preNDA meeting (August 21, 2019) the clinical team addressed the need to demonstrate the time to onset of action. The specific clinical goal was:

> *"for a parenteral analgesic for acute pain, it is expected that onset of action will be within an hour of dosing or less. If this is not the case, you must determine how patients pain will be managed until the onset of action of your product occurs. Onset of action is measured using*

the two stopwatch method, where the first stopwatch is stopped by the patient when they feel the first perceptible pain relief, and the second when they feel the onset of meaningful pain relief. The median time to meaningful pain relief is the time to onset. The duration of effect is measured using time to request of either rescue medication or a second dose of study medication. This is usually measured after the first dose but can also be assessed following subsequent doses. It is expected that the median time to rescue will be consistent with the proposed dosing interval. If it is shorter, the dosing interval may need to be shortened. This may not be possible if the product is already being dosed at the maximum safe dose, and other changes may be necessary. If the time to rescue is longer, consideration can be given to lengthening the dosing interval. If the time to onset is not measured prior to the time to first rescue, you will have to reevaluate whether your product is suitable for the proposed indication."

During a follow-up conference call (October 10, 2019), the Division concluded that the NDA should contain a clear discussion of the time to onset and a discussion of how the various endpoints relating to time to onset corroborate the onset of relief.

2.2 Data Sources

All data were supplied by the applicant to the CDER electronic data room (edr) in SAS transport format. The study reports and data in the electronic submission are archived under the network path location: \\Cdsesub1\evsprod\NDA213231\0001.

3 STATISTICAL EVALUATION

The two clinical studies submitted to support efficacy in this application were similar in many respects. Both were multicenter, randomized, double-blind, three-arm studies designed to compare Tramadol 50mg infusion to placebo. The key differences were the surgical procedure and timepoint after surgery for the primary and secondary comparison of pain intensity.

Both studies included a third treatment arm. In Study 102, it was a lower dose of Tramadol (25mg). The hierarchical closed testing procedure planned to compare the Tramadol 25mg arm to placebo after the comparisons of Tramadol 50mg arm to placebo. Comparisons between the two Tramadol doses were not planned. Study 103 included a morphine 4mg treatment arm but did not plan direct comparison of that arm to the Tramadol 50mg arm.

3.1 Data and Analysis Quality

The study data were submitted in standard formats, along with all documentation needed to complete my review. I was able to confirm the applicant's efficacy analyses. The data were clearly organized to conduct my own analyses without difficulty.

3.2 Evaluation of Efficacy

Studies 102 and 103 were multicenter, randomized, double-blind, parallel group designs and were conducted in the US. The objective was to evaluate the efficacy and safety of tramadol IV

for treatment of post-surgical pain. Both were planned for the primary comparison of tramadol 50mg infusion versus placebo.

Eligible subjects were adults, age 18 to 75, scheduled for the protocol-specific surgical procedure. Presurgical screening determined enrollment eligibility, and randomization was done on the day of surgery. Following surgery, subjects were screened for minimum pain outcomes prior to receiving study treatment. Eligible subjects had study drug administered via IV infusion at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44. Subjects remained at the healthcare facility for at least 48 hours after start of treatment and were not discharged until stable.

The Full Analysis Set (FAS) Population was defined as all randomized patients who received at least one dose of study medication. Patients were analyzed according to the treatment group they were randomized to. Because randomization was done prior to the post-surgical baseline pain scores being collected, between 3-6% of randomized subjects did not receive study medication.

The FAS dataset was designated as the primary analysis population for efficacy endpoints. Pain intensity was recorded on an 11-point, 0-10 numeric pain rating scale (NPRS) at baseline (Time 0; prior to first dose) then at 0.5 hr., 1 hr., 2, 3, 4, 5, 6 hrs., and every 2 hours through 48 hours after first dose. Pain intensity was also recorded prior to any use of rescue medication, which was ibuprofen 400mg every 4 hours (max 2400 mg /day).

The primary efficacy endpoint was the Summed Pain Intensity Difference (SPID) calculated as the weighted average of the difference in pain intensity score at each timepoint, weighted by the length of the time interval. Negative SPID scores indicate a patient's pain decreased over time, with the lower SPID values indicating greater reduction in pain intensity. In both studies the SPID24 and SPID 48 were planned for comparisons, but the priority order for the two timeframes was different. The order of the priority will be described for each study separately (Section 3.2.1.1. and 3.3.1.1).

Pain assessments were adjusted for use of rescue. The pre-rescue pain intensity NPRS score was used to replace the NPRS score obtained within 4 hours post-rescue medication. All other missing NPRS are imputed using multiple imputation method with a pattern mixture approach. For the primary endpoint (SPID), 100 imputed datasets were created, with data imputation for missing values due to missingness at random as well as due to discontinuation due to AE and lack of efficacy (LoE) and to account for use of rescue medication. 1). The intermittent missing data will be imputed using a Markov chain Monte Carlo method. 2). For patients that did not discontinue due to an AE, an imputation using regression-based method for continuous variables was then run to complete the imputed datasets by imputing the remaining monotone missing NPRS scores assuming MAR. 3). For patients with missing data as a result of discontinuation due to an AE, a penalty of 1 was applied to the imputed value based on MAR. The 100 imputed datasets were analyzed using an analysis of covariance (ANCOVA) model to test the primary efficacy endpoint. The model used treatment as the main effect, study center, and baseline NPRS score as covariates. In Study 103 the baseline BMI (<30 kg/m2 versus ≥30 kg/m2) was also included in the model because randomization was stratified by site and BMI category in that study.

A secondary endpoint, Patient Global Assessment (PGA), was recorded at 24 and 48 hours after first dose. This is a 5-point Likert scale assessed as: 0=poor; 1=fair; 2=good; 3=very good; or 4=excellent. This was analyzed using an ANCOVA model with terms for treatment, site and baseline pain.

Two endpoints which were planned as tertiary endpoints, but the clinical team requested several analyses of are the time to first perceptible pain relief and time to first meaningful pain relief. Two stopwatches were started at the start of the infusion of the first dose of study drug. Patients were instructed to stop the first stopwatch when pain relief was first perceptible and the second when pain relief was considered meaningful. These outcomes are intended to demonstrate the onset of action, a clinical concern discussed at the pre-NDA meeting.

The time to confirmed perceptible and meaningful pain relief were analyzed using Kaplan-Meier approach to provide median time to event and the log-rank test for comparisons. Time to pain relief was censored at 6 hours. If a patient did not record perceptible/meaningful pain relief and discontinued from the study prior to 6 hours, then the patient was censored at the time of discontinuation. The time to perceptible pain relief was considered confirmed and treated as an event in the analyses only if the patient also achieved meaningful pain relief.

Total consumption of rescue medication was calculated as the total amount of rescue analgesia (mg) given to the patient between the first dose of study medication through 48 hours post first dose (4 hours after the start of the last dose of study medication). The total consumption of rescue analgesia was analyzed using the nonparametric Wilcoxon rank sum test.

3.2.1. Study 102

3.2.1.1 **Study Design and Endpoints**

Study 102 was conducted from Aug. 2017 through April 2018 at 5 sites in the U.S. Enrollment was adequately distributed across the 5 sites, with the smallest contributing 12% and the largest 35% of the total.

