SPONSOR BRIEFING DOCUMENT FOR TRAMADOL HYDROCHLORIDE INJECTION

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Meeting Date: February 15, 2022

NDA 213231

SPONSOR

Avenue Therapeutics, Inc.

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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Table 1: Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
ATC	Anatomical/Therapeutic/Chemical
BMI	Body mass index
CMH	Cochran-Mantel-Haenszel
CRL	Complete Response Letter
CSR	Clinical study report
CYP	Cytochrome P450
DAAP	Division of Anesthesiology, Addiction Medicine and Pain Medicine
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of Treatment
ER	Extended release
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonization
IM	Intramuscular
IRB	Institutional Review Board
ISS	Integrated Summary of Safety
IV	Intravenous
LoE	Lack of efficacy
LSMean	Least squares mean
M1	O-desmethyl tramadol
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NMU	Non-medical use
NPRS	Numerical Pain Rating Scale

Abbreviation or Specialist Term	Explanation
NSAID	Nonsteroidal anti-inflammatory drugs
OND	Office of New Drugs
ORAE	Opioid related adverse event
PID	Pain intensity difference
PK	Pharmacokinetic(s)
PRN	Pro re nata (As needed)
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SOC	System organ class
SPID	Sum of pain intensity differences
SPID24	Sum of pain intensity differences through 24 hours post first dose
SPID48	Sum of pain intensity differences through 48 hours post first dose
TEAE	Treatment-emergent adverse events
US	United States
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

Tramadol is a centrally acting atypical opioid analgesic with two distinct and synergistic mechanisms of actions for pain relief including both opioid and non-opioid mode of analgesia. This NDA for IV tramadol is a 505(b)(2) application with reference to ULTRAM relying upon both clinical trial data from our own development program as well as the efficacy and safety demonstrated in the ULTRAM NDA (approved in 1995), and 26-year documented efficacy and safety history of oral tramadol, currently a Schedule IV controlled substance. Outside the U.S., parenteral tramadol has been widely used in over 70 countries including most parts of Europe for about 30 years (Grünenthal 2017) with about 370 million doses used in Europe from 2010 to 2019 (IQVIA).

The purpose of this briefing document is to provide the background on intravenous (IV) tramadol developed to provide a Schedule IV opioid alternative for patients with post-operative acute pain in a medically supervised setting (hospitals and surgical centers, etc.). Our focus is to provide a review of the data with specific focus on the issues raised by FDA's review division (Division of Anesthesia, Addiction Medicine, and Pain Medicine or DAAP) in the Complete Response Letters (CRL-1 and CRL-2). The Sponsor submitted a New Drug Application (NDA) for IV tramadol in 2019 and has received two CRLs with the same core clinical deficiency from DAAP.

DAAP acknowledged that IV tramadol met the primary endpoint in both Phase 3 efficacy studies, which were designed with Division input and agreed upon by the Division. DAAP did not describe any specific safety findings from any of the Phase 3 studies that would preclude approval. The core clinical issue cited in the two CRLs is that the Division concluded that IV tramadol's onset of analgesia, delayed according to the two-stopwatch method (but not by other clinical parameters as discussed below), would lead to a safety concern of opioid stacking with excessive use or overdosing of opioids, and as such, "IV tramadol is not safe for the intended population (CR-1)."

The Sponsor submitted a Formal Dispute Resolution Request (FDRR) above the Division level.[1] FDRR above the Division level is a structured process for sponsors that wish to appeal a scientific and/or medical issue to the office or center level. The first step in this appeal process was to submit our appeal to the Office of Neuroscience (ON) which denied the appeal. The appeal was subsequently submitted to the next management level which is the Office of New Drugs (OND). The Sponsor met with the deciding official on September 28, 2021, and subsequently received a Dispute Appeal Interim Response letter dated October 21, 2021, where the deciding official stated:

- "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

[1] Formal Dispute Resolution: Sponsor Appeals Above the Division Level. Guidance for Industry and Review Staff. Good Review Practice. November 2017

> 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 OND deciding official also stated in the letter, "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." Further, "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."

The OND deciding official stated that the Advisory Committee will be asked 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

We provide our perspectives on these issues in the Executive Summary.

This briefing document is structured with an Executive Summary, followed by a detailed description of IV tramadol's clinical development history, clinical pharmacology, efficacy, safety, a summary of a comprehensive epidemiology survey, and references. To facilitate easier review, hyperlinks (in blue) are provided in the Executive Summary to the more detailed information (in the body) or to external references.

1.1. Organization and Nomenclature

This document is organized with the following sections:

There are five items in the appendices:

- Appendix A: Complete Response Letter – 1 (October 9, 2020)
- Appendix B: Complete Response Letter – 2 (June 11, 2021)
- Appendix C: Formal Dispute Resolution Request Submitted to the Office of New Drugs
- Appendix D: ULTRAM label (09/2021)
- Appendix E: Literature search results of clinical trials with IV tramadol (Submitted to the NDA)

Names of studies discussed in this document:

- Study AVE-901-101: Study 101 (Phase 1, pharmacokinetics or PK study)
- Study AVE-901-102: Study 102 (Phase 3 efficacy study, bunionectomy)
- Study AVE-901-103: Study 103 (Phase 3 efficacy study, abdominoplasty)
- Study AVE-901-104: Study 104 (Phase 3 open-label safety study)

2. EXECUTIVE SUMMARY

The Sponsor conducted a robust Phase 3 program with detailed input from the Division, including study designs, outcome measures, and all key parameters that were agreed upon by the Division. IV tramadol demonstrated safety and efficacy in two pivotal Phase 3 studies in two distinct surgical models (Study 102 and Study 103), with a similar overall efficacy on the primary endpoint as IV morphine (Study 103). The open-label study, Study 104, demonstrated safety and effectiveness of IV tramadol in patients undergoing additional types of painful procedures as part of a multimodal analgesic approach. DAAP acknowledged that IV tramadol met the efficacy primary endpoint in both pivotal Phase 3 studies and has not described any specific safety findings from the program that would preclude approval.

The primary deficiency identified by DAAP in the two CRLs (CRL-1 and CRL-2) is a delayed onset of analgesia as measured by the two-stopwatch method. DAAP concluded that this may result in a risk of "opioid stacking," i.e., concomitant use of different opioids, due to the administration of other short-acting opioids to treat delayed analgesia. We understand that DAAP's concern to be that a delay in pain relief and early administration of rescue opioid, which may peak simultaneously with the M1 levels from tramadol, will place patients at increased risk for respiratory depression and opioid overdose.

The Sponsor disagrees with DAAP's conclusions about the safety of concomitant use of IV tramadol and an opioid rescue in patients needing additional analgesia. To provide a framework for a discussion on FDA's concerns, we will first summarize background information on IV tramadol, post-operative pain, IV tramadol PK, Phase 3 efficacy results, safety information in the NDA (Phase 3, ex-U.S. safety summary etc.). Our discussion focusing the core clinical issue and FDA's concern will be provided from the following summary in Section 2.6.

- Onset of action: The stopwatch metric of onset of action was not consistent with other data that informs onset of analgesia. Using the totality of evidence, it is clear that IV tramadol demonstrates a clinically adequate onset of action. We note that there is not a standardized methodology for collecting and analyzing stopwatch data, and the results can be highly dependent and variable based upon data collection and analytical approaches. DAAP's position on the delayed onset is based on the stopwatch metric and does not consider other endpoints (PID, time to first rescue, and PGA) showing IV tramadol provided clinically meaningful pain relief at early timepoints. We will discuss the review and approval of ANJESO (IV meloxicam, approved in 2020), an intravenous NSAID analgesic labeled with a delayed onset, with attention to its stopwatch data in regard to other clinical parameters and how those parameters can be informative in defining a truly delayed onset.
- Risk for harm from opioid stacking: The use of the same or different opioid rescue for additional analgesia is common in the post-operative setting, whether the primary opioid is IV tramadol or other intravenous opioids such as IV morphine, IV hydromorphone, or IV fentanyl. First, there is no evidence that IV tramadol carries a greater likelihood that opioid rescue will be needed, as demonstrated in our clinical trials where pain was successfully managed with rescue ibuprofen or other non-opioids in the vast majority of the patients. Next, there are no data to support the idea that patients will be at risk for opioid overdose if they did receive opioid rescue with a 50 mg dose of IV tramadol, any more than any other IV opioid. As for DAAP's position that "combination therapy of an opioid with a non-opioid is

not consistent with the intended use of intravenous opioids (CR-2)," we will summarize data that show the use of multimodal analgesia with non-opioids and opioids has become standard of care. We will use the recently approved OLINVYK (oliceridine) as an example of FDA approving a Schedule II opioid based on clinical trials with an NSAID rescue and as an example of use of a Schedule II opioid that will rely on additional opioid analgesics to provide analgesia for a full 24-hour period. Further, we describe the 30-year European experience with IV tramadol, which entails the use of hundreds of millions of doses, without any problematic safety signal due to the use of opioid rescue.

- Variability of tramadol metabolism: Formation of M1 from tramadol is mediated by CYP2D6, the polymorphism of which leads to a range of M1 levels in patients. However, our data demonstrates that this does not lead to unpredictability of opioid activities. In Study 103 which included a morphine treatment arm, the onset of opioid related adverse events indicates that the onset of opioid activities of IV tramadol are as predictable as IV morphine. Because of the dual mechanism of action of tramadol, the IV tramadol dosing regimen was able to provide good pain relief with a relatively low quantity of opioid analgesia during the Phase 3 programs, as well as provided predictable PK for both the parent compound tramadol and the key metabolite M1. Because of bypassing first pass effects the opioid activity from IV tramadol is lower than the approved oral dosage, which is used in outpatient use without supervision of medical personnel. The CYP2D6 variability is accepted for oral tramadol and is not a safety risk clinically in our studies.
- Medically supervised setting (hospitals, surgical centers): Inpatient management of post-operative pain provides a setting where patients are monitored allowing for detection of signs and symptoms from opioid-mediated sedation and respiratory depression. Any patient unable to tolerate IV tramadol with or without opioid rescue will be under the care of experienced staff. IV tramadol is intended for use ONLY in a medically supervised setting.
- Public health: There are no currently approved intravenous Schedule IV opioids approved for use in post-operative pain. IV tramadol was developed to provide a therapeutic alternative to Schedule II opioids for patients with post-operative pain who need an opioid for pain management, and as such, could reduce reliance on intravenous Schedule II opioids in this setting. Clinicians in the U.S. have adopted multimodal analgesia to improve pain management and to reduce opioid use in the postoperative setting. Similarly, IV tramadol would provide clinicians with another tool in their armamentarium and the ability to select an opioid with less abuse liability than the usual Schedule II parenteral opioids.

It is therefore the Sponsor's position that IV tramadol has an adequate and acceptable clinical onset of action and does not result in an increased risk of opioid stacking or harm from opioid stacking. The 30-year history of the use of millions of doses of IV tramadol in Europe and other territories along with the 26-year U.S. history of oral use provide additional support for approval of IV tramadol.

2.1. Background on IV Tramadol

The intent of this application is to bring IV tramadol to the US market as a Schedule IV alternative to the intravenous Schedule II opioids for patients with po-operative pain in a medically supervised setting. The IV tramadol NDA was submitted as a 505(b)(2) application

with relying in part on FDA's approval of ULTRAM® (NDA 20281), an oral tramadol product that has been marketed in the U.S. since 1995. The pharmacokinetic, efficacy, and safety data from the IV tramadol NDA are summarized in Sections 2.2, 2.3, and 2.4 and additional details can be found in Section 4, 5, and 6.

2.1.1. IV tramadol's dual mechanism of analgesia

Tramadol is a centrally acting atypical opioid that is differentiated from conventional opioids such as morphine or codeine (which is a pro-drug of morphine) by its dual mechanism of analgesia. It combines weak mu opioid agonist activity and non-opioid mode of pain relief and both opioid and non-opioid mechanisms are important contributors to tramadol's analgesic effect (Raffa 1992, Raffa 1996). In addition to being a weak mu opioid receptor agonist, the parent compound, tramadol, reduces pain signal transmission in the CNS by inhibiting the reuptake of monoamine neurotransmitters, norepinephrine and serotonin. Tramadol is metabolized via CYP2D6 to the active metabolite O-desmethyl tramadol (M1), with an affinity to μ receptors that is higher than that of the parent compound but overall an order of magnitude lower than that of morphine (Raffa 1992, Gillen 2000). The overall analgesic action of tramadol comes from these multiple pharmacological mechanisms of opioid and nonopioid actions that results in 'synergistic potentiation,' i.e., the degree of pain relief is greater than the sum of the individual components of its action (Shipton 2000).

The non-opioid mechanism of pain relief is especially relevant in understanding how IV tramadol provides pain relief at early timepoints, and has been confirmed in both human and nonclinical studies (Dayer 1994). Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests (Ultram label). The role of monoaminergic modulation to the analgesic effect of tramadol has also been studied in humans. In humans, the μ-antagonist naloxone produced only a partial decrease (~30%) of tramadol's antinociceptive effect on pain thresholds. However, the combined administration of both opioid and monoaminergic antagonist yohimbine significantly decrease the effect of tramadol (1996). The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (Ultram label). Further, it has been demonstrated in human volunteers that even poor metabolizers (with low levels of M1) have analgesia via the monoamine reuptake inhibition mode of pain relief (Enggaard 2006).

It is also documented in the literature that at doses that provide similar pain relief as conventional opioids, tramadol shows a lesser degree of opioid mediated effects such as constipation, fewer effects on the respiratory system and a lower abuse and dependence potential Grond 2004).

2.1.2. European and ex-U.S. experience with parenteral tramadol

Tramadol has been available in Germany since 1977. To date, parenteral tramadol is available in over 70 countries in Europe, Asia, the Middle East, Africa, South America, Australia and New Zealand. In Europe alone, approximately 370 million doses of parenteral tramadol were administered in the ten years from 2010 to 2019 (IQVIA).

Clinicians in EU and other territories use tramadol currently with non-opioids to reduce or avoid opioids with stronger abuse potential (Anekar 2021). They use parenteral tramadol because of its documented advantages compared to pure opioids on respiratory function (Bosenberg 1998, Houmes 1992, Langford 1998, Mildh 1999, Tarkkila 1997, Tarkkilla 1998, Vickers 1995),

cardiovascular system (Ellmauer 1994) and gastrointestinal motor function (Wilder-Smith 1997, Wilder Smith 1999).

Approximately 370 million doses of parenteral tramadol were administered in European hospitals from 2010 to 2019 (IQVIA) and there is no setting restriction on the use of parenteral tramadol in Europe (SmPC for Zydol 2020). Intravenously administered tramadol is used both intra-operatively (Teunkens 2016) and post-operatively as it can be used in the PACU soon after completion of surgery and in patients unable to take oral therapy. Tramadol is often the only opioid used in patients with post-operative pain, and its use in combination with non-opioid medicine provides adequate pain relief while reducing the use of more abusable opioids (Grond 2004; Lee 1993).

The safety findings from decades of European and ex-U.S. experience with parenteral tramadol were summarized and submitted to the NDA (Section 2.5).

2.1.3. Scheduling of tramadol in the U.S.

IV tramadol is a new route of administration of a well-known drug in the U.S. and is expected to be in the same schedule as oral tramadol. Oral tramadol's current schedule IV classification reflects the scientific understanding that tramadol has less abuse potential than conventional pure mu opioid agonists and is supported by extensive preclinical, clinical, post-marketing and epidemiological studies conducted by various academic institutions, sponsors, and government agencies, including the recent report on tramadol by the WHO expert committee on drug dependence in November 2018 (WHO 2018), as well as our review of the data on the abuse of tramadol in the U.S. and in European countries where IV formulation is available (Section 7).

2.2. IV Tramadol Fills a Gap in Post-Operative Pain Management

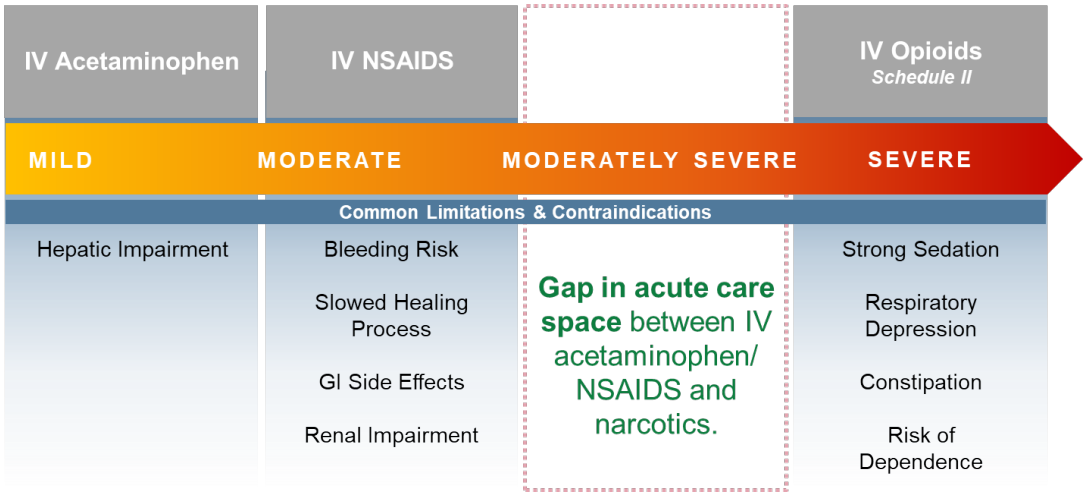
There are currently three approved pharmaceutical classes of intravenous (IV) analgesics in the U.S.: acetaminophen, NSAIDs and conventional (Schedule II) opioids that are pure mu agonists. In situations where non-opioids such as acetaminophen and NSAIDs cannot provide sufficient analgesia, are not tolerated, or are contraindicated, the only available systemic analgesic options for U.S. clinicians and patients are Schedule II opioids.

Research has shown that multimodal analgesia – the use of more than one pharmacological mechanism to alleviate pain -- may provide superior pain relief and decreased consumption of conventional (i.e., Schedule II) opioids (Elia 2005, McLaughlin 2018). The rationale for this approach is to achieve additive or synergistic effects by addressing multiple mechanisms of pain and to reduce side effects (Kehlet 1993) by using lower doses of individual drugs. The practice of multimodal regimens for patients with post-surgical pain is also recommended in the guidelines by multiple professional societies (Chou 2016). In practice, all post-operative patients get multimodal analgesia, but non-opioids may be insufficient on their own and most patients after medium-sized and major surgeries will need repeated doses of opioids in addition to NSAIDs and acetaminophen.

However, there is a gap (Figure 1) between non-opioids and conventional opioids with high abuse potential, which contributes to the fact that intravenous conventional Schedule II opioids are still heavily relied upon in the acute pain setting in the U.S. (Kessler 2013), despite the fact

that short-term exposure to highly abusable opioids can lead to chronic opioid dependence (Brummett 2017; Koepke 2018; Lee 2017; Mehra 2018).

Figure 1: Gap in Intravenous Analgesics for Post-operative Pain Management



Source: Avenue Presentation

IV tramadol is intended to fill this gap for the management of post-operative pain in a medically supervised setting when an opioid is warranted. Notably, contemporary analgesic practice is evolving to embrace the principles of enhanced recovery after surgery (ERAS), in particular shifting away from epidurals, PCA opioid administration to intermittent iv or oral dosing, in the context of a multimodal regimen comprising acetaminophen, NSAIDs, local anesthetics, and selected other adjuvants such as ketamine, magnesium and/or gabapentinoids (Baker 2020, Ljungqvist 2017, Melnyk 2011). These techniques are increasing the proportion of patients for whom tramadol is sufficient, and an opioid with higher abuse potential can be avoided. As such, IV tramadol would offer an alternative to Schedule II opioids when the physician or patient want to avoid the higher abuse potential inherent in Schedule II opioids. The availability of IV tramadol could reduce the extent of exposure of U.S. patients to Schedule II opioids in the post-operative setting, just as it has for millions of patients located in many countries outside the U.S.

Opioids remain an important tool in modern anesthesia and postoperative pain management (Echeverria-Villalobos 2020). There is no direct data to determine that a limited exposure to intravenous Schedule II opioids increases risk for opioid use disorder that may be prevented by using intravenous Schedule IV opioid, however the availability of IV tramadol would allow further advancement of the concepts of multimodal analgesia to reduce exposure to highly addictive opioids. U.S. clinicians are already avoiding or reducing the use of opioids with multimodal analgesia to decrease both ORAEs and addiction/dependence risk to their patients (Nicholas 2022). There is no reason not to provide them with an option for a drug with a lower abuse potential, as IV tramadol would be a further advancement allowing them to use a less addicting opioid before using a more addicting opioid.

2.3. IV Tramadol Pharmacokinetics (PK)

Tramadol exerts its analgesic effect through two complementary and synergistic mechanisms—by binding to the μ-opioid receptor and inhibiting the reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the M1 metabolite to mu-opioid receptors. The non-opioid analgesic effect is mediated through the inhibition of norepinephrine and serotonin by the parent compound, which blocks pain signal transmission in the spinal cord.

M1 is primarily metabolized from tramadol in the liver by cytochrome P450 2D6 (CYP2D6). M1 formation is dependent on CYP2D6. According to the ULTRAM label, about 7% of the population has reduced activity of the CYP2D6 isoenzyme and are therefore "poor metabolizers" whose tramadol levels are 20% higher than "extensive metabolizers" while M1 levels are 40% lower.

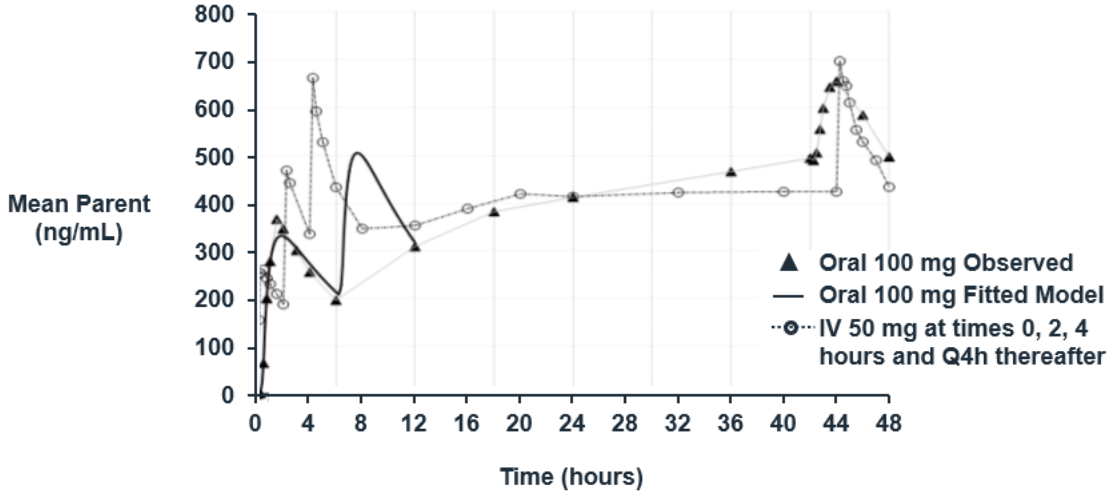
When administered orally, tramadol undergoes first-pass metabolism and approximately 25 to 30% of tramadol is converted to M1 before it has a chance to enter the systemic circulation. In contrast, when tramadol is administered intravenously, no first-pass metabolism occurs resulting in less conversion to M1. This means that IV tramadol has less opioid activity than oral tramadol.

2.3.1. IV tramadol dosing regimen was chosen based on a PK Study (Study 101)

The Sponsor developed IV tramadol in a manner that builds on the documented safety profile of oral tramadol. The IV dosing regimen used in the Phase 3 studies (50 mg given at Hours 0, 2, 4, and every 4 hours thereafter) was discussed in detail with the Division and tested as one of the two IV regimens in a Phase 1 PK study in healthy volunteers (Study 101). The regimen was chosen to move into Phase 3 because it provided a predictable pharmacokinetic (PK) profile resulting in a similar exposure of parent compound tramadol to that of the approved oral tramadol dosage (100 mg Q6H, ULTRAM label) based on Cmax and AUC at steady state.

Compared to oral tramadol 100 mg Q6H, IV tramadol provides a more rapid increase in tramadol concentrations and a quicker analgesic effect attributed to tramadol's ability to block monoamine reuptake. Figure 2 shows the pharmacokinetic modeling of these data from Study AVE-901-101. The concentration vs time curve for the oral 100 mg dose was simulated and is plotted with the actual IV 50 mg curve. These data allow for visual comparison of the concentration vs time curves between the two formulations. Differences in concentrations between the oral and IV regimens are minimal once steady state is reached. The final IV dose in this study was given at Hour 44, and that interval demonstrated the C_{max} was comparable to the oral dosing C_{max}.

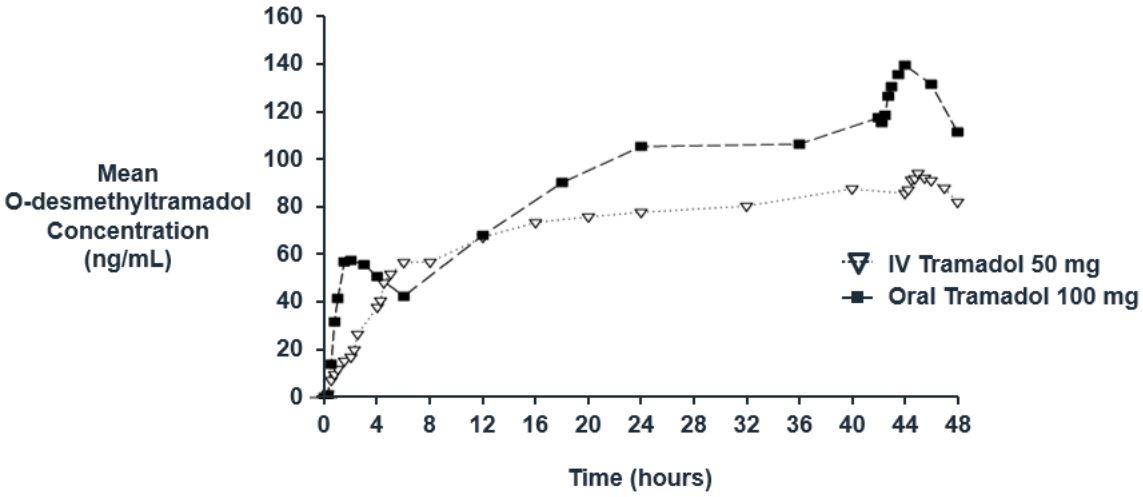
Figure 2: Mean Tramadol Plasma Concentration versus Time Curves for IV 50 mg Dosing Regimen and Oral 100 mg Q6H: Observed and Fitted (Study AVE-901-101)



Source: AVE-901-101 CSR

On the other hand, IV tramadol provides a lower exposure to M1 due to the lack of first pass metabolism (Figure 3). In terms of M1 levels, Cmax is 30% lower and AUC is 20% lower with IV administration than oral tramadol 100 mg Q6H.

Figure 3: Mean M1 Plasma Concentration versus Time Curves for IV Tramadol 50 mg Dosing Regimen and Oral Tramadol 100 mg Q6H (Study AVE-901-101)



Source: AVE-901-101 CSR

Note that only trough concentrations were collected after Hour 8 until the last dosing interval and that near-steady state for M1 is reached by about 12 hours with the IV Tramadol. Beyond that time, trough levels rise only minimally, indicating that the Cmax following each trough would

also increase only minimally. M1 levels decrease fairly rapidly, with a half-life of approximately 6 to 7 hours. Table 2 provides the key pharmacokinetic parameters for parent compound tramadol and key metabolite M1 after administration of oral tramadol 100 mg Q6H or IV tramadol 50 mg over 48 hours.

Table 2: Plasma Pharmacokinetic Parameters of IV and Oral Tramadol and M1 over 48 hours (Study AVE-901-101)

	Intravenous (n=14)		Oral (n=17)	
	Parent Compound Tramadol	Key Metabolite M1	Parent Compound Tramadol	Key Metabolite M1
Parameter	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ng/mL)	736 ±152	96.6 ±24.5	701±178	146±37.4
AUC_{0-48} (h•ng/mL)	20540 ±4906	3427 ±889.9	19140±5172	4349±1139
T_{max} (h)	30.0 ± 19.89	45.0 ± 1.59	44.0 ± 1.01	44.0 ± 1.12

Source: AVE-901-101 CSR

2.3.2. IV tramadol PK parameters were confirmed in Population PK studies

Population PK studies were conducted on approximately 33% of patients in the two Phase 3 efficacy studies (Section 2.4). Blood was collected for pharmacokinetic analysis of tramadol and M1 at 0, 0.25, 0.5, 2.25, 2.5, 4, 4.25, 4.5, 8, 8.25, 24.5, 44, 44.25, 44.5, and 48 hours. CYP2D6 genotyping was not requested by FDA for these studies. Exposure parameters for tramadol and M1 were similar to the PK study (AVE-901-101), as shown in Table 3. Of note, standard deviations of the observed M1 levels were relatively small, indicating low variability due to CYP2D6 polymorphism. The population PK study confirms that exposure to M1 with IV tramadol is lower than that from oral tramadol 100 mg Q6H.

Table 3: Plasma Pharmacokinetic Parameters of Tramadol and M1 in Efficacy Studies (Study AVE-901-102 and Study AVE-901-103)

	Study 102 (n=54)		Study 103 (n=50)	
	Parent Compound Tramadol	Key Metabolite M1	Parent Compound Tramadol	Key Metabolite M1
Parameter	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ng/mL)[1]	1340 ±1580	72.4 ±23.0	846 ±664	76.9 ±23.7
AUClast (h•ng/mL)	24500 ±15300	2690 ±910	22600 ±6340	2850 ±865
T_{max} (h)	19.3 ± 17.8	37.5 ± 11.5	23.9 ± 17.9	35.0 ± 12.9

[1] Mean tramadol levels in Study 102 were higher than in Study 103 due to sampling errors at a few Study 102 clinical study sites (samples were drawn from the arm where tramadol was being infused).

Source: AVE-901-102 CSR and AVE-901-103 CSR

2.3.3. Advantages of fixed dosing regimen

The fixed dosing regimen tested in the IV tramadol Phase 3 program provides a predictable PK profile for both the parent compound tramadol and the active metabolite M1. The synergistic actions of both the monoamine reuptake inhibition and the opioid activity offer two key advantages. First, clinicians can use the regimen in a multimodal approach based on anticipated pain levels post procedures rather than waiting for patients to have moderate to severe break-through pain that will require rescue with bigger doses of opioid. An example is that the traditional way of providing IV opioids with patient-controlled analgesia (PCA) is becoming outdated as the field is moving towards maximizing pain control with preventive analgesia in a multimodal approach. The IV tramadol dosing regimen fits into this strategy by providing a consistent and sustained level of pain control resulting in high-level of patient satisfaction and reducing the need for opioid rescue due to analgesic gaps commonly seen with short-acting IV opioids, as demonstrated in Study 104. Second, just like all other intravenous analgesics for acute pain approved based on doing pivotal studies in post-operative pain, clinicians may decide to administer the first dose of IV tramadol intra-operatively and continue IV tramadol post-operatively. The predictable PK of the dosing regimen makes it very safe for clinicians to fit IV tramadol into their practice.

2.4. Phase 3 Efficacy Results

Although the Division acknowledged that IV tramadol met the primary endpoint in both pivotal studies, the efficacy results will be summarized here to help inform the risk-benefit analysis of IV tramadol. Additional details can be found in Section 5. The Sponsor conducted a robust Phase 3 program and closely followed the Division's advice during development. The Phase 3 program consists of three studies: two double-blind, placebo-controlled efficacy studies in two distinct pain models (Study AVE-901-102 and Study AVE-901-103) and an open-label safety study (Study AVE-901-104).

The IV tramadol Phase 3 program is comparable to recent programs that supported the approval of other intravenous opioid analgesics. In these programs, the efficacy studies were adequate and well-controlled, and designed to assess the efficacy of monotherapy of the product candidate and included the use of a specified rescue analgesic from a different pharmacological class on an as-needed basis. The design of these registrational studies is suited for regulatory approval and used by sponsors in the acute pain space to eliminate confounders and reduces as much as possible the large placebo effect that exists in analgesic trials. It is important to note the studies are not intended to reflect how the agent would be used in the 'real world'; rather, these registrational studies are experimental models (Figure 15 and Figure 17) designed to assess an analgesic's safety and efficacy versus placebo using a number of outcome measures (Table 15). For example, in contrast to clinical practice, patients were withheld post-surgical pain and anesthetic medications until their pain levels reached moderate to severe before treatment initiation. This is compared to current practice where clinicians administer analgesic medication to prevent

anticipated pain from the surgeries. Additionally, even though the study drug is administered intravenously, the rescue medicine is generally oral analgesic.

In the IV tramadol Phase 3 program, Study 102 included two different doses of IV tramadol (Figure 15) and Study 103 had an active comparator (Figure 17), which was IV morphine 4 mg administered as an IV push with the same dosing schedule as IV tramadol. While there is not a regulatory requirement for an investigational drug to be equivalent or superior to an active comparator, IV morphine, an active comparator, was included for assay sensitivity and to assess the safety profile of IV tramadol relative to an approved therapy. The morphine dosage was chosen based on dosing for other development programs and to achieve a similar level of efficacy so we could compare the safety profile of the two active arms. The Sponsor chose the IV morphine dosage based on a literature search of studies conducted in Europe and provided FDA with references and justification prior to study initiation. Additionally, the IV morphine dosage is in the range of other recently conducted abdominoplasty studies (Singla 2017, Singla 2019). Even though there was no formal statistical comparison between the two active arms, Study 103 allowed a general comparison of both safety and efficacy of IV tramadol and IV morphine. In both efficacy studies, rescue medication was an NSAID (ibuprofen 400 mg) allowed once every 4 hours. Study 104, an open-label safety study, provided further safety data and assessed how IV tramadol would fit into the clinical practice of multimodal analgesia without another opioid in 251 patients following major surgeries. It was designed to confirm the clinical experience from European clinicians who use parenteral tramadol to avoid or limit their use of more abusable opioids.

The study populations enrolled in the Phase 3 studies (Table 16 and Table 18) are consistent with the type of patients intended to be treated with IV tramadol and are like those in pivotal clinical trials used to establish efficacy of other analgesic products. The design of the studies, the enrolled population, the surgical models, and statistical analysis method were agreed to by the Division. The three Phase 3 studies enrolled a total of 1030 patients. The Division reviewed the protocols and agreed to the designs for each of the Phase 3 trials before they were initiated. In all our Phase 3 studies, patients knew that they could discontinue at any time to receive another opioid if they were not getting enough pain relief.

IV tramadol was shown to be safe and effective in Phase 3 efficacy studies with established primary endpoints of summed pain intensity difference at 24 and 48 hours (SPID24 and SPID48) from baseline, as shown in Table 4. These endpoints have been accepted by the Division as appropriate and used for the evaluation of other analgesics.

Table 4: Primary Efficacy Endpoints: SPID24 and SPID48 LS Mean[1] (SE) Comparisons between IV tramadol 50 mg vs Placebo by Study

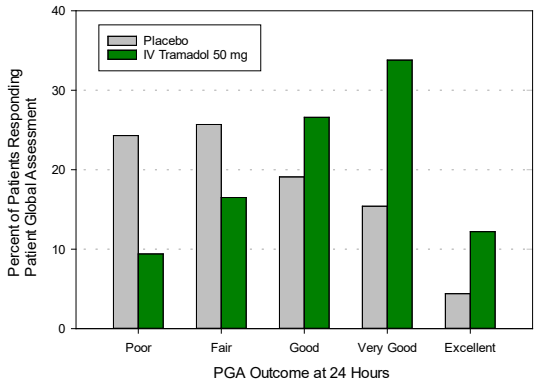
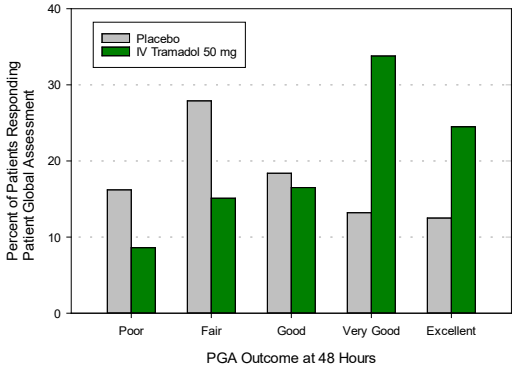
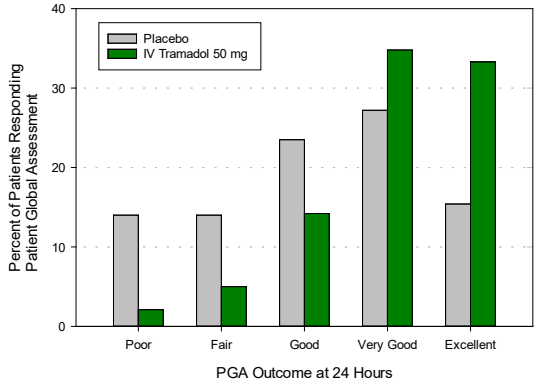
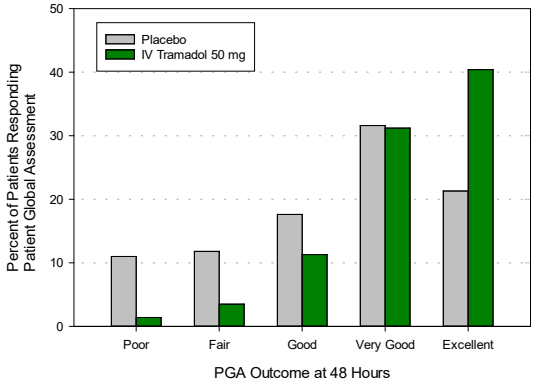
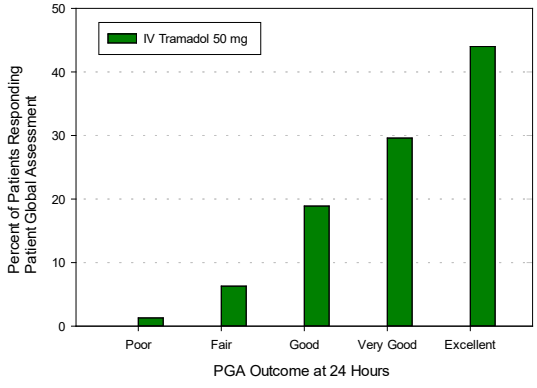
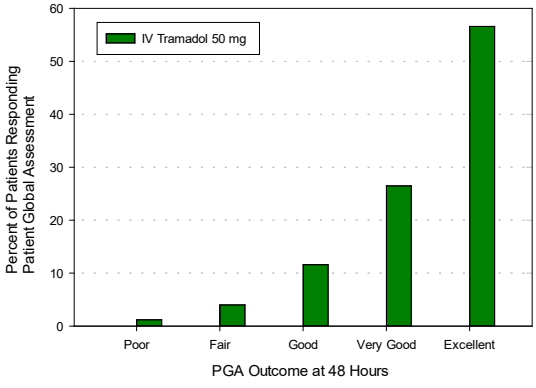
Study	Primary Endpoints	Placebo LS mean (SE)	Tramadol 50 mg LS mean (SE)	Difference in LS mean (SE)	P-value for treatment comparison vs Placebo
AVE-901-102 Bunionectomy	SPID48	-97.8 (6.53)	-122.8 (6.28)	-25.0 (8.81)	**0.005**
AVE-901-103 Abdominoplasty	SPID24	-47.7 (3.89)	-79.0 (3.89)	-31.3 (4.71)	**<0.001**

[1] LS mean, LS mean difference (treatment – placebo), p-values were the combined results obtained from an analysis of the multiply imputed datasets using an analysis of covariance model with treatment as the main effect, pooled study center and baseline Numerical Pain Rating Scale score as covariates.

Source: AVE-901-102 CSR and AVE-901-103 CSR

The key secondary endpoints showed that IV tramadol provided clinically meaningful benefit over the placebo arm on use of rescue medication and Patient Global Assessment (PGA) at 24 and 48 hours (Table 17 and Table 19). The PGA from the Phase 3 studies, which captures patients' perception of the treatment, is presented in Figure 4.

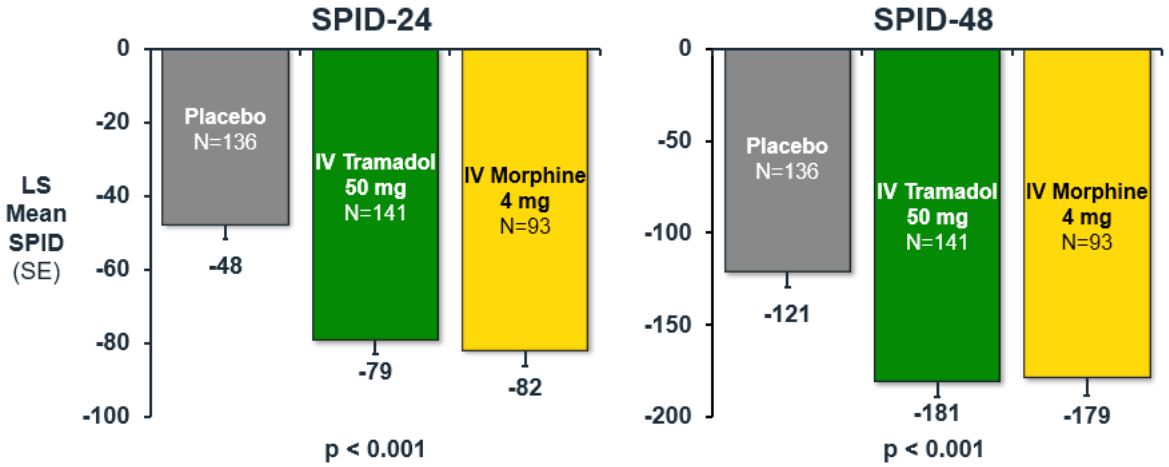
Figure 4: Patient Global Assessment of Treatment for Phase 3 Studies (Studies AVE-901-102, AVE-901-103, AVE-901-104)

	PGA at Hour 24	PGA at Hour 48
AVE-901-102		
AVE-901-103		
AVE-901-104		

Source: AVE-901-102 CSR, AVE-901-103 CSR, and AVE-901-104 CSR

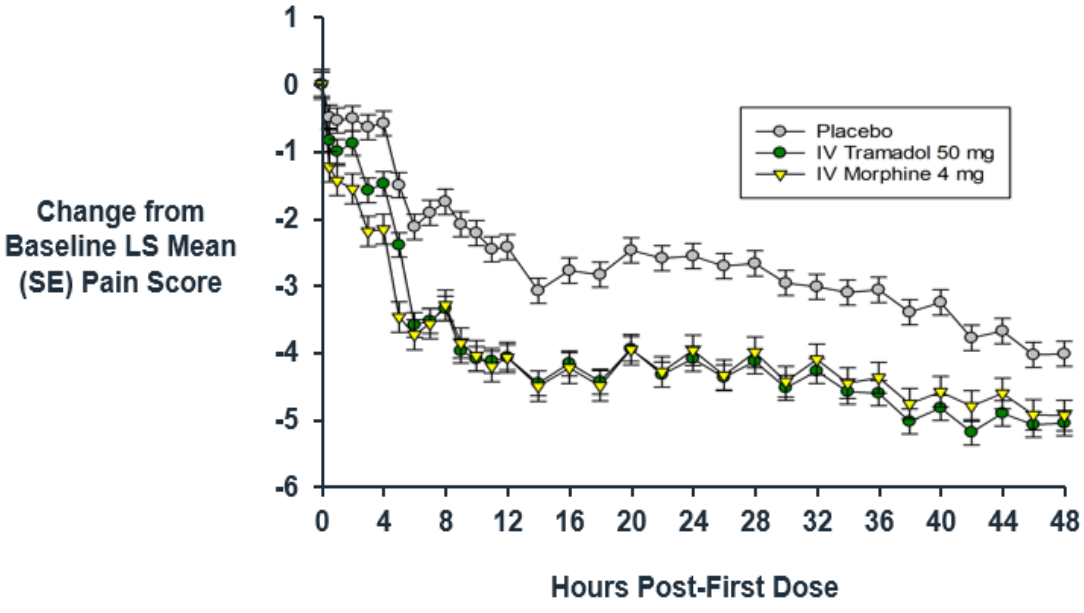
Importantly, IV tramadol demonstrated similar overall analgesic efficacy to IV morphine on the primary (SPID24) and key secondary endpoint (SPID48) in Study 103, as shown in Figure 5. The PID over time profile for both tramadol and morphine (as well as placebo) is shown in Figure 6.

Figure 5: LSMean (SE) SPID24 and SPID48 Comparisons[1] across Treatment Groups (Study AVE-901-103)



[1]P value on both SPID24 and SPID 48 graphs represent IV tramadol versus placebo.
Source: AVE-901-103 CSR

Figure 6: LSMean (SE) Pain Intensity Differences for IV tramadol 50 mg, Placebo and Morphine (Study AVE-901-103)



Source: AVE-901-103 CSR

A detailed discussion of the data relating to pain relief at early timepoints is presented in the discussion on onset in Section 2.6.1.

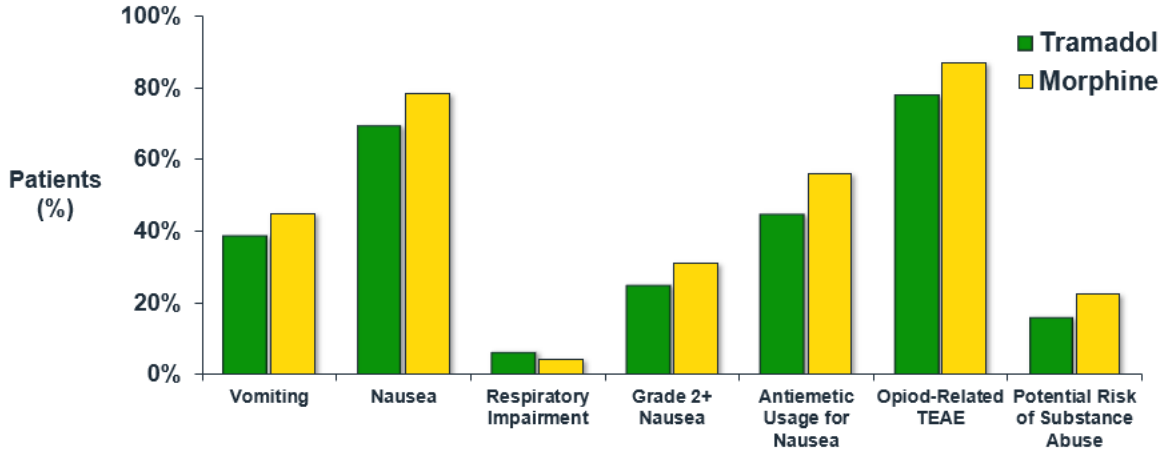
The open-label safety study (Study 104) confirmed the safety and effectiveness of IV tramadol in a multimodal analgesic approach in a variety of patients (Table 20) undergoing painful surgeries such as total joint replacement procedures. None of the 251 patients discontinued due to inadequate analgesia, and at the end of treatment, 95% of the patients rated their treatment (without another opioid) as good, very good, or excellent (Figure 4).

2.5. Phase 3 Safety Results, Safety from Outside the U.S. and Epidemiology on Abuse Potential

Although the safety of IV tramadol as determined in the three Phase 3 studies is not in question, the safety results will be summarized here to help inform the risk-benefit analysis of IV tramadol. The evidence for safety in the NDA consists of three components: (1) clinical trial data from the IV tramadol development program, (2) safety information from outside the U.S., and (3) epidemiological data related to the abuse of tramadol in the US, as well as in countries where tramadol is available in both an IV and an oral formulation. This NDA also relies on the Agency's prior findings of safety for ULTRAM and its 26-year history in the U.S.

The safety database included 533 patients treated with IV Tramadol 50 mg in the Phase 3 development program and exceeded Division's expectation of 500 patients for a 505(b)2 application referencing oral tramadol. IV tramadol was well tolerated with a similar side effect profile as oral tramadol and did not have any unexpected safety findings. It demonstrated a side effect profile similar to IV morphine in Study 103, as shown in Figure 7. Together, the studies demonstrate that IV tramadol is safe and effective in patients with post-operative pain in a medically supervised setting.

Figure 7: Risk of IV tramadol vs Morphine for Key Opioid-Associated Safety Endpoints (Safety Population) (Study AVE-901-103)



Source: AVE-901-103 CSR

The safety findings from the Phase 3 program are consistent with the safety experience from Europe and other regions where parenteral tramadol has been widely used for decades. The safety summary from sources outside the U.S. in the NDA included a literature review (citations provided in Appendix E) and a Vigibase report, which consists of individual case reports from WHO member countries. In the VigiBase analysis, the Sponsor pre-defined three adverse events of interest in reports listing tramadol: seizure, serotonin syndrome and respiratory depression. Table 5, from the Vigibase report in the NDA, shows the relative frequencies of these events from AE reporting of the use of Oral and IV tramadol. The percentages displayed reflect the percentage of total AE reports for each tramadol formulation.

Table 5: Number and percentage of total reports for 3 adverse events of interest in reports listing Tramadol (i.e., tramadol alone, paracetamol/tramadol, ketolorac/tramadol) 2009-2019 (Source: VigiBase)

Adverse event of interest	Oral Tramadol (all)		IV Tramadol (all)	
	Number of reports	Percentage	Number of reports	Percentage
Seizure	553	1.0%	118	0.3%
Serotonin syndrome	242	0.5%	23	0.1%
Respiratory depression	109	0.2%	16	0.04%

Source: VigiBase report (Module 5.3.6 of NDA)

Respiratory depression was an AE of interest for oral and IV tramadol and their commonly prescribed combination products in our review of the VigiBase. It should be noted that no denominator is available for such AE reporting systems, and hence, incidence and prevalence rates cannot be derived. From 2009 to 2019, respiratory depression was reported 109 times for oral tramadol accounting for 0.2 % of all AE reports for oral tramadol worldwide. It was reported 16 times for parenteral tramadol in the same timeframe and accounts for 0.04% of the AE reports for parenteral tramadol worldwide. Despite the potential limitations in this spontaneous reporting database (reporting bias, duplication, confounding, and heterogeneity), IV tramadol in general appears to be comparable to oral tramadol with respect to the number of AE reports. The analysis of the literature and Vigibase data also failed to raise a safety signal regarding respiratory depression.

The Sponsor also conducted an in-depth epidemiology survey with high-quality data from well-known third-party sources to assess the abuse potential of tramadol in the U.S. and in countries where the IV formulation is available (Section 7). The conclusions are that reports of abuse with tramadol are infrequent, both in absolute number and relative to other prescription opioids, and that abuse of tramadol via injection is uncommon relative to oral tramadol in both the U.S. and in countries where it is available.

2.6. Sponsor's discussion of Issues in the CRLs

The core clinical issue that prevented approval in the two CRLs is that the Division concludes that IV tramadol's onset of analgesia, delayed according to the two-stopwatch method, would lead to a safety concern of opioid stacking (i.e., concern of an increased risk of respiratory depression from concomitant use of another opioid). The Sponsor will discuss our perspectives on these issues.

- Section 2.6.1. IV tramadol's onset of action is adequate based on clinically relevant pre-defined endpoints that inform onset.
- Section 2.6.2. IV tramadol does not carry increased risk of opioid rescue and FDA's concern about adverse events from opioid rescue on top of IV tramadol has not been reported as a safety signal in wide clinical use outside the U.S.
- Section 2.6.3. Variability of CYP2D6 does not lead to unpredictability of opioid activities and this variability is accepted for oral tramadol, which has a 26-year history in the U.S.
- Section 2.6.4. Medically supervised setting (hospitals, surgical centers) further mitigates FDA's concern for risk of overdose caused by opioid rescue on IV tramadol.
- Section 2.6.5. Benefit-risk considerations based on the Phase 3 data, foreign safety information, and public health benefit of making a less-abusable IV opioid available supports the approval of IV tramadol.

2.6.1. IV tramadol's onset of action is adequate based on clinically relevant pre-defined endpoints that inform onset.

While there was a delayed onset on the stopwatch metric, IV tramadol consistently showed an adequate onset on clinically meaningful endpoints that inform the pain relief evaluation in the Phase 3 program. These evaluations were pre-defined endpoints in Phase 3 studies and include Pain Intensity Difference (PID) at early timepoints, time to first use of rescue medicine, and PGA 24 which were consistent with each other and across the two studies. The totality of the data demonstrates that IV tramadol provides clinically meaningful pain relief at appropriately early timepoints.

FDA's position on IV tramadol's onset of action is based only on the stopwatch metric, which can yield very different results based on evaluation and analytical methods

The onset of analgesia is conventionally measured in clinical studies with the two-stopwatch method. Patients are instructed to stop the first stopwatch when they first perceive pain relief and stop the second stopwatch when they feel meaningful pain relief. Onset of analgesia is the median time to meaningful pain relief on the second stopwatch (patients must also press the first stopwatch to confirm that they have had a preceding perceptible pain relief to be eligible).

However, the stopwatch metric can provide different results depending on how it is collected and analyzed. There is no guidance on the correct way to collect and analyze the data and FDA has accepted different methods. There is also no guidance or policy on the required threshold of achieving meaningful pain relief within an hour. The Division first indicated to us, in a post-meeting note following a pre-NDA meeting, that their expectation was an IV analgesic must have an onset of action on the stopwatch metric within an hour (This note is on Page 58 of

FDRR). However, it appears that this threshold is arbitrary and, to our knowledge, not driven by any actual data or any guidance or policy on acute pain. While it may be reasonable to have an expectation that a drug used for acute pain treatment will have an onset within a certain time interval, as we will discuss, the onset of pain relief should be evaluated by multiple measures, especially if there is reason to believe that one method may not accurately reflect pain relief. Also, from a regulatory perspective of consistency, as we will discuss with the ANJESCO (IV meloxicam) approval, the Agency has determined that this threshold is not a requirement for approval and can be handled by appropriate labeling.

The stopwatch should be reviewed in the context of other relevant clinical endpoint as there is not clear methodology on the conduct or evaluation of this type of investigation required by the Division. As such results can be quite variable from different methods of data collection and analysis that have been used by different sponsors and accepted by the Division.