Subjects were randomized equally (1:1:1) to the three treatment arms, stratified by site. The protocol planned for 135 subjects per arm (405 total) based on an anticipated difference of 250 units (SD=600; effect size 42%) for the SPID48 with 90% power and a two-sided test at α=0.05.

The primary efficacy endpoint was the Summed Pain Intensity Difference from start of first dose until 48 hours after first (SPID48). If the primary comparison of tramadol to placebo was statistically significant, the hierarchical testing order for secondary endpoints was prespecified as follows: SPID24; total rescue consumption; PGA at 24 and 48 hours. The statistical analysis plan also controlled for multiplicity for the comparisons of each Tramadol dose vs. placebo. Specifically, for each step in the planned primary/secondary order, the Tramadol 50mg vs placebo test would be conducted first, and if successful ($p \leq 0.05$), then the Tramadol 25mg vs.

placebo test would be done. According to the Sponsor, the key secondary endpoints of the high dose arm can be tested even if the test of the primary endpoint fails in the low dose arm. However, to fully control the type I error rate with the hierarchical order the sponsor provided, the key secondary endpoints should not be tested if the p-value for the primary endpoint of the low dose arm is not significant.
The time to first perceptible pain relief and time to first meaningful pain relief were planned as tertiary endpoints. Two stopwatches were started at the start of the infusion of the first dose of study drug. Patients were instructed to stop the first stopwatch when pain relief was first perceptible and the second when pain relief was considered meaningful.

3.2.1.2 **Patient Disposition, Demographic and Baseline Characteristics**

A total of 434 subjects were randomized, of whom 409 received study treatment. All 25 of the randomized subjects who did not receive treatment did not meet the post-surgical eligibility criteria (not related to treatment). One subject randomized to the Tramadol 25mg arm actually received Tramadol 50mg treatment. All treated subjects are included in the efficacy analyses according to the arm they were randomized to.

Table 2. Patient Disposition (Study 102 - Bunionectomy)

Disposition Category	Tramadol 25mg	Tramadol 50mg	Placebo
Randomized	143	142	149
Received study treatment (FAS) *	134 (100%)	139 (100%)	136 (100%)
Completed study	123 (92%)	137 (99%)	120 (88%)
Discontinued (Early Termination)	11 (8%)	2 (1%)	16 (12%)
Adverse event	2 (1%)	1 (1%)	0
Lack of Efficacy	7 (5%)	1 (1%)	11 (8%)
Protocol violation	1 (1%)	0	0
Withdrew consent	1 (1%)	0	3 (2%)
Other	0	0	2 (1%)

* A total of 25 randomized subjects did not receive treatment, all due to not meeting post-surgical eligibility criteria.
All percents calculated using FAS as denominator.
Source: Reviewer
Abbreviations: FAS Full Analysis Set

Overall, 89.7% of patients had complete NPRS assessments. The tramadol 50 mg group had the highest incidence of patients with complete NPRS data (97.8%), followed by the tramadol 25 mg group (88.1%) and placebo group (83.1%). The majority of missing NPRS values were not intermediate time points (only 13 patients had at least one intermediate missing score), but rather assessments following discontinuations from the study.

Baseline Demographics

The three treatment groups were balanced with respect to relevant demographic and baseline characteristics as shown in Table 3. Overall 85% of subjects were female which is typical for a bunionectomy study. The majority were white (69%) or black (25%). The mean baseline pain was 6.8 on the 0-10 NPRS pain scale.

Table 3. Demographic and Baseline Characteristics (Study 102 - Bunionectomy)

All Treated (FAS)	Tramadol 25mg N=134	Tramadol 50mg N=139	Placebo N=136
Age (years)			
Mean (SD)	45 (13.1)	46 (13.5)	45 (13.4)
Range	19 - 74	19 - 69	19 - 69
Gender			
Male	18 (13%)	19 (14%)	23 (17%)
Female	116 (87%)	120 (86%)	113 (83%)
Race			
White	88 (66%)	104 (75%)	88 (65%)
Black	38 (28%)	29 (21%)	37 (27%)
Asian	3 (2%)	2 (1%)	4 (3%)
Other/Multiple	5 (4%)	4 (3%)	7 (5%)
Body Mass Index (BMI) kg/m^2			
Mean (SD)	28 (5.5)	28 (5.0)	28 (4.9)
Range	18 - 40	18 - 40	19 - 40
Post-surgery pain NPRS			
Mean (SD)	6.8 (1.4)	6.7 (1.7)	6.9 (1.6)
Range	5 - 10	5 - 10	5 - 10
Post-surgery Categorical Pain			
Moderate	80 (60%)	89 (64%)	75 (55%)
Severe	54 (40%)	50 (36%)	61 (45%)

Source: Reviewer

3.2.1.3 **Results and Conclusions**

Table 4 presents the applicant's results for the primary efficacy endpoint, which were confirmed. For the NPRS pain scale and the SPID calculation, high scores indicate worse pain. A negative change indicates reduction in pain from baseline. For the Patient Global Assessment, a high score is better (rate the effectiveness in controlling your pain). The results showed Tramadol 50mg is statistically significant superior vs. placebo ($p \leq 0.005$) in the primary endpoint, but Tramadol 25mg was not significantly different from placebo. According to the planned hierarchical testing plan, all the test for the key secondary endpoints stopped.

Table 4. Efficacy Analysis Results (Study 102 - Bunionectomy)

All Treated (FAS)		**Tramadol 25mg N=134**	**Tramadol 50mg N=139**	**Placebo N=136**
Primary: SPID48	LSMean (SE) Diff. vs. placebo (95% CI) p-value	-111 (6.5) -13 (-31, 5) 0.145	-123 (6.3) -25 (-42, -8) 0.005	-98 (6.5)
Secondary: SPID24	LSMean (SE) Diff. vs. placebo (95% CI) p-value	-34 (3.3) -8 (-17, 1) NA	-44 (3.2) -18 (-27, -9) <0.001	-26 (3.3)
Secondary: Total Rescue Medication Consumption 48 hrs (mg)	Mean (SD) Wilcoxon Rank Sum Mean Diff. vs. placebo p-value	1337 (1112) 213 -6 NA	1027 (952) 180 -30 0.002	1371 (960) 223
Secondary: Patient Global Assessment At 24 Hours	LSMean (SE) Diff. from placebo (95% CI) p-value	1.9 (0.1) 0.4 (0.2, 0.7) NA	2.3 (0.1) 0.8 (0.5, 1.1) <0.001	1.5 (0.1)
Secondary: Patient Global Assessment At 48 Hours	LSMean (SE) Diff. vs. placebo (95% CI) p-value	2.3 (0.1) 0.5 (0.2, 0.8) NA	2.6 (0.1) 0.8 (0.5, 1.1) <0.001	1.8 (0.1)
Tertiary: Time to Perceptible Pain Relief (mins)	Had Event (%) Censored (%) Median (95% CI) p-value vs. placebo	57 (43%) 77 (57%) -- (181, --) NA	70 (50%) 69 (50%) 167 (16, --) 0.009	46 (34%) 90 (66%) -- (--, --)
Tertiary: Time to Meaningful Pain Relief (mins)	Had Event (%) Censored (%) Median (95% CI) p-value vs. placebo	57 (43%) 77 (57%) -- (238, --) NA	70 (50%) 69 (50%) 321 (84, --) 0.009	46 (34%) 90 (66%) -- (--, --)