Avenue used the most conservative methods to collect the stopwatch data and the most conservative methods to analyze the stopwatch data

First, there is not a standard way to collect the stopwatch metric. In our Phase 3 studies, we used a conservative approach as our intent was to understand meaningful pain relief driven by IV tramadol or placebo without rescue. If a patient took a rescue ibuprofen before they felt meaningful pain relief, the protocol stated that they were not allowed to stop the 2nd stopwatch and these patients were counted as not achieving meaningful pain relief.

Second, there is also not a standard way of analyzing the stopwatch metric. In our calculation of the median time to meaningful pain relief, we included all patients and counted patients who received rescue medication as if they failed to reach meaningful pain relief at 6 hours (duration for this endpoint). The stopwatch results using our conservative method of analysis, as submitted to the NDA, are summarized in Table 6.

Table 6: Time to Confirmed Perceptible Pain Relief, Meaningful Pain Relief, and First Rescue (Studies AVE-901-102 and AVE-901-103)

	Study AVE-901-102 (Bunionectomy)		**Study AVE-901-103 (Abdominoplasty)**		
	Placebo (N=136)	**IV Tramadol 50 mg (N=139)**	**Placebo (N=136)**	**IV Tramadol 50 mg (N=141)**	**IV Morphine 4 mg (N=93)**
Number (%) achieving confirmed perceptible pain relief	46 (33.8)	70 (50.4)	75 (55.1)	92 (65.2)	69 (74.2)
Median time to confirmed perceptible pain relief (minutes)	Did not achieve	167 minutes	69 minutes	27 minutes	5 minutes
Number (%) achieving meaningful pain relief	46 (33.8)	70 (50.4)	77 (56.6)	93 (70.0)	69 (74.2)
Median time to meaningful pain relief (minutes)	Did not achieve	321 minutes	145 minutes	106 minutes	42 minutes

Source: AVE-90-1-102 CSR, AVE-901-103 CSR

DAAP has not questioned the way we collected or analyzed the stopwatch metric. The Division based its conclusion of delayed onset on the stopwatch data we submitted to the NDA. DAAP's statement in CR-2 that "meaningful pain relief was delayed (accounting for the use of rescue medication, e.g., ibuprofen), and some patients never achieved pain relief" refers to the two-

stopwatch data, as it went on to say that "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." To our knowledge, DAAP has not done any sensitivity analyses or taken other endpoints into consideration.

FDA has accepted different methods of data collection and data analysis on the stopwatch metric

As part of the preparation for the AC, in exploration of the inconsistency of the stopwatch metric to other clinically important data informing onset, we examined the methodology used by ANJESO (based on publicly available information found in ANJESO Review). We note that the FDA accepted the methods used in the ANJESO program. In fact, the time to meaningful pain relief collected and analyzed using their methods appears in ANJESO's labeling (ANJESO label).

In ANJESO's case, patients could stop the second stopwatch indicating meaningful pain relief even after they receive rescue medication. The FDA reviewer stated in the ANJESO Clinical Review(s) (ANJESO Review) that "…the time to meaningful pain relief were evaluated using the double-stop watch method without regarding first use of rescue… The meaningful pain relief was achieved temporally two hours after oral dose of 5 mg oxycodone. Therefore, it could be argued that the meaningful pain relief was, at least partially, achieved by the 5 mg Oxycodone given earlier."

The Division also accepted the calculation of the median time to meaningful pain relief by censoring patients who took rescue medication at the time they took rescue medicine. That is why the time to meaningful pain relief can be calculated (~3 hours) when only 29% of patients in the ANJESO arm experienced meaningful pain relief in one of the studies (ANJESO Review). This contrasts with FDA statement in CR-2 that "(t)he 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…"

Our stopwatch outcome would be considerably better if we used other methods

In the absence of clear guidance from the FDA for this important endpoint, different sponsors have used different methods for data collection and data analysis. Table 7 summarizes how our methods of data collection and analysis compares to ANJESO (based on our interpretation of the publicly available information).

Table 7: Stopwatch Methodology Comparison[1]

	Data collection	
	Data collection	**Data analysis**
ANJESO (IV Meloxicam) NDA	Patients were allowed to stop the 2nd stopwatch even after taking rescue	Censor patients who never reached meaningful pain relief at the time they took rescue
IV Tramadol NDA	If a patient takes a rescue before pressing the 2nd stopwatch, they are not allowed to stop the 2nd stopwatch	Censor patients who needed rescue as if they never achieved meaningful pain relief (uniformly at 6 hours which is the end time for this endpoint)

[1]Based on our interpretation of the publicly available information found in ANJESO Review.

While it is not possible to know what the stopwatch metric would look like if our protocol had allowed patients to stop the 2nd stopwatch after taking rescue, like the sponsor of ANJESO did, we modeled the analysis of the stopwatch metric using the method as we understand it in the ANJESO Review. The results of time to meaningful pain relief for IV tramadol in the two efficacy studies are shown in Table 8. Instead of uniformly censoring patients who needed rescue at 6 hours and keeping the total patient pool steady for 6 hours (duration of the stopwatch metric), we censor them at the time of rescue in this analysis. So if a patient required rescue at one hour, he/she is taken out of the patient pool at one hour.

By this method, the median time to meaningful pain relief becomes considerably shorter for IV tramadol. IV tramadol's onset, still more than an hour on the stopwatch, is 135 minutes (versus 321 minutes with our method in the NDA) in Study 102 and 81 minutes (versus 106 minutes with our method in the NDA) in Study 103. For IV morphine, it does not change because very few patients needed rescue before its time to meaningful pain relief (42 minutes).

Please note that these analyses have not be submitted to the NDA. They are presented here to demonstrate that a different statistical methodology can have a dramatic influence on the median time to meaningful pain relief on the stopwatch outcome of onset of analgesia.

Table 8: Median Time to Meaningful Pain Relief Using Methods Used by Other Sponsors and Accepted by the FDA (Not submitted to the NDA1)

	Study AVE-901-102 (Bunionectomy)		**Study AVE-901-103 (Abdominoplasty)**		
	Placebo (N=136)	**IV Tramadol 50 mg (N=139)**	**Placebo (N=136)**	**IV Tramadol 50 mg (N=141)**	**IV Morphine 4 mg (N=93)**
Median time to confirmed perceptible pain relief	Did not achieve	55 minutes	66 minutes	25 minutes	5 minutes
Median time to meaningful pain relief	Did not achieve	135 minutes	90 minutes	81 minutes	42 minutes

Source: Avenue data.
[1]This analysis is shown here to demonstrate that different statistical methods can yield very different results on the stopwatch outcome.

The stopwatch metric must be reviewed in conjunction with clinical endpoints that inform onset

The above analysis demonstrates the fragility of the stopwatch metric (because it is heavily dependent on the methods of evaluation and analysis), as well as the importance of

demonstrating harmony with other clinical indicators of onset of action for accurate assessment of onset of action Therefore, for IV tramadol's onset of action, like any methodology, the interpretation of the stopwatch results should be guided by the limitations of the method. Focusing on the stopwatch metric alone can give an inaccurate assessment of the drug's onset effect, especially when there are different methodologies that can dramatically influence the outcome. Predefined clinical endpoints such as Pain Intensity Difference (PID) at early timepoints, time to first use of rescue medicine, and PGA 24 should be considered alongside stopwatch data to paint a complete picture of onset of action. ANJESO, discussed below, demonstrates what these other endpoints would look like in the setting of a truly delayed onset.

IV tramadol provided meaningful pain relief at early timepoints based on clinically relevant endpoints that inform onset

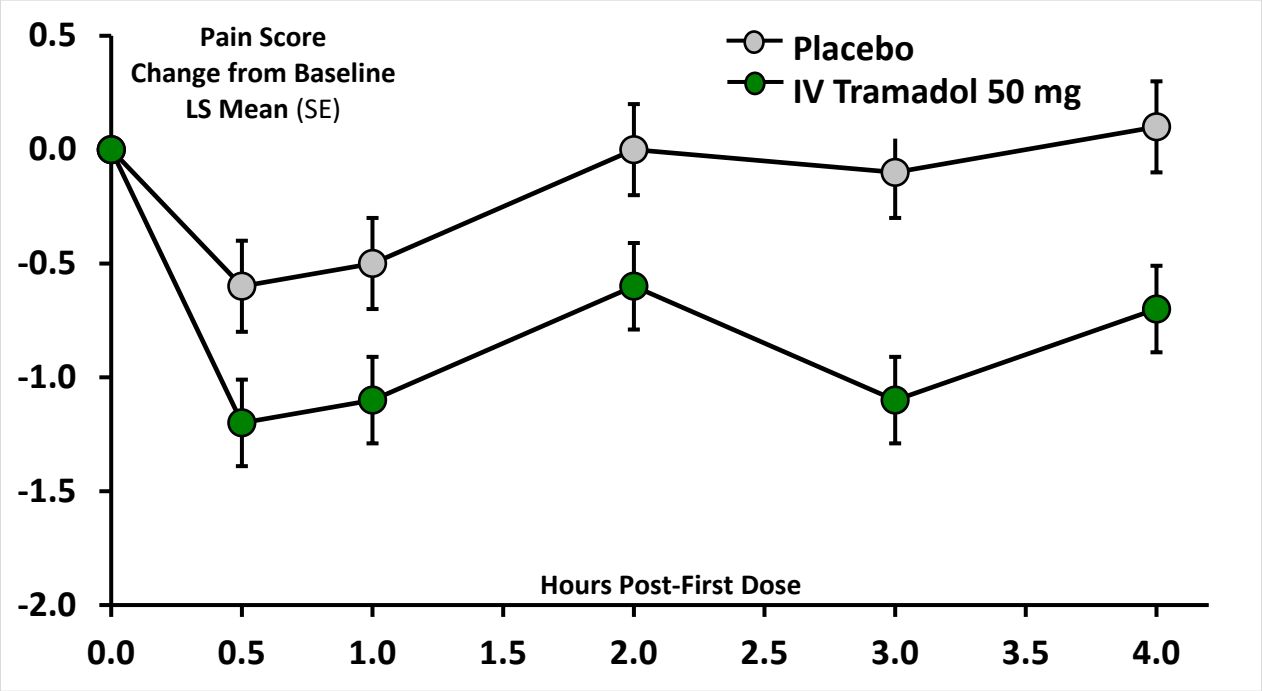
The stopwatch results contrast with the relevant clinical endpoints that fully define IV tramadol's onset of action. These endpoints, pre-defined for the Phase 3 studies include pain intensity difference (PID), time to first rescue and the patient reported outcomes (PGA) findings (Figure 4). These endpoints are directly linked to the ability of a drug to provide clinically meaningful pain relief at early timepoints. IV tramadol demonstrated separation from placebo early on these endpoints, which strongly support a clinically adequate onset of pain relief.

<u>IV tramadol separated from placebo on PID at early timepoints</u>

The pain intensity difference (PID) over the 24 and 48-hour treatment periods was a pre-defined analysis that allowed for assessment of the patient-reported pain intensity at regular and frequent time intervals. This patient reported outcome measure reflects pain levels reported directly from the patient to the study staff, and serves as the basis for the primary and key secondary endpoints. The PID endpoints are different from the stopwatch metric, in that pain scores are obtained on a predefined schedule (e.g., the patient is asked to rate their pain at scheduled times and is awoken if they are asleep to provide that score). Additionally, the PID requires a numerical value and comparison to the baseline that allows assessment of the time-course of pain relief robustly.

In Study 102, IV tramadol produced an average decrease in PI of 1.2 starting at 30 minutes post-start of treatment (the first measured time point). This is compared to an average decrease of 0.6 in the placebo group. The decrease in pain levels continued to be different through early timepoints, as shown in Figure 8.

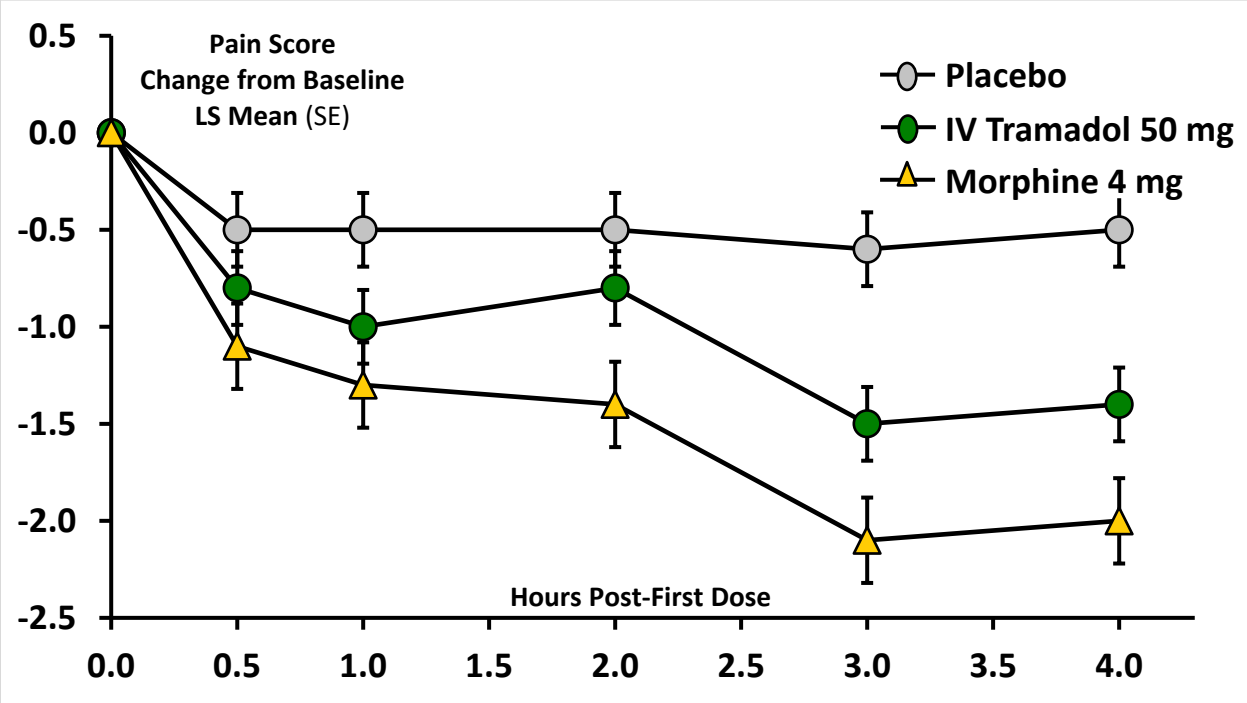
Figure 8: Pain Intensity Differences for IV Tramadol 50 mg versus Placebo 0 to 4 hours in Study AVE-901-102



Source: AVE-901-102 CSR

In Study 103, the IV tramadol PID curve separated from placebo by 30 minutes, as shown in Figure 9. The IV morphine's PID curve also separated form placebo by 30 minutes, although with a greater decrease than IV tramadol.

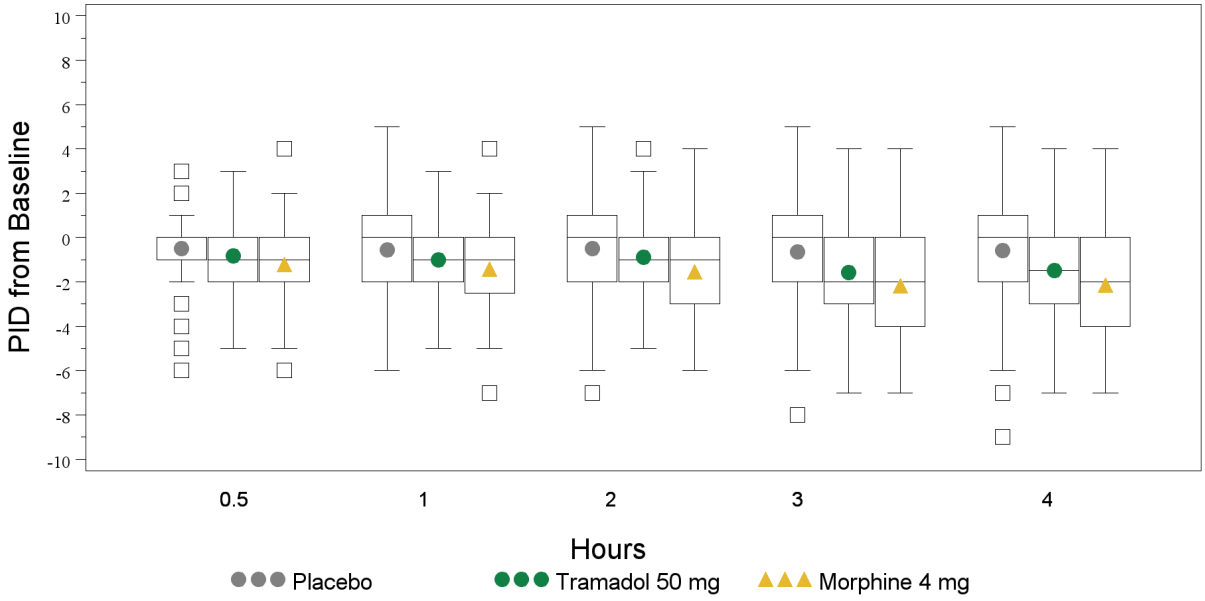
Figure 9: Pain Intensity Differences for IV Tramadol, IV morphine versus Placebo 0-4 hours in Study AVE-901-103



Source: AVE-901-103 CSR

The Sponsor also created a boxplot of the PID from Study 103 to examine the distribution of the response in different arms (Figure 10). The body of the boxplot consists of a box which goes from 25th percentile (Q1) to 75th percentile (Q3). Within the box, a horizontal line is drawn at the median, while a symbol depicts the mean. The two lines extending from the top and bottom go from Q1 to the smallest non-outlier in the data set and from Q3 to the largest non-outlier, respectively. Other outliers are indicated by the square empty box symbols. The PID in the boxplot are without imputation. The boxplot demonstrates that the distribution of the PID with IV tramadol compared to placebo shows a clear and immediate (at the first time point) benefit over placebo that continues throughout. Further, the boxplots shows that the general distribution of changes in PID from baseline (ie, when comparing the box plots to one another) for IV tramadol was generally similar to that of morphine.

Figure 10: Post-hoc Exploratory Analysis of Box Plot of PID from Baseline Without Imputation (Study AVE-901-103)



Source: Study 103 Pain Intensity Scores

A post-hoc exploratory analysis of the PID values from Study 103 at early timepoints (0 to 6 hours) using the same statistical method as the calculation for the primary endpoint was performed to assess the impact of IV tramadol on pain intensity at these early timepoints. For example, SPID 1 is the sum of pain intensity differences from baseline to 1 hour. SPID1, SPID2, SPID3, SPID4, SPID5, and SPID6 indicated that with IV tramadol, SPID2, 3, 4, 5, and 6 were all better than placebo demonstrating better pain relief as early as 2 hours following initiation of treatment (Table 9). SPID1demonstrated that the benefit of numerically improved pain relief had begun and that the trend continued as observed from the SPID2 data onwards.

Table 9: Post-Hoc Exploratory Analysis of Onset of Tramadol Pain Relief as Compared to Placebo During Early Timepoints (Study AVE-901-103)

	Placebo		Tramadol 50 mg		Difference	
	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI
SPID1	-0.2 (0.12)	-0.45, 0.01	-0.5 (0.12)	-0.72, -0.26	-0.3 (0.14)	-0.54, 0.01
SPID2	-0.5 (0.28)	-1.07, 0.01	-1.2 (0.27)	-1.74, -0.66	-0.7 (0.33)	-1.32, -0.02
SPID3	-0.9 (0.47)	-1.82, 0.01	-2.2 (0.47)	-3.16, -1.34	-1.3 (0.56)	-2.45, -0.24
SPID4	-1.3 (0.66)	-2.64, -0.05	-3.5 (0.66)	-4.82, -2.24	-2.2 (0.80)	-3.75, -0.62
SPID5	-2.3 (0.85)	-3.94, -0.60	-5.4 (0.85)	-7.08, -3.74	-3.1 (1.03)	-5.16, -1.12
SPID6	-4.0 (0.99)	-5.95, -2.06	-8.3 (0.99)	-10.20, -6.32	-4.3 (1.20)	-6.61, -1.91

Abbreviations: CI=confidence interval; FAS=Full Analysis Set; LS=least squares; SE=standard error

Source: Summary of Clinical Efficacy (Module 2.7.3 of NDA)

Time to First Rescue Supports an adequate and acceptable onset of action

The median time to first rescue is shown in Table 10. An analgesic with delayed onset would be expected to have a short time to first rescue and similar time to first rescue as placebo in a blinded efficacy study because patients in acute post-surgical pain are expected to request rescue unless they experience pain relief that is clinically meaningful. In Study 102, time to first rescue was 5.1 hours in the IV tramadol arm and 2.5 hours in the placebo arm. In Study 103, time to first rescue was 22.9 hours in the IV tramadol group versus 1.7 hours in the placebo group. These data strongly suggest that the pain relief from IV tramadol was adequate for the patients treated in the study.

Table 10: Median Time to First Rescue (Studies AVE-901-102 and AVE-901-103)

	Study AVE-901-102 (Bunionectomy)		**Study AVE-901-103 (Abdominoplasty)**		
	Placebo (N=136)	**IV Tramadol 50 mg (N=139)**	**Placebo (N=136)**	**IV Tramadol 50 mg (N=141)**	**IV Morphine 4 mg (N=93)**
Median time to first rescue	148 minutes	308 minutes	104 minutes	1371 minutes	Did not reach median

Source: AVE-901-102 CSR, AVE-901-103 CSR

Patients Perception Confirms that IV tramadol has an adequate and acceptable onset

These two clinical endpoints support an adequate and acceptable onset from IV tramadol which is further confirmed by PGA 24. An analgesic with a clinically important delay of onset would be expected to receive a rating that is not different from placebo from the perspective of the patients. Nevertheless, PGA at 24 hours, a key secondary endpoint that is directly linked to clinically meaningful analgesia was also supportive of an adequate and acceptable onset of action in both efficacy trials, as shown in Figure 4.

ANJESO (IV meloxicam injection) data demonstrate what these clinical endpoints look like in the setting of a truly delayed onset.

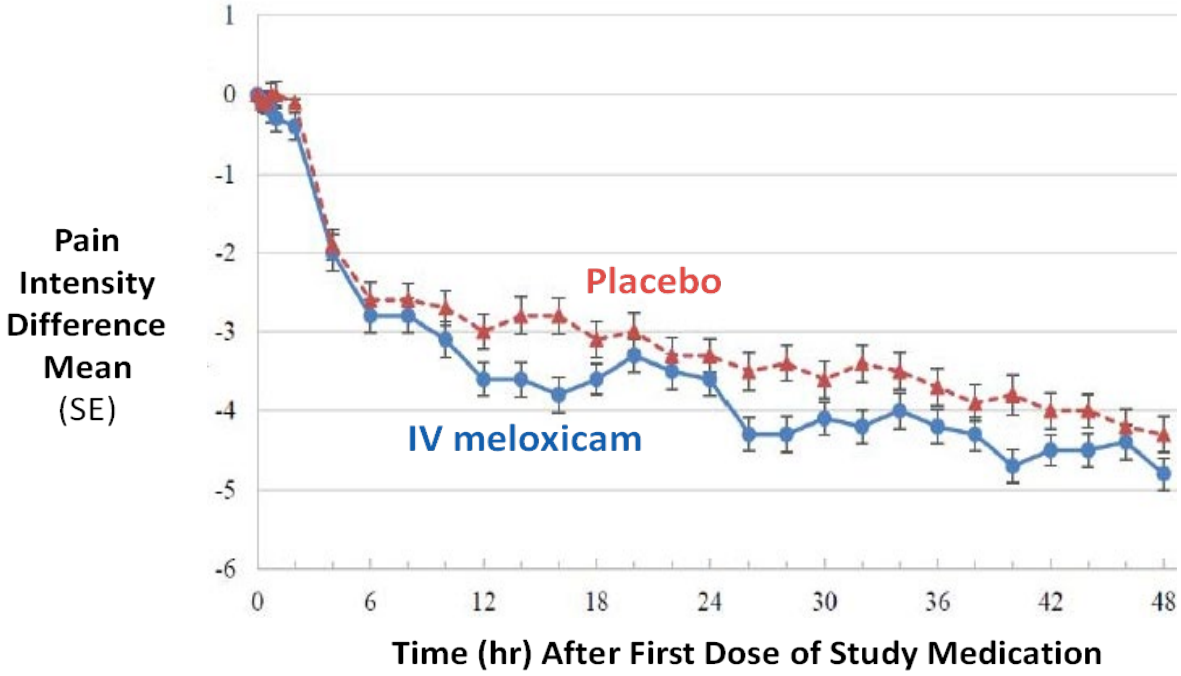
ANJESO Review provided clear discussions of outcomes on these other clinical parameters and is informative of what these clinical endpoints would look like in the setting of a delayed onset.

In contrast to the data with IV tramadol, ANJESO and placebo had a similar median time to meaningful pain relief as measured by the two-stopwatch test (~2 versus ~3 hours). Notably, ANJESO also had a short time to first rescue (2 hours in one study and 1 hour in the other study) that is not different from placebo and was shorter than the time to meaningful pain relief in both studies. Consistent with the short and comparable time to first rescue, patients in the ANJESO arm did not rate their treatment as better than placebo at 24 hours (PGA 24) in either of the efficacy Phase 3 studies. In addition, SPID6 (the sum of pain intensity differences from 0 to 6 hours) was not different from placebo in one of the two efficacy trials. In ANJESO's case, as opposed to our program, all clinical endpoints that inform onset of analgesia reflect a delayed onset and they collectively corroborate the two-stopwatch metric, indicating that ANJESO did not provide clinically meaningful pain relief at early timepoints compared to placebo.

Figure 11 and Figure 12 present the data from the ANJESO's study in abdominoplasty (ANJESO Review), showing the lack of PID separation from placebo in the first 6 hours post first dose,

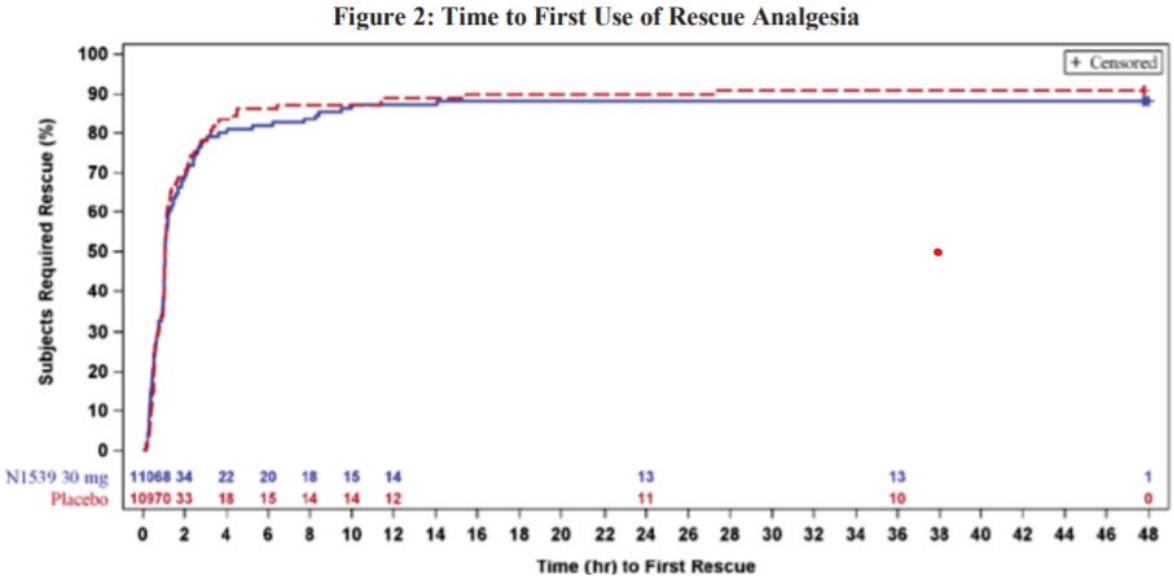
lack of separation from placebo on time to first rescue. Table 11 shows that time to first rescue is earlier than time to meaningful pain relief. It is clear that ANJESO had a delayed onset clinically. The clinical endpoints confirm the stopwatch metric.

Figure 11: IV Meloxicam Pain Intensity Data Demonstrating no difference from Placebo in Time to Onset During first 6 Hours of Treatment (Phase 3 Abdominoplasty Study)



Source: ANJESO labeling

Figure 12: IV Meloxicam Time to First Rescue Analgesia Confirms Delayed Onset (Phase 3 Abdominoplasty Study)



Source: ANJESO Statistical Review(s)

Table 11: IV Meloxicam Median Time to First Rescue and Time to Meaningful Pain Relief Showed no Benefit over Placebo

	Phase 3 Abdominoplasty Study	
Median Time to (hours)	**IV meloxicam 30 mg** (N=110)	**Placebo** (N=109)
First rescue	**1.08**	**1.09**
Meaningful pain relief[1]	**3.02**	**2.92**

Source: ANJESO Summary Basis of Approval (ANJESO)

[1]Based on 29% of patients achieving the endpoint in the ANESO group.

One-hour threshold of time to meaningful pain relief on the stopwatch metric is not a requirement for approval

In ANJESO's case, while the initial action by the Division on this application was a CRL identifying onset of action as a clinical issue, formal dispute resolution (FDR) above the Division level led to approval in 2020. This determination by the Agency involved the same dispute mechanism as we are currently undertaking, a sponsor invoking a Formal Dispute whereupon the Office overruled a Complete Response action taken by the Division and allowed approval of ANJESCO.

The reviewing official found that "(E)even if the onset of action is delayed, that would not preclude the use of Anjeso as an IV analgesic…labeling can be developed to inform prescribers who could then formulate a regimen that would provide adequate analgesic coverage." (ANJESO Review). As such, it was determined that delayed onset is not an approval issue and can be clarified in labeling supporting appropriate use. ANJESO label states that "Because of delayed onset of analgesia, ANJESO alone is not recommended for use when rapid onset of analgesia is required." It further states in Clinical Studies section:

> Onset of Meaningful Pain Relief and Use of Rescue Analgesic Medication
>
> The median time to first rescue analgesic use in patients treated with ANJESO (2 hours in Study 1 and 1 hour in Study 2) came before the median time to patient-reported meaningful pain relief in both studies (2 hours in Study 1 and 3 hours in Study 2). Fifty percent of patients treated with ANJESO and 49% of patients treated with placebo in Study 1 received rescue analgesia medication in the first 2 hours after the start of dosing. Seventy-eight percent of patients treated with ANJESO and 78% of patients treated with placebo in Study 2 received rescue in the first 3 hours after the start of dosing.

Further, as we stated in the Formal Dispute Resolution Request (FDRR) document, the one-hour onset of action requirement has never been formally articulated through guidance or rulemaking, and Avenue is unaware of any public workshops with external clinicians, patients or sponsors that would have helped shape what is a seemingly critical threshold that overrides all other clinical considerations. Had FDA sought input on whether any particular amount of time to onset of meaningful pain relief should be a requisite feature of analgesic drugs, it may have obtained

critical information. For instance, prescribers may have noted that while fast onset is important for drugs routinely used as rescue medicine (such as IV fentanyl) and in situations that require immediate pain relief such as in patients following accident or trauma, it may not be as important for post-operative setting, because patients are already treated with multiple analgesic and anesthetic medications during the surgery and before they leave the operating room. Prescribers may also willingly trade fast onset for other important features such as obviating the need for a Schedule II opioid for patients with post-operative pain in a medically supervised setting.

Summary of IV tramadol's onset of analgesia.'

The parent drug tramadol exerts analgesia via the monoaminergic effect and at the mu receptor providing early analgesia prior to conversion to the more potent mu receptor agonist M1 metabolite with IV administration (Enggaard 2006). This is consistent with the clinical onset data for IV tramadol, the known pharmacology of tramadol (Section 2.1.1), including how FDA describes tramadol pharmacology ("The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound." – ULTRAM label), and the PK profile observed with IV tramadol (Section 2.3). As such, despite the stopwatch data which are inconsistent with other clinical data, IV tramadol has an adequate and acceptable onset of action as demonstrated by the analysis of PID, time to rescue and PGA, where each of these endpoints describes a different aspect of pain relief. The totality of the data indicates that IV tramadol had a sufficiently adequate and appropriate onset of action which is expected from its mechanism of analgesia.

The findings that support the adequacy of IV tramadol's onset are corroborated by the open-label safety study designed to assess how IV tramadol fits into the multimodal analgesic approach in the real world. Patients' pain following a variety of surgeries was successfully managed with IV tramadol plus optional use of non-opioid medications such as NSAIDs and acetaminophen. Patients were informed that they could discontinue the study at any time to receive another opioid but none out of 251 patients did. Approximately 95% of patients in the study rated their treatment (without another opioid) as good, very good, or excellent.

2.6.2. IV tramadol does not carry increased need for opioid rescue and FDA's concern about adverse events from opioid rescue on top of IV tramadol has not been reported as a safety signal in wide clinical use outside the U.S.

The use of opioid rescue on top of another opioid leading to overdose is a risk for all opioids (because different patients respond to an analgesic differently) and is currently recognized in class labeling which warns prescribers to watch for adverse events when using more than one central nervous system depressants. There is no evidence in the current NDA that IV tramadol carries an increased need of opioid rescue as there were very few discontinuations due to inadequate analgesia in Phase 3 trials and IV tramadol demonstrated a similar pattern of rescue use as IV morphine in Study 103. Further, DAAP's position that "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids (CR-2)," which was central to connecting IV tramadol's onset to opioid stacking, runs counter to modern postoperative care, and the use of NSAID rescue in our studies was appropriate. We also provide an example where FDA recently approved OLINVYK (an intravenous Schedule II opioid) despite characteristics that would likely lead to opioid stacking.

Importantly, the FDA's concern about adverse events from concurrent use of IV tramadol and other opioids has not been reported as a safety signal in the clinical experience of parenteral tramadol in Europe (30 years, hundreds of millions of doses).

Opioid stacking leading to overdose is a risk for all opioids and is managed with labeling.

Opioid stacking, using an opioid rescue with a different background opioid, leading to overdose is a risk for all opioids regardless of onset because all opioids may require supplementation with additional unscheduled doses, or with another opioid analgesic in the setting of analgesic gaps during the course of treatment. In the post-operative acute pain setting, most of the opioids have a fast onset of action but it takes time to achieve equilibrium between blood and cerebrospinal (CSF) and there may be a delay of peak effect (Onset, Peak, and Duration of Common Pain Medications Table). As clinicians try to titrate to pain, repeated doses of the same opioid or a different opioid are used as needed as rescue when a patient needs additional pain relief (Peri-Operative Pain Management – MD Anderson Cancer Center). As such, use of concomitant opioids is common, sometimes before peak CNS effects of the initial opioid has occurred. The key question is how to keep patients safe from ORAEs including respiratory depression.

In the setting of postoperative pain, patient safety relies on an experienced prescriber and hospital or surgical center safety monitoring protocols. For patients with post-operative pain in the medically supervised setting where IV tramadol (and other IV opioids) will be used, clinical staff are trained to appropriately monitor patients for opioid-related adverse events. (Section 2.6.4).

Even oral opioid analgesics used by outpatients are labeled with class labeling to alert prescribers to the risks of using more than one opioid or prescribing other central nervous system depressants to patients using opioid analgesics. The labeling for oral tramadol (ULTRAM label), as with class labeling for all opioids, recognizes that some patients may require additional pain relief and warns of the risk of opioid stacking. Oral tramadol contains a "Boxed Warning" indicating that among other things:

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase.
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Thus, the prescriber is informed of the risk of potentially serious opioid-related adverse events such as respiratory depression when a patient receives concomitant CNS depressants including other opioids. Avenue expects similar information to be a component of the labeling for IV tramadol.

There is no evidence that IV tramadol carries an increased need for opioid rescue.

DAAP believes that the risk of harm from opioid stacking could not be evaluated in our NDA because the Sponsor did not allow rescue with another opioid in Phase 3 studies and the only allowed rescue was ibuprofen. The Division's safety concern centers on the use of opioid rescue

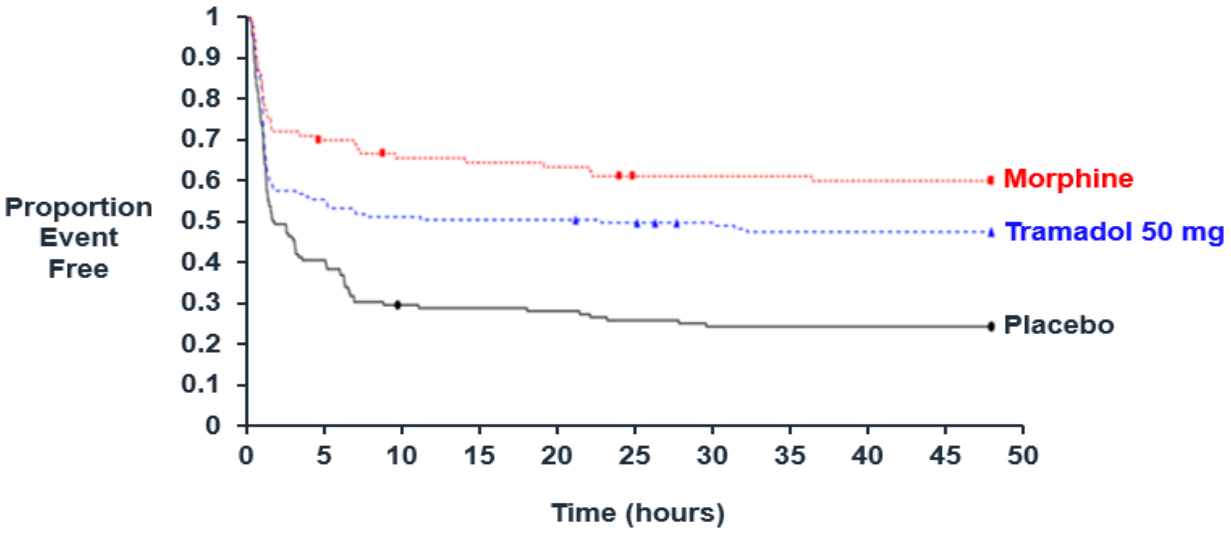
when patients on IV tramadol need additional analgesia. Efficacy trials for analgesics mainly use a monotherapy approach, with specified "rescue" medications. The approach of using NSAIDs as rescue for opioid analgesics is common in efficacy trials and has supported the approval of OLINVYK (approved in 2020, discussed below).

Despite not having a direct evaluation, the need for opioid stacking in Phase 3 clinical trials can be assessed using two surrogates: discontinuation due to lack of efficacy to have access to a rescue opioid and comparing rescue use with IV tramadol versus rescue use with an approved opioid.

If IV tramadol with an NSAID rescue was not able to provide adequate analgesia, we would have expected to see a high drop-out rate because patients knew they could discontinue at any time to get additional analgesics including an opioid in the Phase 3 trials. Very few patients discontinued due to lack of efficacy: 2% in efficacy studies (6 out of 280 patients) and 0% (0 out of 251 patients) in the safety study. Of the 6 patients who did discontinue and received another opioid, none had a serious AE or severe AE. Patients in the safety study were highly satisfied with their treatment without another opioid.

The use of rescue medication was not very different in the IV tramadol arm (52.5%) than the IV morphine arm (39.8%) in Study 103. The average dose of rescue is slightly higher in the IV tramadol group than in the IV morphine group: 312 mg and 409 mg (~ 1 tablet) of ibuprofen in the IV tramadol group versus 189 mg and 271 mg of ibuprofen in the IV morphine group over the first 24 hours and the entire 48-hour treatment period, respectively. Patients receiving rescue in both arms needed it early in the treatment, as shown in Figure 13.

Figure 13: Kaplan-Meier Plot of Time to Use of First Rescue Medication (Ibuprofen), Demonstrating most patients who used Rescue used it in the first few hours of the study whether they received IV tramadol or IV morphine (Study AVE-901-103)



Source: AVE-901-103 CSR

We note that patients in the IV tramadol arm and the IV morphine arm were both adequately

managed with NSAID rescue. Based on the percent of patients needing rescue, timing of rescue, amount of rescue in the IV tramadol arm and the IV morphine arm, the evidence does not support FDA's concern that IV tramadol carries an increased need for opioid rescue versus an approved IV opioid. The rescue use in the IV morphine group shows that significant numbers of patients on approved IV opioids will require additional analgesia for post-operative pain. Patients on IV morphine would be at the same risk for harm from opioid stacking as patients treated with IV tramadol if the treating physician decides to rescue with an opioid.

FDA's position regarding appropriate rescue for IV tramadol is not valid.

DAAP has stated that "(I)it would not be clinically feasible if an opioid analgesic requires a nonopioid product to augment the analgesia," (November 19, 2020 Post-action Type A meeting) and that "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids." (CRL-2). This position is contradicted by our data, FDA's product labeling, clinical practice, and expert opinion.

The data in the NDA demonstrated that clinicians were able to successfully manage all but a handful of patients on IV tramadol with a NSAID rescue medication. The two pivotal Phase 3 efficacy studies demonstrated a low discontinuation rate in patients randomized to IV tramadol due to inadequate analgesia. The Phase 3 safety . It showed that patients reported a favorable impression of the effectiveness of their treatment in the absence of Schedule II opioids in Study 104. These data strongly indicate the satisfactory pain relief from IV tramadol, both from measured clinical outcome assessments (eg, pain intensity differences) as well as patient reported outcomes.

The Division's position regarding appropriate rescue for an opioid is also unexpected given FDA's labeling of multiple non-opioid products that are indicated as adjuncts for opioid analgesics. TORADOL (Ketorolac) IV was approved based on a study where it served as rescue for morphine PCA. CALDOLOR (ibuprofen) for intravenous use is indicated for use in adults and pediatric patients six months and older "for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics," and OFIRMEV (acetaminophen) injection is indicated 'for the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older."

Unlike the artificial environment of an efficacy studies where analgesics may be withheld until a patient's pain level meets certain threshold, in clinical practice, the clinician anticipates the patient's post-operative pain level and may prescribe an opioid, perhaps with a non-opioid medicine in a multimodal approach, if warranted (Hyland 2021). Further, the multimodal analgesic approach is well established in the management of acute pain and is recommended by a taskforce convened by the U.S. Department of Health and Human Services and other government agencies: "To avoid the side effects associated with prescription opioids, it is important to exploit the benefits of multimodal, non-opioid approaches in acute pain management in conjunction with possible opioid therapy." (HHS 2019).

FDA recently approved an intravenous Schedule II opioid despite clear intent for use with another opioid

OLINVYK is a Schedule II intravenous pure mu opioid agonist that serves as an example of a novel opioid approved with labeling for use with another opioid. The overall design of the OLINVYK program was similar to that of IV tramadol. OLINVYK was tested in two efficacy studies (bunionectomy and abdominoplasty) where patients were randomized to OLINVYK, placebo, or an active comparator, morphine. The protocol specified rescue medicine was an oral NSAID (OLINVYK Review).

OLINVYK is labeled for us via patient-controlled analgesia (PCA). PCA allows the patient to titrate the dose as needed (within certain limits). The labeling recognizes that one of the potential risks of PCA is "stacking" the drug on top of itself: "Although self-administration of opioids by PCA may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression." (OLINVYK label)

Second, if the Division's logic used for the potential for stacking in the tramadol program were applied universally, the need for opioid rescue would also apply to OLINVYK as rescue was required in this program. The labeling notes that for the bunionectomy study, "[I]in the 0.1 mg, 0.35 mg and 0.5 mg OLINVYK treatment groups, 41%, 20%, and 17% of patients, respectively, used the protocol-specified rescue medication etodolac" and for the abdominoplasty study "[i]n the OLINVYK 0.1 mg, 0.35 mg, and 0.5 mg treatment groups, 31%, 21%, and 18% of patients, respectively, used protocol-specified rescue medication etodolac." Based on FDA's statement about non opioid medication being inappropriate for an opioid, patients using OLINVYK would have to rescue with an opioid, as FDA suggests will be the case with IV tramadol.

Third, OLINVYK has a daily dose cap (due to QT prolongation issues) and patients who reach that cap will need another analgesic to fill the gap until OLINVYK can be restarted. The labeling states that "[i]f patients reach a 27 mg cumulative daily dose and analgesia is still required, an alternative analgesic regimen should be administered until OLINVYK can be resumed the next day. Alternative analgesia may include multi-modal therapies." Notably, the median times for patients to reach the daily cap ranged from 13.6 to 15.8 hours in the bunionectomy trial and 14.1 to 19.4 hours in the abdominoplasty trial (OLINVYK Review). Therefore, patients on OLINVYK is likely to require another opioid once the daily cap is reached, and this may lead to opioid stacking because another opioid may be needed before OLINVYK is cleared from the blood (half life is up to 3 hours according to OLINVYK label). This did not preclude approval.

Further, there was no other compelling advantage to offset the need for additional analgesics with OLINVYK as The FDA reviewer concluded that "Oliceridine has a benefit-risk profile similar to that of other opioids…there is no evidence for a safety advantage of oliceridine over other opioids…It must also be noted that morphine demonstrated a greater reduction in pain intensity than all three dosing regimens of oliceridine that were tested in the studies" (OLINVYK Review).

FDA's concern that opioid rescue on top of IV tramadol leading to overdose of patients has not been reported as a safety signal in Europe and the rest of the world.

Opioid stacking or the use of multiple opioids is common in the peri-operative setting. The FDA's concern is not just the need for stacking, but the risk of harm resulting from stacking such as respiratory depression and overdose. However, parenteral tramadol has been approved in over 70 countries outside the U.S. including most parts of Europe for about 30 years. Approximately

370 million doses of parenteral tramadol were administered in European hospitals from 2010 to 2019 (IQVIA) and there is no setting restriction on the use of parenteral tramadol in Europe (SmPC for Zydol 2020). It is also widely used in Asia, Middle East, South America, Australia and New Zealand. In these countries, the use of parenteral tramadol with non-opioid medicine provides adequate pain relief while reducing the use of more abusable opioids (Grond 2004; Lee 1993). DAAP's concern regarding stacking has not been realized clinically; nor is that concern supported by our review of the medical literature.

Avenue conducted an extensive literature review and reviewed Vigibase as summarized in Section 2.5. There is not a signal indicating increased safety concern for IV tramadol due to opioid stacking. The Sponsor found one systematic review and meta-analysis of combining tramadol and morphine in adult surgical patients (Martinez 2015). While the studies in the review had limitations (single-site studies, different surgeries and anesthesia protocols, different dosing regimens and comparators), the authors found a limited but significant post-operative morphine-sparing effect and there was no report of a safety signal related to opioid stacking.

2.6.3. Variability of CYP2D6 does not lead to unpredictability of opioid activity

DAAP has stated that IV tramadol has demonstrated a delayed onset of analgesia and wide individual variability in pain relief (possibly due to CYP2D6 polymorphisms) that renders its analgesic effect unpredictable. However, the pharmacokinetic data demonstrate an acceptable range of variability, and the clinical studies demonstrated consistent analgesic efficacy. The dosing regimen provides a predictable PK for both the parent compound tramadol and the key metabolite M1 (Section 2.3).

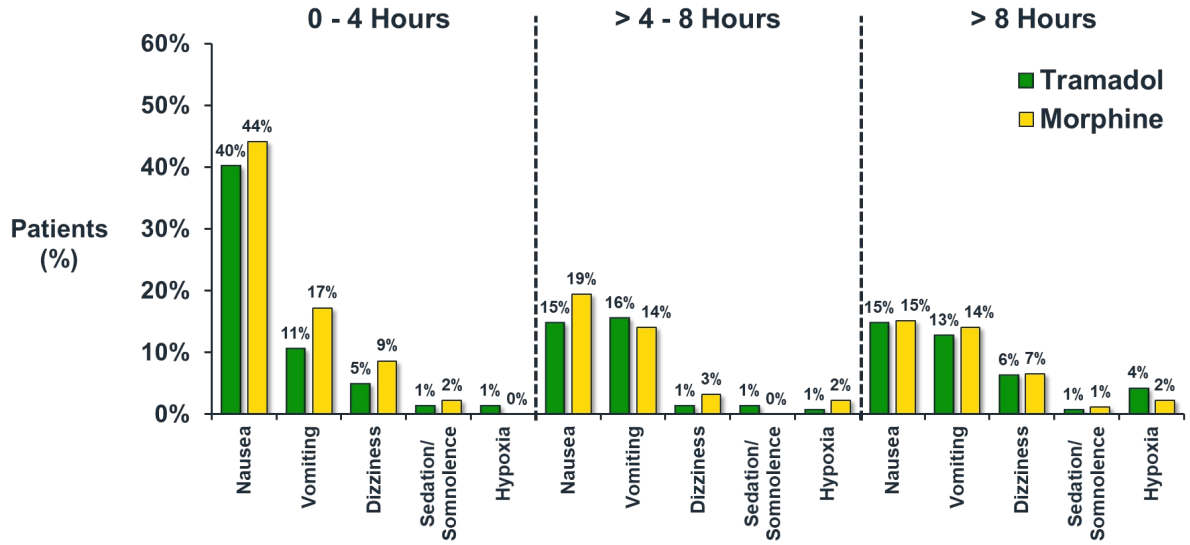
Focusing on M1 exclusively ignores non-opioid mechanism of analgesia

Tramadol has both opioid and non-opioid mechanisms for analgesia. The parent compound has both opioid activity and monoaminergic effect for pain relief. The active metabolite M1, with stronger affinity for the mu receptor than the parent compound, is converted from parent compound tramadol in the liver via CYP2D6. The Sponsor acknowledges CYP2D6 polymorphism and agree that there are poor metabolizers and ultra-rapid metabolizers and that there is a range of M1 levels produced based on CYP2D6 differences (Kirchheiner 2008, Leppert 2011, Miotto 2017, Stamer 2007). However, focusing exclusively on CYP2D6 ignores the monoaminergic mode of analgesia and the weak mu opioid agonist action exerted by parent compound tramadol, both of which may contribute to the clinically acceptable onset of analgesia (Enggaard 2006). As previously discussed, the analgesic effect of IV tramadol was highly rated by patients (Figure 4) and that IV tramadol provides sustained pain relief with relatively low opioid activities because of the non-opioid mode of analgesia by the parent compound tramadol (Section 2.1.1)

Onset of opioid related adverse events (ORAEs) indicate that the opioid activity of IV tramadol are not more unpredictable than IV morphine (Study 103)

To evaluate if there is any clinically relevant unpredictability of opioid activities with IV tramadol, we reviewed the onset of ORAEs during different time intervals in both the IV tramadol arm and the IV morphine arm in Study 103 (Figure 14).

Figure 14: Onset of Relevant ORAEs indicate that the opioid activities of IV tramadol is no more unpredictable than IV morphine (Study AVE-901-103)



Source: AVE-901-103 CSR

During each of the time intervals, the opioid related adverse events from IV tramadol are similar to IV morphine. The most important of these, sedation and somnolence, occur infrequently in both IV tramadol and IV morphine, at frequencies that are not of concern. No patient had clinically significant respiratory depression or needed naloxone to reverse symptoms. The onset of the ORAEs indicates that the opioid activity of IV tramadol was not more unpredictable than IV morphine. The pattern and nature of the events were consistent with usual postoperative care.

Overdose due to opioid stacking is unlikely in patients who receive IV tramadol regardless of their CYP2D6 phenotypes

The Cmax and AUC of M1 from the IV tramadol dosing regimen are lower than that from approved oral tramadol dosage (Section 2.3) due to the lack of first-pass metabolism. This is true for any patient whether they are a 2D6 extensive metabolizer or poor metabolizer. To address the concern expressed by the Division that "(T)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" (CRL-1), the Sponsor notes that patients experiencing rapid onset of analgesia on IV tramadol are less likely to ask for a rescue analgesic. These patients should not have an increased risk of overdose with IV tramadol as compared to approved oral tramadol dosage. On the other hand, if a patient is a poor metabolizer who does not respond to IV tramadol during early treatment, the patient is not at risk for harm resulting from a rescue opioid because that patient generates very low levels of M1 at early and late timepoints, and adding another opioid should cause little additive opioid effects.

Given the amount of opioid activity from IV tramadol, there is no evidence that opioid rescue on top of IV tramadol would lead to overdose in either case. It is already documented that in current clinical practice, patients may be prescribed oral tramadol before surgery without genotyping and receive intravenous opioids both during the surgery and in the post-surgical setting (Vu 2020). Therefore, opioid stacking with oral tramadol already occurs in the peri-operative setting on a

routine basis. IV tramadol would be safer and subject patients to less opioid stacking related harm than oral tramadol in this setting because of the lower M1 levels from the IV administration regardless of the 2D6 genotype. Additionally, the patient is in a medically supervised setting (hospitals and surgical centers) where the use of multiple opioids is common and managed carefully by experienced clinicians (Section 2.6.4).

The CYP2D6 variability is managed with labeling for oral tramadol

The CYP2D6 variability, known for many years (Bertilsson 2002), is managed with labeling for oral tramadol which has a documented safety and efficacy history since its approval 26 years ago (in 1995) in the U.S. There has not been any requirement to genotype patients before oral tramadol is prescribed.

Importantly, the Sponsor did not find evidence in the literature that suggests patients on parenteral tramadol is subject to an increased risk of opioid stacking leading to overdose due to the variability of 2D6. In addition, the IV tramadol dosing regimen will provide further predictability of the PK (Section 2.3) of both the parent compound tramadol and M1.

There is no evidence from our clinical data and vast ex-U.S. experience that the CYP2D6 polymorphisms represents a safety concern for IV tramadol, nor is there any evidence that it renders the effect unpredictable any more in a monitored postoperative setting than in an unmonitored outpatient setting. Oral tramadol has been successfully used in outpatient setting for both acute and chronic pain. Given that CYP2D6 polymorphisms is accepted for oral tramadol in the outpatient setting, it is also acceptable for IV tramadol in a medically supervised setting.

2.6.4. Medically supervised setting (hospitals, surgical centers) further mitigates FDA's concern for risk of overdose caused by opioid rescue with IV tramadol.

DAAP stated in CRL-1 that "(O)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." This statement ignores clinical practice. Opioid stacking leading to overdose is a risk for all opioids regardless of onset and opioid stacking (dose stacking or different opioids) with Schedule II intravenous pure mu opioid agonists already occurs in the post-operative setting (Section 2.6.2). Oral tramadol (with more opioid activity) is already used along with intravenous opioids in the peri-operative setting (Vu 2020).