Source: CSR Tables 15-18 and 22

NA (not applicable): Hierarchical testing stopped for the Tramadol 25mg vs. placebo after the primary endpoint did not meet p ≤0.05 criteria.
For Time to Event outcomes, median time cannot be calculated is less than 50% of subjects had the event.
Abbreviations: SE – Standard Error; CI - confidence interval; SD – Standard Deviation

No sensitivity was performed by the Sponsor. Missing data caused by discontinuation due to AE were handled in the primary analysis. The majority of the remaining discontinuation is due to 'lack of efficacy' (LoE). The Sponsor performed a sensitivity analysis for Study 103 which treated the discontinuation due to LoE the same as due to AE. Because the placebo arm had the most discontinuation due to LoE (8%) compared to the other arms (5% and 1%), this sensitivity analysis will punish placebo arm more than the other arms. Thus, this sensitivity analysis will not change the conclusion.

The high number of censored subjects for the time to perceptible pain relief and time to meaningful pain relief outcomes is problematic for the clinical question of determining the time to onset of action. The applicant's explanation was that subjects may have been asleep or not attentive to using the stopwatches, suggesting it was unrelated to treatment. Dr. Wiltrout and I considered if pain scores and use of rescue could provide further insight. I divided the subjects into subgroups according to whether the time to pain relief outcome was censored.

Table 5 shows the use of rescue and pain endpoints for those subgroups. In all three treatment arms, subjects who were censored by 6 hours for the perceptible pain outcome (columns labelled PPR=No) were more likely to use rescue and had average less improvement for pain relief than the subjects who recorded perceptible pain relief (PPR=Yes) using the stopwatches. Of note, the median time to first rescue was less than 360 minutes for subjects who were censored but was more than 360 minutes for subjects who recorded perceptible pain relief.

The descriptive statistics in Table 5 suggest that the incidence of censoring is related to pain relief. With regards to Dr. Wiltrout's concern, the time to onset of action for the Tramadol 50mg arm was at least 6 hours for half of the subjects. Among subjects who did report perceptible pain relief, the median time was 167 minutes, almost 3 hours after start of treatment.

Table 5. Time to Pain Relief (Study 102 - Bunionectomy)

	TRAM 25mg N=134		TRAM 50mg N=139		Placebo N=136	
Subgroups:	PPR=Yes N=57 43%	PPR=No N=77 57%	PPR=Yes N=70 50%	PPR=No N=69 50%	PPR=Yes N=46 34%	PPR=No N=90 66%
Used Rescue (w/in 48 hrs)	40 70%	68 89%	40 57%	64 93%	37 80%	84 93%
Mean Total Amt Rescue 48 hours (mg)	982	1579	697	1389	1096	1511
Median Time to First Rescue (mins)	441	86	619	87	361	93
SPID48 (mean)	-123	-85	-134	-101	-85	-91
SPID24 (mean)	-47	-19	-52	-30	-21	-25

Source: Reviewer
PPR=Yes: Perceptible Pain Relief was recorded within 6 hours (double stopwatch method)
PPR=No: Perceptible Pain Relief was censored at 6 hours
For SPID24 and SPID48, I report the unadjusted MEAN, not LSMEAN.

3.2.2. Study 103

3.2.2.1 Study Design and Endpoints

Study 103 was conducted from Dec. 2018 through May 2019 at 3 sites in the U.S. Enrollment was adequately distributed across the sites, ranging from 25% to 39% of the total.

Subjects were randomized at a 3:3:2 ratio to the three treatment arms (Tramadol 50mg: Placebo: and morphine 4mg IV). Randomization was stratified by site and BMI (<30; ≥30). The protocol planned for 135 subjects in the Tramadol and placebo arms and 90 in the active-control arm (360 total) based on an anticipated difference of 15 units (SD=38; effect size 40%) for the SPID24 with 90% power and a two-sided test at α=0.05.

The primary efficacy endpoint was the Summed Pain Intensity Difference from start of first dose until 24 hours after first dose (SPID24). If the primary comparison of tramadol to placebo was statistically significant, the hierarchical testing order for secondary endpoints was prespecified as follows: PGA at 24 hours; SPID48; total rescue consumption through 24 hours.

The time to first perceptible pain relief and time to first meaningful pain relief were planned as tertiary endpoints. Two stopwatches were started at the start of the infusion of the first dose of study drug. Patients were instructed to stop the first stopwatch when pain relief was first perceptible and the second when pain relief was considered meaningful.

3.2.2.2Patient Disposition, Demographic and Baseline Characteristics

A total of 380 subjects were randomized, of whom 370 received study treatment. The 10 randomized subjects who did not receive treatment did not meet the post-surgical eligibility criteria (not related to treatment). One subject randomized to the placebo arm actually received Tramadol 50mg treatment. All treated subjects are included in the efficacy analyses according to the arm they were randomized to.

Table 6. Patient Disposition (Study 103 - Abdominoplasty)

Disposition Category	Tramadol 50mg	Placebo	Morphine 4mg
Randomized	142	142	96
Received study treatment (FAS) *	141 (100%)	136 (100%)	93 (100%)
Completed study	124 (88%)	127 (93%)	85 (91%)
Discontinued (Early Termination)	17 (12%)	9 (7%)	8 (9%)
Adverse event	12 (9%)	2 (2%)	6 (7%)
Lack of Efficacy	5 (4%)	6 (4%)	2 (2%)
Protocol violation	0	0	0
Withdrew consent	0	1 (1%)	0
Other	0	0	0

* A total of 10 randomized subjects did not receive treatment, all due to not meeting post-surgical eligibility criteria.
All percents calculated using FAS as denominator.
Source: Reviewer
Abbreviations: FAS Full Analysis Set

Overall, 91.9% of patients had complete NPRS scores between 0 to 24 hours. There were few missing at random (MAR) NPRS scores. Where there were missing NPRS values, the majority were following a discontinuation from the study by the patient.

Baseline Demographics

The three treatment groups were balanced with respect to relevant demographic and baseline characteristics as shown in Table. Overall 99% of subjects were female which is typical for an abdominoplasty study. All 3 males were randomized to the placebo group. The majority were white (75%) or black (17%). The mean baseline pain was 6.5 on the 0-10 NPRS pain scale.

Table 7. Demographic and Baseline Characteristics (Study 103 - Abdominoplasty)

All Treated (FAS)	Tramadol 50mg N=141	Placebo N=136	Morphine 4mg N=93
Age (years)			
Mean (SD)	40 (8.7)	40 (8.8)	39 (8.7)
Range	23 - 71	21 – 69	20 – 60
Gender			
Male	0	3 (2%)	0
Female	141 (100%)	133 (98%)	93 (100%)
Race			
White	102 (72%)	102 (75%)	72 (77%)
Black	25 (18%)	24 (18%)	13 (14%)
Asian	3 (2%)	5 (4%)	3 (3%)
Other/Multiple	11 (8%)	5 (4%)	5 (5%)
Body Mass Index (BMI) kg/m^2			
Mean (SD)	27 (3.3)	27 (3.7)	27 (3.3)
Range	19 - 40	19 – 40	20 – 36
Post-surgery pain NPRS			
Mean (SD)	6.5 (1.4)	6.5 (1.4)	6.7 (1.5)
Range	5 - 10	5 - 10	5 - 10
Post-surgery Categorical Pain			
Moderate	105 (75%)	99 (73%)	67 (72%)
Severe	36 (25%)	37 (27%)	26 (28%)

Source: Reviewer

3.2.2.3 Results and Conclusions

Table 8 presents the applicant's results for the primary and secondary efficacy endpoints, which were confirmed. For the NPRS pain scale and the SPID calculation, high scores indicate worse pain. A negative change indicates reduction in pain from baseline. For the Patient Global Assessment, a high score is better (rate the effectiveness in controlling your pain). The results showed Tramadol 50mg is statistically significant superior vs. placebo ($p \leq 0.001$). Comparisons to morphine 4mg were not prespecified and are not reported here.

Table 8. Efficacy Analysis Results (Study 103 - Abdominoplasty)

All Treated (FAS)		Tramadol 50mg N=141	Placebo N=136	Morphine 4mg N=93
Primary: SPID24	LSMean (SE) Diff. vs. placebo (95% CI) p-value	-79 (3.4) -31 (-41, -22) <0.001	-48 (3.9)	-82 (4.5)
Secondary: SPID48	LSMean (SE) Diff. vs. placebo (95% CI) p-value	-181 (8.2) -60 (-79, -40) <0.001	-121 (8.2)	-179 (9.6)
Secondary: Total Rescue Medication Consumption 24 hours (mg)	Mean (SD) Wilcoxon Rank Sum Mean Diff. vs. placebo p-value	312 (409) 167 -51 <0.001	659 (571) 235	189 (261) 141
Secondary: Patient Global Assessment At 24 Hours	LSMean (SE) Diff. from placebo (95% CI) p-value	3.0 (0.1) 0.9 (0.6, 1.1) <0.001	2.2 (0.1)	3.1 (0.1)
Tertiary: Time to Perceptible Pain Relief (mins)	Had Event (%) Censored (%) Median (95% CI) p-value vs. placebo	92 (65%) 49 (35%) 27 (14, 73) 0.21	75 (55%) 61 (45%) 69 (29, --)	69 (74%) 24 (26%) 5 (4, 7)
Tertiary: Time to Meaningful Pain Relief (mins)	Had Event (%) Censored (%) Median (95% CI) p-value vs. placebo	93 (66%) 48 (34%) 106 (54, 153) 0.28	77 (57%) 59 (43%) 145 (67, --)	69 (74%) 24 (26%) 42 (17, 96)

Source: CSR Tables 17-20 and 22
Abbreviations: SE – Standard Error; CI - confidence interval; SD – Standard Deviation

A sensitivity analysis was performed on SPID24 and SPID 48 to assess the impact of treating missing data due to 'lack of efficacy' (LoE) as MAR as opposed to MNAR for purposes of imputing these missing values. The same assumption of MNAR used for discontinuation due to AE was used. The point estimate of the LS mean treatment difference is very similar between the two methods (treated LoE as MNAR versus MAR).

Table 9: Sensitivity analysis of effect of treating lack of efficacy as MNAR vs MAR for SPID24 and SPID48

Method for Imputation	Endpoint	Placebo		Tramadol		Difference (Tramadol versus Placebo)		P-value for Treatment Comparison
		LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	
MNAR	SPID24	-47.7 (3.89)	-55.32, -40.08	-79.0 (3.89)	-86.63, -71.40	-31.3 (4.71)	-40.55, -22.08	<0.001
MAR	SPID24	-49.8 (3.66)	-56.93, -42.58	-81.4 (3.65)	-88.57, -74.25	-31.7 (4.45)	-40.38, -22.95	<0.001
Absolute Difference between LS Means for MNAR versus MAR Methods of Imputation							**0.17**	
MAR	SPID48	-127.3 (7.55)	-142.09, -112.51	-187.4 (7.51)	-202.14, -172.69	-60.1 (9.17)	-78.08, -42.15	<0.001
MNAR	SPID48	-121.1 (8.23)	-137.24, -104.99	-180.8 (8.23)	-196.94, -164.68	-59.7 (9.97)	-79.24, -40.15	<0.001
Absolute Difference between LS Means for MNAR versus MAR Methods of Imputation							**1.16**	

Source: CSR Tables 21.

3.3 Evaluation of Safety

Dr. Wiltrout will review the body of evidence for safety. She did not request additional analyses for safety questions or concerns.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The majority of subjects enrolled in both studies were female, which is not unexpected for bunionectomy and abdominoplasty surgical procedures. All study sites were in the US.

4.1 Gender, Race, and Age

I produced exploratory analyses for the primary efficacy endpoint by age group, gender, and race (See Tables 10 and 11). These are descriptive analyses only and are not intended for inferential purposes. There were no significant differences in primary endpoint (SPID48 or SPID24, respectively) across the subgroups in either study.

In Study 102, only 19 subjects (5%) were 65 or older. The median age (46) was used to define the age groups. In the Tramadol 50mg arm the SPID48 was larger in the younger age group, which is the opposite of the other two arms, but there was no significant interaction of age by treatment, or for the age factor, when included in the ANCOVA model.

Only 60 (15%) of subjects were male. Although the SPID48 is larger in females than males in the Tramadol 50mg arm, there was no significant interaction of gender by treatment, or for the gender factor, when included in the ANCOVA model.

Overall 69% of subjects were white. The SPID48 results were similar across the race subgroups for all three arms.

Table 10. Subgroup Analyses: (Study 102 - Bunionectomy)

Primary: SPID48 N Mean (SD)	**Tramadol 25mg** **N=134**	**Tramadol 50mg** **N=139**	**Placebo** **N=136**
Age group			
< 46 years	N=72 -85 (80)	N=63 -128 (85)	N=71 -78 (82)
≥ 46 years	N=62 -120 (89)	N=76 -109 (81)	N=64 -101 (86)
Sex			
Male	N=18 -100 (77)	N=19 -76 (78)	N=23 -86 (66)
Female	N=116 -101 (87)	N=120 -124 (82)	N=112 -89 (88)
Race			
White	N=88 -103 (83)	N=104 -117 (79)	N=88 -90 (80)
People of Color	N=46 -98 (90)	N=35 -120 (96)	N=47 -87 (92)

Source: Reviewer

In Study 103, only 3 subjects (<1%) were 65 or older. The median age (40) was used to define the age groups. The SPID24 results were similar across the age subgroups for all three arms.

Only 3 (<1%) of subjects were male, and all were randomized to the placebo arm. I do not calculate subgroup results for gender.

Overall 75% of subjects were white. The SPID24 results were similar across the race subgroups for all three arms.