However, the use of multiple opioids concurrently in a medically supervised setting (hospitals, surgical centers, etc.) is considered safe because patients are closely monitored by clinicians experienced in pain management. Clinicians in this setting are trained to recognize the signs and symptoms of opioid-related side effects. Patients on opioids are regularly assessed for their pain levels, respiratory rate, oxygen saturation, and cognition. Every hospital and ambulatory surgical center have protocols with dosing instructions and safety monitoring in place to ensure safe administration of opioids based on a real time evaluation of the individual patient. Additionally, healthcare professionals, not patients, administer opioids in this setting.

Please note that the Sponsor has always sought an indication in which use would be restricted to a medically supervised setting such as hospitals and surgical centers.

2.6.5. Benefit-risk considerations based on the Phase 3 data, foreign safety information, and public health benefit of making a less-abusable IV opioid available supports the approval of IV tramadol.

At present, there are only three classes of intravenous analgesics available in the U.S.: acetaminophen, NSAIDs and Schedule II opioids. For patients undergoing major surgeries, non-opioid analgesics are not sufficient, and most patients will require opioids even after advancement of local anesthetics and various techniques. The use of opioids is common in the post-operative setting in the hospital, even though short-term use of highly abusable opioids may create long-term issues for patients (Section 2.2).

IV tramadol met primary efficacy endpoint in both efficacy pivotal trials and demonstrated a safety profile similar to that of oral tramadol and IV morphine and consistent with the extensive clinical experience with parenteral tramadol in Europe and the rest of the world. DAAP's safety concern, i.e. the use of additional opioids when patients are on background IV tramadol places them at increased risk for opioid overdose due to the variability in CYP2D6 was not seen in our clinical studies and has not been reported as a safety signal in clinical experience outside the U.S.

Exposure of patients to a schedule IV opioid with a lower abuse potential than a schedule II opioid is relevant in the benefit-risk considerations of the approval of IV tramadol, particularly since the vast majority of patients in the clinical trials were able to achieve adequate analgesia with IV tramadol and NSAID rescue. Our data show that IV tramadol does not lead to an increased use of opioid rescue and the adverse events resulting from concurrent use of other opioids with IV tramadol has not been reported as a safety signal in the vast clinical experience outside the U.S. IV tramadol is a therapeutic alternative to Schedule II opioids for clinicians who wish to minimize the use of Schedule II opioids and for patients who wish to minimize their exposure Schedule II opioids in the post-operative setting. For these groups, IV tramadol (a schedule IV opioid) with an NSAID in the postoperative period, possibly with additional schedule II opioid as needed, is a better option than a schedule II opioid analgesic with an NSAID with additional schedule II opioid as needed.

2.6.6. Conclusion

The Phase 3 studies demonstrated that IV tramadol was safe and effective. IV tramadol's safety profile is similar to oral tramadol, IV morphine and consistent with foreign experience. There were no unexpected safety findings in the NDA.

IV tramadol has an adequate and acceptable clinical onset of analgesia despite showing a delay by one method of evaluation (the stopwatch metric). It does not carry increased risk of opioid rescue versus other approved IV opioids and FDA's concern about adverse events from concurrent use of IV tramadol and other opioids has not been observed clinically in our studies nor has it been reported as a safety signal in hundreds of millions of doses and 30 years of clinical experience outside the U.S. CYP2D6 polymorphism does not lead to unpredictability of opioid activities and this is accepted for oral tramadol, which has a 26-year history in the U.S. The opioid activity from IV tramadol is lower than approved oral dosage and opioid related adverse events from IV tramadol is as predictable as IV morphine. IV tramadol's use will be limited to a medically supervised setting (hospitals, surgical centers) where the use of multiple opioids is common and recognized as safe.

In practice, IV tramadol may be given with non-opioid medicine and will be a therapeutic alternative to Schedule II opioids. The added benefit of approving IV tramadol is that patients could conceivably be managed throughout their entire postoperative period, both inpatient and outpatient with a Schedule IV opioid and with either no schedule II opioid or doses limited to rescue. This benefit of making IV tramadol available outweighs DAAP's safety concern and supports IV tramadol's approval.

3. CLINICAL DEVELOPMENT HISTORY

3.1. Product Overview

Despite being widely prescribed outside the U.S. for decades, IV tramadol is a new route of administration of tramadol in the U.S. Tramadol is a centrally acting atypical opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. The analgesic effect of tramadol is believed to be due to both binding to mu-opioid receptors and inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the key metabolite M1 to mu-opioid receptors. According to ULTRAM label, tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests, demonstrating that reuptake inhibition of norepinephrine and serotonin is important in providing the analgesic effect. The parent compound tramadol is largely responsible for this mechanism, which blocks pain signal transmission in the spinal cord.

It is important to note that M1 is metabolized from tramadol in the liver. When administered orally, tramadol is absorbed and transported to the liver. Approximately 25 to 30% of tramadol does not enter systemic circulation as it gets converted to M1 during this first-pass metabolism. In contrast, when tramadol is administered intravenously, no first pass metabolism occurs resulting in less conversion to M1. Less M1 conversion means that IV tramadol has less opioid activity and abuse potential than oral tramadol; this was also confirmed by the WHO's expert committee on drug dependence in their critical review report of tramadol in November 2018 (WHO 2018).

In the U.S. oral tramadol was first approved in 1995 under the trade name ULTRAM (Ortho-McNeil-Janssen Pharmaceuticals, Inc). It is also an active agent in an extended release (ER) product, ULTRAM ER, and as a combination product with acetaminophen, ULTRACET®. It was not initially scheduled but was placed in Schedule IV in 2014. Schedule IV controlled substance status means tramadol carries a lower abuse liability than conventional opioids, which are Schedule II. The DEA definition of scheduling can be found online at https://www.dea.gov/drug-scheduling. The scheduling reflects the scientific understanding of the abuse potential of tramadol and is supported by extensive preclinical, clinical, post-marketing and epidemiological studies conducted by various academic institutions, sponsors, and government agencies. It was also confirmed by the recent report on tramadol by the WHO expert committee on drug dependence in November 2018.

Oral and parental tramadol have been used outside the United States in more than 70 countries for over 25 years (Grünenthal 2017). According to IQVIA (an independent provider of health information), over 370 million doses of IV tramadol were used in the hospital in Europe in the last 10 years (2010 to 2019).

It is important to note that use of IV tramadol, which is intended to be given *only* in a medically supervised setting (and thus not dispensed directly to patients), would provide even *less* abuse potential than the oral tramadol formulation (which is prescribed and dispensed directly to the patient, and thus intended for home use) due to both the setting and the slower formation of and the lower M1 levels discussed previously.

This NDA is a 505(b)2 application that is intended to bring intravenous (IV) tramadol to the US market, relying upon both clinical trial data and the documented efficacy and safety of oral

tramadol. The advantage of IV tramadol over conventional (ie, Schedule II) opioids is that it carries less abuse liability, an important consideration in the context of the ongoing opioid epidemic in the U.S. This important point was confirmed by the extensive epidemiological study summarized in Section 7. IV tramadol is a potential alternative that could help to avoid exposing patients with acute pain to conventional opioids in a medically supervised healthcare setting.

3.2. Proposed Indication and Dosing

The proposed indication is for management of moderate to moderately severe pain for adults in a medically supervised health care setting. The dosing regimen tested in the Phase 3 program (50 mg given at Hours 0, 2, 4, and every 4 hours thereafter) provides a similar exposure to oral tramadol 100 mg Q6H based on Cmax and AUC at steady state.

3.3. Regulatory History

Tramadol was originally developed by the German pharmaceutical company Grünenthal GmbH in the late 1970's and is marketed globally under the trade names TRAMAL® and others outside of the U.S. (Grünenthal 2017) in both oral and parenteral formulations. In the U.S. oral tramadol was first approved in 1995 under the trade name ULTRAM for moderate to moderately severe pain in adults. It is also an active agent in an extended release (ER) product, ULTRAM ER, and as a combination product with acetaminophen, ULTRACET.

In the development of IV tramadol, the Sponsor met with the FDA at each step in the clinical development process (eg, Pre-IND, End of Phase 2, pre-NDA), and followed all FDA guidance provided during development as suggested. Of note, the FDA confirmed agreement on the surgical models (bunionectomy and abdominoplasty) and design of the Phase 3 pivotal trials (Studies AVE-901-102 and AVE-901-103) for IV tramadol 50 mg with the addition of a 25 mg IV regimen to the first Phase 3 study (Study AVE-901-102) and the addition of an active comparator (morphine) (to assess for safety) in the abdominoplasty study (Study AVE-901-103). A safety study (Study AVE-901-104) was also conducted to meet FDA's requirement that the safety database for IV tramadol must include at least 500 subjects. The resulting data forms the basis for conclusions regarding the efficacy and safety of IV tramadol for the proposed indication.

The Phase 3 program included 271 placebo subjects, 133 tramadol 25 mg subjects, 533 tramadol 50 mg subjects, and 93 morphine subjects, comprising, in total, 1030 subjects. This safety database has well-characterized the safety and tolerability profile of IV tramadol 50 mg, and two well-controlled Phase 3 pivotal clinical studies have provided confirmatory evidence of IV tramadol 50 mg as effective for the management of moderate to moderately severe pain in adults in a medically supervised health care setting. The open-label safety study included treatment up to 5 days of dosing with IV tramadol 50 mg.

Of note, this application is being submitted as a **505(b)(2)** application, with reference to ULTRAM [which is the approved oral formulation of tramadol in the United States (US)]. ULTRAM was approved by the FDA in 1995 and is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

- A 505(b)(2) NDA contains full safety and effectiveness reports (as are included in this application for IV tramadol), but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.
- The provisions of 505(b)(2) were created, in part, to help avoid unnecessary duplication of studies already performed on a previously approved ("reference" or "listed") drug; the section gives the FDA express permission to rely on data not developed by the NDA applicant.

3.4. Clinical Development Program

The IV tramadol development program, which includes 6 clinical studies, builds on data in the ULTRAM NDA as well as extensive post-marketing experience with oral tramadol. Avenue Therapeutics followed all FDA guidance as suggested in these meetings and communications.

A tabulated list that includes a brief summary of the design, objectives, test products and dosages, number of subjects/patients, and duration of treatment for each study can be found in Table 12.

The Phase 1 studies included:

- Study RVG-10-018 was a Phase 1 study performed in healthy adult subjects to assess comparative bioavailability of the IV formulation to the oral formulation of tramadol.
- Study RVG-12-001 was a Phase 1 thorough QT study performed in healthy adult subjects. This rigorous assessment allowed for a thorough understanding of the potential effects of IV tramadol on ECG parameters. The study demonstrated that IV tramadol had no clinically meaningful effects on ECG outcomes.
- Study AVE-901-101 was a Phase 1 study performed in healthy adult subjects to assess the pharmacokinetics of two doses of the IV formulation as compared to an approved dosage of oral tramadol. The dose and dosing regimen that were selected to move into Phase 3 had a similar Cmax and AUC of tramadol versus that of the approved dosage of oral tramadol (100 mg Q6H) at steady state and lower M1 levels versus oral tramadol.

The Phase 3 studies included:

- Study AVE-901-102 Bunionectomy Study was a Phase 3 double-blind study that assessed the effects of 2 doses of IV tramadol (versus placebo): 25 mg and 50 mg in an orthopedic model. The use of two active dose arms was intended to allow for selection of the optimal dose based on both efficacy and safety outcomes. IV tramadol 50 mg dosing regimen statistically superior to placebo with respect to the management of moderate to moderately severe pain, whereas the IV tramadol 25 mg arm, while numerically 'better' than placebo with respect to the pain management, was found not to be statistically different from placebo. Thus the 50 mg regimen was carried forward to Study AVE-901-103 and to the open-label Study AVE-901-104.
- Study AVE-901-103 Abdominoplasty Study was a Phase 3 double-blind study that assessed the effects of IV tramadol 50 mg (versus placebo) as well as versus an active

comparator, IV morphine 4 mg, in a soft tissue model. The use of the single active dose was intended to corroborate findings from Study AVE-901-102 for the IV tramadol 50 mg dose, while use of a morphine treatment arm was intended to provide safety outcomes relative to an active control. Although not powered, efficacy was also assessed to allow for an understanding of the comparability of IV tramadol and an approved opioid IV treatment. The study confirmed the efficacy of the IV tramadol 50 mg dose and, in comparison to the active comparator arm (morphine), showed comparable efficacy on all primary and key secondary efficacy endpoints. This study also demonstrated a similar safety/tolerability profile compared to morphine injection.

- Study AVE-901-104 Safety Study was a Phase 3, single-arm, open-label safety study performed in patients undergoing a variety of elective bone and soft tissue surgeries and included treatment up to 168 hours in duration. The only efficacy measurement in this study was Patient Global Assessment (PGA), an important outcome that reflects patients' view of the treatment.

Table 12: Description of Clinical Studies in IV Tramadol Development Program

Study No.	Study Design	Study Objectives	No. Subjects, Gender, Mean Age (Range)	Treatment (Drug/Dose/Form/ Route/Freq/ Duration
RVG-12-001	Randomized, double-blind, single-dose, positive- and placebo-controlled, three-way crossover study	Effect of IV tramadol on QTc interval	60E/52C M/F = 44/16 IV tramadol = 56 PBO =57 Mox = 57 30.5 yrs (18-45)	Subjects received: IV tramadol: 1 x 200 mg, diluted in 50 mL saline PBO: 1 x 200 mg IV, diluted in 50 mL saline Mox = 1 x 400 mg tablet po, admin w/concurrent IV infusion of PBO
RVG-10-018	Open-label, multi-dose, randomized, parallel treatment study	Comparative BA of oral vs IV tramadol, dose proportionality of IV tramadol at steady-state	32R/31C M/F = 24/8 A: 8 5/3 B: 8 7/1 C: 8 6/2 D: 7 5/2 32.1 yrs (19-48)	Subjects received 1 of the following treatments, q6h for total of 9 doses: A: 50 mg tramadol IV B: 50 mg ULTRAM tablet, po C: 100 mg (2x50) tramadol IV D: 100 mg (2x50 mg tablets) ULTRAM, po
AVE-901-101	Open-label, single center, 3-treatment, 3-period multidose crossover.	PKs of 2 regimens of IV tramadol vs 1 oral regimen over 48 hours of treatment	18R/17C M/F = 11/7 34.9 yrs (24-55)	Each subject received: 1: IV tramadol 75 mg at Hour 0, 3, and 6, then 75 mg q6h thru Hour 42 2: IV tramadol 50 mg at Hour 0, 2, and 4, then 50 mg q4h thru Hour 44 3: Oral tramadol 100 mg (2x50 mg tablets) at Hour 0 and 6, then q6h thru Hour 42
AVE-901-102[a]	Phase 3, multicenter, double-blind, three-arm, randomized, placebo-controlled, multiple-dose, parallel-group	Analgesic efficacy of AVE-901 compared to PBO in the management of postoperative pain following orthopedic surgery	Overall:409R[a]/380C (~135/group) M/F = 60/349 45.2 yrs (19-74)	Treatment groups: 25 mg Tramadol IV 50 mg Tramadol IV PBO Tramadol admin at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 over approximately 15 ±2 minutes.
AVE-901-103[a]	Phase 3, multicenter, double-blind, three-arm, randomized, placebo-controlled, multiple-dose, parallel-group trial.	Analgesic efficacy of AVE-901 compared to PBO in the management of postoperative pain following abdominal surgery	Overall: 380R/336C M/F = 3/367 39.9 yrs (20-71)	Treatment groups: 50 mg Tramadol IV infusion PBO IV infusion 4 mg morphine IV push All treatments administered at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 for a total of 13 doses.

Study No.	Study Design	Study Objectives	No. Subjects, Gender, Mean Age (Range)	Treatment (Drug/Dose/Form/ Route/Freq/ Duration
AVE-901-104	Phase 3, multicenter, single-arm, open-label, repeat-dose safety trial	To evaluate the safety of IV Tramadol in the management of post-surgical pain in patients having various types of elective surgery	Overall 251 patients. 100 (39.8%) males, 151 (60.2%) females Age median 48.0 years, range 18 to 75 years	IV Tramadol 50 mg administered at Hours 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 for a total of 13 doses. There was no control arm in this single-arm, open-label study.

[a]A subset of the study population (approximately 33%) participated in a limited PK analysis portion of the study.
Abbreviations: C = completed, E = enrolled, F = female, M = male, Mox = moxifloxacin, po = by mouth (oral), R = randomized, PBO=Placebo.
Source: Clinical Overview (Module 2.5 of NDA)

4. CLINICAL PHARMACOLOGY

The objective of the Phase 1 program was to identify a dose and dosing regimen suitable for Phase 3 development. Study RVG-10-018 assessed comparative bioavailability of the IV formulation to the oral formulation of tramadol. Study RVG-12-001, a thorough QT study demonstrated that IV tramadol had no clinically meaningful effects on ECG outcomes. Study AVE-901-101 examined the pharmacokinetics of two doses of the IV formulation as compared to an approved dosage of oral tramadol.

The study found that IV tramadol 50 mg administered as a 15-minute infusion at baseline, 2 hours, 4 hours and every 4 hours thereafter had a similar Cmax and AUC of tramadol, and lower M1 levels, as compared to the approved dosage of oral tramadol (100 mg Q6H) at steady state.

4.1. Study RVG-12-001 (Thorough QT Interval Study)

Study RVG-12-001 was a randomized, double-blind, single-dose, positive- and placebo-controlled, three-way crossover study designed to assess the effects of a supratherapeutic dose of 200 mg IV tramadol on the QTc interval. This dose is 4 times the recommended dose that is proposed in the IV tramadol 50 mg dosing regimen. Overall, the effect of the supratherapeutic dose of 200 mg of tramadol on the QTcF was minimal. The upper bound of the 90% CI was below the threshold of regulatory concern, 10 ms, at all timepoints except at 8 hours postdose, where it slightly exceeded the threshold (10.4 ms). Note that a simulation conducted with the 200-mg dose PK data from this study, to estimate the effect of a 100-mg dose of tramadol on the QTc interval showed that the upper 90% CI of the ΔΔQTcF value at 8 hours decreased from 10.4 to 8.0 ms when the dose effect was simulated at 100 mg. This falls below the threshold value of 10 ms for a positive finding according to the ICH E14 guideline.

4.2. Study RVG-10-018 (Phase 1 Dose-Finding)

Study RVG-10-018 was an open-label, multi-dose, randomized, parallel treatment study designed to assess the PK of IV vs oral tramadol for 50 mg and 100 mg doses. Treatments were given every 6 hours for each treatment arm (and thus, for the IV tramadol 50 mg group, were not the same as the proposed dosing regimen for this NDA). Subjects received 1 of the following treatments, q6h for total of 9 doses:

- 50 mg tramadol IV
- 50 mg ULTRAM tablet, orally
- 100 mg (2x50) tramadol IV
- 100 mg (2x50 mg tablets) ULTRAM, orally

Key findings included:

- Tramadol C max concentrations following IV dosing were higher than after the same dose administered orally, while Cmin concentrations were relatively similar after IV and oral administration. Cmin concentrations were approximately 40% of Cmax after IV dosing and approximately 60% of Cmax after oral dosing.
- The oral bioavailability of tramadol tablets was in the range of 70% -85% compared to the IV infusion.

- Tramadol showed dose-proportional PK over the 50 mg to 100 mg dose range after both IV and oral dosing M1 showed dose-proportional PK after IV dosing, but less than dose proportional PK after oral dosing.

4.3. Study AVE-901-101 (Phase 1 Dose-Finding)

This was a Phase 1, open-label, single-center, 3-treatment, 3-period, multiple-dose, crossover study conducted in 18 healthy subjects (11 males and 7 females), 24 to 55 years of age, to evaluate the PK profiles of 2 different regimens of IV tramadol (50 and 75 mg) and to compare them to a single oral regimen of tramadol in order to determine optimal dosing such that exposure would be similar to oral 100-mg tramadol (ULTRAM tablets).

Eligible subjects were randomized into one of six treatment sequences, and each subject was to receive each of the following treatments:

- IV tramadol 75 mg at Hour 0, followed by 75 mg at Hour 3 and Hour 6, and 75 mg q6h thereafter through Hour 42
- IV tramadol 50 mg at Hour 0, followed by 50 mg at Hour 2, 50 mg at Hour 4, and 50 mg every 4 hours (q4h) thereafter through Hour 44
- Oral tramadol 100 mg (50 mg tablets x 2) at Hour 0 and Hour 6, and q6h thereafter through Hour 42

Subjects underwent a minimum 72-hour washout period between the end of Period 1 (Hour 48) and initiation of dosing in Period 2, and between the end of Period 2 (Hour 48) and initiation of dosing in Period 3. Blood sampling for each regimen was performed frequently to ensure a comprehensive concentration-time profile.

Exposure to tramadol based on C_{max}, AUC_{24-48} and AUC_{0-48} was not appreciably different between 50 mg IV and 100 mg oral. There was no substantive difference in overall systemic exposure among the 3 treatments, although a higher C_{max} for tramadol after IV 75-mg treatment compared to the IV 50-mg and oral 100-mg treatments was observed, see Table 13. Steady-state was reached by 12 hours for the IV 75-mg regimen, 16 hours for IV 50-mg regimen, and 24 hours for oral 100-mg regimen.

Over the entire PK sampling period, the C_{max} for IV tramadol 75 mg was somewhat higher, compared to the other 2 treatments, while the C_{max} after IV 50 mg and oral 100 mg were similar. During the last 24-hour sampling period (AUC_{24-48}), the exposure to tramadol after oral 100 mg administration was comparable to that after IV 50 mg (11020 h•ng/mL) administration, while it was somewhat lower for IV 75 mg, see Table 13.

The predicted exposure over 12 hours at steady-state (estimated based on $AUC_{tau\ n}$) was comparable for IV 50 mg q4h (3 x 2228=6684 h•ng/mL) and oral 100 mg q6h (2 x 3475=6950 h•ng/mL), but somewhat lower for the IV 75 mg q6h (2 x 3036=6072 h•ng/mL), see Table 13.

Table 13: Study AVE-901-101: Plasma Pharmacokinetic Parameters of Tramadol (Parent)

Parameter	75 mg IV		50 mg IV		100 mg Oral	
	Mean ± SD	CV%	Mean ± SD	CV%	Mean ± SD	CV%
t_{max} (h)	15.93 ± 17.36	108.96	30.02 ± 19.89	66.27	44.03 ± 1.01	2.29
C_{max} (ng/mL)	932 ± 199	21.30	736 ± 152	20.60	701 ± 178	25.44
AUC_{24-48} (h•ng/mL)	9402 ± 2511	26.71	11020 ± 2852	25.88	11650 ± 3387	29.07
AUC_{0-48} (h•ng/mL)	19330 ± 4427	22.90	20540 ± 4906	23.89	19140 ± 5172	27.02
$AUC_{tau\ n}$ (h•ng/mL)	3036 ± 608.3	20.04	2228 ± 525.6	23.60	3475 ± 902.2	25.97

Note: n=14 for 75 mg IV, n=14 for 50 mg IV, and n=17 for 100 mg oral treatment.
Source: AVE-901-101 CSR

Exposure to M1 was significantly higher after oral 100 mg administration compared to the 2 IV regimens, see Table 14, which was as expected, considering the first pass metabolism after oral administration which results in a higher fraction of the active metabolite in systemic circulation. Although exposure parameters were slightly higher for 75 mg IV q6h compared to 50 mg IV q4h through early time points, exposure to M1 was comparable for the two IV regimens when the entire PK sampling period was considered.

Table 14: Study AVE-901-101: Plasma Pharmacokinetic Parameters of M1 (Metabolite)

Parameter	75 mg IV		50 mg IV		100 mg Oral	
	Mean ± SD	CV%	Mean ± SD	CV%	Mean ± SD	CV%
t_{max} (h)	32.99 ± 16.50	50.01	44.95 ± 1.59	3.53	43.97 ± 1.12	2.54
C_{max} (ng/mL)	99.2 ± 25.6	25.85	96.6 ± 24.5	25.35	146 ± 37.4	25.62
AUC_{24-48} (h•ng/mL)	1896 ± 524.5	27.66	2002 ± 514.9	25.72	2693 ± 750.0	27.85
AUC_{0-48} (h•ng/mL)	3504 ± 931.2	26.58	3427 ± 889.9	25.97	4349 ± 1139	26.20
$AUC_{tau\ n}$ (h•ng/mL)	519.8 ± 142.7	27.45	355.6 ± 89.39	25.14	768.4 ± 209.4	27.26

Note: n=14 for 75 mg IV (except AUCtau n, n=15), n=14 for 50 mg IV, and n=17 for 100 mg oral treatment.
Source: AVE-901-101 CSR

The PK curves for both the parent compound tramadol and M1 for both the IV Tramadol 50 mg and the oral tramadol dosage were shown in Section 2.3.

In conclusion, the IV tramadol 50 mg dosing regimen resulted in a similar Cmax and AUC of tramadol as oral tramadol 100 mg Q6H at steady state. The IV tramadol 50 mg resulted in lower Cmax and AUC, as well as slower onset of M1, as compared to the oral dosing regimen.

5. EFFICACY

The development program provided separate and independent evidence of efficacy in two Phase 3 studies in patients with post-surgical pain and demonstrated the safety profile of IV tramadol in these patients. To support the approval of IV tramadol for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting, two Phase 3 studies were conducted in 2 distinct surgical pain models. Dosing for each study group was at baseline, 2 hours, 4 hours and every 4 hours thereafter through 48 hours.

Study AVE-901-102 bunionectomy was completed prior to initiation of Study AVE-901-103 abdominoplasty, in agreement with FDA advice. Study AVE-901-102 demonstrated that a dose-response existed, with the IV tramadol 50 mg dosing regimen superior to placebo with respect to the management of moderate to moderately severe pain. While the 25 mg dosing regimen demonstrated modest activity and was numerically 'better' than placebo with respect to the pain management, it was found not to be statistically different from placebo. Thus the 50 mg regimen was carried forward to Study AVE-901-103 and to the open-label Study AVE-901-104.

Study AVE-901-103 confirmed the efficacy of the IV tramadol 50 mg dose and, in comparison to the active comparator arm (IV morphine 4 mg), demonstrated a favorable safety/tolerability profile compared to IV morphine 4 mg and showed comparable efficacy on all primary and key secondary efficacy endpoints.

The two Phase 3 trials were run independently and were similar in design and in endpoints, with the following key differences:

1. Study AVE-901-102 assessed the effects of 2 different dose levels of IV tramadol (versus placebo): 25 mg and 50 mg after bunionectomy, an orthopedic model. The use of two active dose arms was intended to allow for selection of the optimal dose based on both efficacy and safety outcomes.
2. Study AVE-901-103 assessed the effects of IV tramadol 50 mg versus placebo as well as versus an active comparator, morphine injection, after abdominoplasty, a soft tissue model. The use of the single active dose level was intended to corroborate findings from Study AVE-901-102 for the IV tramadol 50 mg dose, while use of a morphine treatment arm was intended to provide safety outcomes relative to an active control. The study was not powered to directly compare efficacy of the two active arms. However, the results of the study allow for an understanding of the comparability of IV tramadol and IV morphine.

The endpoints for the two pivotal efficacy studies were similar. The primary endpoint for assessment of efficacy for the bunionectomy model (Study AVE-901-102) was through 48-hours post first dose, whereas it was through 24-hours post-first dose for the abdominoplasty model (Study AVE-901-103) (Table 15). Both studies included a primary endpoint, 3 key secondary endpoints, and tertiary endpoints. Each study included pre-specified methods to control for multiplicity testing for the primary and key secondary endpoints. These endpoints have been frequently used in other registrational trials supporting approval of analgesics for acute pain.

Table 15: Comparison of Efficacy Endpoints Between the Two Phase 3 Efficacy Studies

	Study AVE-901-102	Study AVE-901-103
Primary Endpoint	The Sum of Pain Intensity Differences (SPID) measured at rest through 48 hours post first dose (**SPID48**)	The Sum of Pain Intensity Differences (SPID) measured at rest through 24 hours post first dose (**SPID24**)
Key Secondary Endpoints (ordered in sequence of hypothesis testing)	The Sum of Pain Intensity Differences (SPID) measured at rest through 24 hours post first dose (SPID24)	Patient Global Assessment of efficacy at 24 hours post first dose
	Total consumption of rescue (supplemental) analgesia through 48 hours post first dose.	The Sum of Pain Intensity Differences (SPID) measured at rest through 48 hours post first dose (SPID48)
	Patient Global Assessment of efficacy at 24 and 48 hours	Total consumption of rescue (supplemental) analgesia through 24 hours post dosing
Tertiary Endpoints	Time-specific pain intensity profile over time.	Time-specific pain intensity profile over time
	Clock time (in minutes) to first use of rescue medication from the time of first dose of study medication.	Time (in minutes) to first rescue analgesia from the time of first dose of study medication.
	Number of patients who required no rescue analgesia from T0-T48.	Number (percent) of patients who require no rescue analgesia from T0- T24 and T0-T48.
	The rate of consumption of rescue analgesia.	Rate of consumption of rescue analgesia.
	Time (in minutes) to meaningful pain relief after first dose. Time (in minutes) to confirmed perceptible pain relief after first dose.	Time (in minutes) to meaningful pain relief after first dose. Time (in minutes) to confirmed perceptible pain relief after first dose.
		Total consumption of rescue (supplemental) analgesia through 48 hours post dosing.
		Patient Global Assessment of efficacy at 48 hours post first dose

Source: Clinical Overview (Module 2.5 of NDA)

5.1. Study AVE-901-102 (Bunionectomy, Dose-Finding)

5.1.1. Study Design

The first Phase 3, Study AVE-901-102, was a Phase 3, multicenter, double-blind, three-arm, randomized, placebo-controlled, multiple-dose, parallel-group trial to evaluate the safety, tolerability and the efficacy of IV tramadol (two difference dose levels) versus placebo in the management of postoperative pain in consenting patients undergoing a unilateral primary first metatarsal bunionectomy surgery. Dosing for each treatment group was at Hour 0, 2, 4, and every 4 hours thereafter through Hour 48

A total of 409 patients were randomized and underwent treatment. Randomization was stratified by study center.

Patients underwent the Screening Visit (Day -28 to Day -1), the preoperative assessment (within 24 hours prior to surgery start time), the Surgical/Treatment Visit, the first day of which was when the bunionectomy was performed (Day 0), the primary treatment period through Hour 48 (the last on treatment assessment, and the End of Treatment visit), and the Follow-up Visit (Day 14).

Screening occurred up to 28 days prior to surgery. Following the preoperative assessments, and after the patient met eligibility criteria, patients were randomized in a double-blinded fashion, stratified by study center, in a 1:1:1 ratio to the treatment groups.

Following surgery, a patient that met the post-surgical dosing criteria received his or her assigned study medication infusion regimen over a period of 48 hours. Patients were confined at the healthcare facility during study drug administration and were discharged only if clinically stable. Following surgery, patients had their popliteal block withdrawn approximately between 4 and 5 AM. Post removal of the popliteal block, patients were assessed for the dosing eligibility criteria prior to dosing. Patients must have been awake and alert and must have had a pain intensity of 5 or greater on the Numerical Pain Rating Scale (NPRS) and reported a score of moderate or severe on a 4-point categorical rating scale (with categories of none, mild, moderate, or severe) just before the first dose of the study drug. Patients who did not report pain at this level within 8 hours of the removal of the block were discontinued from the study.

T_0 was the time of start of infusion of first study drug administration. Pain intensity was recorded using an NPRS from 0 to 10, where 0 was no pain and 10 was the worst pain imaginable. Pain intensity assessments were recorded immediately prior to the first dose (baseline) and at frequent intervals through 48 hours after first treatment (ie, post T_0). The patient rested for 15 minutes (±5 minutes) prior to NPRS assessments.

Rescue medication (ibuprofen 400 mg every 4 hours as needed [PRN] up to 2400 mg per day) was available any time after the initial dose of study medication to keep the patient comfortable. However, patients were encouraged to wait at least 60 minutes after the initial dose of study medication before they received rescue therapy. An NPRS measurement was obtained immediately (approximately 5 minutes) prior to each administration of rescue medication. Patient controlled analgesia was not allowed in this study. The time of rescue medication was recorded in the electronic case report form (eCRF). The Investigator and/or study team personnel monitored the patient carefully for 48 hours to assess the patient's condition and provide rescue medication whenever requested, within the above limits. Antiemetic treatment (Reglan or Emend but not Zofran or 5-HT_3 antagonists) were allowed.

The Patient Global Assessment of efficacy was completed by the patient at 24 hours and 48 hours post T0. Ratings were assessed as: 0=poor; 1=fair; 2=good; 3=very good; or 4=excellent. 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.

SPID48 (the sum of the time-weighted pain intensity differences for the time period 0-48 hours) was the primary efficacy endpoint. Pain intensity was recorded using the following NPRS from 0 to 10, where 0 was no pain and 10 was the worst pain imaginable. Patients underwent training on pain assessment and/or watched a video at Screening and prior to surgery.

The key secondary efficacy assessments were:

- SPID24.
- Total consumption of rescue (supplemental) analgesia. This was the total amount of rescue analgesia given to the patient after first dose of study medication through 48 hours post first dose.

- Patient Global Assessment of efficacy at 24 and 48 hours. The Patient Global Assessment of efficacy was completed by the patient at 24 hours and 48 hours post T_0. Ratings were assessed as: 0=poor; 1=fair, 2=good, 3=very good or 4=excellent.

Additional analgesia endpoints included the time-specific pain intensity profile over time and other outcomes.

Safety data included treatment-emergent AEs (TEAEs), clinical laboratory tests (hematology panel, chemistry panel and urinalysis) pre-treatment and discharge, vital signs including respiratory rate, heart rate, temperature, oximetry, and blood pressure, physical examination at pre-treatment and discharge, 12-lead ECG at protocol specified time points, and concomitant treatment assessments.

5.1.1.1. Statistical methods and analysis populations

A prespecified Statistical Analysis Plan (SAP) was prepared and provided to the FDA prior to unblinding the study treatment codes. The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model with contrasts to test the primary efficacy endpoint. The model used treatment as the main effect and investigational center and baseline pain intensity (NPRS scores of 0 to 10) as covariates. Data from all three treatment groups were included in the same ANCOVA model for purposes of the testing procedures. Missing data was accounted for via 'multiple imputation techniques', according to procedures specifically agreed to with the FDA at the end of Phase 2 meeting.

The key analysis populations pre-specified for purposes of the statistical analysis were.

- The Safety Population was defined as all patients who received study medication. Patients were analyzed according to the actual treatment they received. This was the primary analysis population used for assessment of safety.
- 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. This was the primary analysis population used for assessment of efficacy.

Importantly, control for multiplicity was included in the analysis. The high-dose tramadol arm vs placebo comparison will be assessed for the primary endpoint at the 0.05 alpha level. If and only if, the p-value is ≤ 0.05 for this pairwise comparison, will the lower dose tramadol arm vs placebo comparison be assessed.

According to the hierarchical alpha testing strategy described in the pre-specified SAP, if the primary endpoint (SPID48) was significant for the tramadol versus placebo comparison (in favor of the tramadol arm) for the high dose comparison or both pair-wise tests, then statistical testing was to proceed to the key secondary endpoints within each pair-wise grouping, to be tested in the following order:

- SPID24
- Total consumption of rescue analgesia
- Patient Global Assessment of efficacy at 24 and 48 hours (the two time points were to be tested simultaneously)

Thus, the SPID48 for the high dose needed to be statistically significant to proceed to testing of secondary endpoints for the high dose. If a statistical test for a secondary endpoint was significant for the high dose comparison at the nominal 0.05 level, 2-sided (in favor of the tramadol arm), then testing was to proceed to the next endpoint in the list. Once a non-significant test occurred, endpoints lower in the list were to be considered not statistically significant.

If the primary endpoint (SPID48) was statistically significant for the high dose tramadol arm vs placebo, testing of the low dose tramadol arm vs placebo comparison was performed, first for the primary endpoint, and if statistically significant, proceeding to the secondary endpoints in a similar fashion as for the high dose comparisons.

5.1.1.2. Demographics and Patient Disposition

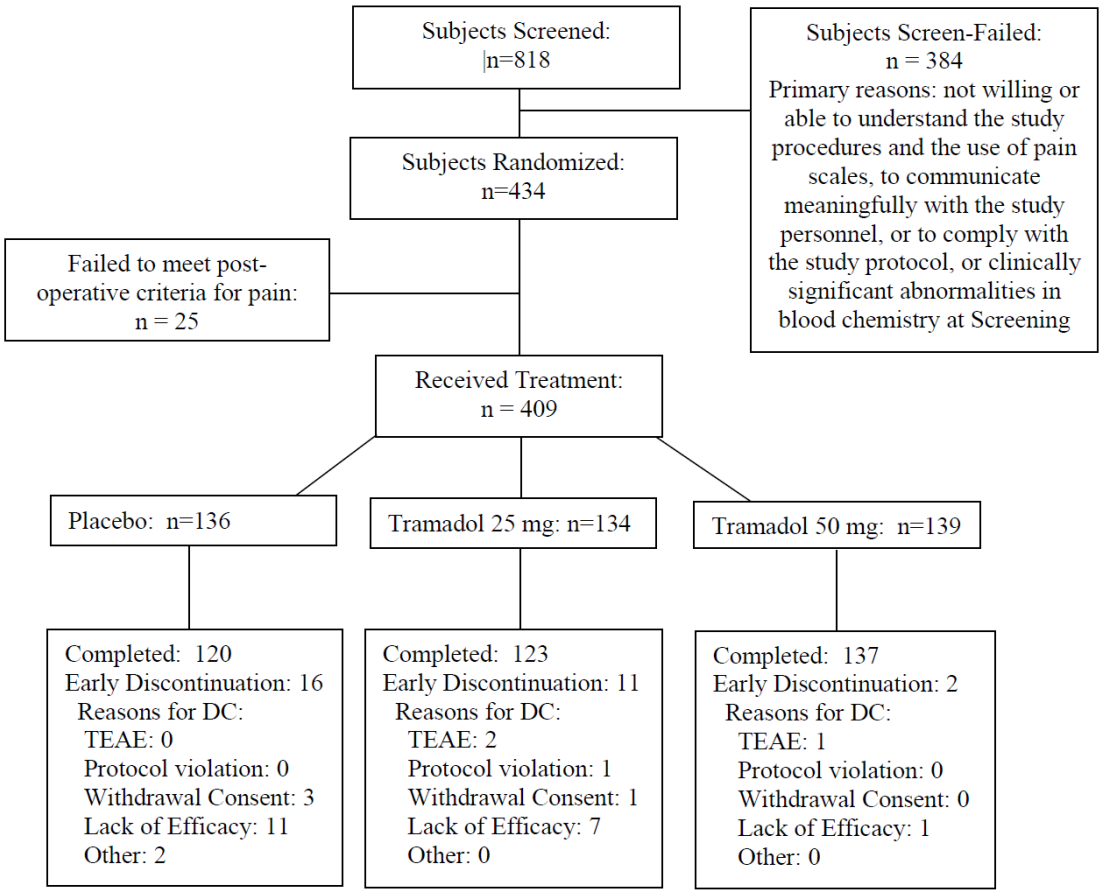
Table 16 shows that the majority of patients were female (85.3%), White (68.5%), and non-Hispanic/non-Latino (63.6%). The median age was 46.0 years and median BMI was 28 kg/m^2. The majority had no prior opioid usage (65.5%), were ASA Physical Class of 1 (52.1%), and had moderate pain (59.7%) at the time of qualifying for randomization. The mean (±SD) qualifying NPRS score was 6.8 (1.56). Enrollment and patient disposition are shown in Figure 15.

Table 16: Demographic and Baseline Characteristics (Study AVE-901-102)

Category	Placebo (N=136) n (%)	IV Tramadol 25 mg (N=134) n (%)	IV Tramadol 50 mg (N=139) n (%)
Age (years) Mean (SD)	45.3 (13.44)	44.5 (13.15)	45.7 (13.51)
Age (range, Min, max)	(19, 69)	(19, 74)	(19, 69)
Female n (%)	113 (83.1)	116 (86.6)	120 (86.3)
Hispanic or Latino n (%)	52 (38.2)	46 (34.3)	51 (36.7)
Race n (%)			
American Indian or Alaskan Native	4 (2.9)	1 (0.7)	2 (1.4)
Native Hawaiian/Pacific Islander	0	1 (0.7)	0
Asian	4 (2.9)	3 (2.2)	2 (1.4)
White	88 (64.7)	88 (65.7)	104 (74.8)
Black or African American	37 (27.2)	38 (28.4)	29 (20.9)
Other	0	1 (0.7)	0
Multiple	3 (2.2)	2 (1.5)	2 (1.4)
Previous use of opioid n (%)	47 (34.6)	52 (38.8)	42 (30.2)
Qualifying categorical pain score			
Moderate	75 (55.1)	80 (59.7)	89 (64.0)
Severe	61 (44.9)	54 (40.3)	50 (36.0)
Qualifying NPRS, mean (SD)	6.9 (1.63)	6.8 (1.39)	6.7 (1.66)
Baseline body mass index (kg/m^2), mean (SD)	28.3 (4.91)	28.1 (5.48)	27.9 (4.97)

max=maximum; min=minimum; NPRS=Numerical Pain Rating Scale; SD=standard deviation
1 NPRS scores ranged from 0 (no pain) to 10 (worst pain).
Source: AVE-901-102 CSR

Figure 15: Enrollment and Patient Disposition (Study AVE-901-102)



Source: AVE-901-102 CSR

5.1.1.3. Efficacy Outcomes

Efficacy outcomes demonstrate that the tramadol 50 mg dose was effective in the management of postoperative pain following bunionectomy.

- In the primary efficacy analyses, tramadol 50 mg was found to be statistically significantly better than placebo with p values <0.05 (in accordance with the pre-defined hierarchical testing strategy). The key secondary endpoints are supportive.
- The tramadol 25 mg was not found to be statistically significantly different from placebo for the primary outcome measure (SPID48); (p-value=0.145).
  - These outcomes demonstrate that while the tramadol 25 mg dose provided some pain relief, it was not statistically significantly different from placebo on the primary outcome (in accordance with the hierarchical testing). Thus, the tramadol 25 mg dosing regimen was not judged to be an effective dose for treatment of postoperative pain following bunionectomy surgery.

A summary of key efficacy findings is presented in Table 17.

Table 17: Summary of Key Efficacy Findings Compared to Placebo, in Accordance with Pre-defined Hierarchical Testing Strategy (FAS Population) (Study AVE-901-102)

	Placebo (N=136)	IV Tramadol 25 mg (N=134)	IV Tramadol 50 mg (N=139)
SPID48[1]			
LSMean	-97.8 (6.53)	-110.9 (6.50)	-122.8 (6.28)
Difference in LS mean (SE) from Placebo		-13.1 (8.98)	-25.0 (8.81)
P-value for difference		0.145	**0.005**
SPID24[1]			
LSMean (SE)	-25.9 (3.33)	-33.9 (3.32)	-43.7 (3.22)
Difference in LS mean (SE) from Placebo		-8.0 (4.57)	-17.8 (4.50)
Total rescue medication use[2]			
Median	1200	1200	800
Difference in rank sum mean from Placebo		-6.4	-30.1
Patient Global Assessment for 24 hours[3]			
LSMean (SE)	1.5 (0.11)	1.9 (0.10)	2.3 (0.10)
Difference in LS mean (SE) from Placebo		0.4 (0.14)	0.8 (0.14)
Patient Global Assessment for 48 hours[3]			
LSMean (SE)	1.8 (0.11)	2.3 (0.11)	2.6 (0.11)
Difference in LS mean (SE) from Placebo		0.5 (0.16)	0.8 (0.15)

Abbreviations: ANCOVA=analysis of covariance; FAS=Full Analysis Set; LS=least squares; NPRS=Numerical Pain Rating Scale; SE=standard error

[1] From combined results obtained from analysis of the 100 multiply imputed datasets using an ANCOVA model with treatment as the main effect, pooled study center and baseline NPRS as covariates.

[2] Rank sum mean difference (treatment – placebo) and p-values are obtained from Pairwise Two-Sample Wilcoxon rank sum test.

[3] From an ANCOVA with treatment as the main effect, pooled study center and baseline NPRS scores as covariates.

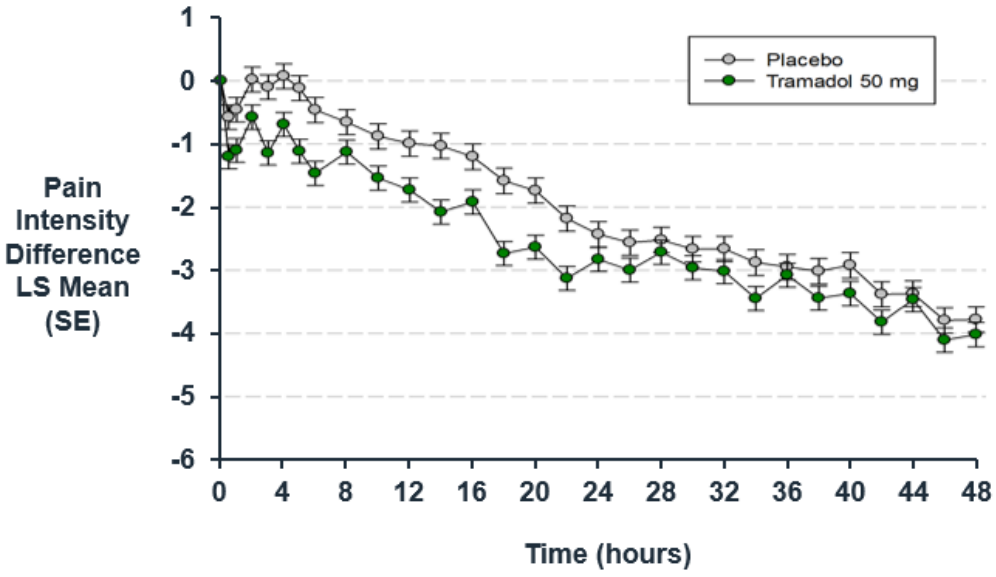
[4] From Cochran-Mantel-Haenszel test (stratified by pooled study center).

Note: P-values in this table are in accordance with the pre-defined hierarchical testing strategy. Since the p-value for tramadol 25 mg compared to placebo was not statistically significant for the primary endpoint, the remaining endpoints were considered not significant.

Source: AVE-901-102 CSR

Figure 16 provides the LSMean (SE) PID values for IV tramadol 50 mg and for placebo from Study AVE-901-102. These data show immediate separation between the treatment groups at the first time point (Hour 0.5), with continued differences throughout the dosing regimen, demonstrating early onset of effect for the IV tramadol treatment arm.

Figure 16: LSMean (SE) Pain Intensity Differences for IV Tramadol 50 mg and Placebo (FAS Population) (Study AVE-901-102)



Abbreviations: FAS=Full Analysis Set; LS=least squares; NPRS=Numerical Pain Rating Scale; SEM=standard error of the LSmean. Notes: A negative pain intensity difference indicates less pain post baseline. Pre-rescue NPRS score was used to replace NPRS obtained within 4 hours post rescue medication. No other missing pain scores were imputed. LS means were obtained from the mixed model for repeated measures (MMRM) with treatment as the main effect, patient as the random effect, pooled study center baseline NPRS, time and treatment by time interaction as covariates.
Source: AVE-901-102 CSR

The PGA 24 and PGA 48 confirmed that patients on IV tramadol 50 mg benefited from clinically meaningful analgesia following orthopedic (bunionectomy) surgery, over both the full 48-hour treatment period as well as over the first 24 hours of treatment (Figure 4).

5.2. Study AVE-901-103 (Abdominoplasty, Active Control)

The major design elements of this study were the same as for Study AVE-901-102 (bunionectomy), with a few key differences.

5.2.1. Study Design

The second Phase 3, Study AVE-901-103, was a Phase 3, multicenter, double-blind, three-arm, randomized, placebo-controlled, multiple-dose, parallel-group trial to evaluate the safety, tolerability and the efficacy of IV tramadol 50 mg versus placebo in the management of postoperative pain in consenting patients undergoing abdominoplasty surgery.

As for the first Phase 3, dosing for each treatment group was at Hour 0, 2, 4, and every 4 hours thereafter through Hour 48.

A total of 380 patients were randomized (142 in the tramadol 50 mg arm, 142 in the Placebo arm, 96 in Morphine arm). Assessments (including timing of pain scoring, type of rescue medication, etc.) were the same as for Study AVE-901-102, and thus are not described in detail here.

The primary objective of this study was to evaluate the analgesic efficacy of intravenous (IV) tramadol compared to placebo in the management of postoperative pain following abdominal surgery. The Sum of Pain Intensity Differences (SPID) measured at rest through 24 hours post first dose (SPID24), was used as the primary measure of efficacy. (This was in contrast to the prior study, in which SPID48 was the primary measure of efficacy. This difference is due to the pain intensity in the surgical models, ie, patients undergoing bunionectomy tend to have pain that lasts a bit longer than the pain for patients undergoing abdominoplasty).

The Key Secondary efficacy endpoints were:

- Patient Global Assessment of efficacy at 24 hours post first dose using a 5-point scale. The question posed was "How would you rate the study medication in terms of its effectiveness in controlling your pain?" (0=poor; 1=fair; 2=good; 3=very good; 4=excellent).
- SPID through 48 hours post first dose (SPID48) measured at rest
- Total consumption of rescue (supplemental) analgesia through 24 hours post dosing. This is the total amount of rescue analgesia given to the patient after first dose of study medication through 24 hours post-first dose.

5.2.1.1. Statistical methods and analysis populations

Statistical methods were generally the same as for the prior Phase 3 study, with minor differences according to the inclusion, in Study AVE-901-103, of an active comparator arm.

Statistical testing for efficacy outcomes was focused on the tramadol to placebo comparison. A hierarchical alpha testing strategy was utilized to control for the overall experiment-wise alpha (as in the prior study, Study AVE-901-102). Comparisons between the IV tramadol and morphine arms were performed in an exploratory fashion, with a focus on the magnitudes of effect and whether there were any material (clinically important) differences between those treatment arms.

5.2.1.2. Demographics and Patient Disposition

Table 18 shows nearly all patients were female (99.2%) (reflecting the demographics most often associated with this surgery type), and the majority of patients were White (74.6%). A little over half were Hispanic or Latino (56.2%), and the median age was 40.0 years (range of 20 to 71 years). The majority of patients had moderate pain at time of qualifying (73.2%), were ASA Physical Class of 1 (65.4%), and 54.9% had no previous opioid history. The mean (SD) qualifying NPRS overall was 6.5 (1.45).

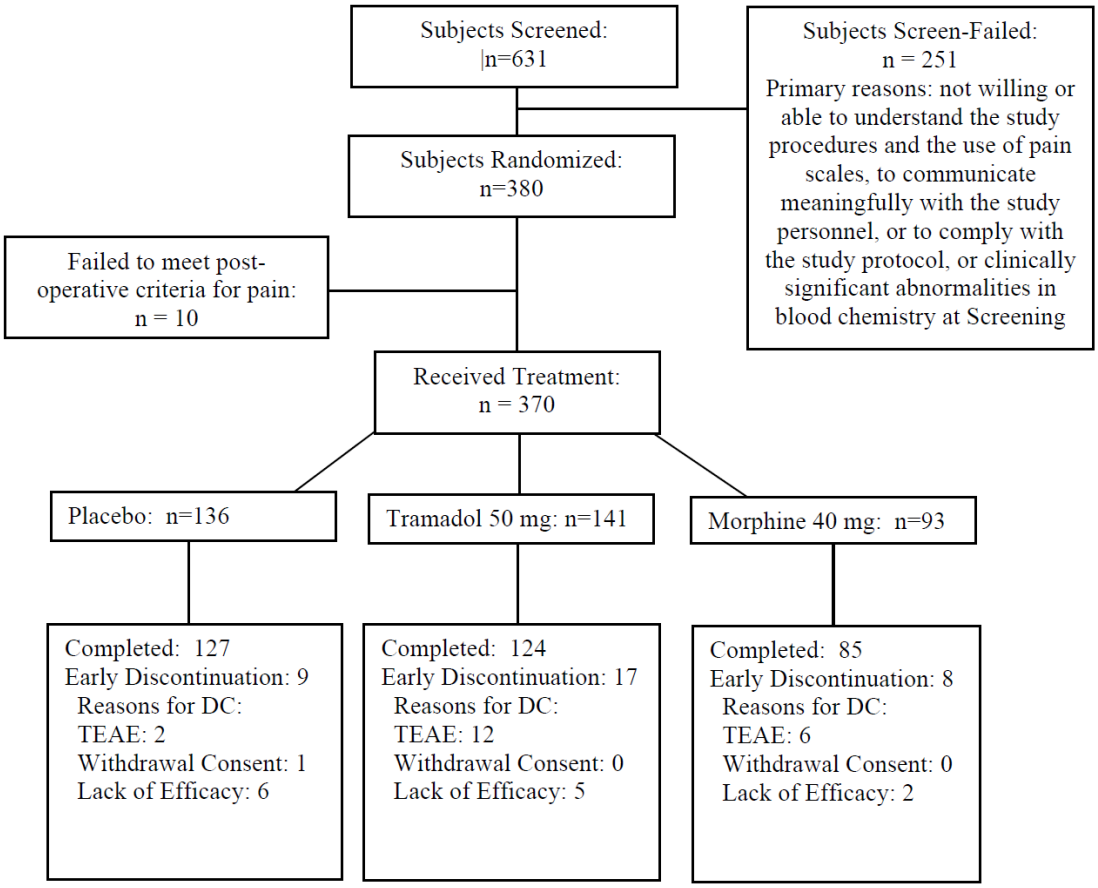
Table 18: Demographic and Baseline Characteristics (Study AVE-901-103)

Category	Placebo (N=136) n (%)	IV Tramadol 50 mg (N=141) n (%)	IV Morphine 4 mg (N=93) n (%)
Age (years), mean (SD)	40.3 (8.77)	39.9 (8.70)	39.1 (8.67)
Age (range) Min, max	(21, 69)	(23, 71)	(20, 60)
Female	133 (97.8)	141 (100.0)	93 (100.0)
Hispanic or Latino	67 (49.3)	85 (60.3)	56 (60.2)
Race			
American Indian or Alaskan Native	0	2 (1.4)	0
Asian	5 (3.7)	3 (2.1)	3 (3.2)
Black or African American	24 (17.6)	25 (17.7)	13 (14.0)
Native Hawaiian/Pacific Islander	1 (0.7)	1 (0.7)	2 (2.2)
White	102 (75.0)	102 (72.3)	72 (77.4)
Other	1 (0.7)	3 (2.1)	2 (2.2)
Multiple	3 (2.2)	5 (3.5)	1 (1.1)
Previous opioid history	63 (46.3)	67 (47.5)	37 (39.8)
Qualifying NPRS,[1] mean (SD)	6.5 (1.43)	6.5 (1.43)	6.7 (1.51)
Baseline body mass index (kg/m^2), mean (SD)	26.8 (3.65)	26.9 (3.26)	26.9 (3.34)

max=maximum; min=minimum; NPRS=Numerical Pain Rating Scale; SD=standard deviation
[1] NPRS scores ranged from 0 (no pain) to 10 (worst pain).
Source: AVE-901-103 CSR

Figure 17 provides a CONSORT diagram of the enrollment and patient disposition. Note that randomization was in a 3:3:2 ratio of IV tramadol:Placebo:Morphine, and thus the morphine arm enrolled fewer patients than the other treatment arms.

Figure 17: Enrollment and Patient Disposition (Study AVE-901-103)



Source: AVE-901-103 CSR

5.2.1.3. Efficacy Outcomes

Efficacy outcomes demonstrate that IV tramadol 50 mg is highly effective in the management of postoperative pain following abdominoplasty. A summary of key efficacy findings (primary and key secondary efficacy endpoints) is presented in Table 19. In each of these key efficacy analyses, IV tramadol 50 mg was found to be statistically significantly better than placebo with all p-values <0.05 (in accordance with the pre-defined hierarchical testing strategy).

Table 19: Summary of Primary and Key Secondary Efficacy Findings (FAS Population) (Study AVE-901-103)

	Placebo (N=136)	IV Tramadol 50 mg (N=141)	IV Morphine 4 mg (N=93)
SPID24[1]			
LS mean (SE)	-47.7 (3.89)	-79.0 (3.89)	-81.7 (4.54)
Difference in LS mean (SE) vs placebo		-31.3 (4.71)	-34.0 (5.28)
P-value for difference versus placebo		**<0.001**	<0.001
Patient Global Assessment for 24 hours[2]			
LS mean (SE)	2.2 (0.11)	3.0 (0.11)	3.1 (0.13)
Difference in LS mean (SE) vs placebo		0.9 (0.13)	1.0 (0.15)
SPID48[1]			
LS mean (SE)	-121.1 (8.23)	-180.8 (8.23)	-178.6 (9.60)
Difference in LS mean (SE) vs placebo		-59.7 (9.97)	-57.5 (11.17)
Total rescue medication use through 24 hours[3]			
Mean Total Rescue (mg)	658.8	312.1	189.2
Rank sum mean	234.7	167.3	141.1

Abbreviations: ANCOVA=analysis of covariance; FAS=Full Analysis Set; LS=least squares; NPRS=Numerical Pain Rating Scale; SE=standard error

[1] From combined results obtained from analysis of the 100 multiply imputed datasets using an ANCOVA model with treatment as the main effect, study center, baseline body mass index (<30 kg/m^2 versus ≥30 kg/m^2), and baseline NPRS as covariates.

[2] From an ANCOVA with treatment as the main effect, study center, baseline body mass index (<30 kg/m^2 versus ≥30 kg/m^2), and baseline NPRS scores as covariates.

[3] Rank sum mean and p-values were obtained from Pairwise Two-Sample Wilcoxon rank sum test.

Note: P-values in this table are in accordance with the pre-defined hierarchical testing strategy.

Source: AVE-901-103 CSR

Comparisons between morphine and tramadol and morphine and placebo were evaluated in this study for exploratory analyses. The magnitude of the differences in the primary and key secondary efficacy outcomes were similar between tramadol and morphine; patients in the morphine group tended to utilize less rescue medication over the first 24 hours and showed earlier time to onset of perceptible pain relief.

An in-depth discussion of the results of Study 103 is found in Section 2.

5.3. Study AVE-901-104 (Various Surgery Types, Open-Label)

5.3.1. Study Design

This study was a Phase 3, multicenter, single-arm, open-label, uncontrolled, repeat-dose trial to assess the safety of IV tramadol 50 mg in the management of postoperative pain. Eligible patients included patients that were undergoing elective surgery and were deemed appropriate to receive IV tramadol for the treatment of post-surgical pain. Two hundred fifty-one patients were enrolled into the study. Patients underwent the Screening Visit (Day -28 to Day -1), the pre-operative assessment (within 24 hours prior to surgery), the surgery (Day 0), the primary treatment period (Hour 0 up through Hour 168), End of Treatment Visit, and the Follow-up Visit (Day 14).

Screening occurred up to 28 days prior to surgery. Eligible patients were made aware of the use of additional pain medication and of the various post-treatment safety measures. These patient training procedures may have been conducted on different days as appropriate during Screening. Surgery occurred on Day 0. There were no restrictions on the agents used for induction, neuromuscular blockade, and maintenance of anesthesia and no restrictions on hypnotics, sedatives, or anxiolytics.

Following surgery, patients who met the post-surgical dosing criteria received their study drug infusion (IV tramadol 50 mg) at T0 (Hour 0), Hour 2, and Hour 4, and then every 4 hours for up to 168 hours after the first study drug administration (a total of up to 43 doses per patient). T0 was the time of start of infusion of first study drug administration. The latest (last) dose that was allowed was at Hour 164. Patients were to continue study treatment until it was no longer needed; however, some patients had consented in advance to stay on treatment for 5 days to allow for safety data collection beyond 48 hours, in order to gain longer-duration experience with IV tramadol 50 mg. Patients were confined at the healthcare facility for as long as they were still using study drug. Following the first dose of study drug, the patients were allowed to use non-opioid pain medication per the treating physician's discretion, if additional pain relief was required.

The primary objective of this study was to evaluate the safety of IV tramadol 50 mg for the management of postoperative pain. In addition, patient global assessment of the treatment was collected at 24 hours and end of treatment, to assess the patient satisfaction with pain relief.

Key inclusion criteria included:

1. The patient is male or female 18-75 years of age
2. Patient is undergoing elective surgery and, in the opinion of the investigator, is an appropriate candidate for IV Tramadol for pain management post-operatively.
3. The study patient is willing to be housed in a healthcare facility capable of administering parenteral analgesia for at least 24 after surgery. Treatment may extend through Hour 168 if deemed appropriate.

Key exclusion criteria included:

1. The patient has current or historical evidence of any clinically significant disease or condition that might place the patient at unacceptable risk due to receiving the study medication, in the opinion of the investigator.
2. The patient has allergy or hypersensitivity (or is intolerant) to opioids or tramadol.
3. The patient has used chronic opioid therapy, defined as >= 20 MEQs of morphine per day >=3 days out of 7 days over the past 4 weeks.
4. The patient has a recent (within 2 years) and/or current history of alcohol, opiate or tranquilizer abuse or dependence.
5. The patient has had a recent (within 6 months) cardiovascular event or clinically significant abnormal ECG finding at screening.
6. The patient has a history of Long QT Syndrome or a relative with this condition

5.3.1.1. Effectiveness Outcomes

Patients in this Phase 3 open-label study had a median age 48.0 years (range 18 to 75 years), with 50 (19.9%) of patients ≥65 years of age. This study enrolled a substantial proportion of male subjects, with 39.8% male and 60.2% female. The majority of patients were non-Hispanic/non-Latino (66.1%) and White (80.9%). Most patients had no prior history of opioid use (80.9%) and were ASA Physical Classification 2 (80.9%). The most common surgery type was breast augmentation (30.7%), followed by total hip replacement (22.7%) and hernia surgeries (19.1%). The demographic and surgery information are summarized in Table 20.

Table 20: Demographic and Surgery Summary (Studies AVE-901-104)

Category	Tramadol 50 mg (N=251) n (%)
Age (years) Mean (SD)	45.6 (17.26)
Gender (Female)	151 (60.2)
Hispanic or Latino	85 (33.9)
Black or African American	43 (17.1)
White	203 (80.9)
Previous opioid history use	48 (19.1)
BMI (kg/m2) Mean (SD)	27.2 (5.09)
Surgery Type	
Total knee replacement	32 (12.7)
Total hip replacement	57 (22.7)
Abdominoplasty	20 (8.0)
Colon surgeries	15 (6.0)
Hernia surgeries	48 (19.1)
Breast augmentation	77 (30.7)
Hysterectomy	2 (0.8)

Source: AVE-901-104 CSR

In Study 104, a variety of non-opioid analgesics were used in addition to IV tramadol in a multimodal approach per treating physicians' discretion. They are listed in Table 21.

Table 21: Non-opioids Used in Studies AVE-901-104

Medicine	Number (%) of Patients
Paracetamol	134 (53.4)
Gabapentin	78 (31.1)
Meloxicam	57 (22.7)
Ketorolac	31 (12.4)
Celecoxib	13 (5.2)
Ibuprofen	5 (2.0)
Ketorolac Tromethamine	4 (1.6)

Acetylsalicylic acid	1 (0.4)
Pregabalin	1 (0.4)

Source: AVE-901-104 CSR

Patient reported outcomes corroborated the findings that patient perception of their pain management with IV tramadol was very good to excellent in most cases, and where rescue was needed, non-opioid medications were sufficient. Figure 4 presents that 95% of patients reporting good, very good, and excellent effectiveness in controlling pain, as reported by the patients themselves in the PGA. Importantly, no patients discontinued due to a lack of efficacy or to switch to a schedule 2 opioid.

6. SAFETY

This NDA is a 505(b)2 application that relies upon both clinical trial data from our own development program as well as the well-documented efficacy and safety of oral tramadol. In the Phase 3 program, IV tramadol was well-tolerated in a variety of surgical models and provides a safety profile consistent with known pharmacology of oral tramadol. As it has been used in more than 70 countries including most parts of Europe for about 30 years, the Sponsor also examined the safety record of IV tramadol outside the U.S. via a review of the available medical literature and an assessment of the VigiBase data. VigiBase is the unique WHO global database of Individual Case Safety Reports (ICSRs) and member countries of the WHO Programme for International Drug Monitoring (WHO PIDM) submit ICSRs electronically to this database.

Each of these approaches demonstrated that adverse effects after IV tramadol are consistent with those of oral tramadol, as reflected in the current ULTRAM label.

6.1. Treatment Exposure

6.1.1. Exposure in Phase 1 Studies

Table 22 provides a summary of the number of subjects by maximum dose of IV tramadol given in these Phase 1 studies.

Table 22: Number of Subjects by Maximum Dose of IV Tramadol Given, for Healthy Subjects in Phase 1 Studies (Studies RVG-10-108, RVG-12-001, AVE-901-101)

	Number of Subjects by Maximum Dose of IV Tramadol Received				Total Subjects Treated with IV Tramadol
Study	**IV 50 mg**	**IV 75 mg**	**IV 100 mg**	**IV 200 mg**	
RVG-10-018 (parallel study)	8	0	8	0	16
RVG-12-001 (single-dose QT)	0	0	0	56	56
AVE-901-101 (crossover study)	0	18	0	0	18
Total Subjects by Maximum IV Tramadol Dose Received	8	18	8	56	90

Note: Study AVE-901-101 was a crossover study in which all patients were to receive treatment with IV tramadol 50 mg, IV tramadol 75 mg, and oral tramadol 100 mg. This table presents the highest IV dose given.
Source: Clinical Overview (Module 2.5 of NDA)

6.1.2. Exposure in Phase 3 Studies (Controlled and Uncontrolled)

Table 23 provides a summary of the number of subjects by dose of IV tramadol given in these Phase 3 (controlled and uncontrolled) studies. The Phase 3 program included 271 placebo subjects, 133 tramadol 25 mg subjects, 533 tramadol 50 mg subjects, and 93 morphine subjects, comprising, in total, 1030 subjects. Note that in the Phase 3 controlled studies, 93.2% of patients completed their full 48-hour treatment, with only 2.1% discontinuing due to lack of efficacy.

Table 23: Number of Subjects by Maximum Dose of IV Tramadol Given in Subjects in Phase 3 Studies (StudiesAVE-901-102, AVE-901-103, and AVE-901-104)

	Number of Subjects by Treatment				Total Subjects Treated by Study
Study	**Placebo**	**IV Tramadol 25 mg**	**IV Tramadol 50 mg**	**IV Morphine 4 mg**	
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 Subjects by Dose Received	271	133	533	93	1030

Source: Clinical Overview (Module 2.5 of NDA)

6.2. Treatment Emergent Adverse Events

Safety outcomes focus on the Phase 3 studies, and specifically on two comparisons:

- The pooled safety database, which included data from both double-blind Phase 3 placebo-controlled studies. The TEAE outcomes from the IV tramadol 50 mg arm and the placebo arm are compared in those presentations.
- Study AVE-901-103 allows for comparison of IV tramadol and morphine safety outcomes, including TEAEs incidence rates, Opioid-Related AEs (ORAEs), and AEs related to Potential Risk of Abuse, and provide context to how IV tramadol safety and tolerability compares to an approved opioid medication.

6.2.1. Pooled Safety Database

Table 24 provides an overview of the overall incidence of TEAEs for the pooled safety database. As expected, the IV tramadol group demonstrated a higher incidence than the placebo group for those TEAEs commonly associated with opioid treatment. The incidence of severe events, SAEs, and events leading to discontinuation were low in these studies. There were no deaths reported during the development program. Study completion rates were very high in these Phase 3 studies, with over 92% of patients randomized to IV tramadol completing their full 48-hour treatment.

Table 24: Overview of Study Completion and Treatment-Emergent Adverse Events (Safety Population) (Studies AVE-901-102 and AVE-901-103 Combined)

	Placebo (N=271) n (%)	IV Tramadol 50 mg (N=282) n (%)
Study Completer	247 (91.1)	261 (92.6)
Number of patients with at least one TEAE[1]	137 (50.6)	215 (76.2)
Number of patients with at least one Grade 3 or higher TEAE	1 (0.4)	6 (2.1)
Number of patients with at least one SAE	0	2 (0.7)
Number of patients with TEAEs leading to study discontinuation	2 (0.7)	13 (4.6)
Number of patients with TEAE leading to drug interruption	0	2 (0.7)
Number of TEAEs leading to death	0	0

Abbreviations: TEAE=treatment-emergent adverse event; SAE=treatment emergent serious adverse event
[1] A TEAE was defined as an adverse event occurring during or after study drug administration and up to 24 hours after the start of the last study drug administration.
[2] At least possibly related TEAEs were defined as TEAEs with relationship of probably, possibly, or definitely related.
Note: Patients experiencing more than 1 TEAE were only counted once under the greatest severity and causality.
Source: Clinical Overview (Module 2.5 of NDA)

TEAEs reported in at least 2.0% of patients in either treatment group, irrespective of relationship to study medication, are reported in Table 25 by preferred term in decreasing order based on incidence rates in the IV tramadol group.

Table 25: Incidence of All TEAEs Regardless of Relationship Reported in at Least 2.0% Patients in Either Treatment Group by Preferred Term in Decreasing Frequency Based on Incidence Rates in the IV Tramadol Group (Studies AVE-901-102 and AVE-901-103 Combined)

	Number of patients (%)	
MedDRA Preferred term	Placebo (N=271) n (%)	IV Tramadol 50 mg (N=282) n (%)
Total patients with at least 1 TEAE	137 (50.6)	215 (76.2)
Nausea	61 (22.5)	144 (51.1)
Vomiting	14 (5.2)	83 (29.4)
Dizziness	13 (4.8)	39 (13.8)
Headache	33 (12.2)	34 (12.1)
Somnolence	5 (1.8)	19 (6.7)
Constipation	6 (2.2)	15 (5.3)
Hypoxia	1 (0.4)	14 (5.0)
Infusion site pain	16 (5.9)	12 (4.3)
Pruritus generalized	4 (1.5)	11 (3.9)

MedDRA Preferred term	Number of patients (%)	
	Placebo (N=271) n (%)	IV Tramadol 50 mg (N=282) n (%)
Respiratory disorder	0	9 (3.2)
Oropharyngeal pain	5 (1.8)	6 (2.1)
TEAE = treatment-emergent adverse event		

Source: Clinical Overview (Module 2.5 of NDA)

6.2.2. Comparison of IV Tramadol to Morphine: Opioid-Related AEs and AEs related to Potential Risk of Abuse

Treatment-emergent ORAEs are summarized in Table 26. ORAEs were identified by the Sponsor and Medical Monitor during a blinded review of all TEAEs (prior to unblinding of the treatment allocation codes) and all events identified were included in this analysis. These events included nausea, vomiting, dizziness/postural, constipation, hypoxia/respiratory disorder, pruritus/generalized, somnolence, sedation, and bradypnea.

The incidence of patients identified as having at least one ORAE was 43.7% in the placebo group, 78.2% in the tramadol group, and 87.1% in the morphine group.

The individual preferred terms were generally reported with a higher incidence in the tramadol and morphine groups as compared to the placebo group. The morphine group tended to have a slightly higher incidence of the more frequent ORAEs, eg, nausea, vomiting, and dizziness. The incidence of the less frequently reported ORAEs was similar between the tramadol and morphine groups.

Table 26: Incidence of Treatment-Emergent Opioid Related Adverse Events by System Organ Class and Preferred Term (Safety Population) (Study AVE-901-103)

MedDRA System Organ Class Preferred Term	Placebo (N=135) n (%)	IV Tramadol 50 mg (N=142) n (%)	IV Morphine 4 mg (N=93) n (%)
Number of patients with at least one ORAE	59 (43.7)	111 (78.2)	81 (87.1)
Nausea	50 (37.0)	99 (69.7)	73 (78.5)
Vomiting	9 (6.7)	55 (38.7)	42 (45.2)
Dizziness	9 (6.7)	18 (12.7)	17 (18.3)
Constipation	3 (2.2)	7 (4.9)	3 (3.2)
Hypoxia	0	9 (6.3)	4 (4.3)
Pruritus generalized	3 (2.2)	7 (4.9)	3 (3.2)
Respiratory disorder	0	9 (6.3)	4 (4.3)
Pruritus	1 (0.7)	4 (2.8)	5 (5.4)
Somnolence	2 (1.5)	3 (2.1)	2 (2.2)
Dizziness postural	1 (0.7)	2 (1.4)	3 (3.2)
Sedation	0	2 (1.4)	1 (1.1)
Bradypnea	0	1 (0.7)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Authorities; TEAE=treatment-emergent adverse events
Notes: A TEAE was defined as an adverse event occurring during or after study drug administration and up to 24 hours after last study drug administration. At each level of summarization (system organ class or preferred term), patients experiencing more than one TEAE are only counted once. All adverse events were coded using the MedDRA, Version 20.1.
Source: AVE-901-103 CSR

Treatment-emergent AEs related to potential risk of substance abuse are summarized in Table 27. Prior to unblinding, the Sponsor and Medical Monitor identified AEs related to potential risk of substance abuse based on the FDA guidance (*Assessment of Abuse Potential of Drugs, Guidance for Industry, January 2017*). In this study, these included: disturbance in attention, dizziness, dizziness postural, dysphoria, somnolence, and sedation. There were no reports of other AEs related to a potential risk for substance abuse, such as euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, thinking abnormal, hallucination, inappropriate affect, mood disorders, drug tolerance, habituation, drug withdrawal syndrome, or substance-related disorders reported in the study.

The incidence of at least one TEAE related to potential risk of substance abuse was 8.1% in the placebo group, 16.2% in the tramadol group, and 22.6% in the morphine group. Dizziness was the most frequently reported TEAE of this type, reported in 6.7% placebo, 12.7% tramadol, and 18.3% morphine patients. No dizziness, somnolence, or sedation occurred in conjunction with euphoria, which was not reported at all.

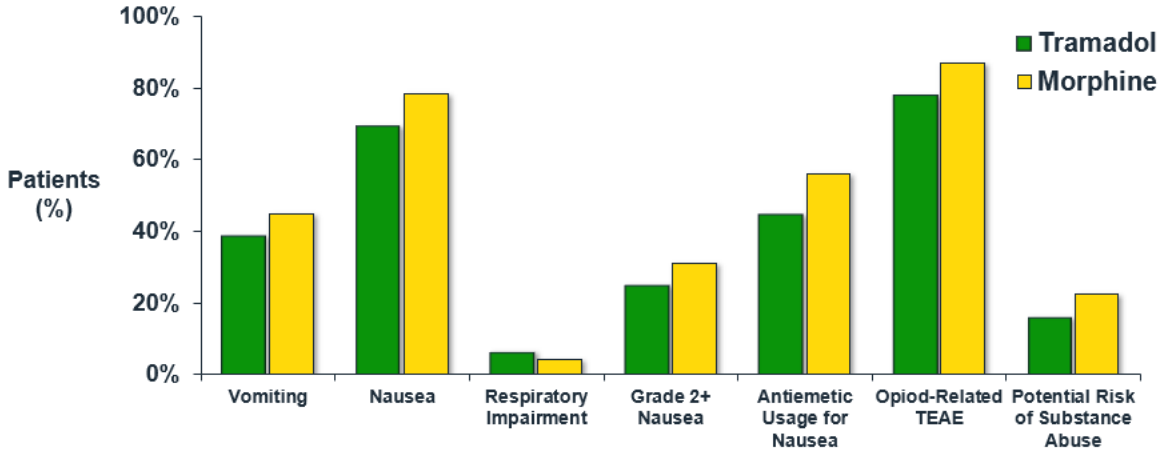
Table 27: Incidence of Treatment-Emergent Adverse Events Related to Potential Risk of Substance Abuse by System Organ Class and Preferred Term (Safety Population) (Study AVE-901-103)

MedDRA System Organ Class Preferred Term	Placebo (N=135) n (%)	IV Tramadol 50 mg (N=142) n (%)	IV Morphine 4 mg (N=93) n (%)
Number of patients with at least one TEAE related to potential risk of substance abuse	11 (8.1)	23 (16.2)	21 (22.6)
Dizziness	9 (6.7)	18 (12.7)	17 (18.3)
Somnolence	2 (1.5)	3 (2.1)	2 (2.2)
Dizziness postural	1 (0.7)	2 (1.4)	3 (3.2)
Sedation	0	2 (1.4)	1 (1.1)
Disturbance in attention	1 (0.7)	0	0
Dysphoria	0	0	1 (1.1)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Authorities; TEAE=treatment-emergent adverse events
Notes: A TEAE was defined as an adverse event occurring during or after study drug administration and up to 24 hours after last study drug administration. At each level of summarization (system organ class or preferred term), patients experiencing more than one TEAE are only counted once. All adverse events were coded using the MedDRA, Version 20.1.
Source: AVE-901-103 CSR

Opioid-related TEAEs included nausea, vomiting, dizziness/postural, constipation, hypoxia/respiratory disorder, pruritus/generalized, somnolence, sedation, and bradypnea. The incidence of these events was similar, but generally higher for the morphine arm for each event type (Figure 18).

Figure 18: Risk of IV Tramadol vs Morphine for Key Opioid-Associated Safety Endpoints (Study AVE-901-103)



Note: Opioid-related TEAEs included nausea, vomiting, dizziness/postural, constipation, hypoxia/respiratory disorder, pruritus/generalized, somnolence, sedation, and bradypnea.
Source: AVE-901-103 CSR

6.2.3. TEAES leading to Discontinuation: IV Tramadol vs Morphine

A comparison of the incidence of TEAEs events leading to study discontinuation are presented in Table 28. There were no meaningful differences in discontinuations due to any TEAE.

Table 28: Incidence of Adverse Events Leading to Study Discontinuation by Preferred Term (Safety Population) (Study AVE-901-103)

MedDRA System Organ Class Preferred Term	Placebo (N=135) n (%)	IV Tramadol 50 mg (N=142) n (%)	IV Morphine 4 mg (N=93) n (%)
Atrial fibrillation	1 (0.7)	0	0
Tachycardia	0	1 (0.7)	0
Nausea	1 (0.7)	4 (2.8)	2 (2.2)
Vomiting	1 (0.7)	2 (1.4)	0
Post procedural hematoma	0	1 (0.7)	0
Dizziness postural	0	1 (0.7)	0
Sedation	0	0	1 (1.1)
Panic attack	0	0	1 (1.1)
Hypoxia	0	4 (2.8)	3 (3.2)
Respiratory disorder	0	4 (2.8)	3 (3.2)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities TEAE=treatment-emergent adverse event
Notes: A TEAE was defined as an AE occurring during or after study drug administration and up to 24 hours after last study drug administration. All adverse events were coded using the MedDRA, Version 20.1.
Source: AVE-901-103 CSR

6.2.3.1. Concomitant Medications: IV Tramadol vs Morphine

Table 29 provides a comparison of anti-emetic usage for nausea as reported from the concomitant medication CRF where treatment was given for nausea related adverse event; these medications included medications from a number of drug classes, primarily antiemetics and antinauseants, and propulsives. The incidence of usage of medications for nausea was highest for the morphine arm, followed by the tramadol arm and then placebo.

Table 29: Comparison of Antiemetic Usage for Nausea (Safety Population) (Study AVE-901-103)

	Placebo (N=135)	IV Tramadol 50 mg (N=142)	IV Morphine 4 mg (N=93)
Number and % of Patients with Antiemetic Usage for Nausea			
Yes	28 (20.7)	64 (45.1)	52 (55.9)

Abbreviations: ORAE=opioid-related adverse event
Note: Anti-emetic usage for nausea is based on concomitant medication CRF where treatment was given for nausea related adverse event.
Source: AVE-901-103 CSR

Upon discharge from the study, approximately half of patients in each treatment arm were dispensed opioids (oral tramadol was the highest-prescribed opioid post-treatment, followed by Vicodin and Panadeine (Tylenol/codeine). Ibuprofen was also frequency prescribed upon discharge.

6.2.4. Safety from Phase 3 Open-Label Study

Table 30 presents the most common TEAEs (those occurring in at least 2% of patients) in Study AVE-901-104. Nausea and vomiting, occurring in 28.7% and 19.5% of patients, respectively, were the most frequently reported TEAEs. Hypoxia was reported in 6.8% of patients; this TEAE was primarily observed in patients who had undergone hernia surgery (16 of the 17 patients with hypoxia) and at one site. Notably, there were no unexpected TEAEs reported (eg, important cardiac or vascular events).

Table 30: Incidence of Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients (Safety Population (Study AVE-901-104)

MedDRA Preferred Term	IV 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)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Notes: A TEAE was defined as an adverse event occurring during or after study drug administration and up to 24 hours after last study drug administration. For each preferred term, patients experiencing more than one TEAE are only counted once. All adverse events were coded using the MedDRA, Version 20.1.
Source: AVE-901-104 CSR

The most frequently reported SOC was gastrointestinal disorders (35.5%) followed by general disorders and administration site conditions (9.2%) and investigations (9.2%). Notably, the incidence of nervous system disorders (7.6%) and psychiatric disorders (1.6%) was low.

There were 2 patients with an SAE in Study AVE-901-104, both post procedural hematoma and each reported in a female patient who had undergone breast augmentation surgery. Neither SAE was considered to be at least possibly related to study drug. Eleven patients had an AE leading to study discontinuation. The most commonly reported AEs leading to discontinuation were nausea (1.2%), vomiting (0.8%), and post procedural hematoma (0.8%). The remaining AEs were reported in 1 patient each (0.4%).

7. EPIDEMIOLOGY FINDINGS ON ABUSE OF TRAMADOL

This section presents the Sponsor's findings on epidemiological data related to the abuse of tramadol in the US, as well as in countries where IV tramadol has been on the market, with a focus when possible on abuse via injection. Note the IV tramadol used ex-US is the same medication but has different dosing instructions.

Overall, the findings from the different epidemiology databases were consistent with one another, and demonstrate that reports of abuse with tramadol are infrequent, both in absolute number and relative to other prescription opioids, such as morphine, oxycodone, hydrocodone (US), and codeine (EU-5). Similarly, reports of oral tramadol misuse are much less common than with alprazolam, another Schedule IV drug, in the U.S. Furthermore, abuse of tramadol via injection is uncommon relative to oral tramadol in both the U.S. and in countries where IV tramadol is available.

The abuse potential of IV tramadol for the intended use is further mitigated by the fact that it is intended for use only in adults in a medically supervised health care setting. It will be administered only by a healthcare provider and not dispensed directly to the patient.

7.1. Introduction

This NDA for IV tramadol is a 505(b)2 application and therefore partially relies on the documented and well-established efficacy and safety of oral tramadol. The abuse potential of oral tramadol, an atypical opioid analgesic with both opioid and non-opioid mechanisms, has been studied multiple times by the FDA and DEA. Prior to the approval of oral tramadol, the Drug Abuse Advisory Committee of the FDA initially recommend that tramadol did not require scheduling as a controlled substance, because preliminary human and animal studies demonstrated a low potential for abuse, recognizing as well its history of extensive utilization in Europe since the 1970's. After ULTRAM was approved in 1995, the manufacturer of tramadol (Ortho-McNeil) set up an independent steering committee to monitor the abuse of tramadol in the U.S., with strict criteria that would allow for unbiased recognition of abuse. Within the first three years of the approval of tramadol, the committee concluded that tramadol was abused at a low rate (Cicero 1999).

Numerous studies and analyses followed (Inciardi 2006, Schneider 2007, Senay 2003, Woody 2003), and in 2014, the DEA designated tramadol as a Schedule IV controlled substance. The scheduling difference between tramadol and conventional opioids reflects both the scientific understanding of the abuse potential of tramadol as well as well as actual data from post-marketing surveillance and other sources.

Finally, the WHO's expert committee on drug dependence in their critical review report of tramadol in November 2018 stated that "parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalised since first-pass metabolism is avoided. Hence, the abuse of tramadol is much reduced through intravenous administration when compared to ingestion." (WHO 2018).

As part of this NDA, the Sponsor discussed with FDA the important issue of evaluating the abuse potential of IV tramadol with real-world evidence. The Sponsor agreed with FDA to obtain epidemiological data related to the abuse of tramadol in the US, as well as in countries where IV tramadol has been on the market, collecting information on routes of administration

when available. The Sponsor engaged experts to understand the complexities of the available epidemiological data on abuse potential and has undertaken multiple steps to identify available epidemiologic evidence that would allow for credible and valid assessments.

7.2. Methods

7.2.1. Approach for Epidemiology Assessment

To assess the abuse of tramadol in the U.S. and in countries where IV tramadol has been on the market, as well as routes of abuse, Avenue Therapeutics used a mosaic approach that collected data from diverse and complementary sources covering key populations and behaviors of interest to create a more complete picture. This approach represents a best-available method to providing a robust analysis of the abuse potential of IV tramadol. The effort consisted of a targeted literature review of abuse of oral tramadol and tramadol for injection, and studies of various epidemiological databases on abuse, misuse, and non-medical use (NMU) of tramadol and comparator opioids in the both the U.S. and the EU-5.

The four databases selected for analyses and the territories they cover are:

- The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system: a system of projects that collects product-and geographic-specific data on abuse, misuse, and diversion of prescription drugs --U.S. and EU-5 (France, Germany, Italy, Spain, and the United Kingdom). The RADARS® database in select European countries is best positioned to answer the question of the abuse of tramadol in countries where intravenous tramadol has been on the market, as it is the most relevant and robust epidemiology database that can provide insight into the abuse potential of IV tramadol and comparator opioids.
- The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO): a database that uses a proprietary survey to capture data from adults assessed for substance abuse problems and treatment planning. NAVIPPRO provides insight into the abuse and non-medical use of tramadol and comparator opioids in a high-risk population with opioid use disorders in the U.S.
- The National Survey on Drug Use and Health (NSDUH): a congressionally mandated population-based US household survey that collects information on tobacco, alcohol, and drug use, mental health and other health-related issues in the U.S. NSDUH provides a snapshot of misuse of tramadol and comparator opioids in a sample of the general population in the U.S.
- Abuse-related Adverse Events from the FDA Adverse Event Reporting System (FAERS): a database that contains spontaneous adverse event (AE) reports, including medication error reports and product quality complaints resulting in AEs. (This data will not be presented due to the limitations of database)

It is important to note that to answer the question of the abuse of tramadol in countries where the product (tramadol hydrochloride injection) has been on the market, Avenue chose the RADARS database on the EU-5, because tramadol for injection is approved in each of these five countries, and their medical practices and availability of medicines are closer to the U.S. than other countries. Furthermore, high-quality epidemiology data from RADARS on abuse, misuse and

diversion of opioids are available. The data from the EU-5 provide insight into the abuse potential of IV tramadol and possibly reflect worst-case scenarios, given that tramadol is not scheduled in the majority of the EU-5.

In the database studies, rates of abuse, misuse, and non-medical use (NMU) in both the general population and the high-risk treatment center population are all assessed to paint a complete picture of abuse potential. Importantly, the comparison of tramadol versus other commonly available opioids provides a contextual framework for the epidemiological data. In the U.S., the comparator opioids across different database studies are: hydrocodone, oxycodone, and morphine. To provide context for the Schedule IV classification of tramadol, its misuse was also compared to that of alprazolam, another well-known Schedule IV drug in the U.S. in the NSDUH survey. In the EU-5, the selected comparator opioids are: codeine, morphine, and oxycodone. The routes of administration and formulation (oral versus injectable) were examined whenever available.

The Sponsor focused primarily on Europe in its survey of ex-US countries. Several geographic areas were not included because of lack of high-quality data and serious issues with the reporting. For example, reports from Africa were not included in this analysis for the following reasons: 1. The standard of care medical practices and availability of medicine are considered to be very different from those in the U.S.; 2, The reports lacked credibility and could not be verified by any high-quality data source; and 3. The "tramadol" mentioned in these reports was generally sourced from manufacturers not legally permitted to produce pharmaceutical grade tramadol and there is no assurance exactly what the "tramadol" contains (Klein 2018).

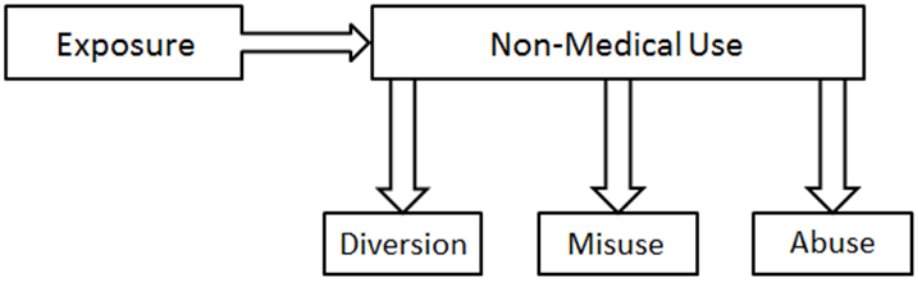
7.2.2. Framework to Understand Prescription Drug Non-Medical Use

Figure 19 illustrates the paradigm for understanding prescription drug non-medical use (NMU).

To understand the abuse potential of a prescription drug, it is important to adjust for exposure or its availability, which is generally expressed as the number of prescriptions and/or the number of pills dispensed.

The reason is that exposure to the prescription drug is required before the subject starts non-medical use (NMU), a broad term that describes use of a drug in a way other than directed by healthcare professionals. Non-medical use (NMU) can be motivated by a variety of reasons, and represents a diverse set of behaviors including diversion, misuse, or abuse. NMU encompasses both misuse (the intentional *therapeutic* use of a drug by an individual in a way other than prescribed or for whom it was not prescribed) and abuse (the intentional, *non-therapeutic* use of a drug, even once, for its desirable psychological or physiological effects).

Figure 19: Prescription Drug Non-Medical Use Paradigm (Source: RADARS)



Crude frequencies of events related to abuse cannot be properly understood without context. The issue of adjusting for availability was discussed in detail in a 2014 paper published by the officials at the Office of Surveillance and Epidemiology of the FDA (Secora 2014). FDA recognizes the importance of normalizing rates based on availability, to provide appropriate context and a complete picture of the abuse of a prescription opioid. FDA further commented that the number of tablets dispensed was the most granular measure and provided the best description of drug availability, because each tablet represents an individual opportunity for abuse, and accounts for nearly all of the drug available in the community. Therefore, for this analysis, the rates were adjusted for availability via pill counts. Importantly, the trends do not change if we use the number of prescriptions to adjust for availability.

Table 31 provides a summary of the databases used, the population covered, routes of use covered and geographical location for data as provided in the discussion of abuse.

Table 31: Data System Sources and Type of Data Extracted for this Summary

Data System	Population	Tramadol Route of Use	Location
RADARS®	High Risk and General Population	IV/Oral	US/EU
NAVIPPRO®	High Risk Population	IV/Oral	US
NSDUH	General Population	Oral	US

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1. Results

7.1.1. RADARS® : Summary of Surveillance of Tramadol in the United States (Oral Formulations) and the EU5 (Oral and Injection Formulations)

The RADARS® System collects data from a variety of sources, to provide a systematic, "mosaic" approach to understanding prescription drug non-medical use. Each RADARS® System program targets and assesses different populations and aspects of drug misuse, abuse, diversion and related medical outcomes.

Data from multiple RADARS® programs were utilized for this study (Table 32).

Table 32: Overview of Data Sources, Surveillance Populations, and Outcomes by RADARS® System Program

RADARS System Program	Surveillance Population	Type of Data	Outcomes	Definition
Poison Center Program (*US Report*)	Exposure cases recorded by regional poison control centers covering people in urban, suburban, and rural regions.	Poison center calls	Abuse, Misuse	*Abuse:* The improper or incorrect use of a substance to gain a high, euphoric or psychotropic effect *Misuse:* The improper or incorrect use of a substance for reasons other than to gain a high, euphoric or psychotropic effect
Treatment Center Programs Combined (*US Report*)	Patients entering treatment for opioid and substance use disorder.	Paper survey of entrants to treatment programs	Abuse	A survey response endorsing use "to get high" in the past month
Drug Diversion Program (*US Report*)	Cases of diverted controlled substances reported by law enforcement agents.	Paper survey of law enforcement activities	Diversion	The illicit acquisition and/or distribution of prescription drugs, resulting in a written complaint or report involving prescription drugs.
Survey of Non-Medical Use of Prescription Drugs Program (*EU Reports, except France*)	Adult general population via an online survey panel company.	Calibrated general population online survey	Non-Medical Use (NMU) Data are also collected on the behaviors associated with NMU: Misuse, Abuse, Diversion	*NMU:* Use in a way not directed by your healthcare provider *Misuse:* NMU for specific reasons ("to reduce pain," "to treat a medical condition or symptom, other than pain," "to relax, reduce stress, or sleep," or "to prevent or treat withdrawal symptoms.") *Abuse:* NMU of a product with a reason of: "for enjoyment or to get high" or "to come down from a high or another drug." *Diversion:* NMU of a product with a source of: "Healthcare provider or pharmacy with a forged prescription," "Friend or family member," "Dealer," "Taken from a pharmacy, clinic, or hospital without permission," "Somewhere without a prescription while you were outside the" country, or "Internet without a prescription."

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.1. U.S.: Oral Tramadol vs Comparator Opioids--Abuse

The data on oral tramadol abuse versus comparator opioids (hydrocodone, morphine and oxycodone) from the poison center program and the treatment center program are presented both in cumulative rates and rates over time reflecting trends. The rates are adjusted for availability via the number of pills/tablets dispensed. The poison center program focuses on exposure (number of cases) recorded by regional poison control centers covering people in urban, suburban, and rural regions. The treatment center program collects data on patients entering treatment for opioid and substance use disorder. Therefore, the two programs reflect different populations.

Intentional abuse rates of tramadol were low both in the poison centers and treatment centers. Tramadol abuse, adjusted for drug availability, has decreased over time, a trend also observed for other opioids.

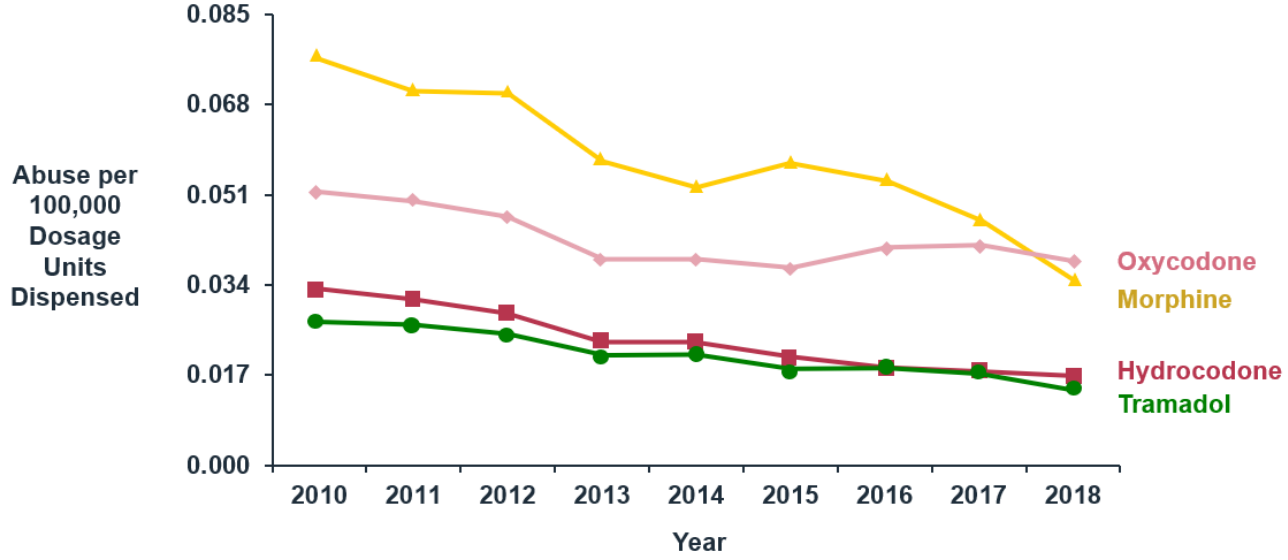
Table 33 shows the cumulative data and Figure 20 illustrates rates over time from the poison center program

Table 33: RADARS® System Poison Center Program: Cumulative Intentional Abuse Exposure Rates of Tramadol and Comparators in the United States. 3rd Quarter 2010 through 4th Quarter 2018

Drug Group	Rate per 100,000 Dosage Units Dispensed (95% CI)
Tramadol	0.022 (0.022, 0.023)
Hydrocodone	0.021 (0.021, 0.021)
Morphine	0.056 (0.054, 0.058)
Oxycodone	0.041 (0.041, 0.042)

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 20: RADARS® System Poison Center Program: Intentional Abuse Exposure Rates of Tramadol and Comparators by Year in the United States (Drug Utilization-Adjusted) 3rd Quarter 2010 through 4th Quarter 2018



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Data collected from the treatment center programs show an advantage for tramadol relative to all three comparators, as show in Table 34.

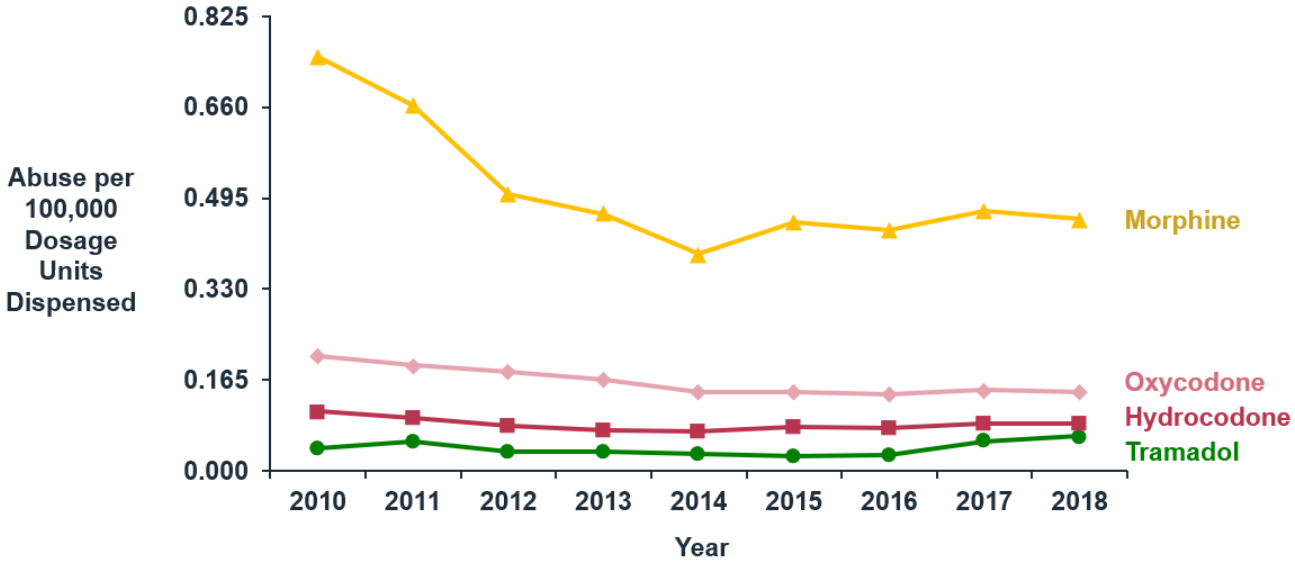
Table 34: RADARS® System Treatment Center Programs Combined: Cumulative Past Month Abuse Rates of Tramadol and Comparators in the United States. 3rd Quarter 2010 through 4th Quarter 2018

Drug Group	Rate per 100,000 Dosage Units Dispensed (95% CI)
Tramadol	0.039 (0.038, 0.041)
Hydrocodone	0.083 (0.082, 0.084)
Morphine	0.494 (0.486, 0.503)
Oxycodone	0.160 (0.158, 0.162)

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 21 shows the trend observed in the treatment center programs data, demonstrating that tramadol consistently had the lowest rate of abuse per dosage units dispensed vs the comparators.

Figure 21: RADARS® System Treatment Center Programs Combined: Past Month Abuse Rates of Tramadol and Comparators by Year in the United States (Drug Utilization-Adjusted) 3rd Quarter 2010 through 4th Quarter 2018



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.2. U.S.: Oral Tramadol vs. Comparator Opioids: Abuse by Injection Route

The injection route of administration was infrequently observed for tramadol in the poison center program (Table 35) as shown in the exposure (number of cases) data. The proportion of tramadol abuse by injection is lower than comparator opioids. Proportions amongst drug groups may not sum to 1 as respondents are able to select multiple products per drug group.

Table 35: RADARS® System Poison Center Program: Cumulative Intentional Abuse Exposure Proportions of Tramadol and Comparators by Route of Administration in the United States. 3rd Quarter 2010 through 4th Quarter 2018

	Tramadol (N=4,753)		Hydrocodone (N=11,348)		Morphine (N=2,505)		Oxycodone (N=12,752)	
Route	Cases	Proportion (95% CI)	Cases	Proportion (95% CI)	Cases	Proportion (95% CI)	Cases	Proportion (95% CI)
Injected (Parenteral)	24	<0.01 (<0.01, <0.01)	89	<0.01 (<0.01, <0.01)	424	0.17 (0.15, 0.18)	879	0.07 (0.06, 0.07)
Oral	4,405	0.93 (0.92, 0.93)	10,074	0.89 (0.88, 0.89)	1,722	0.69 (0.67, 0.71)	9,666	0.76 (0.75, 0.77)
Other	204	0.04	812	0.07	293	0.12	1952	0.15

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.3. U.S.: Oral Tramadol vs. Comparator Opioids: Diversion

Prescription drug diversion is the unlawful channeling of regulated pharmaceuticals to the illicit marketplace and includes transferring drugs to people they were not prescribed for. In general, the

more highly abused drugs will have a higher rate of diversion. Table 36 shows diversion was lowest for tramadol vs the comparators.

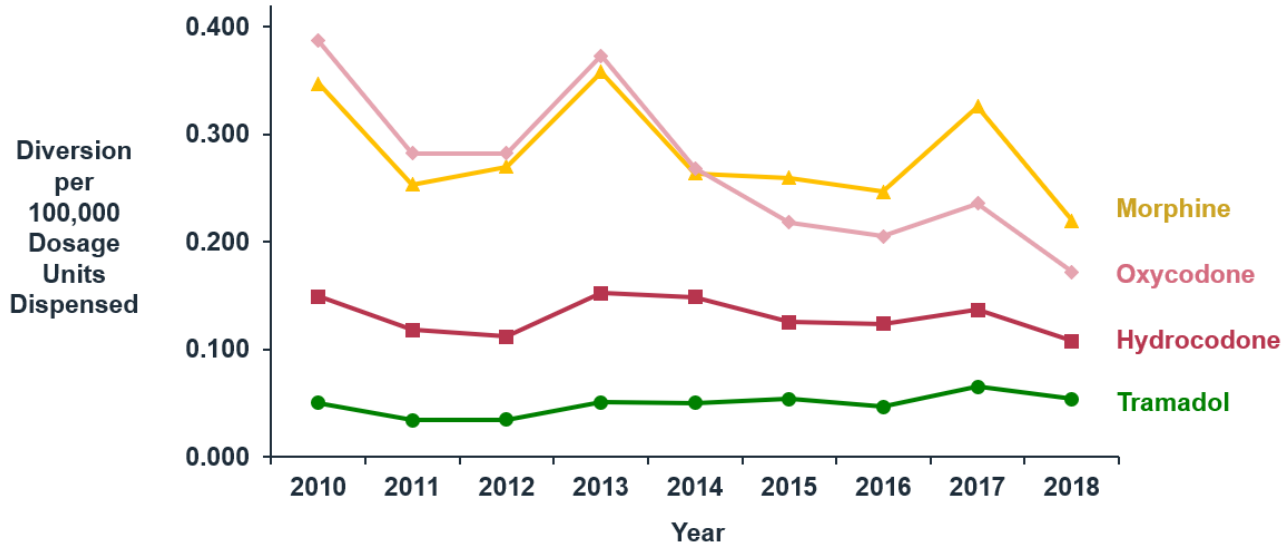
Table 36: RADARS® System Drug Diversion Program: Cumulative Diversion Rates of Tramadol and Comparators in the United States. 3rd Quarter 2010 through 4th Quarter 2018

Drug Group	Rate per 100,000 Dosage Units Dispensed (95% CI)
Tramadol	0.046 (0.045, 0.048)
Hydrocodone	0.129 (0.127, 0.130)
Morphine	0.280 (0.271, 0.288)
Oxycodone	0.273 (0.270, 0.276)

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 22 shows these same data over time. Diversion was consistently lowest for tramadol vs the comparators.

Figure 22: RADARS® System Drug Diversion Program: Diversion Rates of Tramadol and Comparators by Year in the United States (Drug Utilization-Adjusted). 3rd Quarter 2010 through 4th Quarter 2018



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.4. EU Data: Abuse of Tramadol and Comparator Opioids

Data from the Survey of Non-Medical Use of Prescription Drugs Program indicates that abuse of tramadol is generally similar to or lower than comparator opioids, as presented in Table 37; Standard Units include all available formulations in that particular country.

Table 37: RADARS® System Survey of Non-Medical Use of Prescription Drugs Program: Cumulative Abuse Rates of Tramadol and Comparators. 4th Quarter 2018

	Germany	Italy	Spain	UK
Drug Group	**Rate per 100,000 Standard Units Sold (95% CI)**	**Rate per 100,000 Standard Units Sold (95% CI)**	**Rate per 100,000 Standard Units Sold (95% CI)**	**Rate per 100,000 Standard Units Sold (95% CI)**
Tramadol	40.538 (23.657, 57.418)	47.877 (21.143, 74.611)	11.432 (7.126, 15.739)	23.507 (17.287, 29.727)
Codeine	172.197 (115.692, 228.701)	65.607 (39.207, 92.007)	61.354 (46.459, 76.249)	11.613 (8.792, 14.435)
Morphine	93.859 (52.878, 134.841)	827.505 (521.985, 1,133.024)	204.040 (113.019, 295.060)	32.481 (21.987, 42.975)
Oxycodone	24.262 (11.361, 37.163)	54.011 (31.087, 76.935)	52.878 (27.930, 77.825)	39.245 (21.817, 56.673)

Note: Data for France not available.
Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.5. EU Data: NMU of Tramadol and Comparator Opioids by Injection

IV tramadol is available in Europe. However, because the number of cases of abuse by injection is so low that the reported data cannot provide a valid comparison, non-medical use by injection (which has a broader definition) is used to make a more informative comparison between tramadol and other opioids. Table 38 provides the rate per 100,000 units and shows tramadol had low non-medical use by injection.

Table 38: Non-Medical Use rate by injection route per 100,000 Standard Units (NUMRx)

	Germany	Italy	Spain	UK
Drug Group				
Tramadol	21	55	7	10
Codeine	59	35	30	3
Morphine	138	822	310	28
Oxycodone	12	39	33	30

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.1.6. Key conclusion from the RADARS program of studies

This analysis studied the abuse and non-medical use of tramadol in both the U.S. and European countries. In all countries studied, tramadol abuse was uncommon in both the general population and among entrants to treatment or in poison control centers. Injection of tramadol (any formulation) was also uncommon and lower for tramadol vs the comparators. These data indicate that in countries

where tramadol is widely available, it is generally less abused than comparators. The large majority of the data reflect the preferred route of abuse of tramadol is oral as opposed to intravenous route.

7.1.2. The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®)

The objective of this study was to evaluate real-world epidemiological data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®). Specifically the Addiction Severity Index–Multimedia Version (ASI-MV®) was utilized to obtain data related to the nonmedical use (NMU; includes misuse and abuse) of oral tramadol and comparator opioids in the United States. The study included population and drug utilization-adjusted rates of NMU, patient characteristics, route of administration and diversion (measured as source of drug procurement). The patient population in the study represents individuals at high-risk for opioid abuse.