Table 11. Subgroup Analyses: (Study 103 - Abdominoplasty)

Primary: SPID24 N Mean (SD)	Tramadol 50mg N=141	Placebo N=136	Morphine 4mg N=93
Age group			
< 40 years	N=69 -81 (43)	N=63 -45 (39)	N=48 -84 (47)
≥ 40 years	N=72 -76 (42)	N=73 -51 (46)	N=45 -81 (42)
Race			
White	N=102 -81 (40)	N=102 -50 (41)	N=72 -82 (42)
People of Color	N=39 -71 (47)	N=34 -43 (48)	N=21 -87 (46)

Source: Reviewer

4.2 Other Special/Subgroup Populations

In Study 103 randomization was stratified by BMI (<30; ≥30 kg/m^2) along with site. This baseline characteristic is more relevant for the abdominoplasty surgical procedure than for the bunionectomy procedure.

Overall 85% of subjects had BMI <30 kg/m^2 at baseline. The SPID24 results were similar for the two strata across the three treatment arms.

Table 12. Subgroup Analysis by BMI strata: (Study 103 - Abdominoplasty)

Primary: SPID24 N Mean (SD)	Tramadol 50mg N=141	Placebo N=136	Morphine 4mg N=93
BMI strata			
< 30 kg/m^2	N=120 -79 (43)	N=114 -50 (43)	N=79 -83 (44)
≥ 30 kg/m^2	N=21 -72 (38)	N=22 -38 (44)	N=14 -81 (47)

Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Both studies were conducted as planned based on the discussion at the End of Phase 2 meeting in 2016. The results demonstrated Tramadol 50mg was superior to placebo on the primary efficacy endpoint. There is sufficient and consistent evidence of efficacy to support the indication of post-surgical pain treatment. My conclusion is based on the prespecified objectives, hypotheses, and analyses planned in the protocols.

The only issue to arise is the difficulty in adequately characterizing the time to onset of action after first dose with the data collected in the studies. This clinical concern was raised at the pre-NDA meeting, and the sponsor agreed to provide *post hoc* analyses to attempt to address it. Study 102 (bunionectomy) had 50% or higher of subjects censored at Hour 6 for time to perceptible and meaningful pain relief, making estimation difficult. Study 103 did not have censoring issues. Tramadol had numerically shorter times to perceptible and meaningful pain relief than placebo but did not show statistical significance. However, the active-control arm had even shorter times than Tramadol, without planned comparison tests. The clinical team will make the final determination on whether additional evidence for the time to onset of action will be needed to supplement the planned efficacy results.

5.2 Collective Evidence

The two Phase 3 studies were appropriately planned and conducted to evaluate the efficacy of Tramadol 50mg for the indication of treatment of post-surgical pain. Study 102 enrolled patient undergoing bunionectomy, an orthopedic surgical procedure. Study 103 enrolled patients undergoing an abdominoplasty, a soft tissue surgical procedure. The results for the planned primary and secondary endpoints provide consistent evidence to support Tramadol 50mg for this indication. As discussed in Section 5.1, the clinical team will decide if additional data to characterize the time to onset of action is needed.

5.3 Conclusions and Recommendations

The statistical results, as planned in the protocols, provide sufficient evidence of efficacy for Tramadol 50mg for the indication of treatment of post-surgical pain.

5.4 Labeling Recommendations

The applicant's proposed label is shown below. In discussions with the clinical team, I propose the following changes:

a. Both studies included SPID24 and SPID48 in the hierarchical testing plan, but in reverse priority. It is acceptable to include results for both endpoints in this instance. Change Table 4 to remove the p-values. The statistically significant test vs. placebo is in the text.
b. Remove Table 5 (secondary endpoints) and references to it from the text.

c. Figure 1 currently has two plots. Create separate plots for each study to allow for larger font size. Display the plots so that the 48-hour timeframe on the horizontal axes are aligned.
d. Remove the key secondary endpoints from the last sentence of the paragraph of Study 1.

Applicant's proposed label:

14 Clinical Studies

The efficacy of ONPREFA in the treatment of acute pain in adults was evaluated in two randomized, double-blind, placebo-controlled clinical trials in patients with postoperative pain. In the Phase 3 controlled studies (Studies 1 and 2), 93.2% of patients completed their full 48-hour treatment, with only 2.1% discontinuing due to lack of efficacy.

***Study 1** (NCT03290378) evaluated the analgesic efficacy of repeated doses of ONPREFA vs placebo at Hour 0, 2, 4, and every 4 hours thereafter for 48 hours in 409 patients with moderate to severe pain following unilateral primary first metatarsal bunionectomy. The primary efficacy endpoint was the time-weighted summed pain intensity difference over 48 hours (SPID48). ONPREFA was statistically superior to placebo for reduction in pain intensity over 48 hours (Table 13) as well as for all key secondary endpoints (Table 14).*

***Study 2** (NCT03774836) evaluated the analgesic efficacy of repeated doses of ONPREFA vs placebo at Hour 0, 2, 4, and every 4 hours thereafter for 48 hours in 380 patients with moderate to severe pain following elective abdominoplasty. The primary efficacy endpoint was the time-weighted summed pain intensity difference over 24 hours (SPID24). ONPREFA was statistically superior to placebo for reduction in pain intensity over 24 hours (Table 13) as well as for all key secondary endpoints (Table 14).*

Table 13: Primary Efficacy Endpoints: SPID24 and SPID48 LSMean (SE) Comparisons between IV Tramadol 50 mg vs Placebo by Study (Studies 1 and 2)

Study	SPID Endpoints	Placebo LS mean (SE)	IV Tramadol 50 mg LS mean (SE)	Difference in LS mean (SE)	P-value for treatment comparison vs Placebo
Study 1	SPID24	-25.9 (3.33)	-43.7 (3.22)	-17.8 (4.50)	**<0.001**
	SPID48 (Primary endpoint)	-97.8 (6.53)	-122.8 (6.28)	-25.0 (8.81)	**0.005**
Study 2	SPID24 (Primary endpoint)	-47.7 (3.89)	-79.0 (3.89)	-31.3 (4.71)	**<0.001**
	SPID48	-121.1 (8.23)	-180.8 (8.23)	-59.7 (9.97)	**<0.001**

Abbreviations: LS=least squares; SE=standard error; SPID48=sum of pain intensity differences through 48 hours post first dose; SPID24=sum of pain intensity differences through 24 hours post first dose

Least squares mean (standard error) of pain intensity difference from baseline over 48 hours are shown for each Study in Figure 1. For both studies, patient reported outcomes at both Hour 24 and Hour 48 demonstrated statistically significantly better effectiveness of pain control for IV tramadol 50 mg over placebo, and treatment with IV tramadol 50 mg resulted in statistically significantly less rescue medication used than placebo over the treatment periods.

Figure 1: Least Squares Mean (Standard Error) of Pain Intensity Difference by Evaluation Time Point over the 48-Hour Study Period: Bunionectomy and Abdominoplasty ITT Population

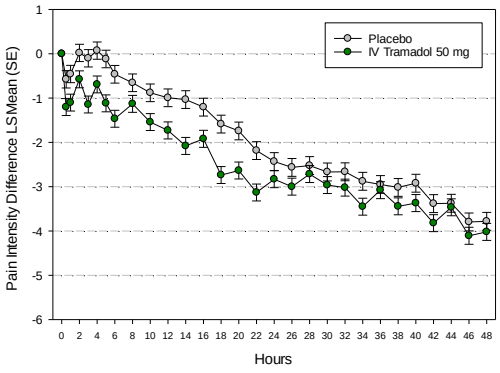
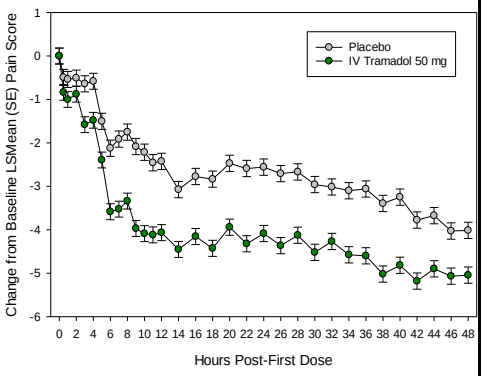
Study 1: Bunionectomy	***Study 2: Abdominoplasty***
	

Table 14: Key Secondary Efficacy Endpoint Comparisons between IV Tramadol 50 mg vs Placebo by Study (Studies 1 and 2)

Study	Endpoints	Statistics	Placebo	IV Tramadol 50 mg	Difference in LS mean (SE)	P-value for treatment comparison
Study 1	48-Hour Total Rescue Used (mg)*	Median	1200	800	N/A	**0.002**
	PGA (24 Hour)	LS mean (SE)	1.5 (0.11)	2.3 (0.10)	0.8 (0.14)	**<0.001**
	PGA (48 Hour)	LS mean (SE)	1.8 (0.11)	2.6 (0.11)	0.8 (0.15)	**<0.001**
Study 2	PGA (24 Hour)	LS mean (SE)	2.2 (0.11)	3.0 (0.11)	0.9 (0.13)	**<0.001**
	PGA (48 Hour)	LS mean (SE)	2.4 (0.11)	3.2 (0.11)	0.8 (0.13)	**<0.001**
	24-Hour Total Rescue Used (mg)*	Median	400	400	N/A	**<0.001**

*Rescue medication was ibuprofen 400mg
Abbreviations: LS=least squares; SE=standard error; PGA=Patient Global Assessment

NDA 213231

COMPLETE RESPONSE

Avenue Therapeutics, Inc.
c/o Veristat, LLC
134 Turnpike Road, Suite 200
Southborough, MA 01772

Attention James Bammert, PharmD
Senior Regulatory Strategist & Authorized US Agent

Dear Dr. Bammert:

Please refer to your new drug application (NDA) dated and received December 10, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tramadol Hydrochloride 50 mg/mL injection.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

(1) Your product, intended to treat patients in acute pain who require an opioid, is not safe for the intended patient population.

You have demonstrated a statistically significant difference between tramadol IV 50 mg and placebo on the primary endpoint in Study AVE-901-102 and primary and secondary endpoints in Study AVE-901-103.

However, in both studies, the pain intensity difference (PID) at early time points and the time to meaningful pain relief indicate that tramadol IV has a delayed onset of analgesia—likely beyond 2 hours. The opioid-related analgesic effect of IV tramadol is exerted mainly through its major metabolite, O desmethyltramadol (M1). When given by the IV route, there is a delay in the formation of M1, explaining the delayed onset of effect.

The delayed onset of analgesia, combined with your product's administration as a standing dose that is not titrated to effect, poses a potentially serious safety issue for the intended patient population. Specifically, your intended patient population requires an opioid. If a patient requires an analgesic between the first dose of your drug and the onset of analgesia, a rescue analgesic would be needed. The likely choice for prescribers would be another opioid, such as an immediate-release formulation. However, this would result in opioid "stacking"

and increase the likelihood of opioid-related adverse effects, including respiratory depression, which is a concern for even tramadol IV alone. Because of this, the benefits of this product do not outweigh the safety concerns. Other intravenous opioids, with a faster onset of effect, are available and can be more flexibly and safely titrated to effect while avoiding the dangerous practice of stacking multiple opioids.

There may be patients, those with genotypes associated with faster and extensive metabolism of M1, who experience onset of relief within approximately an hour. However, it is this same group of patients who may have increased risk of opioid overdose. There are no data in your application that support prospective identification of a population who may have a more favorable benefit-risk profile with this product.

Information needed to resolve the deficiency:
Identify a population for which tramadol IV is safe and effective for the management of acute pain.

PRODUCT QUALITY

(2) In regard to the terminal sterilization of the drug product via autoclave IDs 40750 and 40760, your intention to complete the previously requested terminal sterilization validation studies as part of process validation in November 2020 and submit the validation report as a post-approval commitment is acknowledged. However, review of adequate terminal sterilization validation is required prior to NDA approval.

Information needed to resolve deficiency:
Provide information for additional successful HP/BI challenge runs for a total of 3 runs per load size per autoclave. The information should include:

- Description of the relevant loads.
- Dates of performance.
- Validation cycle parameters.
- Validation acceptance criteria.
- The number and placement of TCs / BIs (a diagram would be helpful).
- Thermal and/or F_0 data.
- BI challenge and control results.
- BI incubation conditions (time and temperature).
- Complete BI information (genus/species, D-value, manufacturer, lot number, expiry, manufacturer's stated spore concentration and confirmed spore concentration).

PRESCRIBING INFORMATION

(3) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

PROPRIETARY NAME

(4) Please refer to correspondence dated, March 9, 2020, which addresses the proposed proprietary name, ONPREFA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing.

If you have any questions, call Jaimin Patel, Regulatory Project Manager, at (301) 796-0412.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
10/09/2020 05:12:15 PM

NDA 213231

COMPLETE RESPONSE

Avenue Therapeutics, Inc.
c/o Veristat, LLC
134 Turnpike Road, Suite 200
Southborough, MA 01772

Attention James Bammert, PharmD
Senior Regulatory Strategist & Authorized US Agent

Dear Dr. Bammert:

Please refer to your new drug application (NDA) dated and received December 10, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride 50 mg/mL injection.

We acknowledge receipt of your amendment dated February 12, 2021, which constituted a complete response to our October 9, 2020, action letter.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

(1) The information provided in the resubmission is not adequate to support the proposed indication for tramadol IV in the management of moderate to moderately severe pain in adults in a medically supervised health care setting, alone or in combination with other analgesics.

As discussed in the complete response letter dated October 9, 2020, there is a delayed onset of analgesia with intravenous administration of tramadol, as demonstrated in clinical trials (Study AVE-901-102 (bunionectomy) and Study AVE-901-103 (abdominoplasty)).

While the primary endpoint was met for both studies, meaningful pain relief was delayed (accounting for the use of rescue medication, e.g., ibuprofen), and some patients never achieved pain relief:

- Study AVE-901-102: The median time to meaningful pain relief (321 minutes) is not interpretable because of the high number of censored outcomes. 50% of patients (69/139) in the tramadol IV arm did not report meaningful pain relief in 6 hours after treatment.

- Study AVE-901-103 (in which a morphine treatment (4 mg every 4 hours) was included to compare Tramadol IV to the standard opioid treatment in a post-operative setting): The median time to meaningful pain relief was 106 minutes for tramadol IV 50 mg, and 42 minutes for morphine IV 4 mg. 34% of patients (48/141) did not report meaningful pain relief in 6 hours after treatment. Evidence from multiple endpoints demonstrated a quicker onset of analgesia for morphine 4 mg than for tramadol 50 mg over the first 2 hours of treatment.