7.1.2.1. NMU of oral tramadol versus comparator opioids

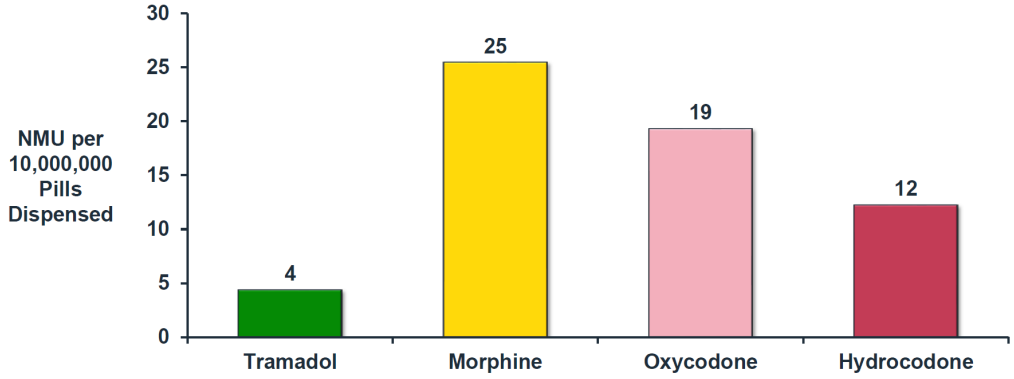
Table 39 provides the prevalence of past 30-day NMU of any tramadol (i.e. tramadol alone or in combination with other drugs) versus that of morphine, oxycodone, or hydrocodone per 100,000 units (each unit is a tablet) dispensed, while Figure 23 provides this data graphically. The overall NMU of any tramadol, based on prescriptions or units dispensed, was 2-3 times lower than hydrocodone, 4-5 times lower than oxycodone, and 5-6 times lower than morphine.

Table 39: Prevalence of past 30-day NMU of any tramadol versus that of morphine, oxycodone, or hydrocodone per 100,000 units dispensed (Source: NAVIPPRO)

Past 30-Day NMU¥	Total NMU cases	Rate/100 ASI-MV Assessments (95% CI)	Total prescriptions dispensed†	Rate/100,000 Prescriptions Dispensed (95% CI)	Total units dispensed††	Rate/10,000,000 Units Dispensed (95% CI)
Tramadol	**8,942**	**1.61 (1.58, 1.65)**	**275,526,568**	**3.25 (3.18, 3.31)**	**20,640,131,569**	**4.33 (4.24, 4.42)**
Tramadol Only	1,105	0.20 (0.19, 0.21)	275,526,568	0.40 (0.38, 0.42)	20,640,131,569	0.54 (0.50, 0.57)
Tramadol plus Any Other Rx Opioid±	7,837	1.41 (1.38, 1.45)	275,526,568	2.84 (2.78, 2.91)	20,640,131,569	3.80 (3.71, 3.88)
Morphine	**10,180**	**1.84 (1.80, 1.87)**	**55,582,130**	**18.32 (17.96, 18.67)**	**4,003,584,090**	**25.43 (24.93, 25.92)**
Oxycodone	**58,115**	**10.49 (10.40, 10.57)**	**405,895,655**	**14.32 (14.20, 14.43)**	**30,141,631,493**	**19.28 (19.12, 19.44)**
Hydrocodone	**53,992**	**9.74 (9.66, 9.82)**	**755,796,049**	**7.14 (7.08, 7.20)**	**44,189,293,091**	**12.22 (12.12, 12.32)**

¥ Opioid categories are not mutually exclusive in that one patient could have endorsed more than one product.
†The total prescriptions dispensed included projected prescriptions dispensed in states participating in the ASI-MV network during the study period.
†† The total number of units dispensed included projected solid oral dosage units (e.g. tablets, capsules, caplets) dispensed in states participating in the ASI-MV network during the study period.
±This category represents past 30-day NMU of tramadol and past 30-day NMU of at least one other prescription opioid compound monitored in the ASI-MV.
Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 23: Oral Tramadol and Comparator Opioids: Non-Medical Use in High-Risk Treatment Center Populations (Source: NAVIPPRO)

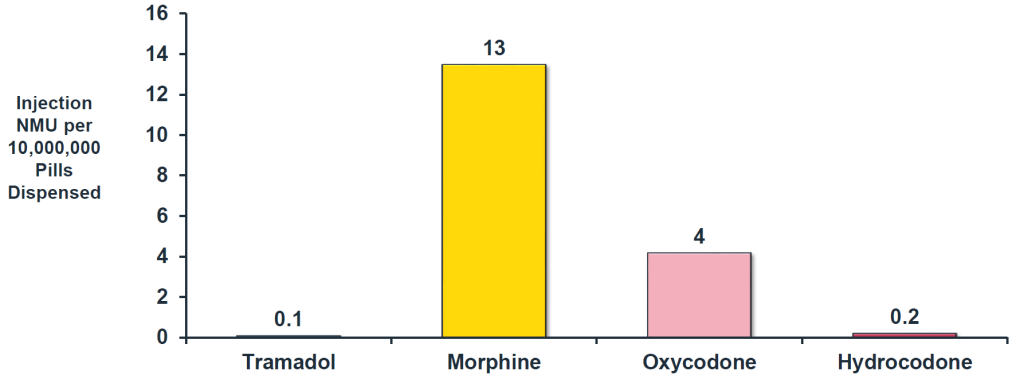


Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.2.2. NMU via Injection

Figure 24 shows that past 30-day NMU of tramadol via injection is lower than comparators. Tramadol, oxycodone and hydrocodone are available only in oral formulation in the U.S. It is apparent that in this high-risk population, nom-medical use of morphine and oxycodone via injection is strongly preferred, and that non-medical use of tramadol via injection is rare. The rate is standardized to oral tramadol)

Figure 24: Oral Tramadol and Comparator Opioids: Past 30-Day Non-Medical Use via Injection (Source: NAVIPPRO)



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.2.3. Key Conclusions from the NAVIPPRO data

This study suggests that tramadol has a significantly lower rate of NMU than morphine, oxycodone, or hydrocodone within a high-risk population of adults assessed for substance abuse problems and treatment planning in the ASI-MV network. Tramadol is less likely to be diverted or used via non-oral routes. These findings support previous evaluations by WHO and DEA which concluded that tramadol has a low potential for abuse.

7.1.3. NSDUH

The National Survey of Drug Use and Health (NSDUH) is an annual, cross-sectional, population-based survey of self-reported alcohol, drug and tobacco use among non-institutionalized persons (≥12 years old). It is a comprehensive nationwide survey and is highly representative of the US population not experiencing homelessness or institutionalization.

We conducted a cross-sectional surveillance study of the NSDUH database to examine lifetime and past-year misuse of oral tramadol and comparators of interest among NSDUH respondents. The past-year misuse analysis includes NSDUH data from 2015-2017 with results adjusted for availability (prescription volume).

For context, commonly prescribed Schedule II opioids including morphine, oxycodone, and hydrocodone were also analyzed as comparators, and an additional analysis compared estimates of reports of oral tramadol misuse with another Schedule IV drug, alprazolam (indicated for management of anxiety disorder).

7.1.3.1. Oral tramadol versus comparator opioids on Past-year Misuse (2015-2017)

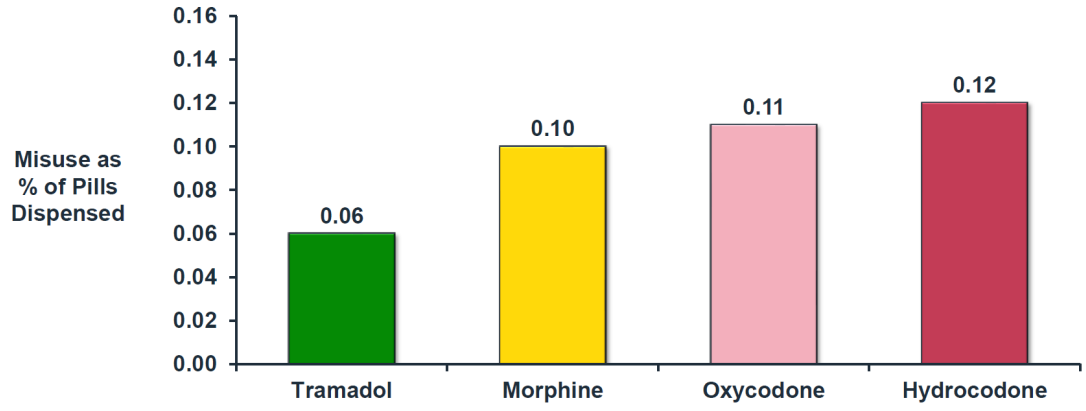
Starting in 2015, NSDHU collected data on reported past-year misuse among individuals reporting past-year use of prescription medicine. Table 40 lists the survey results and those adjusted for availability (prescription volume data provided by Symphony Health). The data from 2015 to 2017 consistently demonstrated that reported misuse of oral tramadol was at approximately 0.06% of total pills dispensed versus approximately 0.10 to 0.12% reported for each of the Schedule II comparator opioids. Figure 25 presents any past-year misuse as a percent of prescriptions.

Table 40: Reported past-year misuse as a percentage of total prescriptions (2015-2017) by product (Source: NSDUH, Symphony Health)

Opioid	Parameter	2015	2016	2017
Tramadol	Any misuse (n)	1,787,180	1,644,875	1,699,088
	Any misuse as a % of those reporting use	9.6%	8.6%	9.2%
	Number of pills	3,226,465,634	3,061,182,270	2,789,570,975
	Any misuse as a % of pills dispensed	**0.06%**	**0.05%**	**0.06%**
Morphine	Any misuse (n)	684,758	562,711	524,847
	Any misuse as a % of those reporting use	9.2%	8.4%	8.7%
	Number of pills	600,240,312	566,061,957	508,176,622
	Any misuse as a % of pills dispensed	**0.11%**	**0.10%**	**0.10%**
Oxycodone	Any misuse (n)	4,310,809	3,964,528	3,788,907
	Any misuse as a % of those reporting use	15.2%	14.6%	14.2%
	Number of pills	3,917,775,735	3,857,224,239	3,548,764,419
	Any misuse as a % of pills dispensed	**0.11%**	**0.10%**	**0.11%**
Hydrocodone	Any misuse (n)	7,132,805	6,995,523	6,184,708
	Any misuse as a % of those reporting use	12.2%	12.8%	12.0%
	Number of pills	6,345,939,344	5,782,622,727	5,060,255,750
	Any misuse as a % of pills dispensed	**0.11%**	**0.12%**	**0.12%**

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 25: Oral Tramadol and Comparator Opioids: Reported past-year misuse as a percentage of pills dispensed (2017) (Source: NSDUH, Symphony Health)



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.3.2. Oral tramadol versus alprazolam on Past-year Misuse (2015-2017)

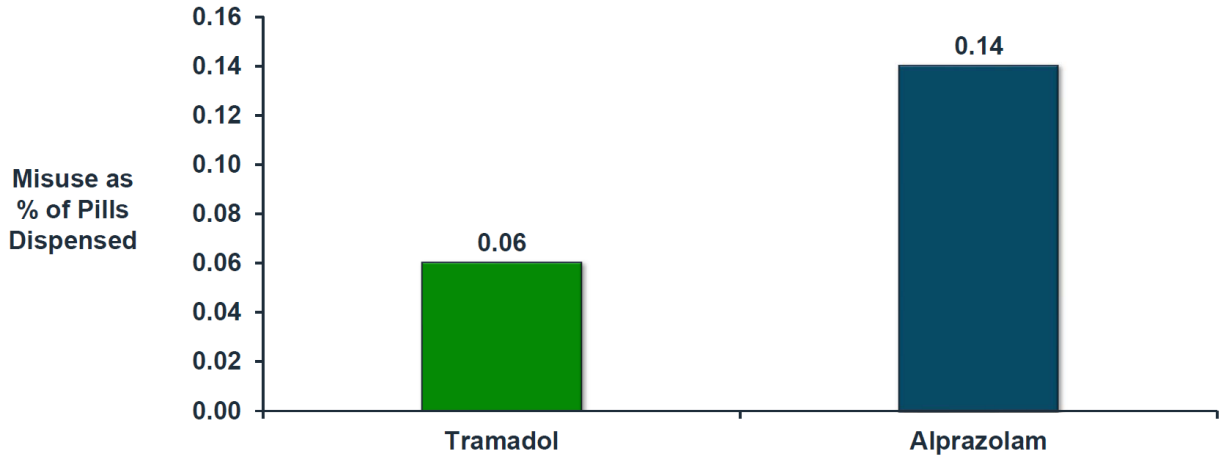
Both tramadol and alprazolam are commonly prescribed Schedule IV drugs. In 2015-2017, alprazolam had approximately 0.14% misuse as a percent of the total number of pills dispensed, versus oral tramadol at approximately 0.06% (Table 41 and Figure 26).

Table 41: Reported past-year misuse of oral tramadol and alprazolam as a percentage of total pills dispensed (2015-2017) (Source: NSDUH, Symphony Health)

Drug	Parameter	2015	2016	2017
Tramadol	Any misuse (n)	1,787,180	1,644,875	1,699,088
	Any misuse as a % of those reporting use	9.6%	8.6%	9.2%
	Number of pills	3,226,465,634	3,061,182,270	2,789,570,975
	Any misuse as a % of pills dispensed	**0.06%**	**0.05%**	**0.06%**
Alprazolam	Any misuse (n)	4,242,532	4,400,878	4,211,257
	Any misuse as a % of those reporting use	24.0%	23.8%	23.3%
	Number of pills	2,857,416,704	2,925,812,470	2,973,195,387
	Any misuse as a % of pills dispensed	**0.15%**	**0.15%**	**0.14%**

Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

Figure 26: Oral Tramadol and Alprazolam: Reported past-year misuse as a percentage of pills dispensed (2017) (Source: NSDUH, Symphony Health)



Source: Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom) (Module 5 of NDA)

7.1.4. Key Conclusion from the NSDUH Data

This analysis demonstrated a low prevalence of self-reported oral tramadol misuse, relative to other commonly prescribed opioids, in a large nationally representative sample of non-institutionalized US residents (≥12 years old). Estimates of reported oral tramadol misuse are substantially lower than those reported for comparators when adjusted for number of pills dispensed. Reports of oral tramadol misuse are also much less than alprazolam, another Schedule IV drug.

7.2. Conclusions

Epidemiologic data demonstrate that reports of abuse with tramadol are infrequent relative to other prescription opioids, such as morphine, oxycodone, hydrocodone (US), and codeine (EU-5). Similarly, reports of oral tramadol misuse are much less common than alprazolam, another Schedule IV drug, in the U.S. Furthermore, abuse of tramadol via injection is uncommon relative to oral tramadol in countries where it is available.

These findings support the use of IV tramadol in a medically supervised healthcare setting, and that in this setting, IV tramadol, with less abuse potential than intravenous Schedule 2 conventional opioids, will provide a valuable alternative to patients in acute pain who require an IV opioid.

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APPENDIX A.COMPLETE RESPONSE – 1 (OCTOBER 9, 2020)

The first complete response can be found here.

APPENDIX B. COMPLETE RESPONSE – 2 (JUNE 11, 2021)

The second part of the complete response can be found here.

APPENDIX C.FORMAL DISPUTE RESOLUTION REQUEST (SUBMITTED TO THE OFFICE OF NEW DRUGS)

The dispute resolution request can be found here.

APPENDIX D. ULTRAM LABEL (09/2021)

The Ultram label can be found here.

APPENDIX E. LITERATURE SEARCH RESULTS OF CLINICAL TRIALS WITH IV TRAMADOL (SUBMITTED TO THE NDA)

The literature review included a total of 27 studies (21 randomized controlled trials and 6 case studies/case series reports) with various design and were published from 1998 to 2019 and revealed no unexpected safety findings relative to oral tramadol. In addition, controlled studies demonstrated few significant differences in rates of AEs between tramadol and opioid comparators, which is consistent with findings in Study 103 abdominoplasty.

Table 42: Literature Review of IV Tramadol Clinical Studies

Baranska-Rybak 2014	Naguib 1998	Sudheer 2007
Broome 1999	Ng 1998	Tantry 2011
Erolcay 2003	Ng 2006	Tarradell 1996
Gan 2007	Pandey 2010	Unlugenc 2008
Hadi 2006	Pang 1999	Vickers 1995
Houmes 1992	Shamim 2006	Vickers 1992
Ilias 1996	Silvasti 2000	Wilder-Smith 1999
Kim 2016	Stamer 2003	
Langford 1998	Stamer 1997	
Mehrpour 2005	Stamer 2008	

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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

August 31, 2021

FORMAL DISPUTE RESOLUTION REQUEST

Applicant:	Avenue Therapeutics, Inc.
Application:	NDA 213231
Product:	Tramadol hydrochloride Injection 50 mg/mL
Reviewing Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office:	Office of Neuroscience
Review Level Requested:	Office of New Drugs Director
Indication:	Management of moderate to moderately severe pain in adults in a medically supervised health care setting.

Counsel to Avenue Therapeutics, Inc.:
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Adverse event	AE
Alanine transaminase	ALT
Aspartate transaminase	AST
Baseline-adjusted, placebo-corrected QTcF	ΔΔQTcF
Central nervous system	CNS
Complete Response Letter from June 11, 2021	CRL 2
Complete Response Letter from October 9, 2020	CRL 1
Corrected QT	QTc
Division of Anesthesiology, Addiction Medicine, and Pain Medicine	DAAP or the Division
FDA Adverse Event Reporting System	FAERS
Federal Food, Drug, and Cosmetic Act	FD&C Act
Formal Dispute Resolution	FDR
Formal Dispute Resolution Request	FDRR
Individual Case Safety Report	ICSR
Lack of efficacy	LOE
O-desmethyltramadol	M1
Medical Subject Heading	MeSH
New Drug Application	NDA
Nonsteroidal anti-inflammatory drug	NSAID
Office of Neuroscience	ON
Office of New Drugs	OND
Outside the U.S.	OUS
Pain Intensity differences	PID
Patient global assessment	PGA
Patient-controlled analgesia	PCA
Post-Anesthesia Care Unit	PACU
Postmarketing Requirements and Postmarketing Commitments	PMRs/PMCs

Potentially clinically significant	PCS
Prescription Drug User Fee Act	PDUFA
Risk Evaluation and Mitigation Strategy	REMS
Serious AE	SAE
Sum of pain intensity differences measured at baseline through # hours after the first dose (e.g. 6)	SPID# (e.g. SPID6)
The National Addictions Vigilance Intervention and Prevention Program	NAVIPPRO
The National Survey on Drug Use and Health	NSDUH
The Researched Abuse, Diversion and Addiction-Related Surveillance	RADARS
Treatment-Emergent Adverse Event	TEAE

FORMAL DISPUTE RESOLUTION REQUEST

On behalf of our client, Avenue Therapeutics, Inc. (Avenue, Sponsor, or the Applicant), we hereby submit this Formal Dispute Resolution Request (FDRR) seeking the Office of New Drugs (OND) review of a scientific and regulatory disagreement between Avenue and the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP or the Division), and the Office of Neuroscience (ON), regarding the approvability of Tramadol Hydrochloride 50 mg/mL injection. "IV tramadol" will be the nomenclature used to describe the product, with the dosage (in mg) indicating the dose level (e.g., IV tramadol 50 mg).

Avenue submitted New Drug Application (NDA) 213231, a 505(b)(2) application for IV tramadol that references FDA's previous findings of safety and efficacy for oral tramadol (ULTRAM®; NDA 20281), 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 on December 10, 2019. Avenue received a Complete Response Letter (CRL 1) on October 9, 2020, which set forth a clinical deficiency related to the safety of IV tramadol 50 mg, and a product quality deficiency.[1] Following a post-action Type A meeting on November 19, 2020, Avenue resubmitted the NDA for IV tramadol with proposed labeling that was revised based on the Division's comments during the first post-action Type A meeting. The resubmission was designated a complete, Class 1 response to the CRL 1 and was assigned a Prescription Drug User Fee Act (PDUFA) goal date of April 12, 2021. The Division did not allow interaction with the sponsor regarding any potential deficiencies during the second review period or present any remaining concerns, however. DAAP missed the PDUFA date by 2 months and issued a second Complete Response Letter (CRL 2) on June 11, 2021, which contained only a clinical deficiency that is essentially identical to that stated in CRL 1. A second post-action Type A meeting was conducted on July 23, 2021 without an acceptable outcome. It was attended by the Division and the ON. To resolve the disparity of how the Division interpreted the data in the NDA and what is known clinically regarding IV tramadol, the Sponsor submitted a FDRR to the ON on July 27, 2021 and received an Appeal Denied Letter on August 26, 2021. The ON Appeal Denied Letter reiterated DAAP's position, failed to take the totality of our data into account, and ignored key points presented in the FDRR.

As this document will demonstrate, the Sponsor conducted a robust clinical program designed with Division input and submitted an NDA that fulfilled all requirements for approval with an appropriate risk to benefit consideration of IV tramadol, a Schedule IV opioid analgesic. This FDRR requests that OND determine that the NDA provides sufficient evidence of effectiveness and safety and should be approved with appropriate labeling. The Sponsor is requesting a meeting with the deciding official of OND and is not requesting advisory committee review. No new clinical information has been submitted in support of the FDRR, although the FDRR does reference publicly available documents that were not submitted to NDA 213231 (e.g., labeling of approved analgesic drugs and certain published articles). This document provides hyperlinks to documents previously submitted to the NDA that are deemed necessary for resolution of the matter.

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[1] The product quality deficiency was resolved in the Sponsor's resubmission and is not germane to this FDRR.

I. Executive Summary

The clinical deficiency identified in the two CRLs is that IV tramadol's onset of action, as measured by the two-stopwatch method, exceeds the Division's expectation of one hour for an analgesic for acute pain. The Division concluded that this hypothetically could lead to inappropriate opioid "stacking." Opioid stacking, or the use of multiple opioids concurrently, occurs when an opioid drug is administered while the patient is under the influence of a previously administered opioid drug. Opioid stacking can also occur with the same opioid due to inappropriate dosing intervals (dose stacking). The principal clinical risk of use of multiple opioids or dose stacking of the same opioid is respiratory depression.

The clinical issue cited in the CRLs appears to be based on the Division's narrow focus on only the two-stopwatch method of measuring onset, and its arbitrary threshold requirement of onset within an hour while disregarding other endpoints. As demonstrated in the NDA, IV tramadol provides an adequate onset and clinically meaningful analgesia at early timepoints. The only datapoint showing delayed onset was the two-stopwatch method and we will discuss the limitation of this methodology. Further, the Sponsor will examine the recent approval of ANJESO (meloxicam) injection, a drug with delayed onset, to illustrate the relationship between onset as measured by the two-stopwatch method and other endpoints, as well as why ANJESO sets a regulatory precedent that even a drug with a real delayed onset can be approved with appropriate labeling and that there should not be a one-hour expectation of onset for IV analgesics as a threshold for approval. The case demonstrates that the labeling can fully inform healthcare providers of the performance characteristics regarding delayed onset of action such that the drug can be used in a safe and efficacious manner.

Notably, the Division's concern regarding opioid stacking (the use of multiple opioids) did not directly result from any safety signal from the NDA because clinicians were able to successfully manage all but a handful of patients without another opioid. The Division's concern was a theoretical one based on its assumption that "it would not be clinically feasible if an opioid analgesic requires a nonopioid product to augment the analgesia."[2] We note that the Division's assumption regarding appropriate rescue for an opioid analgesic is invalid according to multiple sources including our data from our two efficacy studies and real-world safety study, product labeling, and current clinical practice. In addition, parenteral tramadol has been widely used outside the U.S. for decades (~370 million doses in EU from 2010-2019[3]) and opioid stacking has not been noted as a safety concern.[4]

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[2] Type A meeting minutes at 20. CRL 1 states "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 [and] would result in opioid 'stacking' . . . ." (CRL 1 at 1); CRL 2 states "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids" (CRL 2 at 2).

[3] Data purchased from IQVIA and available upon request. Countries included in the figure are France, Germany, Italy, Spain, UK, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Sweden.

[4] Literature review of safety findings (1998 to 2019) and AE assessment of VigiBase (2009 to 2019) were

The Sponsor notes that all opioid analgesics, regardless of onset, may require supplementation with additional doses, or with another opioid analgesic, and are therefore also subject to the risk of opioid stacking. We note that similar percentages of patients asked for rescue in the IV morphine arm and the IV tramadol arm in one of the efficacy studies submitted in the NDA. Current opioid labeling addresses the concomitant use of CNS depressants with opioid analgesics with class labeling such as the language found in the WARNINGS and PRECAUTIONS section of the oral tramadol labeling. The Sponsor will examine another relevant precedent, OLINVYK (oliceridine) injection, which showed that concurrent use of more than one opioid analgesic occurs even in opioids with fast onset, and that the FDA approved OLINVYK despite the fact that OLINVYK carries the risk of opioid stacking in three different ways, as discussed below. This is followed by a discussion of the regular use of multiple opioids concurrently in a medically supervised setting (for which IV tramadol is intended) and why such practice is common and accepted as safe because of the setting.

We conclude 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. (OUS). Consistent with the results of our "real-world" safety study, decades of OUS experience supports the notion that IV tramadol either alone or in concurrent use with non-opioid medicine reduces the use of opioids with greater abuse potential. This is consistent with the finding from the Phase 3 clinical trials submitted in support of the NDA. Compared to IV tramadol, the intravenous Schedule II opioids are more likely to cause psychological or physical dependence even with short-term exposure. The Division did not focus on this feature of IV tramadol during the review,[5] but epidemiology data submitted in the NDA, which confirm IV tramadol has less abuse potential than approved Schedule II opioids, along with the FDA's stated approach to considering abuse liability in conducting benefit-risk analysis of opioid analgesics,[6] support our view that the potential benefit of IV tramadol outweighs the Division's hypothetical (and disproven) safety concern.

A. Background on IV tramadol

This NDA was submitted as a 505(b)(2) application with reference to FDA's approval of ULTRAM® (NDA 20281), an oral tramadol product that has been approved in the U.S. since 1995. Tramadol is a centrally acting atypical opioid with two mechanisms of action including activation of the mu opioid receptor by the parent drug, more potent activation of the mu receptor by its primary metabolite M1 (produced by metabolism of tramadol in the liver), and inhibition of the reuptake of serotonin and norepinephrine. Both opioid and non-opioid mechanisms contribute to tramadol's analgesic effect. The pharmacological difference between tramadol and pure mu agonists (conventional Schedule II opioids such as morphine) explains its lower abuse liability and its ultimate placement in Schedule IV. Compared to oral tramadol, IV

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submitted to the NDA (Module 5.3.6) and are discussed later in the document.

5 FDA response to Question 2b of Type A meeting (Type A meeting minutes at 19-20).

6 FDA, Draft Guidance for Industry – Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (June 2019).

tramadol provides a more rapid increase in tramadol concentrations but lower exposure to M1 and a slower onset of exposure to M1 due to the lack of first pass metabolism.

IV tramadol is intended for the management of post-operative pain in a medically supervised setting when an opioid is warranted. It would offer an option when the physician believed that a Schedule II opioid may not be necessary, or when the physician or patient wanted to avoid the higher abuse liability potential inherent in Schedule II opioids for pain relief. At present, all the commonly used intravenous opioid analgesics for post-operative pain in the U.S. are pure mu agonists placed Schedule II indicating their high potential for abuse.[7] The use of these drugs is ubiquitous in the post-operative setting,[8] even though short-term exposure to highly abusable opioids can lead to chronic opioid dependence.[9] The availability of IV tramadol would reduce the exposure of U.S. patients to Schedule II opioids in the post-operative setting, just as it does for millions of patients located in many countries outside the U.S.

Notably, parenteral tramadol has been approved in over 70 countries outside the U.S. including most parts of Europe for over 25 years. Approximately 370 million doses of parenteral tramadol were administered in European hospitals from 2010 to 2019 and there is no setting restriction on the use of parenteral tramadol in Europe.[10] Outside the U.S. where parenteral tramadol is available, it is often the only opioid used in the majority of patients in the post-operative setting, and its use in combination with non-opioid medicine provides adequate pain relief while reducing the use of more abusable opioids.[11]

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7 Butorphanol tartrate injection is a schedule IV opioid, but it is not commonly used in the post-operative acute pain setting.

8 Kessler, E. R., Shah, M., Gruschkus, S. K., & Raju, A. (2013). Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: Opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy*, *33*(4), 383–391. https://doi.org/10.1002/phar.1223

9 *See, e.g.,* Brummett, C. M., Waljee, J. F., Goesling, J., Moser, S., Lin, P., Englesbe, M. J., Bohnert, A. S. B., Kheterpal, S., & Nallamothu, B. K. (2017). New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surgery*, *152*(6), e170504. https://doi.org/10.1001/jamasurg.2017.0504; Koepke, E. J., Manning, E. L., Miller, T. E., Ganesh, A., Williams, D. G. A., & Manning, M. W. (2018). The rising tide of opioid use and abuse: The role of the anesthesiologist. *Perioperative Medicine*, *7*(1), 16. https://doi.org/10.1186/s13741-018-0097-4; Lee, J. S.-J., Hu, H. M., Edelman, A. L., Brummett, C. M., Englesbe, M. J., Waljee, J. F., Smerage, J. B., Griggs, J. J., Nathan, H., Jeruss, J. S., & Dossett, L. A. (2017). New Persistent Opioid Use Among Patients With Cancer After Curative-Intent Surgery. *Journal of Clinical Oncology*, *35*(36), 4042–4049. https://doi.org/10.1200/JCO.2017.74.1363; Mehra, M., *Why Opioid Addiction Will Persist Until Physicians Have A Panoramic View Of Opioid Exposure* (Oct. 4, 2018) https://www.healthaffairs.org/do/10.1377/hblog20180928.934819/full/ (last accessed July 22, 2021).

10 Datapharm, *SmPC (Summary of Product Characteristics) for Zydol 50 mg/ml Solution for Injection (Grunenthal Ltd)* (last revised March 16, 2020) https://www.medicines.org.uk/emc/product/82/smpc (last accessed July 22, 2021).

11 *See, e.g.,* Grond, S., & Sablotzki, A. (2004). Clinical pharmacology of tramadol. *Clinical Pharmacokinetics*, *43*(13), 879–923. https://doi.org/10.2165/00003088-200443130-00004; Hartman, F. C., LaMuraglia, G. M., Tomozawa, Y., & Wolfenden, R. (1975). The influence of pH on the interaction of inhibitors with triosephosphate isomerase and determination of the pKa of the active-site carboxyl group. *Biochemistry*, *14*(24), 5274–5279. https://doi.org/10.1021/bi00695a007; Lee, C. R., McTavish, D., & Sorkin, E. M. (1993). Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*, *46*(2), 313–340.

As a 505(b)(2) NDA, Avenue developed IV tramadol in a manner that builds on the documented safety profile of oral tramadol. The IV dosing regimen used in the Phase 3 studies (50 mg given at Hours 0, 2, 4, and every 4 hours thereafter) was discussed in detail with the Division and provides a predictable and similar exposure to the approved oral tramadol dosage (100 mg Q6H) based on C_{max} and AUC at steady state (Study AVE-901-101). The Sponsor closely followed the Division's advice during development. Two efficacy studies in two pain models with similar design used to support the approval of other intravenous opioid analgesics were conducted sequentially. One Phase 3 study included dose ranging (Study AVE-901-102) and the other had an active comparator (Study AVE-901-103; IV morphine was included to compare safety and the study was not powered for direct efficacy comparison). An additional open-label safety study (Study AVE-901-104) provided further safety exposure and assessed how IV tramadol would fit into the real-world practice of multimodal analgesia in patients undergoing major surgeries. The Division agreed to the design of the Phase 3 trials and reviewed the protocols for each of the Phase 3 trials.

As explained in more detail below, IV tramadol was shown to be safe and effective in two positive adequate and well-controlled Phase 3 efficacy studies (Study AVE-901-102 and Study AVE-901-103) with established primary and key secondary endpoints in two distinct pain models. Importantly, IV morphine 4 mg (a widely used Schedule II opioid) was included as an active comparator in Study AVE-901-103.[12] IV tramadol met the primary efficacy endpoint and key secondary efficacy endpoints (SPID24 and SPID48) in both efficacy studies (Table 3 and Table 4) and demonstrated similar analgesic efficacy to IV morphine on these endpoints (Figure 1), which have been accepted by the Division as appropriate and used for the evaluation of other acute pain drugs. IV tramadol was well tolerated with a similar side effect profile as oral tramadol and no unexpected safety findings. The additional safety study (Study AVE-901-104) demonstrated safety and effectiveness in patients undergoing a variety of painful surgeries, such as total joint replacement procedures, and demonstrated how IV tramadol can fit into the multimodal analgesic approach used in "real-world" clinical practice. In that study, patients could choose to exit the study at any time to get another opioid if they did not experience adequate pain relief yet not a single patient out of 251 patients did that. Together, the studies demonstrate that IV tramadol can be used for predictable and satisfactory pain relief while also avoiding Schedule II opioids as rescue medications for the great majority of patients. Thus, IV tramadol can help reduce the exposure to Schedule II opioids with higher abuse potential in the post-operative setting, just as it does for patients outside the U.S.

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https://doi.org/10.2165/00003495-199346020-00008; Radbruch, L., Grond, S., & Lehmann, K. A. (1996). A risk-benefit assessment of tramadol in the management of pain. *Drug Safety*, *15*(1), 8–29. https://doi.org/10.2165/00002018-199615010-00002; Scott, L. J., & Perry, C. M. (2000). Tramadol: A review of its use in perioperative pain. *Drugs*, *60*(1), 139–176. https://doi.org/10.2165/00003495-200060010-00008; Stamer, U. M., Maier, C., Grond, S., Veh-Schmidt, B., Klaschik, E., & Lehmann, K. A. (1997). Tramadol in the management of post-operative pain: A double-blind, placebo- and active drug-controlled study. *European Journal of Anaesthesiology*, *14*(6), 646–654. https://doi.org/10.1046/j.1365-2346.1994.00214.x; Teoh, S. W. K., Payne, C., McDonnell, N., & Petrovski, M. (2021). Postoperative pain management on discharge after day case gynaecologic laparoscopy. *Journal of Pharmacy Practice and Research*, *51*(1), 62–66. https://doi.org/10.1002/jppr.1690

[12] The study was not powered to directly compare IV tramadol to IV morphine.

B. First CRL (CRL 1 issued October 9, 2020) and Type A Meeting

The Division agreed that Avenue had demonstrated statistical significance on the primary efficacy endpoint in Study AVE-901-102 and the primary and secondary efficacy endpoints in Study AVE-901-103. CRL 1 does not describe any specific safety finding noted in any of the Phase 3 studies. Instead, the sole clinical reason for the CRL is a "potentially serious safety issue for the intended patient population" that results from a "delayed onset of analgesia" combined with administration of IV tramadol as a standing dose.[13] The CRL stated that if a patient needs an analgesic between the first dose of IV tramadol and onset of analgesia, the patient would likely be prescribed another opioid such as an immediate-release formulation, which would result in opioid "stacking" (the use of multiple opioids concurrently). The Division did not provide any evidence of this likelihood.

During the first post-action Type A meeting, the Division provided somewhat contradictory guidance regarding the path forward for this NDA. On the one hand, the Division appeared to agree with Avenue that appropriate labeling with clear language describing onset of analgesia could lead to approval. For example, the Division said that "[r]evision of the labeling may help address the Division's concerns" and "ultimately, the issue is how tramadol IV will be labeled to make it operational and safe in the postmarket environment."[14] On the other hand, the Division also stated that "[t]he labeling approach was considered during the NDA review; however it was not successful" and "the Division could not identify a patient population who can safely and effectively use this product."[15] The Sponsor proposed to submit revised labeling and the Division did not counsel them regarding any hesitation that this path would be successful.

C. Resubmission and Second CRL (CRL 2 issued June 11, 2021)

Based on the Division's feedback during the first post-action Type A meeting, Avenue revised labeling for IV tramadol in the NDA resubmission. The language was revised to reflect the clinical trial experience with regard to time to onset and be consistent with ANJESO and included information and additional instruction such as "[b]ecause of delayed onset of analgesia in some patients, ONPREFA[16] may be supplemented with a rapid-onset analgesic such as a non-steroidal anti-inflammatory drug [see Dosage and Administration (2.1)]" in Section 1. INDICATIONS AND USAGE, "[w]hen initiating 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)]" in Section 2 DOSAGE AND ADMINISTRATION, and "[t]he 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

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13 CRL 1 at 1.

14 Type A meeting minutes at 5.

15 *Id*. at 8.

16 Proposed proprietary name for IV tramadol.

Study 1 and 106 minutes in patients treated with ONPREFA and 145 minutes in patients treated with placebo in Study 2" in Section 14 CLINICAL STUDIES.[17] The revised labeling also clarified that IV tramadol can be used "alone or in combination with other analgesics," and described more clearly the "medically supervised" setting.[18] The explanation and support for the revised language were provided in the resubmission. The Division accepted Avenue's NDA resubmission and assigned it a complete, class I response to the CRL 1 with a PDUFA date of April 12, 2021. However, the Division did not provide any feedback on the submission, a discipline review letter, nor allow for any exchange of viewpoints. The Division missed the PDUFA action by two months and issued a CRL 2 on June 11, 2021. CRL 2 contained only a clinical deficiency that is essentially identical to that stated in CRL 1.

Consistent with the CRL 1, CRL 2 again focuses on "the delayed onset of analgesia" noting that "meaningful pain relief was delayed (accounting for the use of rescue medication, e.g., ibuprofen), and some patients never achieved pain relief" based on the two-stopwatch metric while disregarding other endpoints in the NDA.[19] The Division again noted that "the potential risk of opioid 'stacking' is a serious safety concern . . . ."[20]

A second post-action Type A meeting on July 23, 2021 did not resolve the issues. The Division stated "that the Applicant's presentation and arguments were clear and that the discussion had been useful in helping the Division understand the Applicants position. The Division recognized that the Applicant was providing reasoning for what contributed to the data that was seen in the NDA submission." The Division asked the Sponsor to "send a formal response to the June 11, 2021, CR letter with the arguments presented during the teleconference and that the Division would review the response." We note that DAAP never provided an opportunity during either the original NDA review cycle or the second review cycle for us to elaborate the rationale for why the data supported approval. Further, DAAP ignored certain key data such as the very low percent of patients who had to get another opioid in the NDA, the similar percentages of patients who asked for rescue in the IV morphine arm and in the IV tramadol arm in Study AVE-901-103. It did not appear that the Division is familiar with the current standard of care for postoperative pain with knowledge of the use of multimodal therapy and the monitoring of postoperative inpatients. As such, even a resubmission to the second CRL would lead to us going through the same exercise with the Division, which appeared fruitless. Accordingly, we submitted the FDRR to the Office of Neuroscience (ON). As ON's Appeal Denied Letter indicates, it can safely be predicted that the outcome of having DAAP review again would yield another CR.

D. ON's Appeal Denied Letter and Why We are Appealing That Decision

We do not believe that the Division or ON have accurately represented the totality of the data in the IV tramadol NDA or responded adequately to various aspects of the FDRR. The reason we pursued FDRR is that we could not resolve the disparity of how the Division

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17 Proposed labeling at 4-5, 34.

18 *Id*. at 4.

19 CRL 2 at 1.

20 *Id*. at 2.

interpreted the data and what is known clinically regarding IV tramadol, because the Division appeared to not take certain data into account and have made key assumptions and suppositions that are not supported by data or current clinical practice. We are disappointed that the ON Appeal Denied Letter includes some of the same misconceptions as has been expressed by the review Division and we note that many key points in the FDRR (see below) were not discussed by the ON.

To help the Office of New Drugs (OND) fully understand how the data from the clinical trials and general knowledge about modern postoperative pain support the potential for IV tramadol to improve the safety of managing patients in this situation, we provide a brief response to the ON Appeal Denied Letter in this section and point out ON's statements/opinions that failed to take into account data/facts. We will also summarize the other key issues relevant to the approvability of IV tramadol that should have been discussed by the ON but were not. Below, we have indented the ON comments, copied verbatim from the Appeal Denied Letter and underlined for emphasis.

The ON stated in the Appeal Denied Letter:

> …the data are clearly consistent with a delayed onset of effect <u>compared to IV morphine</u>.

While we agree that IV morphine has a faster onset of effect compared to IV tramadol (Figure 7 and Table 7), the faster onset of action of IV morphine contributes to its greater abuse potential. We note that there is <u>no</u> regulatory requirement to have an onset of action equivalent to IV morphine, which was an active comparator in Study AVE-901-103 to provide important information regarding the level of pain control (efficacy) and rate of adverse events to IV tramadol. The clinically relevant question is whether the onset has any consequence as it relates to opioid stacking potentially caused by patients asking for rescue. In Study AVE-901-103, approximately 40% of IV morphine patients versus approximately 50% of IV tramadol patients required rescue (Table 11). DAAP and ON never explained why additional doses of opioids added to tramadol are more dangerous than when added to IV morphine. During the second Type A meeting, the Sponsor stated that opioid-related adverse events for IV morphine and IV tramadol are similar in Study AVE-901-103 and asked DAAP what was different regarding the risk of opioid stacking between IV tramadol and IV morphine when they had similar rates of rescue. <u>The Division could not answer the question</u>. ON's Appeal Denied Letter did not address these questions. Additionally, in the studies for the approval of OLINVYK, rescue medication was also required by approximately 20% of the patients at the recommended dose. DAAP and ON have not articulated the arbitrary nature of why opioid stacking is a bar to approval of IV tramadol but not a concern in their recent actions on other applications.

The ON stated in the Appeal Denied Letter:

> 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 analgesia—likely beyond 2 hours after treatment initiation in a substantial proportion of patients taking IV tramadol for acute pain relief.

While the time to meaningful pain relief (Table 7) as measured by the two-stopwatch method showed a delayed onset (the limitation of the method is discussed in the FDRR), other valid endpoints providing a framework of how onset translates clinically demonstrate that patients on IV tramadol experienced clinically meaningful pain relief at early timepoints. These include PID (Figure 6 and Figure 7), Patient Global assessment at 24 hours (PGA 24, Figure 2) and time to first rescue (Table 12). Notably, in the Acknowledgement letter to the FDRR, ON was to determine the core clinical issue "concerning the delayed and unpredictable onset of analgesia with tramadol hydrochloride injection communicated in the Agency's Complete Response letters dated October 9, 2020 and June 11, 2021 . . . ." However, the ON Appeal Denied Letter does not address any of the evidence we summarized in the FDRR regarding the limitation of onset as measured by the two-stopwatch method or other valid endpoints clearly indicating that patients on IV tramadol experienced clinically meaningful pain relief at early timepoints. It did not appear that the ON reviewed these datapoints as there was no meaningful discussion of the clinical meaning of these endpoints in the Appeal Denied Letter. Instead, the ON stated in the Appeal Denied Letter:

> 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.

The ON did not explain why it agrees with the Division's position regarding "delayed onset." The ON ignored our arguments regarding the limitation of the two-stopwatch method in measuring onset. The ON did not discuss other datapoints demonstrating that patients on IV tramadol experienced clinically meaningful pain relief at early timepoints in the NDA. Concerning the risk of opioid stacking, the ON ignored that in the Phase 3 program: (1) only 2% (6 out of 280) patients on IV tramadol discontinued due to inadequate analgesia in the efficacy studies (and none had a serious AE or SAE upon receiving a different opioid); and (2) none of the patients discontinued (0 of 251 patients) due to inadequate analgesia in the safety study and 95% of the patients rated their treatment as good, very good, or excellent (Figure 2). Further, the ON did not discuss the vast outside-the-U.S. (OUS) experience (summarized in the NDA) that does not show a signal for opioid stacking.

The ON stated in the Appeal Denied Letter:

> …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.

IV tramadol's Phase 3 program, designed with Division input, was comparable to other programs that supported recent approvals of IV analgesics. All of the products including both opioid and non-opioid in this space have been tested as monotherapy versus placebo with rescue provided upon patient request in two distinct surgical models in addition to a safety study designed to assess its real-world usage. The Division reviewed the protocols for Phase 3 studies [FDA advice letter (August 4, 2017)] before they were initiated and never raised a concern that another opioid should have been the rescue. The studies were allowed to proceed, indicating that they were adequately designed to meet the study objectives.

The IV tramadol efficacy trials demonstrated that IV tramadol provided adequate analgesia with NSAIDs as appropriate rescue, that IV tramadol performed similarly on primary and key secondary efficacy endpoints as compared to IV morphine, and that the risk of opioid stacking was no greater for IV tramadol than for IV morphine (Study AVE-901-103). Only 6 out of 280 patients (2%) discontinued IV tramadol due to lack of efficacy and none had a severe AE or SAE upon receiving a different opioid. The open-label safety Study AVE-901-104 reflecting real-world practice also informed that IV tramadol in multi-modal analgesia with non-opioids were safe and effective in patients undergoing painful procedures (such as total joint replacement surgeries): none of the 251 patients discontinued to receive another opioid and 95% of the patients rated their treatment as good, very good, and excellent (Figure 2). As such, the data in the NDA clearly demonstrates that a second opioid is rarely needed in the first place. The data is consistent with the vast OUS experience where clinicians use parenteral tramadol with non-opioids to reduce the use of more abusable opioids, as discussed in the NDA and FDRR. Therefore, the NDA clearly informs that NSAIDs are appropriate rescue for IV tramadol, and that IV tramadol is safe and effective in multimodal regimens with non-opioid analgesics.

Importantly, as multiple clinical experts we consulted with stated in first post-Action Type A meeting and second post-Action Type A meeting, for an inpatient post-operative patient population, opioid stacking is currently practiced. Patients routinely receive more than one opioid over the postoperative course when they transition from parenteral opioids used intra-operatively and in the immediate postoperative period (morphine, hydromorphone, fentanyl) to oral opioids (oxycodone or oxycodone and acetaminophen combinations). Therefore, opioid stacking is a concern for all opioids and is already part of the class labeling. We note that the Division has apparently never required a "stacking" study.

The ON stated in the Appeal Denied Letter:

> 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.

Both the ANJESO and the OLINYK precedents are relevant and ON's comments attempt to skirt the true issue. ANJESO received a Complete Response letter because there was no evidence of onset in many patients before a rescue opioid was required, and in those with onset measured with the help of rescue opioid, the time to onset was 2 to 3 hours. Through the process of a dispute resolution, it was determined that labeling can adequately inform prescribers about what to expect regarding the time to onset of ANJESO and what to do in the event of delayed onset for the treatment of moderate to severe pain. In our NDA resubmission we provided labeling language with encouragement from DAAP (discussed further below) to adequately inform prescribers about what to expect regarding the time to onset of IV tramadol, and to recommend that an NSAID be used initially as rescue.

OLINVYK, a recently approved Schedule II opioid, carries three distinct risks of opioid stacking as discussed in the FDRR. First, it is administered via patient-controlled analgesia (PCA) which can cause opioid dose stacking. Second, about 20% of patients in the Phase 3 studies required rescue at the recommended dose. Finally, there is also a limit for the total daily dose of OLINVYK (due to the QT concern) with the median time to reaching the cap of approximately 14 hours. It can be expected that patients will likely receive another opioid once the daily cap is reached while still having a substantial amount of OLINVYK "on board." Nevertheless, DAAP and ON did not require a "stacking" study for OLINVYK. It is completely unclear why the risk of opioid stacking (sequential use of different opioids in a short amount of time) with two Schedule II opioids (one with a QT concern) was found acceptable, while the hypothetical risk of opioid stacking with a Schedule IV and a Schedule II opioid was found to be unacceptable.

The ON stated in the Appeal Denied Letter:

> 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 postoperative 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.

ON states that DAAP has considered the "risks and benefits" but there has been no discussion by the Division on the benefit of adequately managing postoperative pain in a vast majority of patients undergoing painful procedures with a Schedule IV opioid and a nonopioid

analgesic and how it is outweighed by the hypothetical risk of opioid stacking, particularly as opioid stacking routinely occurs with approved Schedule II opioids in clinical practice today. The Division never explained why the possible opioid stacking of a Schedule II opioid on IV tramadol presents a greater clinical risk than the use of two Schedule II opioids in clinical practice today.

As stated in the second post-action Type A meeting, it is not realistic to expect most patients undergoing painful procedures to have adequate analgesia with just non-opioid medicine bridged by one or two doses of opioids. They will need repeated doses of opioids in addition to NSAIDs. Exposure of patients to a Schedule IV drug with a lower abuse potential (Figure 11, Figure 12, and Module 5.3.6 Epi Abuse Summary Report) than a Schedule II drug should be exactly relevant to any benefit/risk calculation in the approval of IV tramadol. That is precisely the scenario we explored in Study AVE-901-104. If IV tramadol was approved with appropriate labeling identifying appropriate patients, almost all would be managed throughout their entire postoperative period, both inpatient and outpatient, with tramadol (a less abusable opioid than Schedule II opioids) and avoid Schedule II opioids for post-operative pain management. This clearly will be a benefit to patients, as well as to public health during an ongoing and worsening opioid crisis because even short-term exposure to highly abusable opioids can cause chronic opioid (references previously provided).

As such, the data from our clinical trials, and the vast clinical experience outside the U.S. with parenteral tramadol as summarized in our NDA (Module 5.3.6) provide clear evidence of an acceptable balance of benefit and risk.

The ON stated in the Appeal Denied Letter:

> 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's assumption regarding appropriate rescue is neither supported by the data in the NDA nor clinical practice. As explained in more detail below, DAAP's assumption, central to connecting time to onset to opioid stacking, contradicts the data in the NDA, product labeling, and clinical practice. Further, DAAP's understanding regarding other intravenous opioids in the post-operative setting is incorrect because they are routinely stacked in the post-operating setting as multiple experts discussed in the first Type A meeting and second Type A meeting. DAAP and ON have not provided any evidence that opioid stacking is "avoided" by the use of other intravenous opioids. There is certainly nothing in the labeling of approved opioid medications that would prohibit a physician from using a second opioid. To the contrary, the uncontroverted evidence we presented is that stacking does occur, and not uncommonly so with Schedule II opioids, but at least in the context of a medically supervised setting, opioid-related adverse events including respiratory depression are appropriately managed and do not constitute a significant risk.

The ON stated in the Appeal Denied Letter:

> A type A post-action meeting was held on November 19, 2020. According to the meeting minutes, you . . . disagreed with DAAP's concerns about opioid stacking.

We did not disagree that opioid stacking is a potential occurrence, or that such an occurrence could be a risk that is concerning depending upon setting and circumstance. Our NDA did not demonstrate an unusual circumstance in the results (withdrawals etc.) that may anticipate an increased risk of opioid stacking. It was unfulfilling that the Division could not answer our questions regarding the difference of opioid stacking risk between the 40% of IV morphine patients and the 50% of IV tramadol patients who required rescue in Study AVE-901-103. It is not clear to us why the Division and ON are not concerned with the risk of opioid stacking in the 40% of IV morphine patients who needed rescue or with the 20% of patients in the OLINVYK studies that required rescue.

We disagree with DAAP, however, regarding the underlying basis for DAAP's concern about opioid stacking. DAAP's concern is based on IV tramadol's onset of analgesia according to the two-stopwatch metric and DAAP's assumption regarding appropriate rescue for opioid analgesics. We note that: (1) multiple endpoints indicated that patients experienced clinically meaningful analgesia at early timepoints; (2) DAAP's assumption regarding appropriate rescue for opioid analgesics contradicts clinical data, product labeling, and clinical practice; and (3) the NDA demonstrated that there is low risk for opioid stacking, and no greater risk for the use of additional opioids with IV tramadol than with IV morphine. Further, we disagree with DAAP's presumption that opioid stacking is an invariable consequence following IV tramadol (a presumption contradicted by our data and the E.U. experience), and neither DAAP nor the Appeal Denied Letter address our point that even if stacking would occur, it could be managed appropriately in a medically supervised setting just as that potential risk is routinely managed now. We note that in a medically supervised setting, patients are closely monitored, opioids are administered by healthcare professionals, and the use of multiple opioids is considered routine and within the standard of care in the post-operative setting.

The ON stated in the Appeal Denied Letter:

> 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.
> . . .
> 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".

Our NDA resubmission did not include new data because our NDA already adequately demonstrates the safety and effectiveness of IV tramadol. Regarding revised labeling of "alone or in combination with other analgesics," and "delayed onset of analgesia," the Sponsor only modified labeling based on the discussion during the first Type A meeting with the Division. The Sponsor was led to believe that the revised language of the proposed labeling would satisfy the concerns of the Division, and so it was a compromise that we were willing to accept to gain approval of the product. It seems that the revised labeling, intended to be a concession based on DAAP's comments in the first Type A meeting, caused confusion.

For OND's consideration of approvability, the Sponsor would like to suggest that the phrase "alone or in combination with other analgesics," be considered in light of the fact that IV tramadol was studied in the same manner as other recently approved intravenous analgesics such as ANJESO and OLINVYK (i.e., as monotherapy versus placebo with pre-determined rescue allowed). We request that OND consider the totality of the data in the NDA and evidence presented in the FDRR regarding onset to reach the conclusion that IV tramadol has an adequate onset of action. We note that there is no regulatory requirement for an IV analgesic to match the onset (as measured by the two-stopwatch method) of an approved Schedule II pure mu agonist.

The ON stated in the Appeal Denied Letter:

> 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.

Our substantial discussion in the FDRR regarding DAAP's second concern ("a combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids") was not addressed in the ON Appeal Denied Letter. We note that OLINVYK studies used an NSAID as rescue. Our studies clearly demonstrated that physicians were able to manage the vast majority of IV tramadol patients with NSAID rescue and that IV tramadol used concurrently with non-opioids in a multimodal approach was safe and effective. Importantly, multimodal therapy has now become the standard of care. Further, IV tramadol represents an opportunity to improve the safety of postoperative multimodal analgesia. Our data show that, consistent with years of experience in the E.U., a combination therapy of an opioid

(IV tramadol) with a non-opioid (when needed) does provide adequate pain relief. Adopting this approach will reduce the use of intravenous Schedule II opioids in the U.S., just as they have been in the E.U., as we discuss in the FDRR.

In terms of the path forward outlined in the Appeal Denied Letter, it first suggests that:

> 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.

We note that our NDA already demonstrated adequate safety and effectiveness with no findings that would lead to an unusual risk of opioid stacking in a real-world setting. Alternatively, the Appeal Denied Letter suggests that:

> … 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.

The original NDA includes a literature review as well as a Vigibase report (Module 5.3.6) which did not demonstrate any unusual safety signals nor any unusual risk of opioid stacking in the decades of OUS experience with parenteral tramadol.

In summary, we are disappointed that the ON Appeal Denied Letter merely reiterated DAAP's prior comments and failed to provide an independent assessment of the data. ON did not provide thoughtful comments on issues that DAAP was unable to answer. The Sponsor is hopeful that OND will provide a careful review of the FDRR.

E. Sponsor's Perspective and Rationale

The core clinical issue that prevented approval in the two CRLs is that the Division concludes that IV tramadol's onset of analgesia, delayed according to the two-stopwatch method, would lead to a hypothetical safety concern of opioid stacking. The Sponsor believes that DAAP did not consider the totality of the data available for IV tramadol regarding onset of analgesia and instead focused on that one issue to the exclusion of the positive attributes of IV tramadol. Avenue requests that OND reconsider the CRL action in the context of the totality of data, which would also include considerations of the true risk of theoretical opioid stacking in a medically supervised setting and how that risk is managed by labeling for other opioid products. In this context, we highlight the recent precedents set by the approval of ANJESO regarding delayed onset and the approval of OLINVYK regarding the risk of opioid stacking. Further, the benefit-risk assessment of making IV tramadol available to reduce the reliance on Schedule II opioids in light of the OUS experience should not be overlooked and Avenue requests OND consider the public health benefit of allowing access to an opioid with less abuse potential for post-operative pain in the ongoing opioid crisis in the U.S.[21] The benefit of approving IV tramadol outweighs

[21] Ahmad F.B., Rossen L.M., & Sutton P. *Provisional drug overdose death counts*. National Center for Health

the hypothetical safety concern of opioid stacking and it should be approved with appropriate labeling.

1. IV tramadol demonstrated adequate onset and clinically meaningful pain relief at early timepoints and throughout the trials in the NDA

The Division communicated to the Sponsor late in the development of IV tramadol in a post meeting note to the pre-NDA meeting that it expects that the onset of an IV analgesic should be less than an hour. This came as somewhat of a surprise as this expectation does not appear in published FDA guidance or policy on acute pain drugs and to the Applicant's knowledge, does not appear in any practice guidelines for pain control.

The onset of analgesia is conventionally measured with the two-stopwatch method. Patients are instructed to press the first stopwatch to record when they first perceive pain relief and the second stopwatch to record time to meaningful pain relief. Onset of analgesia is time to meaningful pain relief when confirmed by a preceding perceptible pain relief. The Division has previously indicated that an IV analgesic must have an onset of action within an hour to "meet prescriber expectation,"[22] however a specific threshold seems arbitrary and to our knowledge is not driven by any actual data. Like any methodology, the interpretation of the results should be guided by the limitations of the method, and the other datapoints that are informative. As an example, in Avenue's studies, patients were not actively reminded to stop the stopwatch, and if the patient was asleep, they were not awakened to record the endpoint. Importantly, if the patient took a rescue, they were counted as not having achieved meaningful pain relief. As such, the statement in CRL 2 that "meaningful pain relief was delayed (accounting for the use of rescue medication, e.g., ibuprofen), and some patients never achieved pain relief"[23] refers to the two-stopwatch data, and specifically to the fact that that some patients did not press the second stopwatch or took a dose of ibuprofen before they pressed the second stopwatch.

This is very different from the collection of pain intensity scores that serve as the basis of the primary and key secondary endpoints of the studies, as pain scores are obtained more rigorously (e.g., the patient is asked to rate their pain at scheduled times and is awoken if they are asleep to provide that score). Examining Pain Intensity differences (PID) and other endpoints such as time to first rescue and patient global assessment (PGA) can help inform how the onset based on the two-stopwatch method translates clinically and if there is clinically meaningful pain relief at early timepoints.

The Sponsor believes that there is other evidence throughout the NDA that IV tramadol provides clinically meaningful pain relief at early timepoints consistent with its pharmacology (i.e. parent drug tramadol exerting an effect via the monoamine pathway and at the mu receptor

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Statistics (last reviewed July 14, 2021) https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm (last accessed July 22, 2021).

[22] Complete Response Letter for Meloxicam from Sharon Hertz, Division of Anesthesia, Analgesia, and Addiction Products Director, Office of Drug Evaluation to Diane P. Myers, Regulatory and Quality Senior Vice President, Recro Pharma Inc., 1 (March 22, 2019).

[23] CRL 2 at 1.

prior to conversion to the more potent M1 metabolite). This is evidenced by endpoints such as time to first use of rescue medicine, PID, and PGA, all of which show statistically significant and clinically meaningful benefit over placebo, including at timepoints as early as 30 minutes in one study. To understand why the two-stopwatch metric should be considered in the context of other endpoints, it is useful to consider ANJESO (meloxicam), which is an intravenous analgesic labeled with a limitation of use that states: "Because of delayed onset of analgesia, ANJESO alone is not recommended for use when rapid onset of analgesia is required."[24] In the case of ANJESO, the onset of analgesia by the two-stopwatch method did not account for the use of rescue oxycodone (e.g. patients were still allowed to stop the second stopwatch after they took rescue oxycodone). The onset of analgesia by this method was not different from placebo and ANJESO also had a short time to first rescue that is not different from placebo; the PGA 24 was not different from placebo; and a SPID6 (the sum of pain intensity differences from 0 to 6) was not different from placebo in one of the two efficacy trials. In the ANJESO bunionectomy study, ANJESO and placebo had a similar median time to meaningful pain relief as measured by the two-stopwatch test (~2 versus ~3 hours) as well as similar median time to first rescue of ~2 hours .[25] In the ANJESO abdominoplasty study ANJESO and placebo had similar time to meaningful pain relief (~3 hours in both groups), and similar time to first rescue (2.6 versus 2.5 hours).[26] SPID6, indicative of pain relief at early timepoints, was not different from placebo. In addition, patients in the ANJESO arm did not rate their treatment as better than placebo at 24 hours (PGA 24) in the ANJESO studies reflecting the delay to the onset of therapeutic effect. Collectively, the delayed onset of ANJESO as measured by the two-stopwatch method was corroborated by a short time to first rescue, and the absence of statistically significant differences in PGA24 and SPID6. These data consistently and clearly indicate that ANJESO did not provide clinically meaningful pain relief at early timepoints compared to placebo.

However, this was not the case for IV tramadol. The two-stopwatch metric of time to meaningful pain relief was done using the most conservative approach. In Study AVE-901-102, time to meaningful pain relief was 5 hours in the IV tramadol group while the placebo group never reached meaningful pain relief using the two-stopwatch test ($p<0.01$). Time to first rescue was 308 minutes (5.1 hours) in the IV tramadol group versus 148 minutes (2.5 hours) in the placebo group ($p<0.001$). In the PID, IV tramadol produced a statistically significant decrease in PID versus placebo starting at 30 minutes (the first measured time point) and continued to be significantly different through early timepoints (Figure 6). PGA at 24 hours, a key secondary endpoint, was also better than placebo ($p<0.001$). In Study AVE-901-103, time to meaningful pain relief was 1.8 hours in the IV tramadol group versus 2.4 hours in the placebo group (not statistically significant). However, time to first rescue was 22.9 hours in the IV tramadol group versus 1.7 hours in the placebo group ($P<0.001$) and patients in the IV tramadol arm had greater pain relief at 30 minutes than placebo with results showing statistical significance at 3 hours (Figure 7). Post-hoc analysis indicated that with IV tramadol, SPID6, as well as SPID2, 3, 4, and 5, were better than placebo (Table 8). IV tramadol was again better than placebo on PGA at 24

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[24] ANJESO (meloxicam), Prescribing Information, NDA 210583, Section 1: Indications and Usage, 3 (Feb. 2020) https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210583s000lbl.pdf.

[25] ANJESO (meloxicam), Clinical Review(s), NDA 210583, 135-140 (Feb. 20, 2020) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000MedR.pdf.

[26] *Id*. at 105-114.

hours ($p<0.001$). In summary, despite the Division's concern regarding the time of onset on the two-stopwatch metric, the other endpoints related to pain relief at early timepoints and the totality of the data in the NDA indicated that IV tramadol has a clinically adequate onset of action and provides clinically meaningful analgesia at early timepoints and throughout the trials. This is consistent with known pharmacology of tramadol where the parent drug tramadol would have an initial effect and contribute to pain relief.

2. 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

The data in the NDA also demonstrated that clinicians were able to successfully manage all but a handful of patients on IV tramadol with a non-opioid rescue medication. In the two Phase 3 efficacy studies, patients could withdraw from the study and receive an opioid, but only 6 out of 280 patients (2%) on IV tramadol withdrew due to inadequate analgesia. In other words, in 98% of the patients, there was no use of additional opioids. Of the 6 patients who received other opioids after discontinuing IV tramadol, none had serious or severe adverse events reported during the follow-up period.

Further, IV morphine 4 mg was included as an active comparator to IV tramadol in Study AVE-901-103 to compare the safety profiles of the two drugs. Although the study was not powered to directly compare the efficacy of IV tramadol to IV morphine, the drugs were similar on the primary and key secondary efficacy endpoints (Figure 1, Figure 4). We note that approximately 40% of IV morphine patients and approximately 50% of IV tramadol patients requested rescue (Table 11). The fact that IV tramadol produced similar pain relief as IV morphine 4 mg over the 48-hour treatment period is significant because it demonstrates that IV tramadol has the potential of providing patients with effective pain relief with lower abuse liability than Schedule II opioids. As discussed below, in the approval of OLINVYK, the Division approved a Schedule II opioid despite concluding that "there is no evidence for a safety advantage," and that "morphine demonstrated a greater reduction in pain intensity"[27] than the approved doses for OLINVYK. Further, OLINVYK has a daily dose cap which can easily lead to opioid stacking.

The Phase 3 open-label safety study (Study AVE-901-104) further highlights the utility of IV tramadol in the "real-world" setting of multimodal analgesia in the treatment of post-operative acute pain. A total of 251 patients had a variety of painful surgeries (such as total joint replacement procedures) and received post-surgical IV tramadol in conjunction with non-opioid analgesics. Patients could exit the study at any time to receive another opioid if they needed more analgesia. However, not a single patient did. At the End of Treatment, 95% of the patients rated their study treatment as good, very good, or excellent for controlling pain (Figure 2). This data further supports the safety and effectiveness of IV tramadol in the setting of multi-modal analgesia and provides no evidence of opioid "stacking." Notably, the data from the safety study is consistent with clinical experience from decades of parenteral tramadol use in Europe and

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[27] OLINVYK (oliceridine), Multi-Discipline Review, NDA 210730, 7, 31 (Aug. 7, 2020) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210730Orig1s000MultidisciplineR.pdf.

other regions where its use along with non-opioid analgesics reduces the need for strong opioids.[28]

The data in the NDA demonstrated that despite the hypothetical concern of the Division, IV tramadol's onset of action did not lead to opioid stacking, that its effectiveness is similar to Schedule II opioids in the post-operative setting, and that patients receiving IV tramadol concurrent with other non-opioid medicine following painful procedures did not require Schedule II opioids and are satisfied with their treatment.

3. 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

The Division's position that a nonopioid cannot bridge or augment the analgesia of an opioid and that a rescue for an opioid has to be another opioid was underscored by its statements in both the CRL 1 and the CRL 2. This position seems central to connecting IV tramadol's onset to the concern of opioid stacking. The Division stated in the CRL 1 that "[i]f 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 [and] would result in opioid 'stacking' . . . ."[29] The Division stated in CRL 2 that "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids."[30] The Division also stated that "[n]on-opioid treatment options should be considered as first line therapy for pain management unless it is clear that these options will be inadequate," and that "[i]t would not be clinically feasible if an opioid analgesic requires a nonopioid product to augment the analgesia" in the Type A meeting.[31]

The Division's position on what is a feasible rescue for an opioid analgesic is contradicted by the data from our three Phase 3 studies in the NDA that clearly demonstrated that IV tramadol with non-opioid analgesics provided effective pain relief without another opioid for post-operative pain. In the efficacy studies, if a rescue medication is needed at all, ibuprofen is sufficient rescue for IV tramadol in most patients. In the safety study (Study AVE-901-104), IV tramadol in concurrent use with non-opioid analgesics provided effective pain relief without another opioid and patients' high level of satisfaction was captured on PGA.

Additionally, the FDA approved Toradol (ketorolac tromethamine) IV, an NSAID, based on a post-operative study that used it as rescue for morphine.[32] FDA has approved multiple non-opioid products labeled as adjuncts for opioid analgesics. Examples include CALDOLOR (ibuprofen) for intravenous use, which is indicated for use in adults and pediatric patients six months and older for the "[m]anagement of mild to moderate pain and the management of

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28 *Supra* note 11.

29 CRL 1 at 1.

30 CRL 2 at 2.

31 Type A meeting minutes at 7.

32 TORADOL (ketorolac), Prescribing Information, NDA 19645, Clinical Studies (Suppl. 19, Mar. 26, 2013) https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019645s019lbl.pdf.

moderate to severe pain as an adjunct to opioid analgesics,"[33] and OFIRMEV (acetaminophen) injection, which is indicated for the "[m]anagement of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older."[34]

The Division's position is also contradicted by established role of multimodal analgesia in clinical practice in post-operative pain.[35] In this setting, the clinician anticipates the patient's pain level and prescribes an opioid in a multimodal analgesic approach, if warranted. Multimodal analgesic approach including "combination therapy of an opioid with a non-opioid"[36] is well established in the management of acute pain and is recommended by taskforce convened by the U.S. Department of Health and Human Services and other government agencies. The taskforce recommended: "To avoid the side effects associated with prescription opioids (e.g., nausea, vomiting, constipation, sedation, OUD), it is important to exploit the benefits of multimodal, non-opioid approaches in acute pain management in conjunction with possible opioid therapy."[37]

4. 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

The labeling proposed for IV tramadol highlights the experience in the clinical studies where, if a rescue medication was used at all, an NSAID was sufficient. Nevertheless, it is true that once approved, another opioid may be prescribed following IV tramadol because concomitant use of opioids is known to occur currently with all IV opioid analgesics and use of multiple opioids sequentially to achieve pain control in the management of post-operative acute pain is not unusual in the hospital setting.[38] This was discussed extensively by multiple clinical experts in the first post-action Type A meeting and the second post-action Type A meeting. The use of multiple opioids is recognized to be safe in a medically supervised setting such as hospitals and ambulatory surgical centers because these facilities must meet certain requirements for performance and monitoring following IV opioid therapy with pre-specified monitoring criteria for patients receiving IV opioids.[39] In this setting, patients are closely monitored by trained clinicians for signs and symptoms of opioid related adverse effects including parameters such as pain levels, respiratory rate, oxygen saturation, and cognition. Healthcare professionals experienced in pain management administer opioids as needed in this setting. The clinicians in

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33 CALDOLOR (ibuprofen), Prescribing Information, NDA 22348, Section 1: Indications and Usage, 3 (Suppl. 18, Apr. 28, 2021) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022348s018lbl.pdf.

34 OFIRMEV (acetaminophen), Prescribing Information, NDA 22450, Section 1: Indications and Usage, 3 (Suppl. 11, Apr. 6, 2018) https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022450s011lbl.pdf.

35 See discussion in NDA 213231 Module 2.5.

36 CRL 2 at 2.

37 Department of Health & Human Services, Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations, 21 (May 2019).

38 An example of a Post-Anesthesia Care Unit (PACU) order sheet showing two different opioids being prescribed simultaneously was provided in Type A meeting.

39 *See* The Joint Commission, *Pain assessment and management standards for ambulatory care*, R3 Report, Issue 14, June 25, 2018, https://www.jointcommission.org/-/media/tjc/documents/standards/r3-reports/r3_14_pain_assess_mgmt_ahc_6_20_18_final.pdf.

this setting are able to ascertain the performance characteristics of the drug, including onset of action, duration, and tolerability profile, from the labeling such that the appropriate patient population can be selected. As such, any risks of concurrent use of opioids are effectively managed in an inpatient setting by experienced clinicians and close monitoring, and that includes the risks related to concurrent use of Schedule II opioids.

In the case of IV tramadol, the Division is concerned about the need for rescue medication following the first dose (e.g., the first two hours) because IV tramadol is administered as a standing dose (Hours 0, 2, 4, 8, etc.), not titrated to effect. The dosing regimen, developed in close collaboration with the Division, provides a predictable pharmacokinetic profile of both the parent compound tramadol and the key metabolite M1 (Study AVE-901-101). Due to the lack of first-pass metabolism, M1 levels increase more gradually with IV tramadol, and M1 C_{max} and AUC following IV tramadol are lower than oral tramadol. Therefore, the risk of opioid-related adverse events is limited even if another dose of short-acting opioid is required in a setting where patients are monitored.

In the IV morphine arm of the abdominoplasty study (Study AVE-901-103), approximately 40% of the patients required rescue versus approximately 50% in the IV tramadol arm. If the treating physician decides to use another opioid as rescue following morphine, the morphine patients also would be at risk for the additive effects of concomitant use of more than one opioid. There is no difference between patients on IV morphine asking for rescue versus patients on IV tramadol. In the second post-action Type A meeting, the Sponsor asked the Division what is different about the risk of opioid stacking in the ~50% of tramadol patients and the ~40% of morphine patients who requested rescue in Study AVE-901-103 and the Division could not provide an answer in the meeting or meeting minutes.

The case of OLINVYK, discussed as a precedent for IV tramadol below, further illustrates that all opioids carry the risk of additive effects of concomitant use of more than one opioid. Class labeling already exists to warn prescribers of the risk of using multiple opioids concurrently. The labeling for oral tramadol (mainly used in the outpatient setting) and all approved opioids informs prescribers of the risk of "concomitant use" with other CNS depressants (e.g., . . . other opioids . . .) under WARNINGs AND PRECAUTIONS. Specifically, the labeling for oral tramadol states that "[p]rofound sedation, respiratory depression, coma, and death may result from the concomitant use of ULTRAM with benzodiazepines or other CNS depressants (e.g., . . . other opioids , alcohol)" (emphasis added).[40] Thus, FDA has already determined that the prescription drug labeling is capable and appropriate to inform healthcare providers of the risk of what has been referred to as "stacking" for tramadol. In fact, labeling is used to routinely manage and warn of this risk for all approved opioids, IV and oral. Avenue expects similar information to be a component of the labeling for IV tramadol, as reflected in the proposed draft labeling.

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[40] ULTRAM (tramadol hydrochloride), Prescribing Information, NDA 20281, Section 5.7: Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants, 13 (Suppl. 48, Mar. 4, 2021) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020281s048lbl.pdf.

5. The ANJESO approval set a precedent that labeling is sufficient to address delayed onset of an IV analgesic

The Division's refusal to approve IV tramadol due to the threshold clinical issue regarding onset (as measured by the two-stopwatch test), is unexpected and inconsistent with FDA's recent decision to approve IV meloxicam (ANJESO) in February 2020 despite having a clear case of delayed onset of analgesia. During the review of the ANJESO NDA, the Division initially expressed an arbitrary one-hour standard for onset of action for IV analgesics and cited it as one of the reasons it could not approve the drug. This expectation was reversed in an FDRR process as Dr. Thanh-Hai (Acting Office Director) found that "even if the onset of action is delayed, . . . that would not preclude the use of Anjeso as an IV analgesic. . . . [L]abeling can be developed to informer prescribers who could then formulate a regimen that would provide adequate analgesic coverage."[41] Thus, the one-hour onset is no longer a threshold approval issue. The approval of ANJESO sets a precedent that labeling can appropriately inform physicians about time to onset, and that when an intravenously administered analgesic actually has a delayed onset, that delay is not a bar to approval.

In the ANJESO clinical studies, fewer patients achieved time to meaningful pain relief than IV tramadol,[42] and the analysis of time to pain relief did not take rescue medication use into consideration,[43] meaning that patients were allowed to press the second stopwatch to achieve meaningful pain relief even after they took rescue oxycodone 5 mg. This contrasts with the IV tramadol studies where a patient taking a rescue prior to pressing the second stopwatch is counted as never achieving meaningful pain relief.

Opioid rescue clearly contributed to meaningful pain relief in the ANJESO studies and the reviewer concluded that "the contribution of Anjeso to the outcome of meaningful analgesia is uncertain."[44] Overall, ANJESO had delayed onset with less than 50% of patients achieving meaningful pain relief (even with the help of opioid rescue) in both Phase 3 studies. As previously discussed, other endpoints related to pain relief corroborated ANJESO's delayed onset. For example, the ANJESO labeling states that because of delayed onset of analgesia, "ANJESO alone is not recommended for use when rapid onset of analgesia is required" and includes a clear description of median time to first rescue analgesic.[45] The Sponsor understands

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41 ANJESO (meloxicam), Summary Basis of Approval, NDA 210583, 7 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000SumR.pdf.

42 ANJESO (meloxicam), Statistical Review(s), NDA 210583, 14, 21 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000StatR.pdf. In the ANJESO trials, only 46% of patients achieved time to meaningful pain relief in the Phase 3 bunionectomy study and 29% of patients achieved time to meaningful pain relief in the Phase 3 abdominoplasty study after patients took oxycodone 5 mg rescue. In contrast, 50% and 66% of the patients in the IV tramadol bunionectomy and abdominoplasty study respectively reported meaningful pain relief without the contribution of rescue medicine.

43 ANJESO (meloxicam), Clinical Review(s), NDA 210583, 137 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000MedR.pdf.

44 *Id*. at 18.

45 ANJESO (meloxicam), Prescribing Information, NDA 210583, Section 1: Indications and Usage, 3 (Feb. 2020) https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210583s000lbl.pdf.

that ANJESO is an NSAID while IV tramadol is an opioid but this precedent is relevant to IV tramadol because IV tramadol treatment did not lead to the use of multiple opioids concurrently in the studies in the NDA, opioid stacking has not been a concern in OUS experience, and even when it does occur the use of multiple opioids is recognized as safe in a medically supervised setting.

6. The 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.

Another relevant precedent is the recent approval of OLINVYK, an intravenous Schedule II pure mu opioid agonist administered via patient-controlled analgesia (PCA) with onset between 2 and 5 minutes. OLINVYK carries the potential risk of opioid stacking in three different ways. First, the labeling states that PCA carries the risk of dose stacking of opioids by stating that "PCA administration has resulted in adverse outcomes and episodes of respiratory depression."[46] Second, 20 % of patients required rescue when they take recommended dose according to the labeling. These patients, like the patients administered IV tramadol, are subject to the risk of opioid stacking if the treating physician chooses another opioid as rescue. Third, the labeling states that"[i]f patients reach a 27 mg cumulative daily dose and analgesia is still required, an alternative analgesic regimen should be administered until OLINVYK can be resumed the next day. Alternative analgesia may include multi-modal therapies."[47] OLINVYK's daily cap was based on FDA's concern for QT prolongation but it does not change the fact the daily cap exposes patients to the risk of opioid stacking because patients will still require opioid-level analgesia once the cap is reached. The median times for patients to reach the daily cap ranged from 13.6 to 15.8 hours in one trial and 14.1 to 19.4 hours in another trial.[48] Therefore, a substantial portion of patients on OLINVYK will require additional opioid-level analgesia with a different opioid when they reach the daily cap with approximately 10 hours of the day left. The sequential use of OLINVYK and another opioid puts patients at clear risk for opioid stacking. It is also puzzling that the Division would recommend multi-modal therapies for patients who have reached the cap on OLINVYK because our CRL 2 stated "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids." The OLINVK labeling seems to indicate that the Division does not discourage the use of concomitant Schedule II opioid therapies, which is inconsistent with its approach to Avenue's NDA.

Remarkably, the FDA approved OLINVYK despite the potential risk of opioid stacking even when the reviewers concluded that "Oliceridine has a benefit-risk profile similar to that of other opioids . . . there is no evidence for a safety advantage of oliceridine over other opioids. . . . It must also be noted that morphine demonstrated a greater reduction in pain intensity than all three dosing regimens of oliceridine that were tested in the studies."[49] Its refusal to approve IV

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46 OLINVYK (oliceridine), Prescribing Information, NDA 210703, Section 5.15 Patient-Controlled Analgesia (PCA), 11 (Aug. 7, 2020) https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210730s000lbl.pdf.

47 *Id.* at Section 2.2: Dosing Information, 5.

48 OLINVYK (oliceridine), Multi-Discipline Review, NDA 210703, 39 (Aug. 7, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210730Orig1s000MultidisciplineR.pdf.

49 *Id.* at 7, 46.

tramadol again suggests a narrow focus on the two-stopwatch test showing that IV tramadol had a slower onset than morphine while discounting all the benefits of IV tramadol such as its lower abuse potential while providing similar pain relief to morphine on the primary and key secondary endpoints. The Sponsor notes that the slower onset of IV tramadol compared to IV morphine is expected based on their mechanisms of action and explains tramadol's lower abuse potential, a benefit of IV tramadol.

7. 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

In FDA's landmark draft guidance document entitled "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment," the Agency emphasized that

> because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others.[50]

The guidance also states that "[a]s part of the benefit-risk assessment for a particular drug and proposed indication, FDA considers the benefits and risks relative to other available therapies for the condition."[51] Tramadol was placed in Schedule IV in 2014 after both the FDA and the DEA conducted the mandatory 8-factor analysis. The Schedule IV reflects the scientific understanding that the abuse potential of tramadol is lower than Schedule II conventional opioids. This is supported by extensive preclinical, clinical, post-marketing studies conducted by academic institutions, sponsors, and government agencies as well as years of marketing experience by other sponsors. As mentioned in the NDA, the low abuse potential of IV tramadol was also confirmed by the recent report on tramadol by the WHO expert committee on drug dependence in 2018, which stated "parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalised since first-pass metabolism is avoided. Hence, the abuse of tramadol is much reduced through intravenous administration when compared to ingestion."[52] Recent epidemiology data presented in the NDA demonstrate that reports of abuse with tramadol are infrequent, both in absolute number and relative to other prescription opioids, and that abuse of tramadol via injection is uncommon relative to oral tramadol in both the U.S. and in countries where it is available (Module 5.3.6 Epi Abuse Summary Report).

The benefits of IV tramadol to the broader public health relative to available approved analgesic drugs is that clinicians and patients will be able to use an opioid with lower abuse

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50 FDA, Draft Guidance for Industry – Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework, 2 (June 2019).

51 *Id.* at 4.

52 World Health Organization, Critical Review Report: Tramadol; Expert Committee on Drug Dependence (Nov. 2018), https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf (last accessed Jul. 22, 2021).

potential in place of one with higher abuse potential in the post-operative setting. The experience outside the U.S. highlights this potential public health benefit. Parenteral tramadol has been widely available in over 70 countries for decades. As reported in the NDA (Module 5.3.6), its ex-U.S. safety profile is similar to oral tramadol with no special concerns regarding opioid stacking. It has been successfully used concurrently with non-opioid medicine to postpone or avoid the use of more abusable opioids. Their experience is also supported by the safety study (Study AVE-901-104) which demonstrated that IV tramadol can be used concomitantly with non-opioid analgesics in an effective and safe manner and help avoid exposing more abusable opioids in this patient population.

Clinicians in the US are currently limited in their choices of IV analgesics in the post-operative setting because only three pharmacological classes (acetaminophen, NSAIDs, and Schedule II opioids) are widely used. Post-operative opioid use is ubiquitous among patients who underwent common surgical procedures in the hospital setting.[53] 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.[54] However, intravenous Schedule II opioids are still used widely in the acute pain setting in the U.S. due to the lack of effective options, which is exacerbated in part because many patients have contraindications to one or more classes of non-opioid medications. The availability of IV tramadol would be a useful option for clinicians who wish to minimize their use of Schedule II opioids and for patients who would like to minimize their exposure to Schedule II opioids in a medically supervised setting.

Therefore, a properly labeled Schedule IV opioid analgesic option would benefit the public health by offering U.S. clinicians and patients a safe and effective therapeutic alternative to Schedule II opioids in the post-operative setting. IV tramadol, a less abusable opioid, used in a multimodal approach as practiced by clinicians outside the U.S. for decades and supported by the studies submitted in the NDA, can play an important role in protecting the public health by reducing the use of intravenous Schedule II opioids in light of the continuing opioid epidemic in the U.S. This broader public health and real advantage of avoiding the use of Schedule II opioids should be an important consideration in the risk-benefit analysis as opposed to a hypothetical concern that has been disproven by multiple data streams including our NDA, setting limitation and worldwide experience.

8. Summary

IV Tramadol meets the statutory standard for approval. The NDA includes substantial evidence of safety and effectiveness for its intended use through adequate and well-controlled investigations. IV Tramadol demonstrated a safety profile similar to oral tramadol and will have the effect described in the proposed labeling. The totality of the data in the NDA demonstrated that IV tramadol provided clinically meaningful pain relief with an adequate onset of analgesia.

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[53] Kessler, E. R., Shah, M., Gruschkus, S. K., & Raju, A. (2013). Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: Opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy*, *33*(4), 383–391. https://doi.org/10.1002/phar.1223.

[54] *Supra* note 9.

The Division's concern regarding the use of multiple opioids concurrently due to IV tramadol's onset of analgesia in the two CRLs is a hypothetical risk that was not encountered in the 3 large Phase 3 studies, not documented in the OUS experience, can be routinely managed in a medically supervised setting, and can be addressed with labeling, as exemplified by the labeling for ANJESO and OLINVYK. The broader public health consideration that IV tramadol would offer U.S. clinicians and patients a safe and effective Schedule IV intravenous option that can reduce the use of more abusable opioid analgesics in the post-operative setting (as parenteral tramadol has been used throughout the world) supports its benefit-risk profile and should be considered in the OND's decision.

II. Background

A. Oral Tramadol

Oral tramadol (ULTRAM) was approved in the U.S. in 1995 and is "is indicated in adults for the management of pain severe enough to require an opioid."[55] Tramadol is a centrally acting atypical opioid with two mechanisms of action including weak activation of the mu opioid receptor by the parent drug, more potent activation by its primary metabolite (M1), and inhibition of the reuptake of serotonin and norepinephrine. These two distinct mechanisms function serve to make tramadol an effective analgesic with a good tolerability profile.[56] Therefore, tramadol is generally considered a weak or atypical opioid and has been found to have a low risk of abuse compared to conventional (i.e., Schedule II) opioids such as morphine.[57]

Oral tramadol was placed in Schedule IV in 2014 after both the FDA and the DEA conducted its 8-factor analysis. Placing tramadol in Schedule IV and therefore designating it with less abuse liability than Schedule II and III opioids reflects the scientific understanding of the abuse potential of tramadol versus conventional opioids and is supported by extensive preclinical, clinical, post-marketing studies conducted by academic institutions, sponsors, and government agencies, as well as recent epidemiology data included in the NDA (Module 5.3.6 Epi Abuse Summary Report).

1. Managing the Risk of Respiratory Depression for Oral Tramadol

The labeling for oral tramadol (ULTRAM), as with class labeling for all opioids, recognizes that some patients may require additional pain relief and warns of the risk of opioid stacking. Oral tramadol contains a "Boxed Warning" indicating that among other things:

- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase.

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55 ULTRAM (tramadol hydrochloride), Prescribing Information, NDA 20281, Section 1: Indications and Usage, 4 (Suppl. 48, Mar. 4, 2021) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020281s048lbl.pdf.

56 Grond 2004.

57 WHO 2014, Grunenthal 2017, Schneider 2009.

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.[58]

Physicians are also instructed that "[p]rofound sedation, respiratory depression, coma, and death may result from the concomitant use of ULTRAM with benzodiazepines or other CNS depressants (e.g., . . . other opioids, alcohol)" (emphasis added).[59] When transitioning a patient from ULTRAM to extended-release formulations of tramadol, the physician is informed that "[t]he relative bioavailability of ULTRAM compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression."[60] Thus, the physician is informed that the risk of stacking (i.e., respiratory depression) can occur when a patient is transitioned from the immediate-release formulation of tramadol to an extended-release formulation.

In summary, FDA has already determined that labeling is the mechanism to be used to inform healthcare providers of the risk of stacking for tramadol. As will be discussed later in this FDRR, labeling is used to warn of the risk of stacking for all approved opioids, IV and oral. Avenue expects similar information to be a component of the labeling for IV tramadol, as reflected in the proposed draft labeling.

2. Summary

Obviously, when prescribing oral tramadol—or any oral opioid for that matter—for use in an out-patient setting, it is difficult for a physician to "monitor closely, especially during initiation or following a dose increase" for signs of respiratory depression, or to "follow patients for signs and symptoms of respiratory depression and sedation," and to "monitor regularly" for signs of abuse. And yet in the case of oral tramadol and other opioids intended for home use, FDA has accepted labeling as the appropriate tool to manage these risks. IV tramadol will have similar labeling instructions. Importantly however, IV tramadol will be used only in a medically supervised health care setting where patients are closely monitored by clinicians experienced in post-operative pain management. In this setting, healthcare professionals experienced in post-operative pain management, not patients, administer opioids, providing another layer of safety. Therefore, it can be expected that the use of IV tramadol in a medically supervised setting and not dispensed directly to patients would carry less risk related to opioid stacking than oral tramadol.

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58 ULTRAM (tramadol hydrochloride), Prescribing Information, NDA 20281, Boxed Warning, 1 (Suppl. 48, Mar. 4, 2021) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020281s048lbl.pdf.

59 *Id.* at Section 5.7: Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants, 13.

60 *Id.* at Section 2.3: Initial Dosage, 6.

III. Development of IV tramadol

A. Pharmacokinetics of IV tramadol

As a 505(b)(2) NDA, Avenue developed IV tramadol in a manner that builds upon the documented safety profile of oral tramadol. The IV dosing regimen used in the Phase 3 studies (50 mg given at Hours 0, 2, 4, and every 4 hours thereafter) was discussed in detail with the Division and provides a predictable and similar exposure to the approved oral tramadol dosage (100 mg Q6H) based on C_{max} and AUC at steady state. As demonstrated in Study AVE-901-101, a Phase 1 pharmacokinetics study, IV tramadol provides a more rapid increase in tramadol concentrations but lower exposure to M1 and a slower onset of exposure to M1 due to the lack of first pass metabolism.

Table 1 describes the key pharmacokinetic parameters for oral tramadol 100 mg and IV tramadol 50 mg over 48 hours from Study AVE-901-101. M1 C_{max} from IV tramadol is 30% lower than from oral tramadol and M1 AUC from IV tramadol is 20% lower than from oral tramadol.

Table 1: Plasma Pharmacokinetic Parameters of IV and Oral Tramadol and M1 Over 48 hours

	Intravenous		Oral	
	Tramadol	**M1**	**Tramadol**	**M1**
Parameter	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C_{max} (ng/mL)	736 ±152	96.6 ±24.5	701±178	146±37.4
AUC_{0-48} (h•ng/mL)	20540 ±4906	3427 ±889.9	19140±5172	4349±1139

Source: Study AVE-901-101 CSR

Thus, IV tramadol would be expected to result in less abuse potential than oral tramadol due to the lower M1 levels shown above and further supports the view by WHO expert committee on drug dependence that "parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalised since first-pass metabolism is avoided. Hence, the abuse of tramadol is much reduced through intravenous administration when compared to ingestion."[61]

B. Efficacy of IV tramadol

Although the efficacy of IV tramadol is not in question, the efficacy results will be summarized here to help inform the risk-benefit analysis of IV tramadol. To support the approval of IV tramadol for the management of moderate to moderately severe pain in adults in a

[61] World Health Organization, Critical Review Report: Tramadol; Expert Committee on Drug Dependence (Nov. 2018), https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf (last accessed Jul. 22, 2021).

medically supervised healthcare setting, three Phase 3 studies were conducted: two efficacy studies in two distinct surgical pain models of pain and an open-label, "real world" safety study. The overall design of the studies was similar to those that supported other recent approvals of IV analgesics and the study protocols were reviewed by the Division. In the efficacy studies, patients were randomized to either IV tramadol (50 mg given at Hours 0, 2, 4, and every 4 hours thereafter) or placebo, and they could request an NSAID rescue for additional analgesia. Patients could also discontinue at any time due to inadequate analgesia. The safety study reflects how IV tramadol would be used in the real world. The study populations enrolled in the Phase 3 studies are consistent with the type of patients intended to be treated and are similar to those in pivotal clinical trials used to establish efficacy of other analgesic products. The design of the studies, the enrolled population, the surgical models, and statistical analysis method were agreed to by the Division. Further, the efficacy studies were done sequentially per Division's advice (Module 2.7.4 Section 1.4). The three Phase 3 studies enrolling a total of 1030 patients are:

- Study AVE-901-102 (Bunionectomy) was a Phase 3 double-blind study that assessed the effects of 2 doses of IV tramadol (25 mg and 50 mg) versus placebo in an orthopedic pain model. The use of two IV tramadol arms was intended to allow for selection of the optimal dose for further study based on both efficacy and safety outcomes. Study AVE-901-102 was completed prior to initiation of Study AVE-901-103, in agreement with DAAP's advice. A total of 409 patients were enrolled in the study and randomized 1:1:1 to IV tramadol 50 mg, IV tramadol 25 mg or placebo. The primary efficacy endpoint was the sum of pain intensity differences measured at baseline through 48 hours after the first dose (SPID48). The key secondary endpoints included the sum of pain intensity differences at baseline through 24 hours (SPID24), total consumption of rescue analgesia through 48 hours, and the PGA of efficacy at 24 and 48 hours. In this study, the only rescue medicine allowed was ibuprofen 400 mg up to Q4H. The results demonstrated a dose-response effect, with the IV tramadol 50 mg dosing regimen statistically and clinically superior to placebo with respect to the management of pain on the primary and key secondary endpoints. While the 25 mg demonstrated a decrease in pain intensity that was numerically greater than placebo, it was not statistically different from placebo. Thus the 50 mg regimen was carried forward to Study AVE-901-103 and to the open-label Study AVE-901-104.

- Study AVE-901-103 (Abdominoplasty) was a Phase 3 double-blind study that assessed the effects of IV tramadol 50 mg (versus placebo) as well as versus an active comparator, IV morphine 4 mg, in a soft tissue pain model. The use of the single IV tramadol 50 mg arm was intended to replicate the findings from Study AVE-901-102. Consistent with DAAP's recommendation, IV morphine 4 mg (administered at the same timepoints) was included as an active comparator to better understand IV tramadol's side effect profile in the context of an approved therapy. A total of 370 patients were enrolled in the study and randomized 3:3:2 to IV tramadol 50 mg, placebo and IV morphine 4 mg. The primary efficacy endpoint was SPID24. The key secondary endpoints included the PGA of efficacy at 24 and 48 hours, SPID48, and the total consumption of rescue analgesia through 24 hours. In this study, the only rescue medicine allowed was ibuprofen 400 mg up to Q4H. Although not powered for a formal comparison, the study allowed for an understanding of the comparability of IV tramadol to morphine. Study AVE-901-103 confirmed the efficacy of the IV

tramadol 50 mg dose and, in comparison to the active comparator arm (IV morphine 4 mg), demonstrated a favorable safety/tolerability profile and showed comparable efficacy on all primary and key secondary efficacy endpoints.

- Study AVE-901-104 (referred to as the Safety Study) was a Phase 3, single-arm, open-label safety study performed in patients undergoing a variety of elective bone and soft tissue surgeries (total knee replacement, total hip replacement, colon surgeries, hysterectomy, and breast augmentation, etc.) that are typically treated with Schedule II opioids. This study was designed to be a 'real-world' study in which patients were administered IV tramadol after surgery as deemed appropriate by their treating physician. Unlike the efficacy studies, patients did not have to have pain that meets certain threshold to receive treatment, reflecting real-world practice in post-operative setting. Physicians were allowed flexibility in terms of concomitant pain medications in a multimodal fashion, with the specific exclusion of use of other opioids. Study AVE-901-104 enrolled 251 patients and provided additional exposure and safety data including treatment up to 168 hours. The only effectiveness measurement in this study was PGA, an important outcome that reflects the patient's view of the treatment. In this "real-world" study where IV tramadol is used in combination with non-opioid medications in treating patients undergoing a variety of surgeries including total joint replacement surgeries, patients reported high levels of satisfaction. Patients could discontinue the study at any time due to inadequate analgesia and receive another opioid but not a single patient did.

The endpoints for the two pivotal efficacy studies were similar. The primary endpoint for assessment of efficacy for the bunionectomy model (Study AVE-901-102) was through 48-hours post first dose, whereas it was through 24-hours post-first dose for the abdominoplasty model (Study AVE-901-103) (Table 2). Both studies included a primary endpoint, 3 key secondary endpoints, and tertiary endpoints. Each study included pre-specified methods to control for multiplicity testing for the primary and key secondary endpoints. These endpoints have been frequently used in other registrational trials supporting approval of analgesics for acute pain.

Table 2: Comparison of Efficacy Endpoints Between the Two Phase 3 Efficacy Studies

	Study AVE-901-102	Study AVE-901-103
Primary Endpoint	The Sum of Pain Intensity Differences (SPID) measured at rest through 48 hours post first dose (**SPID48**)	The Sum of Pain Intensity Differences (SPID) measured at rest through 24 hours post first dose (**SPID24**)
Key Secondary Endpoints (ordered in sequence of hypothesis testing)	The Sum of Pain Intensity Differences (SPID) measured at rest through 24 hours post first dose (SPID24)	Patient Global Assessment of efficacy at 24 hours post first dose
	Total consumption of rescue (supplemental) analgesia through 48 hours post first dose.	The Sum of Pain Intensity Differences (SPID) measured at rest through 48 hours post first dose (SPID48)
	Patient Global Assessment of efficacy at 24 and 48 hours	Total consumption of rescue (supplemental) analgesia through 24 hours post dosing
Tertiary Endpoints	Time-specific pain intensity profile over time.	Time-specific pain intensity profile over time
	Clock time (in minutes) to first use of rescue medication from the time of first dose of study medication.	Time (in minutes) to first rescue analgesia from the time of first dose of study medication.
	Number of patients who required no rescue analgesia from T0-T48.	Number (percent) of patients who require no rescue analgesia from T0- T24 and T0-T48.
	The rate of consumption of rescue analgesia.	Rate of consumption of rescue analgesia.
	Time (in minutes) to meaningful pain relief after first dose. Time (in minutes) to confirmed perceptible pain relief after first dose.	Time (in minutes) to meaningful pain relief after first dose. Time (in minutes) to confirmed perceptible pain relief after first dose.
		Total consumption of rescue (supplemental) analgesia through 48 hours post dosing.
		Patient Global Assessment of efficacy at 48 hours post first dose

1. Primary Efficacy Endpoint: SPID24 and SPID48

Table 3 provides a summary of the comparison of the SPID48 and SPID24 primary efficacy endpoints between the studies for the IV tramadol 50 mg and placebo arms for the two efficacy Phase 3 studies. Both studies demonstrated that IV tramadol 50 mg provided statistically significant and clinically meaningful improvement over the placebo arm with respect to SPID48 and SPID24. In addition:

- Study AVE-901-102 (bunionectomy) demonstrated a statistically significant linear dose-response across the treatment groups placebo-Tramadol 25 mg-Tramadol 50 mg for both these endpoints (see Module 2.7.3 section 3.2).

- Study AVE-901-103 (abdominoplasty) demonstrated similar clinically meaningful and statistically significant benefit for tramadol 50 mg and morphine (over placebo) for both of these endpoints. The point estimates for SPID48 and SPID24 were remarkably similar between tramadol 50 mg and morphine (Figure 1; Module 2.7.3 section 3.2).

Table 3: Primary Efficacy Endpoints: SPID24 and SPID48 LS Mean[1] (SE) Comparisons between IV tramadol 50 mg vs Placebo by Study (Study AVE-901-102 and AVE-901-103)

Study	SPID Endpoints	Placebo LS mean (SE)	Tramadol 50 mg LS mean (SE)	Difference in LS mean (SE)	P-value for treatment comparison vs Placebo
AVE-901-102 Bunionectomy	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**
AVE-901-103 Abdominoplasty	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**

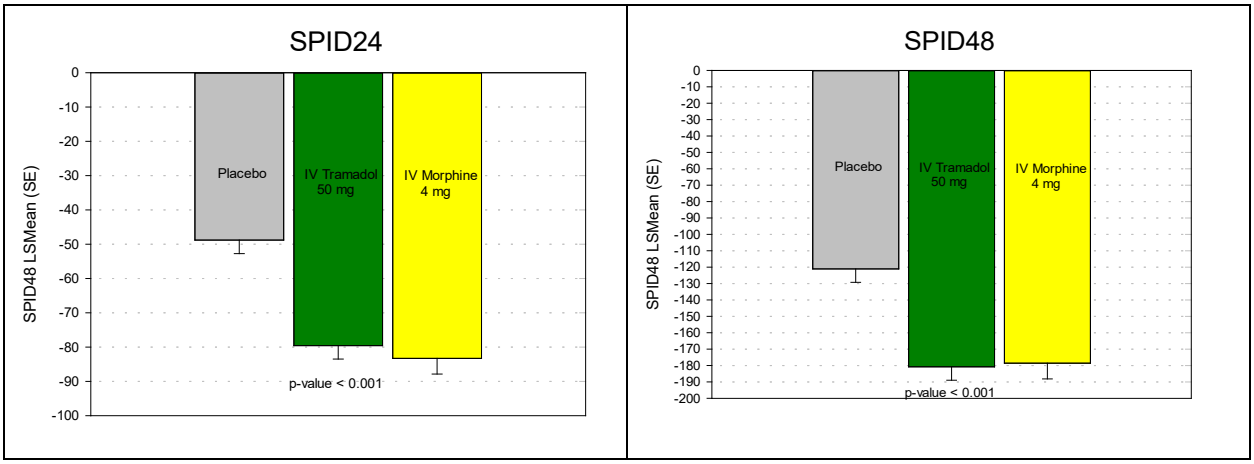
[1] LS mean, LS mean difference (treatment – placebo), p-values were the combined results obtained from an analysis of the multiply imputed datasets using an analysis of covariance model with treatment as the main effect, pooled study center and baseline Numerical Pain Rating Scale score as covariates.

Notes: SPID was the sum of pain intensity difference from baseline (PID) using the standard trapezoidal rule. As higher pain scores indicate worse pain, a negative PID indicates less pain (improvement from baseline). Thus, SPID scores are expected to be negative if a patient's pain decreases over time, with the lower SPID values indicating greater reduction in pain intensity. Pre-rescue Numerical Pain Rating Scale (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. The findings in this table are a result of the combination of outcomes from the analysis of the 100 imputed datasets.

Source: Study AVE-901-102 Table 14.2.1.1 and 14.2.1.2, and Study AVE-901-103 Table 14.2.1.1 and 14.2.1.2

Figure 1 provides the LSMean (SE) SPID24 and SPID48 values for the 3 treatment groups (placebo, IV tramadol 50, and morphine) in Study AVE-901-103.

Figure 1: LSMean (SE) SPID24 and SPID48 Comparisons across Treatment Groups (FAS Population) (Study AVE-901-103)



Source: Study AVE-901-103 CSR Table 14.2.1.1 and 14.2.1.2

2. Secondary and Other Efficacy Endpoints

Table 4 provides a summary of the comparison of the key secondary efficacy outcomes including use of rescue medication and PGA at 24 and 48 hours for the IV tramadol 50 mg and placebo arms for the two pivotal Phase 3 efficacy studies. The statistical analysis corrected for multiplicity. In both studies, IV tramadol 50 mg provided statistically significant and clinically meaningful improvement over the placebo arm with respect to each key secondary efficacy endpoint. Thus, both studies met all primary and key secondary efficacy endpoint expectations under the hypothesis that tramadol provides better pain relief than placebo.[62]

[62] Avenue is aware that CRL 1 states: "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" (CRL 1 at 1). Although the Division has not provided Avenue with a rationale for why it believes that Study AVE-901-102 did not statistical significance for its secondary endpoints, Avenue believes that both pivotal efficacy studies showed statistical significance on the primary and secondary endpoints.

Table 4: Key Secondary Efficacy Endpoint Comparisons between IV tramadol 50 mg vs Placebo by Study (Study AVE-901-102 and AVE-901-103)

Study	Endpoints	Statistics	Placebo	Tramadol 50 mg	Difference in LS mean (SE)	P-value for treatment comparison
AVE-901-102	48-Hour Total Rescue Used (mg)	Median	1200	800	N/A	**0.002**[1]
	PGA (24 Hour)	LS mean (SE)	1.5 (0.11)	2.3 (0.10)	0.8 (0.14)	**<0.001**[2]
	PGA (48 Hour)	LS mean (SE)	1.8 (0.11)	2.6 (0.11)	0.8 (0.15)	**<0.001**[2]
AVE-901-103	PGA (24 Hour)	LS mean (SE)	2.2 (0.11)	3.0 (0.11)	0.9 (0.13)	**<0.001**[2]
	PGA (48 Hour)	LS mean (SE)	2.4 (0.11)	3.2 (0.11)	0.8 (0.13)	**<0.001**[2]
	24-Hour Total Rescue Used (mg)	Median	400	400	N/A	**<0.001**[1]

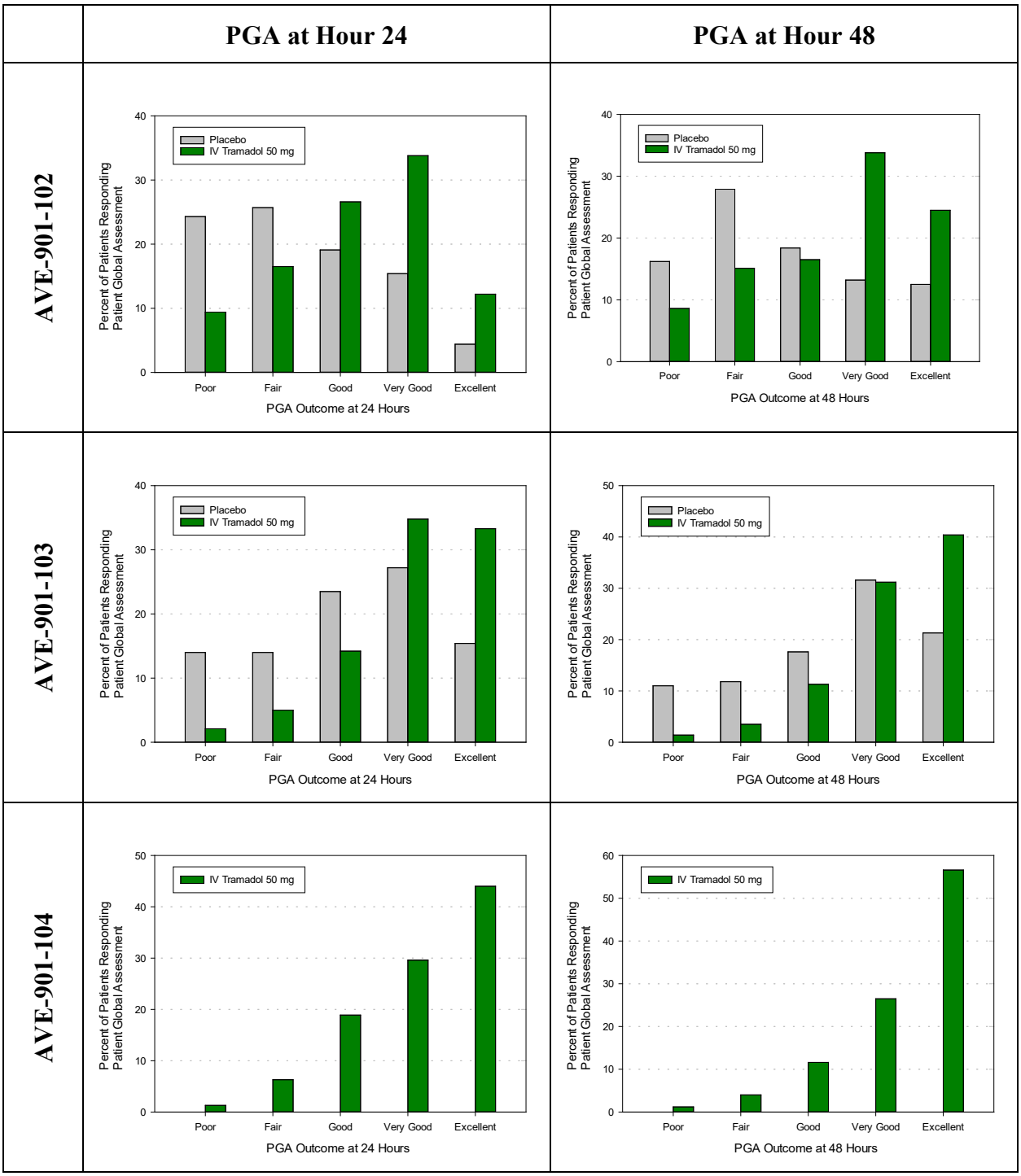
[1] Rank sum mean was obtained from Wilcoxon rank sum test.

[2] LS mean, LS mean difference (tramadol – placebo and p-values were obtained from an ANCOVA model with treatment as the main effect, study center, baseline body mass index for Study AVE-901-103 (<30 kg/m^2 versus ≥30 kg/m^2), and baseline Numerical Pain Rating Scale as covariates.

Source: Study AVE-901-102 and Study AVE-901-103 CSR Table 14.2.5. and 14.2.6

In the pivotal controlled studies, the PGA at both Hour 24 and Hour 48 demonstrated statistically significantly better effectiveness of pain control for IV tramadol 50 mg over placebo. Study AVE-901-104 (open-label), designed to assess how IV tramadol fits into the multimodal analgesic approach in the real world, corroborated these findings. Patients' pain following a variety of painful surgeries was successfully managed with IV tramadol in conjunction with non-opioid medications such as NSAIDs and acetaminophen, and with no early discontinuation due to inadequate analgesia. Patients could discontinue the study at any time to receive another opioid but not a single patient out of 251 did. Approximately 95% of patients in the study rated their treatment as good, very good, or excellent. Figure 2 presents percent of patients reporting poor, fair, good, very good, and excellent effectiveness in controlling pain, as reported by the patients themselves in the PGA patient reported outcome in the three Phase 3 studies. In Study AVE-901-103, morphine also demonstrated statistically significantly better effectiveness of pain control than placebo on PGA 24. On this measure, IV tramadol and IV morphine had similar results.