These studies were not designed to study the analgesic effect of tramadol IV combined with another analgesic. Therefore, the data do not support an indication for tramadol IV alone or in combination with other analgesics to manage moderate to moderately severe pain.

Intravenous opioid products are intended to be used in the management of pain that is not controlled by analgesics in other drug classes. Therefore, combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids. In addition, combining tramadol IV with another opioid increases the risk of opioid "stacking" and of additive adverse reactions, including over-sedation and respiratory depression. The delayed and unpredictable formation of the active metabolite M1 adds another variability factor. The potential risk of opioid "stacking" is a serious safety concern that may not be mitigated with a Risk Evaluation and Mitigation Strategy (REMS) or Postmarketing Requirements and Postmarketing Commitments (PMRs/PMCs).

In summary, the delayed and unpredictable onset of analgesia with tramadol IV does not support its benefit as a monotherapy to treat patients in acute pain, and there is insufficient information to support that tramadol IV in combination with other analgesics is safe and effective for the intended patient population.

PRESCRIBING INFORMATION

(2) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm

response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

PROPRIETARY NAME

(3) Please refer to your correspondence dated, February 12, 2021, which addresses the proposed proprietary name, ONPREFA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jaimin Patel, Regulatory Project Manager, at (301) 796-0412.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
06/11/2021 12:30:15 PM

NDA 213231

APPEAL DENIED

Avenue Therapeutics, Inc.
c/o Veristat, LLC
134 Turnpike Road, Suite 200
Southborough, MA 01772

Dear Dr. Bammert:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride 50 mg/ml injection (Onpefra).

I also refer to your July 27, 2021, request for formal dispute resolution received on July 27, 2021. The appeal concerned the Complete Response (CR) letters issued for your application by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on October 9, 2020, and June 11, 2021.

Billy Dunn, MD, Director of the Office of Neuroscience, has delegated your Office of Neuroscience level appeal to me, the Deputy Director of the Office of Neuroscience.

I have carefully reviewed the materials you submitted in support of your appeal, as well as reviews, meeting minutes, decision memoranda prepared by FDA staff and the CR letters. I have also consulted with staff in DAAP and other relevant Agency staff.

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

You submitted New Drug Application 213231, a 505(b)(2) application, on December 10, 2019, to seek approval of IV tramadol 50 mg for the management of moderate to moderately severe pain in adults in a medically supervised health care setting. Your application references FDA's previous findings of safety and efficacy for oral tramadol (Ultram; NDA 20281).

DAAP issued a CR Letter to your original application on October 9, 2020. DAAP concluded that your product, intended to treat patients in acute pain who require an opioid, is not safe for the intended patient population. DAAP agreed that you have demonstrated a statistically significant difference between IV tramadol 50 mg and placebo on the primary endpoint in Study AVE-901-102 and primary and secondary endpoints in Study AVE-901-103. However, DAAP noted that in both studies, the pain intensity difference (PID) at early time points, and the time to meaningful pain relief,

both indicate that tramadol IV has a delayed onset of analgesia—likely beyond 2 hours after treatment initiation in a substantial proportion of patients taking IV tramadol for acute pain relief. DAAP concluded that the delayed onset of analgesia, combined with the fact that your product is not titrated to effect, poses a potentially serious safety issue for the intended patient population. DAAP noted that your intended patient population requires an opioid, and that if a patient requires an analgesic between the first dose of your drug and the onset of analgesia, a rescue analgesic would be needed. In DAAP's opinion, the likely choice for prescribers would be another opioid, such as an immediate-release formulation, which may result in opioid "stacking," and increase the likelihood of opioid-related adverse effects, including respiratory depression. DAAP noted that other intravenous opioids, with a faster onset of effect, are available, and can be more flexibly and safely titrated to effect while avoiding the stacking of multiple opioids. DAAP also noted that there are no data in your application to support the prospective identification of a population that may have a more favorable benefit-risk profile with your product. DAAP offered as a possible path forward the identification by you of such a population. The Complete Response Letter also included a product quality issue related to terminal sterilization of the drug product.

A type A post-action meeting was held on November 19, 2020. According to the meeting minutes, you disagreed with DAAP's thinking that opioid level analgesia is needed if a patient requires an analgesic between the first dose of IV tramadol and the onset of analgesia, and disagreed with DAAP's concerns about opioid stacking. The minutes note your belief that communication in labeling should be an effective way to address the clinical deficiency, and DAAP's reaction that the labeling approach was explored during the NDA review, but not considered feasible given the nature of the deficiency. DAAP, however, agreed to review your proposed revised labeling and justifications for the labeling revisions.

Following the post-action Type A meeting, you resubmitted the NDA for IV tramadol with revised proposed labeling. Your resubmission did not include any new data. You revised the proposed indication to "the management of moderate to moderately severe pain in adults in an NDA medically supervised setting, **alone or in combination with other analgesics** [emphasis added]". You also proposed a new "limitations of use" section in labeling, describing that the product is "for use only in a medically supervised setting, such as hospitals, ambulatory surgical centers, and emergency departments", and that "because of delayed onset of analgesia in some patients, Onprefa may be supplemented with a rapid onset analgesic such as a non-steroidal anti-inflammatory drug." DAAP issued a second CR Letter on June 11, 2021. In that letter, DAAP noted that the studies you conducted were not designed to study the analgesic effect of IV tramadol combined with another analgesic, and do not support an indication for IV tramadol alone or in combination with other analgesics to manage moderate to moderately severe pain. DAAP continued to be concerned about the delayed onset of analgesia with intravenous administration of tramadol, and also expressed a concern that, as intravenous opioid products are intended to be used in the management of pain that is not controlled by analgesics in other drug classes, a combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids.

DAAP further noted that combining IV tramadol with another opioid increases the risk of opioid "stacking" and of additive adverse reactions, including over-sedation and respiratory depression. DAAP also described their conclusion that the potential risk of opioid "stacking" is a serious safety concern that may not be mitigated with a Risk Evaluation and Mitigation Strategy. The product quality issue noted in the first CR letter was resolved in the second review cycle.

A second post-action Type A meeting, in which you presented arguments similar to those from your formal dispute resolution request (FDRR), was conducted on July 23, 2021. As you know, Dr. Dunn and I attended that meeting.

In your FDRR, you state that "IV tramadol demonstrated adequate onset and clinically meaningful pain relief at early timepoints and throughout the trials in the NDA". While I agree with you, and with DAAP, that you have demonstrated a statistically significant difference between IV tramadol 50 mg and placebo on the primary endpoint in Study AVE-901-102 and primary and secondary endpoints in Study AVE-901-103, establishing an analgesic effect of the product, the data are clearly consistent with a delayed onset of effect compared to IV morphine. I note that your proposed labeling in the resubmission recognizes the delayed onset of effect, as it includes a statement that "because the median time to meaningful pain relief was two hours or more after Onprefa administration in clinical studies, an additional analgesic may be needed after the initial dose to more rapidly achieve the desired analgesic effect in some patients". I agree with DAAP's position that the delayed onset of effect raises a safety concern about a risk of opioid "stacking," with potentially serious opioid-related adverse reactions, that has not been adequately addressed in your application.