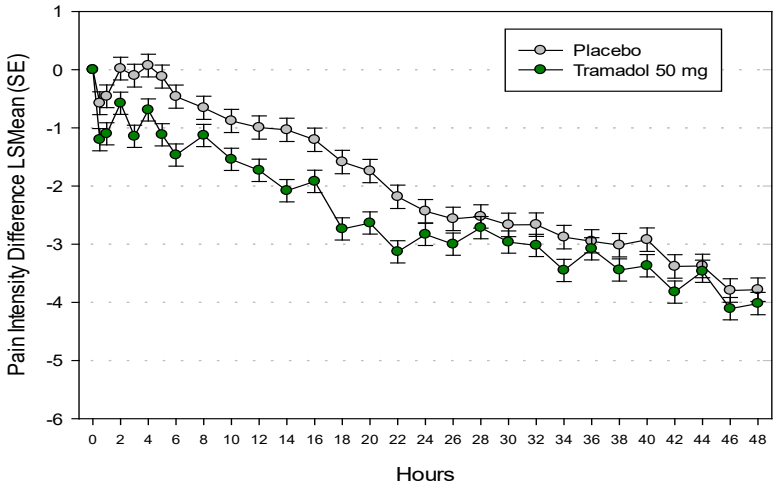
Figure 2: Patient Global Assessment of Treatment for Phase 3 Studies (FAS Populations) (Studies AVE-901-102, AVE-901-103, AVE-901-104)



Source: Study AVE-901-102 Table 14.2.6, Study AVE-901-103 CSR Table 14.2.6, Study AVE-901-103 Table 14.2.6, Study AVE-901-104 Table 14.2

Figure 3 provides the LSMean (SE) PID values for IV tramadol 50 mg and for placebo from the bunionectomy study, Study AVE-901-102. These data show immediate separation between the treatment groups at the first time point (Hour 0.5), with continued differences throughout the dosing regimen which is what would be expected from the analgesia provided by the parent tramadol. An expanded version of this graph highlighting the first 0-4 hours is provided in Figure 6.

Figure 3: LSMean (SE) Pain Intensity Differences for IV tramadol 50 mg and Placebo (FAS Population) (Study AVE-901-102)

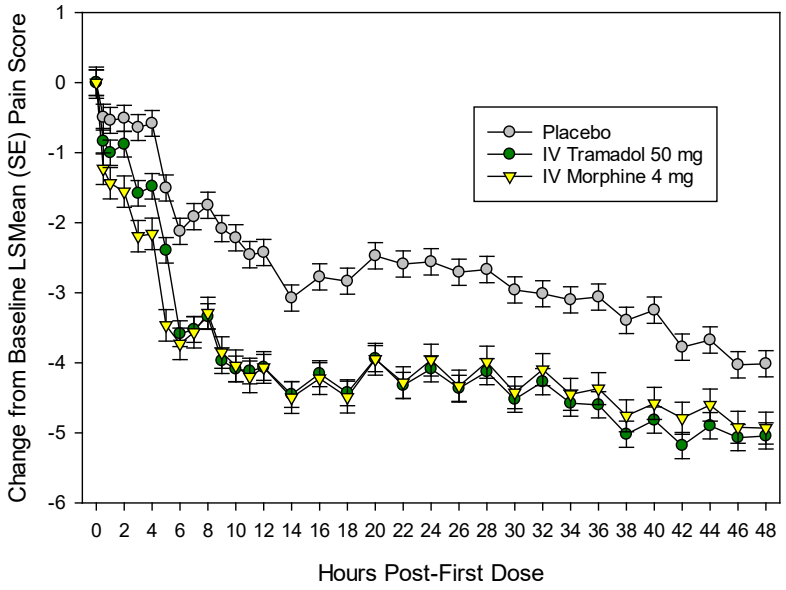


Abbreviations: FAS=Full Analysis Set; LS=least squares; NPRS=Numerical Pain Rating Scale; SEM=standard error of the LSmean. Notes: A negative pain intensity difference indicates less pain post baseline. Pre-rescue NPRS score was used to replace NPRS obtained within 4 hours post rescue medication. No other missing pain scores were imputed. LS means were obtained from the mixed model for repeated measures (MMRM) with treatment as the main effect, patient as the random effect, pooled study center baseline NPRS, time and treatment by time interaction as covariates.

Source: Study AVE-901-102 CSR Figure 14.2.7.a

Figure 4 provides the LSMean (SE) PID values for IV tramadol 50 mg, placebo, and morphine from the abdominoplasty study, Study AVE-901-103. These data show early separation between the tramadol and placebo with continued differences throughout the dosing regimen, and that tramadol provided similar pain relief as morphine across the dosing regimen. An expanded version of this graph highlighting the first 0-4 hours for IV tramadol, IV morphine, and placebo is provided in Figure 7.

Figure 4: LSMean (SE) Pain Intensity Differences for IV tramadol 50 mg, Placebo and Morphine (FAS Population) (Study AVE-901-103)



Abbreviations: FAS=Full Analysis Set; LS=least squares; NPRS=Numerical Pain Rating Scale; SEM=standard error of the LSmean. Notes: A negative pain intensity difference indicates less pain post baseline. Pre-rescue NPRS score was used to replace NPRS obtained within 4 hours post rescue medication. No other missing pain scores were imputed. LS means were obtained from the mixed model for repeated measures (MMRM) with treatment as the main effect, patient as the random effect, study center, baseline body mass index (<30 kg/m^2 versus ≥30 kg/m^2), baseline NPRS, time, and treatment by time interaction as covariates.

Source: Study AVE-901-103 CSR Figure 14.2.3.a

A detailed discussion on the data relating to pain relief at early timepoints is provided in Section VI.A.2. of this document.

C. Safety of IV tramadol

Although the safety of IV tramadol as determined in the three Phase 3 studies is not in question, the safety results will be summarized here to help inform the risk-benefit analysis of IV tramadol. The evidence for safety in the NDA consists of three components: (1) clinical trial data from the IV tramadol development program, (2) safety information from outside the U.S., and (3) epidemiological data related to the abuse of tramadol in the US, as well as in countries where tramadol is available in both an IV and an oral formulation. Briefly, IV tramadol was well-tolerated in the clinical development program with no unexpected safety findings and demonstrated a similar side effect profile to oral tramadol, consistent with the safety experience from outside the U.S. where parenteral tramadol has been widely used in over 70 countries for over 25 years. The safety summery from the OUS experience with parenteral tramadol is submitted in Module 5.3.6 and include a literature review and a Vigibase Report. The epidemiology data (Module 5.3.6 Epi Abuse Summary Report) demonstrate that reports of abuse with tramadol are infrequent, both in absolute number and relative to other prescription opioids, and that abuse of tramadol via injection is uncommon relative to oral tramadol in both the U.S. and in countries where it is available.

1. Treatment-Emergent Adverse Events (TEAEs) in the Controlled Efficacy Studies

The safety database included 533 patients treated with IV tramadol 50 mg in the Phase 3 development program. More than 100 of the patients were male and 50 were over the age of 65 among those exposed to IV tramadol 50 mg. The Phase 3 program included 271 placebo subjects, 133 tramadol 25 mg subjects, 533 tramadol 50 mg subjects, and 93 morphine subjects, comprising, in total, 1030 subjects (Study AVE-901-102 CSR Table 26, Study AVE-901-103 CSR Table 31, Study AVE-901-104 CSR Table 17).

TEAEs reported in at least 2.0% of patients in either IV tramadol 50 mg group or the placebo group, irrespective of relationship to study medication, are reported in Table 5 by preferred term in decreasing order based on incidence rates in the IV tramadol group. For most TEAE classifications, the tramadol group demonstrated a higher incidence than the placebo group. Of note (Module 2.7.4):

- There were two patients with treatment emergent SAEs (each a hematoma following the abdominoplasty procedure) during the controlled Phase 3 efficacy studies.
- There were no TEAEs leading to deaths in these studies.

Table 5: Incidence of all treatment-emergent adverse events (TEAEs) Regardless of Relationship Reported in at Least 2.0% Patients in Either Placebo or IV Tramadol 50 mg Group by Preferred Term in Decreasing Frequency Based on Incidence Rates in the IV Tramadol Group (Studies AVE-901-102 and AVE-901-103 Combined)

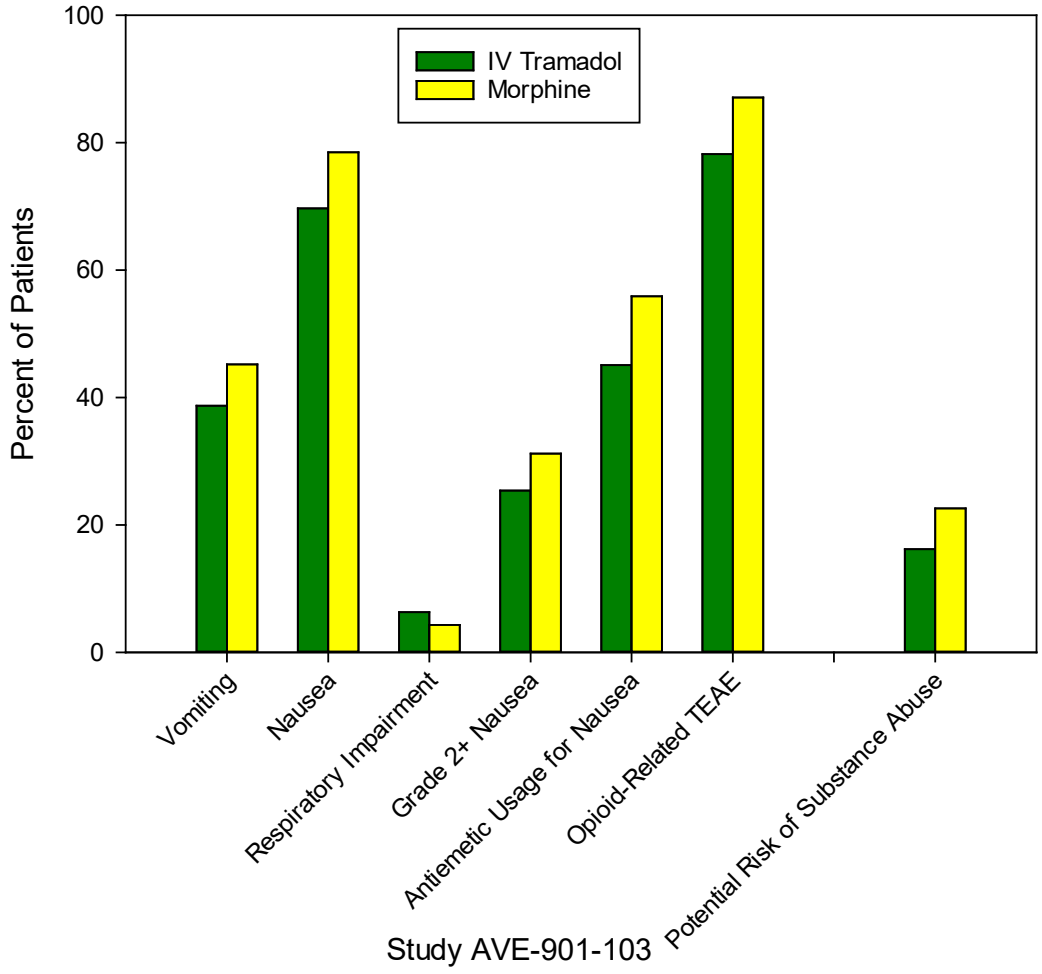
MedDRA Preferred term	Number of patients (%)	
	Placebo (N=271) n (%)	Tramadol 50 mg (N=282) n (%)
Total patients with at least 1 TEAE	137 (50.6)	215 (76.2)
Nausea	61 (22.5)	144 (51.1)
Vomiting	14 (5.2)	83 (29.4)
Dizziness	13 (4.8)	39 (13.8)
Headache	33 (12.2)	34 (12.1)
Somnolence	5 (1.8)	19 (6.7)
Constipation	6 (2.2)	15 (5.3)
Hypoxia	1 (0.4)	14 (5.0)
Infusion site pain	16 (5.9)	12 (4.3)
Pruritus generalized	4 (1.5)	11 (3.9)
Respiratory disorder	0	9 (3.2)
Oropharyngeal pain	5 (1.8)	6 (2.1)

Source: ISS Table 14.3.1.1.1

Study AVE-901-103 included an active (morphine) comparator arm and thus allows for comparison of specific types of TEAEs between IV tramadol 50 and an approved opioid product. Opioid-related TEAEs included nausea, vomiting, dizziness/postural, constipation, hypoxia/respiratory disorder, pruritus/generalized, somnolence, sedation, and bradypnea. Respiratory disorder relates to an exploratory endpoint (respiratory impairment) that had not been validated and was driven largely by oxygen saturation on pulse oximetry, a biomarker. The endpoint should not be confused with respiratory depression which is a clinical event and a serious AE (SAE).

Figure 5 provides a summary of the incidence of key opioid-associated safety endpoints for IV tramadol 50 versus morphine in Study AVE-901-103. Module 2.7.4 provides a detailed comparison of the safety comparison between IV tramadol and morphine.

Figure 5: Risk of IV tramadol vs Morphine for Key Opioid-Associated Safety Endpoints (Safety Population) (Study AVE-901-103)



Source: Study AVE-901-103 CSR Table 14.3.1.5.3 and 14.3.1.5.2

Note: Opioid-related TEAEs included nausea, vomiting, dizziness/postural, constipation, hypoxia/respiratory disorder, pruritus/generalized, somnolence, sedation, and bradypnea.

2. Clinical Laboratory Findings

See ISS Section 5 for a detailed presentation of clinical laboratory data from the clinical development program. The same central lab was used for all three Phase 3 studies, and in the statistical analysis, the same potentially clinically significant ranges were used across these three studies, thus allowing for consistent comparison of outcomes between these studies. The development program also included an active comparator arm (morphine) in Study AVE-901-103 and thus allows for an assessment of the tramadol outcomes in comparison to morphine (see ISS Section 5.5 for more details).

Overall findings of potentially clinically significant (PCS) abnormalities for hematology, serum chemistry, and urinalysis were infrequent and without meaningful differences between groups (including between IV tramadol and morphine). Mean changes in all parameters were generally small and similar among the treatment groups, with no meaningful group-mean changes observed at any time. Further, while there were some patients with shifts in laboratory parameters from baseline to end of study, these shifts were not judged to be related to study treatment, and there were no trends towards a higher incidence of shifts with increasing tramadol dosage (see ISS Section 5.4 for a description of the dose-response outcomes from Study AVE-901-102). As anticipated from the ULTRAM labeling, the incidence of increased liver function tests was greater in the IV tramadol arm as compared to the placebo arm, although the incidence did not exceed 2% for either AST or ALT. No patient had a PCS increase in bilirubin during the development program.

3. Vital Signs

See ISS Section 6 for a detailed presentation of vital sign data from the clinical development program. There were no individual changes in vital sign data for healthy adult subjects (in the Phase 1 studies) that were considered clinically significant or were reported as TEAEs by the Investigator. The integrated Phase 3 efficacy/safety studies provide the most robust data regarding vital signs. Vital signs were collected frequently (including over 20 unique times during each Phase 3 study).

For the integrated Phase 3 assessment, mean changes from baseline tended to follow a similar pattern regardless of treatment group with limited exceptions. Mean heart rate declined slightly more in the tramadol arm compared to the placebo arm, whereas there were no meaningful differences for respiratory rate, oxygen saturation, and blood pressure. While there were minor differences in the incidence rates of specific PCS criteria (of note, low heart rate new-onset PCS was higher in the tramadol arm), the differences were not clinically meaningful, and overall, the proportion of patients with PCS abnormal values was similar between the placebo and IV tramadol 50 mg groups for both blood pressure values. Notably, the incidence of PCS low blood pressure (systolic and diastolic) demonstrated no meaningful difference between the treatment groups.

4. ECGs

See ISS Section 7 for a detailed presentation of ECG data from the clinical development program. ECG monitoring was performed throughout the clinical development program and specifically, as suggested in advice from the Division at the Type B EOP2 meeting, ECG monitoring included ECGs 20-30 minutes following each dose of IV tramadol for the first 24 hours in the Phase 3 studies. The clinical experience demonstrated that IV tramadol has a benign profile regarding ECG parameters.

A high single-dose QT study was performed (Study RVG-12-001), in which the primary objective was to assess the effects of a supra-therapeutic dose of 200 mg IV tramadol (i.e., 4 times the proposed dose) on the QT/corrected QT (QTc) interval in healthy volunteers. Endpoints included the baseline-adjusted, placebo-corrected QTcF ($\Delta\Delta$QTcF), heart rate, PR, QRS, QT, and RR intervals. Frequency of T-wave morphology changes, categorical analysis of

QTcF, heart rate, PR, and QRS were also performed. Moxifloxacin was used as the active control. The relationship between tramadol plasma concentrations and ΔΔQTcF was also assessed. The tramadol infusion caused a small increase in the QTcF interval, with mean ΔΔQTcF above 5 msec between 4 and 12 hours post-dosing, with a peak of 8.5 msec at 8 hours. The upper bound of the 90% CI was below the threshold of regulatory concern, 10 msec, at all timepoints except at 8 hours post-dose, where it slightly exceeded the threshold (10.4 msec). Tramadol did not have a clinically relevant effect on the PR or QRS intervals.

The Phase 3 randomized double-blind studies showed that, specifically for QTcF, there was no meaningful difference between the tramadol and placebo groups with respect to incidence rates of QTcF for any of the four interval categories. ISS Table 14.3.4.1

5. Assessment of AEs potentially related to abuse in clinical trials.

The clinical trials in the tramadol development program included identification of TEAEs based on the FDA guidance *Assessment of Abuse Potential of Drugs, Guidance for Industry*.[63] A comparison of these types of events with morphine was performed in Study AVE-901-103. The incidence of at least one TEAE related to potential risk of substance abuse was 8.1% in the placebo group, 16.2% in the tramadol group, and 22.6% in the morphine group. Dizziness was the most frequently reported TEAE of this type, reported in 6.7% placebo, 12.7% tramadol, and 18.3% morphine patients. No dizziness, somnolence, or sedation occurred in conjunction with euphoria, which was not reported at all. The incidence of the individual preferred terms was low for each treatment group and generally reported with similar incidence among the treatment groups.[64]

6. Safety Summary from Parenteral Tramadol from Outside the U.S.

IV tramadol has been widely used throughout the world, having been approved for use in more than 70 countries for over 25 years[65] at doses from 50 mg up to 100 mg. The Sponsor does not commercialize tramadol in any country and therefore does not have direct access to adverse event reports that may be conveyed to sponsors marketing tramadol outside the U.S.

Additional safety information was provided in the NDA, as agreed in the Type B pre-NDA Meeting, from:

1. A review of the available medical literature including ex-US product labels of tramadol for injection, and;

2. An examination of the most frequently reported AEs associated with IV tramadol use in the VigiBase submitted to the Uppsala Monitoring Center database. VigiBase is the unique WHO global database of Individual Case Safety Reports (ICSRs) and member

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63 FDA, Guidance for Industry – Assessment of Abuse Potential of Drugs (Jan. 2017).

64 *See* Study AVE-901-103 Table 14.3.1.5.2.

65 Grünenthal 2017.

countries of the WHO Programme for International Drug Monitoring submit ICSRs electronically to this database.

The literature review used AE-related Medical Subject Heading (MeSH) terms in the PubMed database to identify AEs associated with parenteral tramadol reported in the published literature. The review includes articles published from 1998 to 2019 and was based on 21 randomized controlled trials and 6 case study reports.[66] These studies had various indications and dosing regimens, and some had higher total daily doses than what was tested in our Phase 3 program including with and without patient-controlled anesthesia. Comparator drugs in the trials generally included morphine, fentanyl, codeine, oxycodone, lornoxicam, and/or meperidine. In the 21 controlled studies, there were few significant differences in rates of AEs between IV tramadol and opioid comparators. Three case studies reported on patients with respiratory depression or disturbances in respiratory parameters with doses of tramadol ranging from 50 mg to 400 mg. Though varied in terms of design, analysis, and reporting, the literature appears to show that IV tramadol is generally comparable to other opioids with respect to the types and number of AEs observed and the AEs reported in the literature are consistent with the oral tramadol labeling. The literature review did not demonstrate a safety signal regarding opioid stacking.

In the VigiBase analysis, respiratory depression was an AE of interest for oral and IV tramadol and their commonly prescribed combination products. It should be noted that no denominator is available for such AE reporting systems, and hence, incidence and prevalence rates cannot be derived. From 2009 to 2019, respiratory depression was reported 109 times for oral tramadol accounting for 0.2 % of all AE reports for oral tramadol worldwide and 58 and 0.5% for Europe. It was reported 16 times for parenteral tramadol in the same timeframe and accounts for 0.04% of the AE reports for parenteral tramadol worldwide and 10 and 1.0% for Europe. Despite the potential limitations in this spontaneous reporting database (reporting bias, duplication, confounding, and heterogeneity), IV tramadol in general appears to be comparable to oral tramadol with respect to the number of AE reports in all regions. The analysis of the Vigibase data also failed to raise a safety signal regarding respiratory depression, the most serious side effect of opioid stacking.

Both approaches demonstrate that adverse effects after IV tramadol are consistent with those of oral tramadol and are already reflected in the current ULTRAM labeling. Additional details can be found in Module 5.3.6.

D. Regulatory Interactions with the Division

The IV tramadol development program builds upon the extensive experience with oral tramadol (ULTRAM) and demonstrated safety consistent with known safety profile of oral tramadol. The six clinical studies were conducted in alignment with the Division's guidance regarding the scope of the program required to support approval, and the design of the Phase 3 studies was discussed in several interactions between the Sponsor and DAAP.

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[66] References provided and discussed in NDA 213231 at Module 5.3.6.

Table 6 lists the key DAAP-Sponsor interactions regarding the Phase 3 clinical development program and data requirement for approval. At each step during the development program, Avenue Therapeutics collaborated with the Division including selection and design of the clinical study pain models used to assess the safety and efficacy of IV tramadol.

Table 6: DAAP-Sponsor Interactions in Collaboration for Clinical Development Program for IV tramadol

Interaction	Purpose	Date
Teleconference	Discuss post-meeting note in the pre-NDA meeting minutes regarding time to onset	October 10, 2019 Sponsor meeting minutes
Face to Face meeting	Pre-NDA meeting	August 20, 2019
Advice following IND submission of the Phase 3 studies	Advice letter on current program Phase 3 Protocols	August 4, 2017
Face to Face meeting	End of Phase 2 meeting	June 21, 2016

The key agreements regarding the Phase 3 program were achieved at the EOP 2 meeting (June 21, 2016) included:

1. The analgesic models (bunionectomy and abdominoplasty) and design of the Phase 3 pivotal trials (Studies AVE-901-102 and AVE-901-103) for IV tramadol 50 mg with the addition of a 25mg IV regimen to the first Phase 3 study (Study AVE-901-102) and the addition of an active comparator (morphine) to the abdominoplasty study (Study AVE-901-103).

2. An increase in ECG monitoring (ECGs 20-30 minutes following each dose of IV tramadol for the first 24 hours) and to monitor antiemetic and adjunct medication use during the studies.

3. The Phase 3 trials (Studies AVE-901-102 and AVE-901-103) would support a general acute pain indication.

4. The size of the clinical safety database of at least 500 subjects receiving the "labeled" dosing for up to 48 hours.

5. Data imputation in the presence of rescue medication and for all other missing data in the primary analysis and time-specific PID as a key secondary endpoint for Studies AVE-901-102 and AVE-901-103.

6. No new studies to evaluate the abuse potential of IV tramadol are needed. The ISS will include an analysis of the abuse-related adverse events from all clinical studies and an assessment of the abuse potential of the product via epidemiology data related to the abuse of oral tramadol in the U.S. as well as in countries where oral and IV tramadol are marketed.

7. No reason for a Risk Evaluation and Mitigation Strategy (REMS) for IV tramadol for use in an inpatient setting has been identified.

In the FDA advice letter (August 4, 2017), the Division provided comments on the Phase 3 protocols including both the efficacy studies as well as the open-label safety study. In addition, the Sponsor followed Division's advice to conduct the Phase 3 studies sequentially and added additional PK sampling times in efficacy studies to capture C_{max} after the first four doses.

A face-to-face pre-NDA meeting was held with the Division in August 2019. Key agreements were:

1. Adequacy of the efficacy and safety package from the Phase 3 pivotal studies (Study AVE-901-102 and Study AVE-901-103) as well as the open-label safety study (Study AVE-901-104) to support the submission for the indication.

2. Scope of epidemiological data to be provided as related to the potential abuse of tramadol (including routes of abuse and abuse in countries where the IV product has been on the market), as requested by the Division (FDA letter, November 22, 2010).

In addition, Avenue was informed on May 20, 2020 that there was no need to take the NDA to an Advisory Committee meeting and that the meeting for this NDA was therefore cancelled.

IV. NDA 213231 Provides Substantial Evidence of Efficacy of IV tramadol in the Management of Moderate to Moderately Severe Pain in Adults in a Medically Supervised Health Care Setting and Should be Approved.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that FDA approve an NDA unless the NDA includes any of seven specific deficiencies, three of which are related to safety.[67] Specifically, an NDA must be approved unless:

> (1) the investigations, reports of which are required to be submitted [in the NDA] do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions . . . [or] (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions.[68]

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67 FD&C Act § 505(d).

68 *Id.* § 505(d)(1), (2) and (4).

Likewise, an NDA may not be approved if based on the information submitted in the NDA "and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[69] The FD&C Act defines "substantial evidence" as

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[70]

As discussed above, NDA 213231 contains substantial evidence that IV Tramadol will be safe and effective when used as described in the draft labeling. Studies AVE-901-102 and AVE-901-103 are undeniably adequate and well-controlled clinical investigations, the designs of which were agreed upon with DAAP. Both studies met their agreed-upon primary endpoint in a population and pain models accepted by the Division. The studies also demonstrate evidence of pain relief in secondary endpoints that, while not required as part of substantial evidence, provide further confirmation of such. The information submitted in the NDA establish the safety of IV tramadol when used according to the proposed draft labeling in a medically supervised healthcare setting. The proposed draft labeling contained in the NDA, like the labeling for morphine, oral tramadol, ANJESO, OLINVYK, and other opioids, ensures that prescribers have sufficient information about the drug's effect to use it safely and effectively. However, the Division determined that IV tramadol, intended to treat patients who require an opioid in a medically supervised setting, is not safe for the intended patient population because the Division identified opioid stacking as a hypothetical safety concern. The concern stems from the fact that IV tramadol did not meet an arbitrary threshold of onset of action as measured by the two-stopwatch method, which the Division seems to elevate over the benefits demonstrated in the NDA. Other methods of evaluation showed IV tramadol provided adequate analgesia that is clinically meaningful at early timepoints (see discussion of SPID, use of rescue medication, and PGA in Section III.B.) for patients with post-operative pain. The hypothetical concern of adverse events related to opioid stacking is not borne out by the data in the NDA or by the considerable foreign experience covering multiple years of parenteral tramadol use in the same population (see discussion in Section III.C.6.) where this hypothetical concern has not been an issue. The Sponsor requests ON consider the totality of the data in the NDA, the clinical benefit of IV tramadol, the medically supervised setting for which IV tramadol is to be used, the two precedents (ANJESO and OLINVYK), and the public health benefit of allowing a safe and effective Schedule IV therapeutic alternative to Schedule II opioids in the post-operative setting.

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69 *Id.* § 505(d)(5).

70 *Id.* § 505(d).

V. DAAP's Position

A. CRL 1

Avenue received CRL 1 on October 9, 2020, which identified a single clinical deficiency. The relevant portion of CRL 1 is reproduced below.

> 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 [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.

B. CRL 2

In CRL 2 (June 11, 2021), the Division repeated the same clinical deficiency. The relevant portion of CRL 2 is reproduced below.

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 [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.

VI. Avenue's Response

IV Tramadol meets the statutory standard for approval. The NDA includes substantial evidence of safety and effectiveness for its intended use through adequate and well-controlled investigations. The clinical deficiency identified in the two CRLs is that IV tramadol's onset of action, as measured by the two-stopwatch method, exceeds the Division's expectation of one hour for an analgesic for acute pain. The Division concluded that this would lead to opioid stacking or the use of multiple opioids concurrently that poses a potentially serious safety concern to patients, even in a medically supervised setting. As discussed in more detail below, the data in the NDA demonstrated that IV tramadol has an adequate onset of analgesia and provided clinically meaningful pain relief at early timepoints. Clinicians were able to manage the vast majority of the patients with an NSAID rescue in Phase 3 trials and not a single patient discontinued the "real-world" safety study to receive another opioid. The facts that rescue with an NSAID provided adequate pain relief, patients reported a high satisfaction rating for IV tramadol, and decades of foreign use have not shown stacking to be an issue should minimize the Division's concern. Even if an opioid was used following IV tramadol, the use of multiple opioids is accepted as safe in a medically supervised setting and the theoretical risk of opioid stacking can be addressed with labeling as is routine for opioids. Notably, an analgesic drug with delayed onset (ANJESO) was recently approved by the FDA; and a Schedule II pure mu agonist (OLINVYK) that carries clear risk of opioid stacking was approved. IV tramadol would provide an option for U.S. clinicians and patients to consider for post-operative pain management, a setting where the majority of intravenous opioids are used. The public health benefit of approving a Schedule IV intravenous opioid with lower abuse potential than the alternatives, all of which are Schedule II opioids, should also be a factor in FDA's risk-benefit analysis.

A. IV tramadol demonstrated adequate onset and clinically meaningful pain relief at early timepoints

1. Background

As a preliminary matter, the first time the Division mentioned to the Sponsor that their expectation of onset for a parenteral analgesic for acute pain is less than an hour was in a post-meeting note that DAAP added to the minutes of the September 29, 2019 pre-NDA meeting minutes. That post-meeting note is reproduced here.

Post meeting note:

> As 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 requesting 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.
>
> Note that 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.

The Division never informed Avenue of the "one-hour onset expectation" before that point. Notably, Avenue and DAAP had an End of Phase 2 meeting on June 21, 2016, and Avenue received an advice letter on the Phase 3 protocols on August 4, 2017. The design of the pivotal Phase 3 studies was an important component of those meetings, but the 1-hour "expectation" was never mentioned, and as a result, the onset (i.e., the time to meaningful pain relief by the two-stopwatch method) was a tertiary endpoint in the efficacy studies and the data collection for this endpoint was not emphasized. Putting aside the lack of notice issue, the genesis of this requirement is murky as it had never been formally articulated through guidance or rulemaking, and Avenue is unaware of any public workshops with external clinicians, patients or sponsors that would have helped shape what is a seemingly critical threshold that overrides all other clinical considerations. DAAP has not provided any basis for its view that an analgesic for acute pain must provide meaningful pain relief within some arbitrary timeframe as measured by the two-stopwatch method, particularly in a post-operative setting.

In 2014, a draft guidance on analgesic indications was "distributed for comment purposes only" by FDA although it was recently withdrawn as part of its efforts to provide more specialized guidance for different types of analgesics.[71] Nevertheless, it is noteworthy that

[71] FDA, Draft Guidance for Industry – Analgesic Indications: Developing Drug and Biological Products (Feb. 2014).

despite DAAP's proclamations of the need for meaningful pain relief within any arbitrary period, this guidance discusses onset of action only as a feature of efficacy that the Agency recommends measuring along with change in pain intensity and time to first rescue or re-medication. The draft guidance afforded an optimal opportunity to obtain input on issues related to onset from a wide variety of potentially affected stakeholders. It is odd that such a critical requirement, at least in the eyes of the Division (as it was the only identified clinical issue in both CRLs), should be omitted from a guidance without seeking public input. That left DAAP without any input from critical stakeholders including healthcare providers and patients about how an analgesic that may not meet the arbitrary time to onset expectation can be incorporated into clinical practice or labeling. Further, had FDA sought input on whether any particular amount of time to onset of meaningful pain relief should be a requisite feature of analgesic drugs, it may have obtained critical information. For instance, prescribers may have noted that while fast onset is important for drugs routinely used as rescue medicine (such as IV fentanyl) and in situations that require immediate pain relief such as in patients following accident or trauma, it may not be as important for post-operative setting, because patients are already treated with multiple analgesic and anesthetic medications during the surgery and before they leave the operating room. Prescribers may also willingly trade fast onset for other important features such as obviating the need for a Schedule II opioid in a medically supervised setting.

2. Time to Onset Data from the NDA

In addressing DAAP's interpretation of the data expressed in the two CRLs, it is important to understand how the data is collected in clinical studies of analgesics compared to how the drugs are used in clinical practice. In Study AVE-901-102 and Study AVE-901-103, patients must meet a moderate to severe pain level after surgery before they are eligible to receive treatment. The design, while artificial, allows valid comparison to placebo in efficacy studies. In contrast, in actual clinical practice as well as in Study AVE-901-104, patients would start their post-surgical pain medications immediately after surgery, as opposed to waiting to reach a certain pain level before dosing. In this setting, the physician may prescribe an opioid concurrently with non-opioid medicine, if warranted. The clinical goal is to treat patients before they have pain.

a. Onset as Assessed by the Two-Stopwatch Method

The onset of analgesia is conventionally measured with the two-stopwatch test. Patients press the first stopwatch to record when they first perceive pain relief. They press the second stopwatch to record time to meaningful pain relief. Onset of analgesia is time to meaningful pain relief when confirmed by a preceding perceptible pain relief. In a telephone call on October 10, 2019 to discuss the post-meeting note added by DAAP described above, Avenue noted that time to onset in the two pivotal studies had been consistently described as a tertiary endpoint collected in a passive approach, and as a result, the data collection for this metric was not emphasized during studies. Avenue noted that the sites did not prompt or wake patients to assess their pain relief on stopwatch outcomes; patients were only awoken and reminded for the pain intensity measurements, which directly contributed to primary endpoint and key secondary endpoint calculations. In Study AVE-901-102 and Study AVE-901-103, if a subject received rescue ibuprofen before pressing the second stopwatch, that event was recorded as the subject not having achieved meaningful pain relief. As such, the CRL 2's statement that "meaningful pain

relief was delayed (accounting for the use of rescue medication, e.g., ibuprofen), and some patients never achieved pain relief" refers specifically to the two-stopwatch data, specifically the fact that some patients did not press the second stopwatch or took a dose of ibuprofen before they did. The onset of analgesia (time to meaningful pain relief by the two-stopwatch method) for the two pivotal studies requested by FDA is shown in Table 7.

Table 7: Time to Perceptible Pain Relief and Time to Meaningful Pain Relief (Two-Stopwatch Method) in the Efficacy Studies

Study AVE-901-102 Bunionectomy		PBO (n=136)	Tramadol 50 mg (n=139) and P value versus PBO	
	Median time to Perceptible Pain Relief	Not reached	167 minutes <0.05	
	Median time to Meaningful Pain Relief	Not reached	321 <0.05	
Study AVE-901-103 Abdominoplasty		PBO (n=136)	Tramadol 50 mg (n=141) and P value versus PBO	Morphine 4 mg (n=93) and P value versus PBO
	Median time to Perceptible Pain Relief	69 minutes	27 minutes Not Significant	5 minutes <0.05
	Median time to Meaningful Pain Relief	145 minutes	106 minutes Not Significant	42 minutes <0.05

Source: AVE-901-102 CSR and AVE-901-103 CSR

b. Other Data in NDA 213231 Demonstrated Pain Relief for IV Tramadol at Early Timepoints

The Sponsor notes that while the two-stopwatch test is a direct measure of onset and the onset of analgesia of IV tramadol was longer than one-hour in the two-stopwatch test, there is other evidence throughout the application that IV tramadol provides clinically meaningful pain relief at early timepoints and for the duration of treatment. These metrics, discussed in Module 2.7.3 Section 3.2.4 and the Briefing Book for the Type A meeting, include time to rescue medicine, PID, and the PGA of the pain relief. When the time to meaningful pain relief is considered with these other endpoints in mind, a more complete picture of the effectiveness of the drug is possible. The usefulness of considering the totality of data is demonstrated by examining the case of ANJESO in the next section.

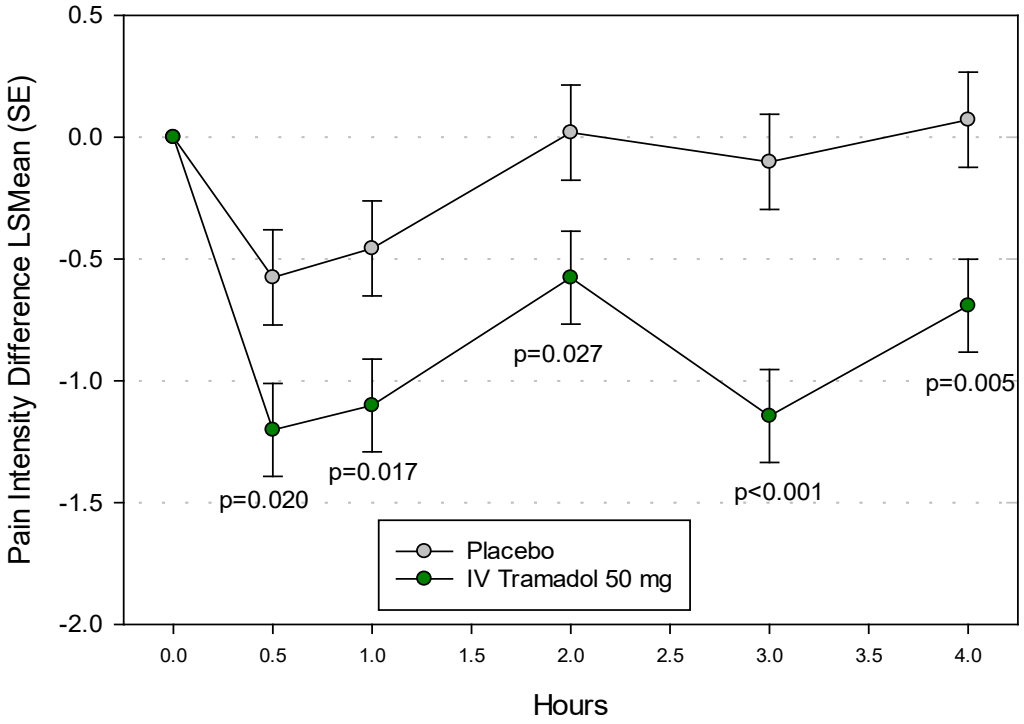
An analgesic with delayed onset would be expected to have a short time to first rescue and similar time to first rescue as placebo in a blinded efficacy study because patients in acute post-surgical pain are expected to request rescue unless they experience pain relief that is clinically meaningful. However, as discussed in more detail at section VI.B.1. below, in both efficacy studies for tramadol IV, time to first rescue was longer in the IV tramadol group versus the placebo group and the results were statistically significant. The endpoint was 5.1 hours in the IV tramadol group versus 2.5 hours in the placebo group in Study AVE-901-102 ($p < 0.001$), and

22.9 hours in the IV tramadol group versus 1.7 hours in the placebo group in Study AVE-901-103 ($p < 0.005$).

An analgesic with a clinically important delay of onset would be expected to receive a low rating from the perspective of the patients. However, the PGA at 24 hours, the primary endpoint in Study AVE-901-103 and a key secondary endpoint in Study AVE-901-102, was statistically better than placebo (Figure 2). In the pivotal controlled studies, the PGA at both Hour 24 and Hour 48 demonstrated better effectiveness of pain control for IV tramadol 50 mg over placebo. Study AVE-901-104 (open-label), designed to assess how IV tramadol fits into the multimodal analgesic approach in the real world, corroborated these findings. Patients' pain following a variety of surgeries was successfully managed with IV tramadol in conjunction with non-opioid medications such as NSAIDs and acetaminophen, and with no early discontinuation due to inadequate analgesia. Patients could discontinue the study at any time to receive another opioid but not a single patient out of 251 did. Approximately 95% of patients in the study rated their treatment as good, very good, or excellent (Figure 2).

As discussed previously, in Study AVE-901-102, statistically significant differences between tramadol 50 mg and placebo, favoring greater pain relief in the tramadol 50 mg group, were observed as early as the first measured time point (Hour 0.5, $p=0.020$) and continued to be significantly different through most of the 48-hour treatment period. Figure 6 show pain relief over the first 4 hours in Study AVE-901-102. Onset of effect occurred well within the one-hour time period for this endpoint.

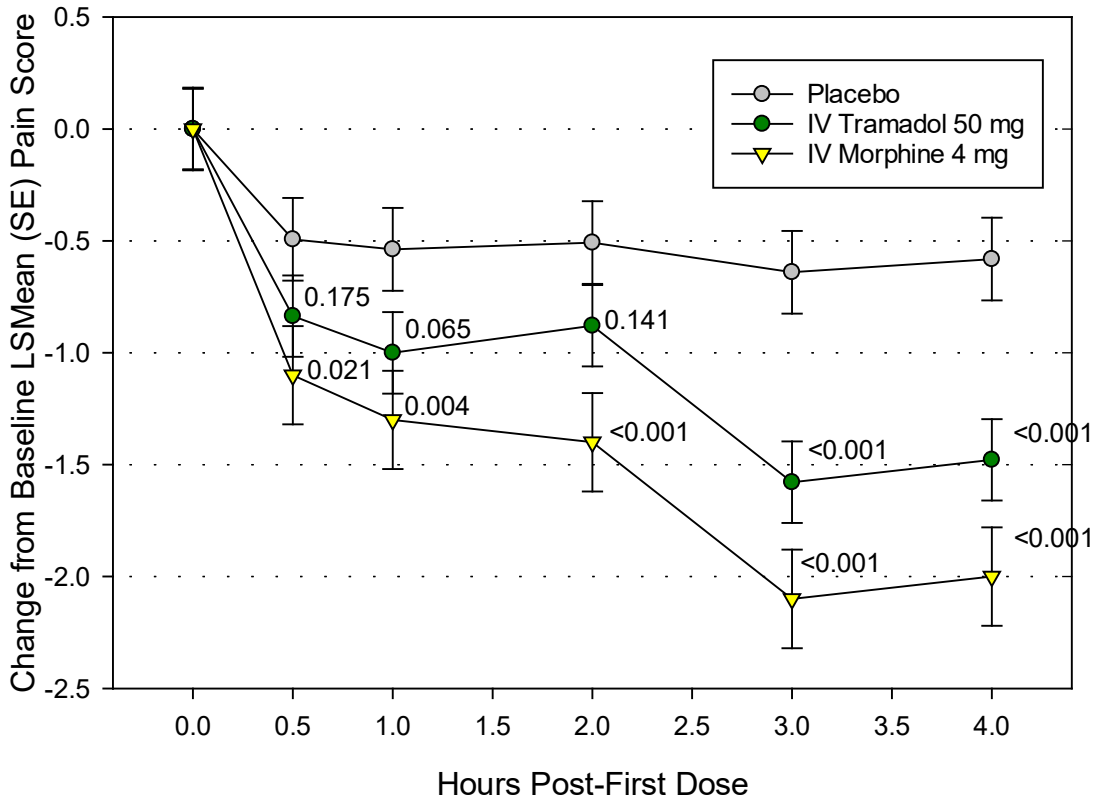
Figure 6: LSMean (SE) Pain Intensity Differences for IV Tramadol 50 mg versus Placebo 0 to 4 hours (and P-Values for Treatment Difference) (FAS Population)
Study AVE-901-102



Note: LS mean, LS mean difference (treatment – placebo), 95% CI and p-values are obtained from the MMRM model with treatment as the main effect, subject as the random effect, pooled study center, baseline NPRS, time and treatment by time interaction as covariates.
Source: Study AVE-901-102 CSR Table 14.2.7

In Study AVE-901-103, a similar magnitude of improvement over the placebo arm was seen although the difference was not statistically significant until Hour 3 (Figure 7).

Figure 7: LSMean (SE) Pain Intensity Differences for IV Tramadol, IV morphine versus Placebo 0-4 hours (FAS Population)
Study AVE-901-103



Source: Study AVE-901-103 CSR Table 14.2.6.1

As presented in the NDA, a post-hoc analysis of the PID values was performed to assess the impact of IV tramadol on pain intensity versus placebo. In a manner similar to the SPID24 and SPID48, calculation of SPID1, SPID2, SPID3, SPID4, SPID5, and SPID6 indicated that with IV tramadol, SPID2, 3, 4, 5, and 6 were all better than placebo (p-values <0.05) demonstrating better pain relief as early as 2 hours following initiation of treatment (Table 8). SPID1, while not statistically significant (p=0.063), demonstrated that the benefit of better (and therefore faster) pain relief as observed from SPID2 onwards was already becoming evident in the first hour after initiation of treatment. The post-hoc analysis did not include the morphine arm.

Table 8: Post-Hoc Analysis of Onset of Tramadol Pain Relief as Compared to Placebo During Early Timepoints (FAS Population) (Study AVE-901-103)

	Placebo		Tramadol 50 mg		Difference		P-value for Treatment Comparison
	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	LS Mean (SE)	95% CI	
SPID1	-0.2 (0.12)	-0.45, 0.01	-0.5 (0.12)	-0.72, -0.26	-0.3 (0.14)	-0.54, 0.01	0.063
SPID2	-0.5 (0.28)	-1.07, 0.01	-1.2 (0.27)	-1.74, -0.66	-0.7 (0.33)	-1.32, -0.02	0.043
SPID3	-0.9 (0.47)	-1.82, 0.01	-2.2 (0.47)	-3.16, -1.34	-1.3 (0.56)	-2.45, -0.24	0.017
SPID4	-1.3 (0.66)	-2.64, -0.05	-3.5 (0.66)	-4.82, -2.24	-2.2 (0.80)	-3.75, -0.62	0.006
SPID5	-2.3 (0.85)	-3.94, -0.60	-5.4 (0.85)	-7.08, -3.74	-3.1 (1.03)	-5.16, -1.12	0.002
SPID6	-4.0 (0.99)	-5.95, -2.06	-8.3 (0.99)	-10.20, -6.32	-4.3 (1.20)	-6.61, -1.91	<0.001

Abbreviations: CI=confidence interval; FAS=Full Analysis Set; LS=least squares; SE=standard error

Source: Study AVE-901-103 CSR Table 14.2.1.8

In summary, despite the time of onset on the two-stopwatch metric, there is other evidence throughout the application that IV tramadol provides clinically meaningful pain relief at early timepoints and for the duration of treatment. The assessment of time to onset in the context of other endpoints related to pain relief at early timepoints and the totality of the data in the NDA, as detailed in Module 2.7.3, indicated that IV tramadol has an adequate onset of action.

3. Onset of Action: ANJESO as An Informative Precedent

The Division highlighted the onset of action as measured by the two-stopwatch method in CRL 2, stating:

> 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.

To understand the onset as measured by the two-stopwatch method and how it fits into the totality of data related to pain relief at early timepoints, it is useful to consider the case of ANJESO. ANJESO (IV meloxicam) was recently approved by the FDA (February 2020) “for the management of moderate-to-severe pain, alone or in combination with non-NSAID

analgesics."[72] The Phase 3 program for ANJESO was similar to the IV tramadol program. The programs used the same pain models (bunionectomy and abdominoplasty) and same primary and key secondary endpoints (SPID48 and SPID24), although the rescue medicine in the ANJESO studies was oxycodone, a Schedule II opioid.

It appears that ANJESO's onset of action by the two-stopwatch metric was not measured correctly because patients were not censored after taking oxycodone rescue. The Division wrote that "the contribution of ANJESO to the outcome of meaningful analgesia is uncertain," due to the fact that "the rescue opioid was administered two hours prior to meaningful analgesia."[73] In contrast, the onset of analgesia in the IV tramadol studies is all from IV tramadol, because a patient who took a rescue prior to pressing the second stopwatch was recorded as never having achieved meaningful pain relief. Even with the help of oxycodone rescue, fewer patients achieved time to meaningful pain relief with ANJESO than with IV tramadol. In the ANJESO trials, only 46% of patients achieved time to meaningful pain relief (~2 hours) in the Phase 3 bunionectomy study and 29% of patients achieved time to meaningful pain relief in (~3 hours) in the Phase 3 abdominoplasty study. In contrast, 50% and 66% of the patients in the IV tramadol bunionectomy and abdominoplasty study respectively reported meaningful pain relief (time not reached and ~2.5 hours, respectively) without the contribution of rescue medicine.

Notably, ANJESO's onset of action as determined by the two-stopwatch measure is corroborated by short time to rescue (~2 hours), pain scores not separating from placebo, and PGA 24 not better than placebo. In contrast, the IV tramadol program demonstrated much longer time to rescue (5 hours and 23 hours, respectively), pain scores that separated from placebo as early as 30 minutes in one of the two studies, and a positive PGA 24 in both studies.

The sponsor of ANJESO received a CRL that identified onset of action as a clinical issue, but clearly thought that ANJESO provided benefit to patients with post-operative pain as it sought formal dispute resolution (FDR). The reviewing official recommended labeling which set an important precedence for IV analgesics that do not meet the onset threshold of one hour. The approval documents for ANJESO explain:

> After review of the FDR, Dr. Thanh-Hai (Acting Office Director), found that "accurate labeling can convey the limitations of Anjeso as an intravenous analgesic used in combination with other modalities of analgesia" to address the concerns raised by the Division. The key reasons for her decision follow.
>
> a. Onset of action:
>
> > i. Dr. Thanh-Hai took greater account of the shape of the early portion of the pain curves in assessing the onset of analgesia. She noted that separation between

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72 ANJESO (meloxicam), Approval Letter, NDA 210583, 1 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/210583s000ltr.pdf.

73 ANJESO (meloxicam), Clinical Review(s), NDA 210583, 18 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000MedR.pdf.

Anjeso and placebo occurred sooner in the bunionectomy study than abdominoplasty and inferred that procedure may influence the treatment effect.

ii. Dr. Thanh-Hai acknowledged precedents of other IV drugs and noted that some other drugs do not produce a rapid effect when administered IV.

iii. Even if the onset of action is delayed, Dr. Thanh-Hai found that would not preclude the use of Anjeso as an IV analgesic. She suggested that labeling can be developed to informer prescribers who could then formulate a regimen that would provide adequate analgesic coverage.[74]

The approval of ANJESO demonstrates that labeling can appropriately inform physicians about time to onset, and that a delayed onset in an intravenously administered analgesic is not a bar to approval. For example, the ANJESO labeling states that because of delayed onset of analgesia, "ANJESO alone is not recommended for use when rapid onset of analgesia is required" and includes a clear description of median time to first rescue analgesic. The ANJESO precedent also stands for the proposition that a specific proportion of patients who do not respond is not a bar to approval.

IV tramadol is now in a similar situation as ANJESO, but the Division is not willing to follow the precedent set by the office-level reviewer. It is recognized that, as an NSAID, the respiratory risk of opioid "stacking" is not the same as for IV tramadol but the data from the clinical development program of IV tramadol clearly demonstrated that rescue with another opioid is not needed when IV tramadol is used in the multimodal analgesic setting. Like the ANJESO labeling, clear communication regarding onset of effect was included in the proposed labeling for IV tramadol, but the Division has foreclosed this approach for IV tramadol.[75]

B. If a patient requires rescue, it is <u>not</u> "likely" to be another opioid.

Avenue does not agree with DAAP's assessment that the consequence of IV tramadol's time to onset is "likely" to be rescue with another opioid that would result in opioid stacking. The data in the NDA demonstrated that clinicians were able to successfully manage all but a handful of patients on IV tramadol with a non-opioid rescue medication such as an NSAID and showed that patients reported a favorable impression of the effectiveness of their treatment in the absence of Schedule II opioids. Summary safety information from outside the U.S., where parenteral tramadol is routinely used for management of post-operative pain, was submitted in

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74 ANJESO (meloxicam), Summary Basis of Approval, NDA 210583, 6 (Feb. 20, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000SumR.pdf.

75 The Sponsor wishes to clarify that the phrase "alone or in combination with other analgesics" was added to the proposed indication in the resubmission of the NDA following discussion with the Division in the Type A meeting (11/19/20) to be consistent with the ANJESO labeled indication "for the management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics" as the two programs had very similar designs. The Sponsor notes that it is not proposing "combination therapy" in the sense that IV tramadol will be used in a fixed dose combination with another drug. Rather, the proposal is to label the drug as it was studied – i.e. as initial therapy if the clinician believes that the pain warrants an opioid, with rescue with an NSAID (ibuprofen) allowed for patients who require additional analgesia. As such, the Sponsor has determined that the original proposed indication was more appropriate.

the NDA (Module 5.3.6 Tramadol AE Literature Summary Report and Module 5.3.6 Tramadol Vigibase Report) and is similar to oral tramadol with no special concerns regarding opioid stacking.

To address the Division's concern, Avenue examined the use of rescue, time to first rescue, patients who discontinued due to lack of efficacy and took other opioids in the efficacy trials, and rate of discontinuation due to inadequate analgesia in the safety study that utilized the real-world practice of multi-modal analgesia (Briefing Book for Type A meeting). As explained below, the data supports Avenue's view: (1) Ibuprofen, an NSAID, was effectively used in conjunction with IV tramadol to provide adequate analgesia for the vast majority of patients; (2) The very small percent of patients (2%) who discontinued due to inadequate analgesia and received other opioids in the efficacy trials did not experience SAE or severe AE (Study AVE-901-102 and Study AVE-901-103); and (3) No patient discontinued the safety study due to inadequate analgesia requiring rescue with another opioid (Study AVE-901-104) in a study that utilized the real-world multi-modal analgesic approach.

1. Use of Rescue Medications in the Pivotal Clinical Trials demonstrates that NSAIDs can adequately supplement IV tramadol analgesia.

Clinical trials of efficacy for analgesics mainly use a monotherapy approach, with specified "rescue" medications. The approach of using NSAIDs as rescue for opioid analgesics is common in registrational trials and has supported other recent approvals of intravenous opioids.[76] In Study AVE-901-102 and Study AVE-901-103, only ibuprofen 400 mg up to Q4H was allowed as a rescue medication. If a patient required another opioid due to inadequate analgesia, they were discontinued from the study and followed for adverse events.

Table 9 provides the total use of rescue medication during the controlled trials. Notably, in Study AVE-901-103, the average dosage of ibuprofen (the rescue medication) was equivalent to a single 2-tablet dosage (400 mg) over the course of the entire 48-hour treatment period, which compares favorably with the morphine arm average ibuprofen dosage (271 mg). The use of concomitant ibuprofen would be considered a natural part of a multimodal approach to pain relief post-surgery.