In your FDRR, you also argue that "IV tramadol's onset of action did not lead to opioid stacking in the studies submitted in the NDA and the data demonstrated IV tramadol's effectiveness against Schedule II opioids and its utility in the post-operative setting." Your further state that "the Division's position that rescue for IV tramadol must be another opioid contradicts the data in the NDA, labeling for other drug products, and clinical practice," and that "while there is no evidence of unusual risk with IV tramadol, the use of multiple opioids concurrently is common and recognized as safe in a medically supervised setting." It must be noted, however, that your Phase 3 clinical trials were designed to assess the safety and efficacy of IV tramadol as a monotherapy, and that opioid "stacking" could not be adequately evaluated in the trials because the use of another opioid as rescue medication was not allowed. There is a lack of data in your application to inform what rescue therapies may be used in a real-world setting, or to rule out that opioids would be used in addition to (and possibly concomitantly with) your product in a substantial number of patients. As you know, DAAP acknowledged at the July 23, 2021, type A meeting that multimodal regimens are important and useful, but noted the lack of data to inform the safety of using IV tramadol along with another opioid therapy, which is an important deficiency in the context of the delayed onset of efficacy.

You also argue in your dispute resolution request that "the Anjeso approval set a precedent that labeling is sufficient to address delayed onset of an IV analgesic," and

note that “FDA recently approved Olinvyk despite the risks of opioid stacking, and despite noting that the drug had no safety advantage and showed less pain reduction than morphine.” As DAAP discussed with you at the type A meeting, Anjeso is not relevant to the situation with your product, as Anjeso is an NSAID, and does not raise a concern for opioid “stacking.” Olinvyk also presents a different clinical scenario, in which a daily cap in dosing is present because of concerns about QT prolongation. There is also a clear expectation based on the approved labeling that Olinvyk and other opioids would be used sequentially, and not concomitantly. Therefore, I do not find these precedents relevant to your product.

Finally, you argue that “the theoretical risk of opioid stacking must be weighed against the benefit of IV tramadol to the broader public health relative to available approved analgesic drugs in the post-operative setting.” Specifically, you concluded by “highlighting the potential public health benefit of approving a Schedule IV opioid that can serve as a therapeutic alternative to Schedule II intravenous opioids for post-operative pain in light of the parenteral tramadol experience outside the U.S.” However, it is important to note that the clinical deficiency that precluded IV tramadol’s approval is not relevant to its abuse potential or scheduling, and that DAAP has clearly considered the risks and benefits of your product in the context of the pain control armamentarium.

As a path forward, you should discuss with DAAP the design of a potential study(ies) to assess the safety of IV tramadol in combination with other analgesics, including opioids, reflecting use in a real-world setting. Alternatively, as the product is marketed in a number of countries, you may be able to leverage existing large postmarketing databases to estimate the risk of opioid “stacking” with IV tramadol. This approach would require a careful consideration of the applicability of those data to the U.S. proposed indication and dosing recommendations. Whether such an approach based on postmarketing data would acceptably address the issues in the CR letters would be a matter of review, and I encourage you to discuss the content of such a resubmission with DAAP prior to its official submission to the Agency.

Questions regarding next steps as described in this letter should be directed to Jaimin Patel, Regulatory Health Project Manager, Division of Regulatory Operations for Neuroscience- Anesthesiology, Addiction Medicine and Pain Medicine at (301) 796-0412.

This constitutes the final decision at the Office of Neuroscience level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center’s Formal Dispute Resolution Program Manager, Melissa Sage.

Any questions concerning your appeal should be addressed to Melissa Sage at 301-796-6449 or via e-mail at Melissa.Sage@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
08/26/2021 05:22:06 PM

NDA 213231

INTERIM RESPONSE TO APPEAL–-
INPUT NEEDED FROM ADVISORY COMMITTEE

Attention: James Bammert, Pharm.D.
Senior Regulatory Strategist

Avenue Therapeutics, Inc.
c/o Veristat, LLC
134 Turnpike Road, Suite 200
Southborough, MA 01772

Dr. Bammert:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride 50mg/mL injection (Onpefra).

I also refer to your August 31, 2021, request for formal dispute resolution received on August 31, 2021. The appeal concerned the Complete Response (CR) letters issued for your application by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on October 9, 2020, and June 11, 2021.

I also refer to your request for formal dispute resolution, received on July 27, 2021, to the Office of Neuroscience (ON), and the denial of the appeal by Eric Bastings, MD, on August 26, 2021.

I have reviewed your appeal and conclude that additional input is needed to reach a decision. Accordingly, we will convene an advisory committee meeting and seek advice from the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management (DSARM) Advisory Committee. We will notify you when the meeting is scheduled and work with you on the planning, as appropriate.

As outlined in the aforementioned CR letters, the Division acknowledged that tramadol IV met the primary endpoint, sum of pain intensity difference (SPID), and a weighted average of the change in pain scores at time intervals across the 24- or 48-hour timeframe after start of study treatment in both pivotal trials. However, the primary deficiency identified by the Division is a delayed onset of analgesia attributed to a delay in formation of the M1 metabolite (O desmethyltramadol) which provides most of the mu-opioid receptor agonist activity of tramadol. M1 is formed by O-demethylation of

tramadol in the liver by cytochrome P450 2D6 which has high genetic polymorphism. The intravenous administration of tramadol bypasses this first-pass metabolism to the active metabolite. The Division concluded that the delayed onset of action of your product may result in a risk of "opioid stacking" due to the administration of other short-acting opioids to treat delayed analgesia. This potential risk could not be explored in your clinical trials because rescue with an opioid was not permitted.

The Division and Office of Neuroscience also noted the faster onset of analgesia with morphine, the active comparator in Study AVE-901-103. This observation along with the fixed dosing regimen of tramadol IV led to their conclusion that other intravenous opioids with a faster onset of effect are available and can be more flexibly and safely titrated to effect while avoiding the stacking of multiple opioids.

Your August 31, 2021, FDRR to the Office of New Drugs level requested a meeting with the deciding official. This meeting was held on September 28, 2021. The summary of your clinical development program, including findings from your open-label safety study and experience with tramadol IV used outside of the United States was very informative; however, I believe a discussion at an advisory committee meeting is warranted to address certain issues. Also, as part of the Opioids Action Plan, FDA announced on April 26, 2018, the expanded use of advisory committees before approving any NDA for an opioid that does not have abuse-deterrent properties. Although tramadol is approved in the United States, you are seeking a new formulation and new use of an opioid for which the review division has identified a potential risk that outweighs its benefit. To reach a decision on your appeal, I have determined that I need additional input from the Advisory Committee.

The Advisory Committee will be asked to discuss a number of issues that may include:

- Importance of time of onset of action and risks related to delayed onset of action of an opioid analgesic for the management of acute pain
- Appropriate methods for evaluating onset of action of an analgesic
- The mechanism of analgesia and complex metabolism of tramadol and its role in acute pain management in the inpatient setting
- The relevance of opioid scheduling in the management of acute pain in an inpatient setting

I will respond to your appeal within 30 calendar days after the Advisory Committee meeting.

If you have any questions, call Cathryn Lee, MSN, CRNP at (301) 796-1394.

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, MD
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY T THANH HAI
10/21/2021 04:40:43 PM