[76] For example, as reflected in the labeling, the Phase 3 program that supported the approval of OLINVYK used etodolac, an NSAID, as rescue medicine. (OLINVYK (oliceridine), Labeling, NDA 210703, 32 (Aug. 7, 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210730Orig1s000lbl.pdf)

Table 9: Phase 3 Studies Amount of Ibuprofen Rescue (mg)
Studies AVE-901-102 and AVE-901-103

	Study AVE-901-102 (Bunionectomy)			Study AVE-901-103 (Abdominoplasty)		
	Placebo (N=136)	**Tramadol 25 mg** (N=134)	**Tramadol 50 mg** (N=139)	**Placebo** (N=136)	**Tramadol 50 mg** (N=141)	**Morphine (N=93)**
48-Hour Total rescue analgesia used (mg)						
Mean (SD)	1370.6 (959.79)	1337.3 (1112.18)	1027.3 (952.25)	997.1 (994.20)	408.5 (616.85)	271.0 (413.52)
Median	1200.0	1200.0	800.0	800.0	400.0	0.0
Min, max	0, 3600	0, 4400	0, 4000	0, 4400	0, 3200	0, 1600
Rank sum mean[1]	223.4	212.6	179.7	235.9	164.8	143.3

Source: Module 2.7.3

Table 10 and Table 11 provide data on the percentages of patients receiving rescue ibuprofen in Study AVE-901-102 and Study AVE-901-103, respectively. The percent of patients receiving rescue ibuprofen was only slightly higher in the IV tramadol arm than the morphine arm in Study-901-103. IV morphine had a fast onset but approximately 40% of the patients required rescue in the first 24 hours and in the real world, they would be subject to opioid stacking based on the Division's position.

Table 10: Cochran-Mantel-Haenszel Analysis of Proportion of Patients Receiving No Rescue Medication (FAS Population) (Study AVE-901-102)

	Placebo (N=136) n (%)	**Tramadol 50 mg (N=139) n (%)**
Patients with rescue medication use from 0 to 48 hours		
Yes	121 (89.0)	103 (74.1)
No	15 (11.0)	36 (25.9)
P-value versus placebo[1]		0.002

Source: Study AVE-901-102 CSR

Table 11: Cochran-Mantel-Haenszel Analysis of Proportion of Patients Receiving No Rescue Medication (FAS Population) (Study AVE-901-103)

	Placebo (N=136)	Tramadol 50 mg (N=141)	Morphine (N=93)
Patients with rescue medication use from 0 to 24 hours			
Yes	101 (74.3)	71 (50.4)	36 (38.7)
No	35 (25.7)	70 (49.6)	57 (61.3)
P-value versus placebo[1]		<0.001	<0.001

Source: Study AVE-901-103 CSR

2. Time to First Rescue.

As shown in Table 12, the median time to first rescue in the IV tramadol arms in the double-blind studies was about 5 hours and 22 hours, respectively, for Study AVE-901-102 and Study AVE-901-103 and both are statistically better than placebo.

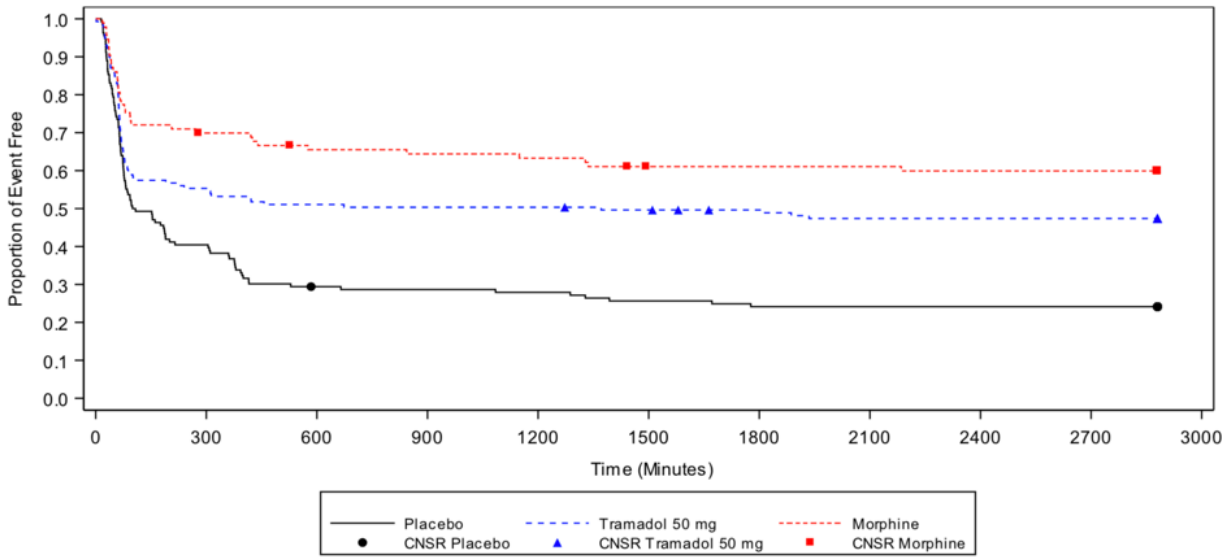
Table 12: Time to Use of First Rescue (Study AVE-901-102 and AVE-901-103)

Study	Placebo	Tramadol 50 mg	Tramadol vs Placebo
Study AVE-901-102 Bunionectomy	148 minutes	308 minutes	P<0.001
Study AVE-901-103 Abdominoplasty	104 minutes	1371 minutes	P<0.05

Source: Module 2.7.3

Based on the Kaplan-Meier curve (Figure 8), most patients who needed rescue in either IV tramadol or morphine arms in Study AVE-901-103 were provided it in the first two hours (approximately 40% of IV tramadol and approximately 28% of IV morphine patients). A hypothesized "delayed onset of effect" does not explain why 28% of subjects in the morphine arm also required rescue medication within the first few hours of morphine administration. Moreover, every patient in the morphine arm who requested rescue would be at the same potential risk of "stacking" that DAAP finds is a bar to approval for IV tramadol. It is also important to note that as explained above, most patients only required one or two doses of 400 mg ibuprofen during the course of the 48-hour treatment period (Table 9).

Figure 8: Kaplan-Meier Plot of Time to Use of First Rescue Medication (Ibuprofen), Demonstrating most patients who used Rescue used it in the first few hours of the study whether they received IV tramadol or IV morphine (Study AVE-901-103)



Source: Study AVE-901-103 CSR

3. Low rate of discontinuation due to lack of efficacy (LOE) with only NSAIDS allowed as rescue.

In the Phase 3 efficacy trials for tramadol IV, ibuprofen 400 mg up to Q4H was the only allowed rescue medication. Patients could discontinue at any time if they needed additional pain relief. A patient would not be expected to stay in the study if they were not getting clinically meaningful and adequate onset of pain relief.

However, a low discontinuation rate due to LOE in patients on IV tramadol 50 mg was observed. A total of only 6 out of 280 patients (2%) on IV tramadol 50 mg discontinued due to LOE as follows:

- In Study AVE-901-102 (bunionectomy), one patient out of 139 patients (0.7%) in the IV tramadol 50 mg arm discontinued due to LOE, versus 11 patients out of 136 patients (8.1%) patients in the placebo arm.

- In Study AVE-901-103 (abdominoplasty), five patients out of 141 patients (3.5%) in the IV tramadol 50 mg arm discontinued due to LOE, versus 6 out of 135 patients (4.4%) in the placebo arm and 2 out of 93 (2.2%) patients in the morphine arm. The rate of discontinuation due to LOE in the IV tramadol arm was similar to the IV morphine arm.

None of the 6 patients (2%) who withdrew due to LOE on IV tramadol 50 mg and received other opioid analgesics experienced an SAE, severe AE or any unexpected TEAEs within the follow-up period of the studies, which was one to two weeks post discharge.

Specifically, Table 13 lists the few patients who discontinued IV tramadol treatment, the number of doses of IV tramadol they received before dropping out, their subsequent opioid medication(s), along with the TEAEs reported. The number of patients discontinuing was very low, and no unexpected TEAEs were observed in these patients. The treating physicians were fully able to manage these patients.

Table 13: Patients taking other opioids after Discontinuation from Phase 3 Studies (Study AVE-901-102 and AVE-901-103)

Study/Patient Number	Number Doses of IV Tramadol	Other Opioids Taken Post-Treatment	Adverse Events Reported Prior to Discharge
AVE-901-103 Abdominoplasty			
10-107	1	morphine sulfate, Oxycocet (acetaminophen/oxycodone)	Nausea, Vomiting, constipation. This patient received only a single dose of IV tramadol. Vomiting and nausea were 11 hours after the dose of tramadol and thus were associated with the morphine/oxycocet treatment.
10-110	1	hydormorphone hydrchloride, Oxycocet (acetaminophen/oxycodone)	Nausea, Vomiting
10-130	1	Vicodin (hydrocodone/acetaminophen)	None
10-221	3	Oxycet (acetaminophen/oxycodone), Vicodin (hydrocodone/acetaminophen)	Nausea
10-325	1	fentanyl citrate, Procet (hydrocodone/acetaminophen)	None
AVE 901-102 Bunionectomy			
01-113	4	morphine sulfate, Procet (hydrocodone/acetaminophen)	Nausea, Hypoxia. Each of these events occurred at least 16 hours AFTER the last dose of IV tramadol and thus were related to the morphine.

Source: CSRs for Studies AVE-901-102 and AVE-901-103

Further, not a single patient discontinued due to inadequate analgesia in the open-label Phase 3 safety study (Study AVE-901-104) that did not allow another opioid as a rescue medication. The study was designed to address how IV tramadol would fit into actual clinical practice and to assess the safety and effectiveness of IV tramadol across a wide range of surgeries in a "real-world" multimodal analgesic setting. In the study, IV tramadol was given with non-opioid medicine in patients who had painful procedures that are typically managed with Schedule II opioids, such as total knee replacement surgeries and colon surgeries. Patients were allowed non-opioid pain medication (per treating physicians' discretion) in addition to IV tramadol and there were no restrictions on agents used for anesthesia, hypnotics, sedatives, or anxiolytics.

Table 14 provides a list of these medications and demonstrates the wide range of non-opioids physicians may use to treat acute pain in the post-surgical setting.

Table 14: Non-opioid medicines used in conjunction with IV tramadol in multi-modal analgesic approach (Study AVE-901-104)

WHO Drug Class/Preferred Term	Number (%) of Patients
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	104 (41.4)
Meloxicam	57 (22.7)
Ketorolac	31 (12.4)
Celecoxib	13 (5.2)
Ibuprofen	5 (2.0)
Ketorolac Tromethamine	4 (1.6)
Naproxen	2 (0.8)
OTHER ANALGESICS AND ANTIPYRETICS	147 (58.6)
Paracetamol	134 (53.4)
Gabapentin	78 (31.1)
Acetylsalicylic acid	1 (0.4)
Pregabalin	1 (0.4)

Source: Study AVE-901-104 CSR Table 14.1.6.2

Patients in the study knew that they could exit the study at any time and receive another opioid. Not a single patient out of 251 patients in this study discontinued due to inadequate analgesia. As shown in Figure 2, at 24 hours, 92.5% of patients reported that study medication was good, very good, or excellent for controlling pain. At the End of Treatment timepoint, 94.8% reported that study medication was good, very good, or excellent for controlling pain. This study provides compelling evidence supporting the effectiveness of IV tramadol in the setting of multi-modal analgesia and shows that another opioid is not required for treatment of pain with IV tramadol.

In summary, based on the data in the NDA, IV tramadol's time to onset does not necessarily lead to rescue with another opioid. Appropriate labeling for IV tramadol should emphasize that in most cases another opioid may not be necessary for adequate pain relief. Importantly, IV tramadol is to be used in a medically supervised setting where patients are monitored by physicians and other skilled clinicians who understand the risk and can transition patients to other opioids safely, if needed. That is precisely what happened in the clinical development program for IV tramadol. This information could be included in the labeling for IV tramadol, but the Division has foreclosed this approach.

C. The Division's position regarding an appropriate rescue medication following treatment with an opioid drug including IV tramadol is unexpected and contradictory to labeling for other drug products

The Division's assessment that IV tramadol's onset could lead to opioid stacking is based on its position that a nonopioid analgesic cannot bridge or augment the analgesia of an opioid and that a rescue for an opioid has to be another opioid in the post-operative setting. The Division stated in the CRL 1 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. The likely choice for prescribers would be another opioid, such as an immediate-release formulation [and] would result in opioid 'stacking' . . ." The Division stated in the CRL 2 that "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids."

The Division's position on this issue is contradicted by the data in the NDA that clearly demonstrated that if a rescue medication is needed at all, ibuprofen and other non-opioid medicines are usually sufficient rescue for IV tramadol. As discussed previously, this is also the experience of physicians in the E.U. and around the world. The Division's statement is also unexpected given FDA's labeling of multiple non-opioid products that are indicated as adjuncts for opioid analgesics. Ketorolac IV was approved based on a study where it served as rescue for morphine PCA.[77] Other examples of approved labels include CALDOLOR (ibuprofen) for intravenous use, which is indicated for use in adults and pediatric patients six months and older "for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics,"[78] and OFIRMEV (acetaminophen) injection, which is indicated 'for the management of moderate to severe pain with adjunctive opioid analgesics in adult and pediatric patients 2 years and older."[79] Avenue agrees that historically, an opioid is usually given for rescue when an NSAID alone is ineffective, but three Phase 3 studies with IV tramadol along with the extensive experience of physicians in the E.U and around the world demonstrate that at least in a post-operative health care setting, an NSAID can serve as an appropriate rescue for IV tramadol. The studies for IV tramadol were designed to fulfill the requirement to demonstrate efficacy and all recently approved IV analgesics utilized a similar design. Clinicians experienced in pain management can ascertain the performance characteristics of the drug, including onset of action, duration and tolerability profile, from the labeling in order to select the appropriate patient population for its use. In the post-operative setting, the clinician anticipates the patient's pain level and may prescribe an opioid, perhaps with a non-opioid medicine in a multimodal approach, if warranted. Further, the multimodal analgesic approach including combination therapy of an opioid with a non-opioid is well established in the management of acute pain and is recommended by a taskforce convened by the U.S. Department

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77 TORADOL (ketorolac), Prescribing Information, NDA 019645, (Mar. 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019645s019lbl.pdf (last accessed Jul. 22, 2021).

78 CALDOLOR (ibuprofen), Prescribing Information, NDA 022348, (Apr. 2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022348s018lbl.pdf (last accessed Jul. 22, 2021).

79 OFIRMEV (acetaminophen), Prescribing Information, NDA 022450, (Apr. 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022450s011lbl.pdf (last accessed Jul. 22, 2021).

of Health and Human Services and other government agencies: "To avoid the side effects associated with prescription opioids (e.g., nausea, vomiting, constipation, sedation, OUD), it is important to exploit the benefits of multimodal, non-opioid approaches in acute pain management in conjunction with possible opioid therapy."[80]

D. Opioid Stacking: OLINVYK as an informative precedent.

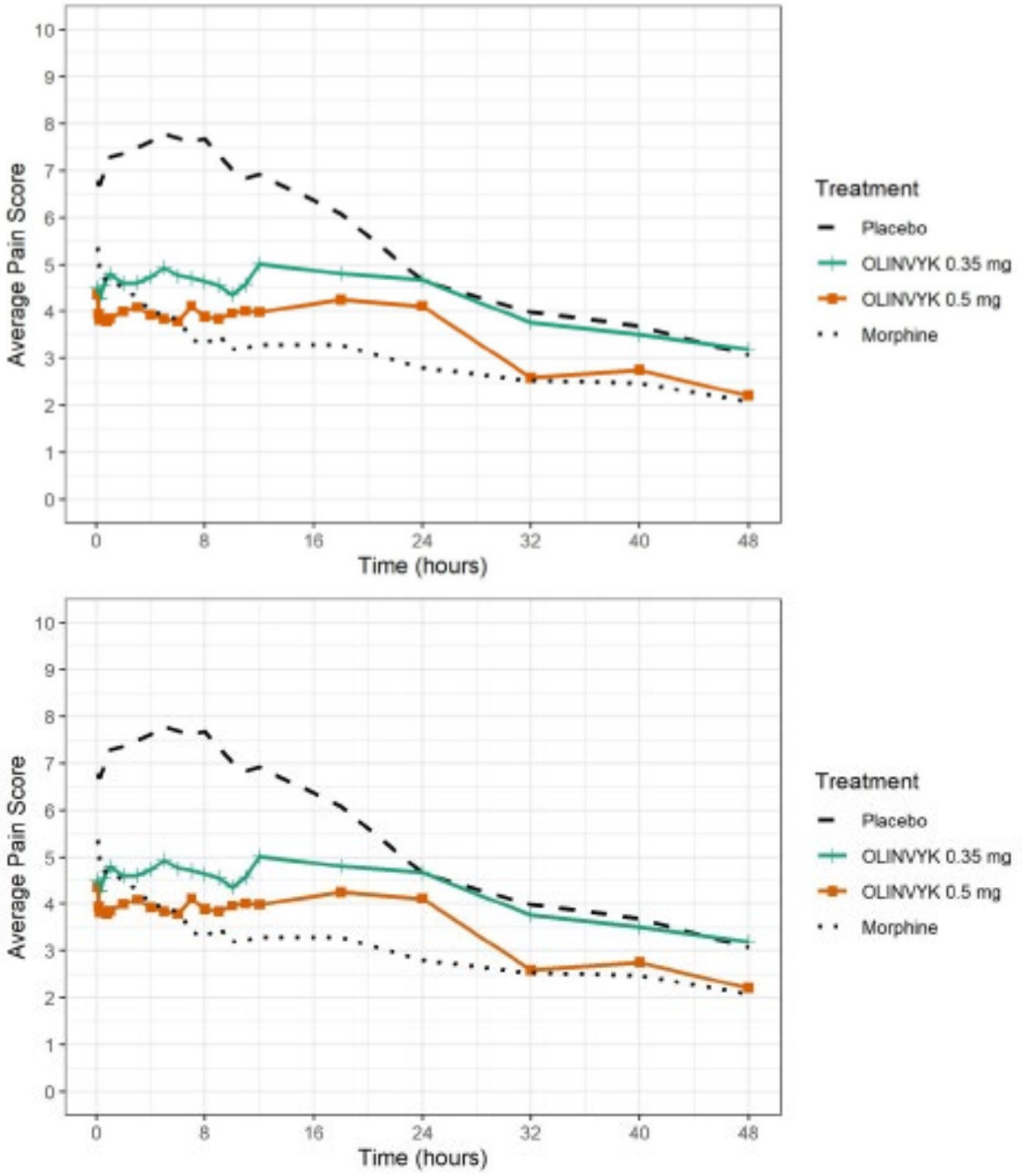
Opioid stacking occurs when an opioid is administered on top of a different opioid or when the same opioid analgesic is administered too soon. In both cases, the principal clinical risk is the same: respiratory and CNS depression. All opioid analgesics are subject to the risk of stacking regardless of its onset because patients receiving opioids with very fast onset also need rescue medicine. Class labeling already exists to manage this risk.

In Study AVE-901-103, IV morphine, a Schedule II pure mu opioid analgesic, demonstrated good onset of action according to the two-stopwatch method (42 minutes and below the Division's expectation for an IV analgesic). However, approximately 40% of patients in the IV morphine arm in Study AVE-901-103 required rescue (versus approximately 50% of the patients in IV tramadol). If the treating physician chooses another opioid, patients in the morphine arm would be subject to opioid stacking.

FDA recently approved OLINVYK, a Schedule II pure mu agonist intravenously administered via a PCA. The overall design of the OLINVYK program was similar to that of IV tramadol. OLINVYK was also tested in two efficacy studies (one in bunionectomy and one in abdominoplasty) where patients were randomized to OLINVIK, placebo or active comparator morphine and the rescue medicine was an NSAID. In the Phase 3 studies, morphine demonstrated a greater reduction in pain intensity, as the figures below from the OLINVIK labeling confirms (Figure 9).

[80] Department of Health and Human Services, Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations, (May 2019), https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf (last accessed Jul. 22, 2021).

Figure 9: OLINVYK Mean Pain Intensity versus Time Plots in the 2 Phase 3 Efficacy Studies



Source: OLINVYK labeling (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210730s000lbl.pdf)

Further, OLINVYK carries the risk of opioid stacking despite having a fast onset of action, which according to the labeling is "expected within 2 to 5 minutes after the initial dose."[81] OLINVYK carries the potential risk of opioid stacking in three different ways. First,

[81] OLINVYK (oliceridine), Prescribing Information, NDA 210730, (Mar. 2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022450s011lbl.pdf (last accessed Jul. 22,

PCA administration allows the patient to titrate the dose (within certain limits). The labeling recognizes that one of the potential risks of PCA is "stacking" the drug on top of itself: "Although self-administration of opioids by PCA may allow each patient to individually titrate to an acceptable level of analgesia, PCA administration has resulted in adverse outcomes and episodes of respiratory depression."[82]

Second, the labeling notes that for the bunionectomy study, "[I]in the 0.1 mg, 0.35 mg and 0.5 mg OLINVYK treatment groups, 41%, 20%, and 17% of patients, respectively, used the protocol-specified rescue medication etodolac" and for the abdominoplasty study "[i]n the OLINVYK 0.1 mg, 0.35 mg, and 0.5 mg treatment groups, 31%, 21%, and 18% of patients, respectively, used protocol-specified rescue medication etodolac."[83] These patients, like the rescued patients administered IV tramadol, are subject to the risk of opioid stacking if the treating physician chooses another opioid as rescue.

Third, the labeling states that "[i]f patients reach a 27 mg cumulative daily dose and analgesia is still required, an alternative analgesic regimen should be administered until OLINVYK can be resumed the next day. Alternative analgesia may include multi-modal therapies."[84] The median times for patients to reach the daily cap ranged from 13.6 to 15.8 hours in the bunionectomy trial and 14.1 to 19.4 hours in the abdominoplasty trial,[85] therefore a substantial portion of patients on OLINVYK require additional opioid level analgesia once the daily cap is reached and they are subject to the risk of opioid stacking if the treating physician chooses another opioid. It is also puzzling that the Division would recommend multi-modal therapies for patients who have reached the cap on OLINVYK because our CRL 2 stated "combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids." The OLINVK labeling seems to indicate that the Division does not discourage the use of concomitant Schedule II opioid therapies, a very different approach from the one it took for the IV tramadol NDA.

Remarkably, the FDA approved OLINVYK despite the potential risk of opioid stacking even when the reviewers concluded that "Oliceridine has a benefit-risk profile similar to that of other opioids . . . there is no evidence for a safety advantage of oliceridine over other opioids. . . . It must also be noted that morphine demonstrated a greater reduction in pain intensity than all three dosing regimens of oliceridine that were tested in the studies."[86] The Division's refusal to approve IV tramadol again shows its narrow focus on that fact that IV tramadol showed a slower onset than morphine while disregarding the benefits of IV tramadol such as its lower abuse potential while providing similar pain relief to morphine on the primary and key secondary

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2021).

82 *Id.*

83 *Id.*

84 *Id.*

85 *Id.*

86 OLINVYK (oliceridine), Multi-Discipline Review, NDA 210730 (Aug. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210730Orig1s000MultidisciplineR.pdf (last accessed Jul. 22nd, 2021)

endpoints. The Sponsor notes that the slower onset of IV tramadol compared to IV morphine is expected based on their mechanisms of action and explains tramadol's lower abuse potential, a benefit of IV tramadol.

Finally, the labeling for all opioids warn the physician of this potential risk of stacking. Morphine, for example, instructs:

- Morphine: Morphine should be administered cautiously to avoid additive effects when other central nervous system depressants, including other narcotic analgesics, general anesthetics, phenothiazines, tricyclic antidepressants, tranquilizers, sedatives, hypnotics, antiemetics, and alcohol are given concomitantly. When given concomitantly the risks of respiratory depression, hypotension, profound sedation and coma are increased.[87]

In the absence of any Clinical Studies section of the labeling for morphine, the physician considering intravenous administration is advised to "[a]djust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience" and "[i]n the selection of the initial dose of Morphine Sulfate Injection USP, give attention to . . . the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously."[88]

Likewise, the labeling for fentanyl alerts the physician to the potential risk of stacking.

- Fentanyl: To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential. As with other potent opioids, the respiratory depressant effect of Fentanyl Citrate Injection may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia. . . . Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Citrate Injection with benzodiazepines or other CNS depressants (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol).[89]

The labeling for morphine and fentanyl also take the post-surgery setting into account, but even then, the labeling also highlights the possibility of overdose ("stacking") despite having the ability to titrate these drugs to effect. For example:

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87 Morphine sulfate (morphine sulfate), Prescribing Information, NDA 202515, (Nov. 2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202515s000lbl.pdf (last accessed Jul. 22, 2021).

88 *Id.*

89 Sublimaze Preservative Free (fentanyl citrate), Prescribing Information, NDA 016619 (Oct. 2019), https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/016619s043lbl.pdf (last accessed Jul. 22, 2021)

> Morphine Sulfate Injection should be limited to use by those familiar with the management of respiratory depression. . . . Selection of patients for treatment with Morphine Sulfate Injection USP should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.[90]

In any event, FDA's approach to managing the risk for every other opioid is through labeling and OLINVYK demonstrates FDA's willingness to approve a Schedule II pure mu opioid analgesic that carries the risk of opioid stacking while having no advantage over morphine. However, the Division has completely foreclosed this option for IV tramadol.

E. IV tramadol is to be used in a medically supervised setting, further reducing the risks related to "stacking"

As multiple clinical experts discussed with the Division in the first Type A meeting and second Type A meeting, use of concomitant opioids is common and considered the standard of care in a medically supervised setting such as a hospital or ambulatory surgery center. Patients typically receive multiple opioids in the post-operative care unit to control their pain, and then are often transitioned to yet another opioid when they are transferred to the floor. It is safe to do so in this setting as it is the standard of care for medical professionals to continuously assess patients on opioids with regular assessments of their pain levels, respiratory rate, oxygen saturation, and cognition. The medical professionals are trained to monitor for the clinical signs and symptoms of opioid-related side effects. Proper monitoring for IV opioid therapy is mandatory at every hospital and ambulatory surgical center, with pre-specified monitoring criteria for patients receiving IV opioids. In this setting, there are protocols with dosing instructions in place to ensure safe administration of opioids based on a real time evaluation of the individual patient. Importantly, healthcare professionals, not patients, administer opioids in this setting, and the health care professionals are trained to hold doses and notify physicians if patients are showing any signs or symptoms of an adverse reaction. The use of multiple opioids is common, and the risks of opioid stacking is effectively managed in an inpatient setting. As with other opioids, the labeling of IV tramadol will contain important information such as onset, potency, duration and side effect profile, etc. that will help clinicians to understand how to administer IV tramadol safely.

VII. Refusal to Approve IV Tramadol is Inconsistent with Public Health Policy.

Parenteral tramadol has been approved in over 70 countries outside the U.S. for over 25 years and widely prescribed at doses from 50 mg up to 100 mg (Grünenthal 2017). According to

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[90] Morphine sulfate (morphine sulfate), Prescribing Information, NDA 202515, (Nov. 2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202515s000lbl.pdf (last accessed Jul. 22, 2021).

IQVIA (an independent data provider), approximately 370 million doses of parenteral tramadol have been used in Europe over the last ten years (2010-2019). IV tramadol is not a new product but rather a new route of administration of an existing opioid, scheduled as a Schedule IV and thus with less potential for abuse than existing Schedule II products (all approved IV opioids for acute pain are currently placed in Schedule II). IV tramadol is intended as an option where a Schedule II may not be necessary or where physicians would like to use a less abusable intravenous pain relief in the in-clinic setting. IV tramadol is not intended to be used at home, and thus the risk of abuse is reduced accordingly.

The scheduling difference between tramadol (Schedule IV) and all other IV opioids for acute pain (Schedule II) reflects the scientific understanding of the abuse potential of tramadol and is supported by extensive preclinical, clinical, post-marketing and epidemiological studies conducted by various academic institutions, sponsors, and government agencies. It was also recognized in a recent report on tramadol by the WHO expert committee on drug dependence, which stated: "Parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalised since first-pass metabolism is avoided. Hence, the abuse of tramadol is much reduced through intravenous administration when compared to ingestion."[91] As discussed in more detail below, the lower abuse potential of tramadol as compared to Schedule II opioids is also supported by epidemiological data (Module 5.3.6 Epi Abuse Summary Report) related to the abuse of tramadol in the US, as well as in countries where IV tramadol has been on the market.

Clinicians in the US are currently limited in their choices of intravenous analgesics, which are widely used in the acute pain setting because of their pharmacokinetics and the fact that many patients cannot take medications orally. The approved IV analgesics in the U.S. for post-surgical pain generally include three pharmacological classes: acetaminophen, NSAIDs, and Schedule II opioids. The lack of options contributes to the fact that intravenous Schedule II opioids are still used heavily in the acute pain setting where many patients have contraindications to one or more classes of non-opioid medications. 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.[92] Use of IV tramadol in the medically supervised setting will help avoid this situation, which is consistent with parenteral experience outside the U.S.[93] and demonstrated in our Phase 3 safety study (Study AVE-901-104), where IV tramadol in concurrent use with non-opioid analgesics provided safe and effective pain control without another opioid. Therefore, any potential risk of opioid stacking following IV tramadol use in a medically supervised setting will likely be no more than what is currently occurring with Schedule II opioids and should be considered in the context of benefit by avoiding the use of more abusable opioids.

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91 World Health Organization, Critical Review Report: Tramadol; Expert Committee on Drug Dependence (Nov. 2018), https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf (last accessed Jul. 22, 2021).

92 Reference provided previously.

93 Reference provided previously.

A. Epidemiological data.

In an advice letter (22 Nov 2010), and reaffirmed at the Type B EOP2 meeting, the Division requested the following:

> In your NDA submission, provide an update of epidemiological data related to the abuse of tramadol in the US, as well as in countries where the product (tramadol hydrochloride injection) has been on the market. Any information regarding routes of abuse of tramadol, such as by ingestion, intravenous injection or snorting would be helpful.

An epidemiologic assessment of the abuse of tramadol (both in the U.S. as well as ex-US) was performed. A report entitled "Summary of Epidemiologic Findings on Abuse of Tramadol (oral and injection): United States and European Union 5 (France, Germany, Italy, Spain, United Kingdom)" was written to describe the epidemiological data related to abuse of tramadol both in the US as well as ex-US (see Module 5.3.6 Epi Abuse Summary Report for the complete report),

To address the Division's request the Sponsor conducted a targeted literature review of abuse of oral tramadol and tramadol for injection, and examined studies of various epidemiological databases on abuse, misuse, and non-medical use of tramadol and comparator opioids in the both the U.S. and the EU-5. The four databases selected for analyses and the territories they cover are:

- The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system: a system of projects that collects product-and geographic-specific data on abuse, misuse, and diversion of prescription drugs (U.S.), and EU-5 (France, Germany, Italy, Spain, and the United Kingdom)

- The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO): a database that uses a proprietary survey to capture data from adults assessed for substance abuse problems and treatment planning (U.S.).

- The National Survey on Drug Use and Health (NSDUH): a congressionally mandated population-based US household survey that collects information on tobacco, alcohol, and drug use, mental health and other health-related issues in the U.S. (U.S.).

- Abuse-related Adverse Events from the FDA Adverse Event Reporting System (FAERS): a database that contains spontaneous adverse event (AE) reports, including medication error reports and product quality complaints resulting in AEs (U.S.).

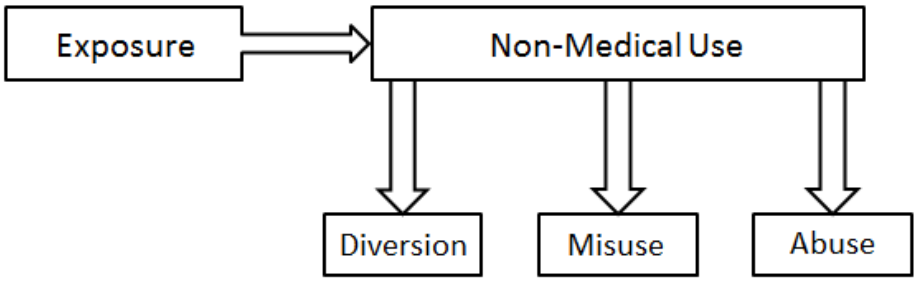
Avenue chose the RADARS database and the EU-5 as the most relevant and robust epidemiology database to answer the question of the abuse of tramadol in countries where the product (tramadol hydrochloride injection) has been on the market. The abuse of tramadol and IV tramadol in the EU-5 were most relevant for this purpose because tramadol for injection is approved in each of these five countries, and their standard-of-care medical practices and availability of medicine are generally considered to be closer to the U.S. than other regions. The

data from the EU-5 provide insight into the abuse potential of IV tramadol and reflects worst case scenarios since tramadol is not scheduled in the majority of the EU-5.

In the database studies, rates of abuse, misuse, and non-medical use in both the general population and the high-risk treatment center population are all assessed. In the EU-5, the comparator opioids are codeine, morphine, and oxycodone. The routes of administration and formulation (oral versus injectable) were examined whenever available. In the U.S., the comparator opioids across different database studies are hydrocodone, oxycodone, and morphine. To provide an additional context, the misuse of tramadol was also compared to that of alprazolam, another well-known Schedule IV drug in the U.S. in the NSDUH survey.

The framework to understand prescription drug non-medical use is illustrated in Figure 10. Below are representative data that illustrate that tramadol has lower potential for abuse than comparator opioids. The numbers are adjusted with units dispensed to provide a valid framework because each tablet represents an opportunity for misuse or abuse. This approach is consistent with how the FDA reviews surveillance data.[94]

Figure 10: Prescription Drug Non-Medical Use Landscape

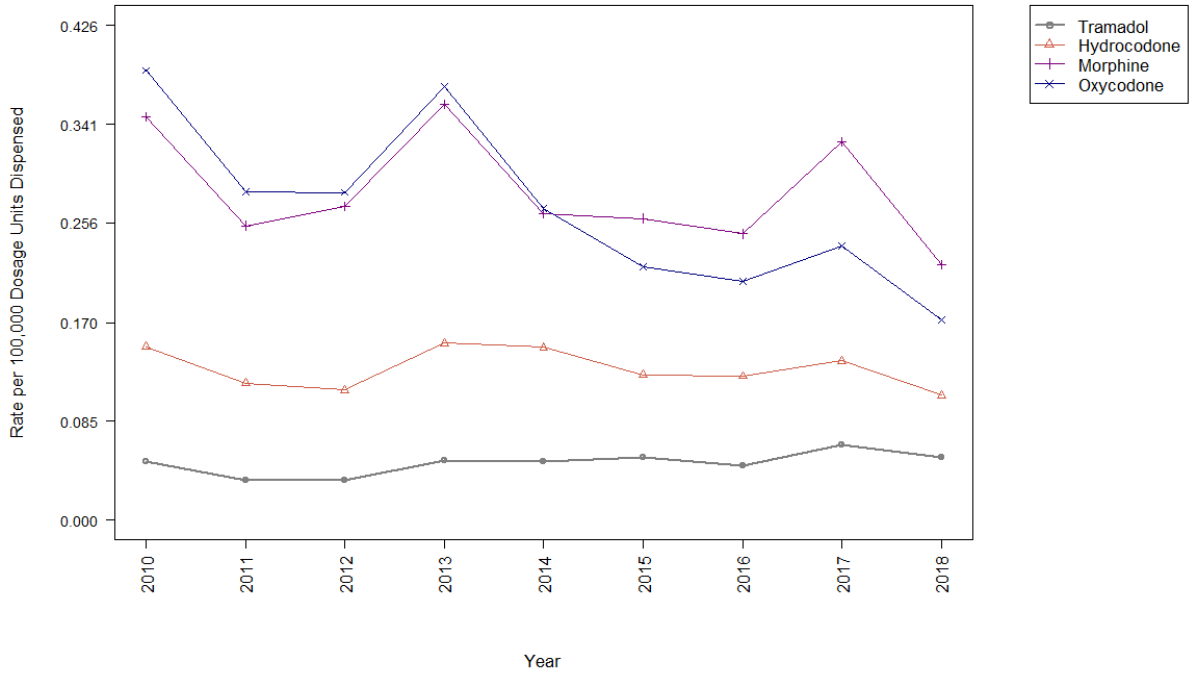


Source: Module 5.3.6 Epi Abuse Summary Report

Figure 11 shows the rate of diversion of tramadol and comparator opioids in the U.S. In general, drugs with higher abuse potential have higher street value and more diversion.

94 Gerald J. Dal Pan, *Real-World Data, Advanced Analytics, and the Evolution of Postmarket Drug Safety Surveillance*, 106 CLINICAL PHARMACOLOGY AND THERAPEUTICS 28-30 (2019).

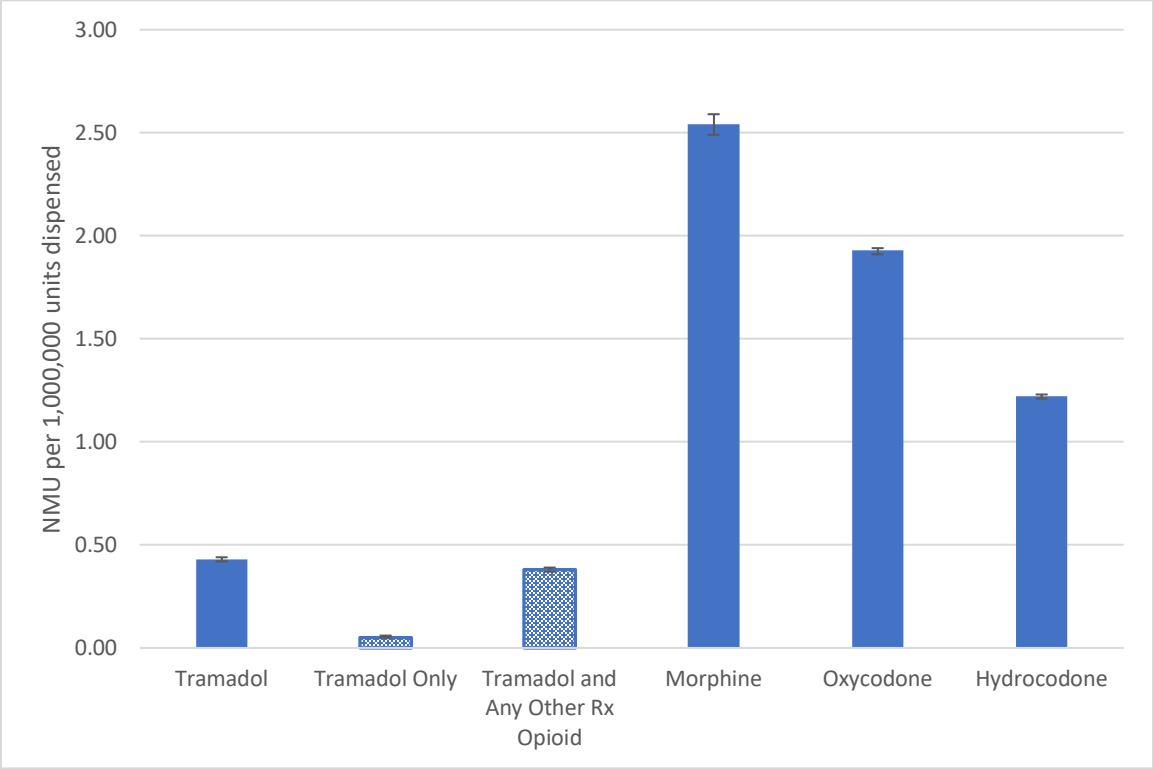
Figure 11: Diversion Rates of Tramadol and Comparators by Year in the United States (Drug Utilization-Adjusted) RADARS® System Drug Diversion Program 3rd Quarter 2010 through 4th Quarter 2018



Source: Module 5.3.6 Epi Abuse Summary Report

Figure 12 shows the past 30-day non-medical use for tramadol and comparator opioids in a high-risk treatment center population.

Figure 12: Past 30-day NMU per 1,000,000 units dispensed for tramadol and comparators within the ASI-MV network (1/1/2010 – 12/31/2018)



Source: Module 5.3.6 Epi Abuse Summary Report

Overall, the data summarized in the epidemiology review of studies and the literature search were consistent with one another and demonstrate that reports of abuse with tramadol are infrequent, both in absolute number and relative to other prescription opioids, such as morphine, oxycodone, hydrocodone (US), and codeine (EU-5). Furthermore, abuse of tramadol via injection is uncommon relative to oral tramadol in both the U.S. and in countries where it is available. These data are support tramadol's placement in Schedule IV and the clinical data supported these findings; TEAEs related to potential abuse were rare in the IV tramadol development program and were lower as compared to IV morphine.

B. Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry.

The clinical program for IV tramadol strongly supports the value of treatment with IV tramadol as a less abusable opioid for relief of post-surgical pain and that IV tramadol can be safely and effectively incorporated into routine multimodal postoperative analgesic regimens where patients can be spared the administration of Schedule II opioids. Therefore, the benefit of IV tramadol, as an effective alternative to intravenous Schedule II opioids, but with lower abuse potential, outweighs its known risks. As such, the Division's view on benefit-risk of IV tramadol, based on the known potential risk of opioid stacking with no mention of abuse liability of Schedule IV versus Schedule II opioids, was unexpected, given the Agency's landmark 2019 draft guidance *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework*

Guidance for Industry. This guidance highlights the consideration of the abuse liability of opioids as it relates to the misuse and abuse in the benefit-risk determination. If patients in acute pain, who require an opioid in an inpatient setting, can be managed effectively using a Schedule IV opioid like IV tramadol, then there is public benefit in reducing the prescribing of Schedule II opioids. The IV tramadol Phase 3 studies demonstrated precisely that: Tramadol IV, a Schedule IV opioid, can effectively manage their pain especially in the context of multi-modal analgesia.

A decision on the approvability of the NDA for IV tramadol must consider that the use of this product will be limited to medically supervised setting, where medications are administered by healthcare professionals and patients are monitored by physicians and other skilled clinicians who understand this potential issue and can safely transition patients to another opioid if needed.

C. Labeling is used to manage risk for all opioid analgesics, and IV tramadol should be no different.

Prescriber expectations are best informed by clear and complete labeling. The purpose of drug labeling is to provide healthcare professionals with the information they need to prescribe drugs appropriately.[95] Based on the information included in the NDA, IV tramadol is safe and effective for the proposed population and indication. As with all opioid analgesics, the appropriate means to address risks such as a potential risk of opioid stacking is through the labeling. In framing time to onset as an approvability issue and dismissing the ability of labeling to adequately describe this pharmacodynamic characteristic of IV tramadol, the Division interferes with the practice of medicine by inserting itself into the realm of prescriber preferences and expectations, which is outside FDA's regulatory mandate.

The opioid class labeling includes language in Section 5 of all opioid analgesic that addresses concomitant use of CNS depressants such as opioids with another opioid. This section is included in the proposed IV tramadol labeling. As shown in Section VI.C. above, labeling can be uniquely crafted to address the unique circumstances of every analgesic. However, the Division has completely foreclosed this possibility for IV tramadol. For the vast majority of patients who will not require Schedule II opioid analgesics, having an alternative to Schedule II opioids using a multimodal analgesic approach would be a safe and effective option for the treatment of post-operative pain in a medically supervised setting. The information in the proposed draft labeling allows prescribers to appropriately place IV tramadol into an MMA paradigm. Time to onset of action and meaningful pain relief can be adequately conveyed in labeling (MELOXICAM). Appropriate non-opioid rescue medications consistent with the multimodal management of pain can be adequately conveyed in labeling (OLINVYK). The risk of "stacking," even for products that may be titrated, can be adequately conveyed in labeling (morphine, fentanyl, OLINVYK).

Multimodal management of pain is the standard of care in the inpatient setting.[96] Indeed, as DAAP has recognized in its review of other analgesics, "[p]rescription medications are often a

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95 Mary E. Kremzner & Steven F. Osborne, U.S. Food and Drug Admin., *An Introduction to the Improved FDA Prescription Drug Labeling*, https://www.fda.gov/files/about%20fda/published/Prescription-Drug-Labeling-Course-Slides.pdf (last accessed Jul. 22, 2021).

96 Jeffrey L. Apfelbaum et al., *Practice Guidelines for Acute Pain Management in the Perioperative Setting:*

component of a multimodal analgesic approach, which is standard in many institutions. Pharmacologic options include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), topical agents (e.g., local anesthetics), and opioids."[97] Further, despite a prescriber's expectations for a particular level of analgesia, patients present differently and experience pain differently. Because patients can articulate their experience in real time while in inpatient care, pain treatment can be tailored on the spot to the needs of the patient as expressed by that patient. Consequently, having a Schedule IV option with informative labeling allows the prescriber the option of fashioning an appropriate treatment plan for patients without exposing them to a Schedule II opioid.

IV tramadol has novel pharmacokinetic characteristics. The differences in onset between IV tramadol and other IV pain medications do not mean that IV tramadol does not meet the statutory standard for approval. It means only that the IV tramadol labeling should describe how IV tramadol can be expected to act in practice. DAAP's narrow focus on time to onset elevates pharmacodynamic data from a somewhat artificial clinical trial setting above the benefits of providing a safe and effective Schedule IV opioid that can be expected to obviate the need for Schedule II opioids in many cases. In determining whether to use a particular analgesic at a given time, practitioners will take into consideration the information provided in labeling, as well as previous clinical experience with the drug. In addressing pain following surgery, practitioners looking to provide an IV analgesic that is not a Schedule II opioid would have another option with IV tramadol. Clearly, there is a place for IV tramadol in the armamentarium of drugs to treat acute pain. As the United States remains in the throes of an opioid epidemic, innovative alternatives for pain management must be encouraged.

* * * * *

Avenue is eager to resolve the issues raised in this FDRR and would be pleased to provide the ON with any additional information it may need during its review.

An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management, 116(2) ANESTHESIOLOGY 248 (2012).

97 Dsuvia (sufentanil) tablets, Cross Discipline Team Leader Review, NDA 209128, 6 (Nov. 1, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209128Orig1s000CrossR.pdf (last accessed Jul. 22 2021).

VIII. LIST OF DOCUMENTS

A list of documents previously submitted to the sponsor's application that are deemed necessary for resolution of the matter.

Date	From	Description
11/22/2010	DAAP	FDA letter
08/04/2017	DAAP	Advice following IND submission of the Phase 3 studies
06/21/2016	DAAP	End of Phase 2 Meeting Minutes
09/23/2019	DAAP	Pre-NDA Meeting Minutes
10/10/2019	Avenue	Sponsor's meeting minutes of a teleconference to discuss the post-meeting note regarding time to onset
12/10/2019	Avenue	NDA 213231
	Avenue	Clinical Study Report Study AVE-901-101
	Avenue	Clinical Study Report Study AVE-901-102
	Avenue	Clinical Study Report Study AVE-901-103
	Avenue	Clinical Study Report Study AVE-901-104
10/09/2020	DAAP	Complete Response Letter (CRL 1)
10/16/2020	Avenue	Briefing Book for the Type A meeting
11/19/2020	DAAP	First Type A Post Action Meeting
02/12/2021	Avenue	NDA 213231 Resubmission
02/26/2021	DAAP	Acknowledge - Class 1 Complete Response
06/11/2021	DAAP	Complete Response Letter (CRL 2)
07/23/2021	DAAP	Second Type A Post-Action Meeting
08/26/2021	ON	Appeal Denied Letter

DAAP= Division of Anesthesiology, Addiction Medicine, and Pain Medicine

ON= Office of Neuroscience

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULTRAM® safely and effectively. See full prescribing information for ULTRAM.

ULTRAM (tramadol hydrochloride) tablets, for oral use, C-IV
Initial U.S. Approval – 1995

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **ULTRAM exposes users to the risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRAM, and monitor regularly for these behaviors or conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase. (5.3)**
- **Accidental ingestion of ULTRAM, especially by children, can result in a fatal overdose of tramadol. (5.3)**
- **Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. (5.4)**
- **ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4). Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. (5.4)**
- **Prolonged use of ULTRAM, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.5)**
- **The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRAM requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1. (5.6, 7)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.7, 7)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2)	03/2021
Warnings and Precautions (5.1, 5.3, 5.7)	03/2021
Warnings and Precautions (5.19, 5.20)	09/2021

----------INDICATIONS AND USAGE----------

ULTRAM is an opioid agonist indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate (1).

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (5.1), reserve ULTRAM 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.

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse (2.1).
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ULTRAM and adjust the dosage accordingly (2.1).
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with ULTRAM. Consider prescribing naloxone based on the patient's risk factors for overdose (2.2, 5.1, 5.3, 5.7).
- Start at 25 mg/day and titrate 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** (2.3, 2.4).
- Severe Renal Impairment: increase the ULTRAM dosing interval to 12 hours, and limit maximum daily dose to 200 mg (2.3).
- Severe hepatic impairment: Recommended dose is 50 mg every 12 hours.
- Do not abruptly discontinue ULTRAM in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 50 mg (3).

----------CONTRAINDICATIONS----------

- Children younger than 12 years of age (4).
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (4).
- Significant respiratory depression (4).
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4).
- Hypersensitivity to tramadol, any other component of this product or opioids (4).
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4).

----------WARNINGS AND PRECAUTIONS----------

- Serotonin Syndrome: May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol (5.8).
- Risk of Seizure: Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures (5.9).
- Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients (5.10).
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid (5.11).
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration (5.12).
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ULTRAM in patients with circulatory shock (5.13).
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ULTRAM in patients with impaired consciousness or coma (5.14).

----------ADVERSE REACTIONS----------

The most common incidence of treatment-emergent adverse events (≥15.0%) in patients from clinical trials were dizziness/vertigo, nausea, constipation, headache, somnolence, vomiting and pruritus (6).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with ULTRAM because they may reduce analgesic effect of ULTRAM or precipitate withdrawal symptoms (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

ADDICTION, ABUSE AND MISUSE

ULTRAM exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRAM, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

OPIOID ANALGESIC RISK EVALUATION AND MITIGATION STRATEGY (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to:

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

LIFE-THREATENING RESPIRATORY DEPRESSION

Serious, life-threatening, or fatal respiratory depression may occur with use of ULTRAM. Monitor for respiratory depression, especially during initiation of ULTRAM or following a dose increase *[see Warnings and Precautions (5.3)]*.

ACCIDENTAL INGESTION

Accidental ingestion of ULTRAM, especially by children, can be fatal. *[see Warnings and Precautions (5.3)]*.

ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN

Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at

least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism *[see Warnings and Precautions (5.4)]*. ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*. Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol *[see Warnings and Precautions (5.4)]*.

NEONATAL OPIOID WITHDRAWAL SYNDROME

Prolonged use of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.5)]*.

INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRAM requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 *[see Warnings and Precautions (5.6); Drug Interactions (7)]*.

RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.7); Drug Interactions (7)]*.

- **Reserve concomitant prescribing of ULTRAM and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit treatment to the minimum effective dosages and durations.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

ULTRAM is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve ULTRAM 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Do not use ULTRAM concomitantly with other tramadol-containing products.
- Do not administer ULTRAM at a dose exceeding 400 mg per day.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5.1)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ULTRAM and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with ULTRAM *[see Warnings and Precautions (5.3), Patient Counseling Information (17)]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. However, the presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.3, 5.7)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose.

2.3 Initial Dosage

Initiating Treatment with ULTRAM

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 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

Conversion from ULTRAM to Extended-Release Tramadol

The relative bioavailability of ULTRAM compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression.

Dosage Modification in Patients with Hepatic Impairment

The recommended dose for adult patients with severe hepatic impairment is 50 mg every 12 hours.

Dosage Modification in Patients with Renal Impairment

In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

Dosage Modification in Geriatric Patients

Do not exceed a total dose of 300 mg/day in patients over 75 years old.

2.4 Titration and Maintenance of Therapy

Individually titrate ULTRAM to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ULTRAM to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as to monitor for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the ULTRAM dosage. 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.

2.5 Safe Reduction or Discontinuation of ULTRAM

Do not abruptly discontinue ULTRAM in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking ULTRAM, there are a variety of factors that should be considered, including the dose of ULTRAM the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on ULTRAM who are physically opioid-dependent, initiate the taper by a small enough increment, (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with a lower dosage strength to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.17), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

ULTRAM (tramadol hydrochloride) 50 mg (equivalent to 43.9 mg of tramadol) tablets are white, capsule-shaped, coated, with a functional score. The tablets are imprinted "ULTRAM" on one side and "06 59" on the scored side.

4 CONTRAINDICATIONS

ULTRAM is contraindicated for:

- all children younger than 12 years of age *[see Warnings and Precautions (5.4)]*.
- postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Warnings and Precautions (5.4)]*.

ULTRAM is also contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.12)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)]*.
- Hypersensitivity to tramadol, any other component of this product or opioids *[see Warnings and Precautions (5.16)]*.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

ULTRAM contains tramadol, a Schedule IV controlled substance. As an opioid, ULTRAM exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ULTRAM. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ULTRAM, and monitor all patients receiving ULTRAM for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ULTRAM, but use in such patients necessitates intensive counseling about the risks and proper use of ULTRAM along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing

naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ULTRAM. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counselling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: *www.fda.gov/OpioidAnalgesicREMSPCG*.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to *www.opioidanalgesicrems.com*. FDA Blueprint can be found at *www.fda.gov/OpioidAnalgesicREMSBlueprint*.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately

recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ULTRAM, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ULTRAM.

To reduce the risk of respiratory depression, proper dosing and titration of ULTRAM are essential *[see Dosage and Administration (2)]*. Overestimating the ULTRAM dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of ULTRAM, especially by children, can result in respiratory depression and death due to an overdose of tramadol.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with ULTRAM. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)]*.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. However, the presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental exposure or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Warnings and Precautions (5.1, 5.7), Patient Counseling Information (17)]*.

5.4 Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol and codeine are subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol or with codeine, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol. Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- ULTRAM is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.
- Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.
- As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose *[see Use in Specific Populations (8.4), Overdosage (10)]*.

Nursing Mothers

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of the active metabolite *O*-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking ULTRAM could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with ULTRAM *[see Use in Specific Populations (8.2)]*.

CYP2D6 Genetic Variability: Ultra-rapid Metabolizer

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (e.g., gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and

may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). These individuals convert tramadol into its active metabolite, *O*-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) *[see Overdosage (10)]*. Therefore, individuals who are ultra-rapid metabolizers should not use ULTRAM.

5.5 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ULTRAM during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

5.6 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from ULTRAM are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRAM requires careful consideration of the effects on the parent drug, tramadol which is a weak serotonin and norepinephrine reuptake inhibitor and μ-opioid agonist, and the active metabolite, M1, which is more potent than tramadol in μ-opioid receptor binding *[see Drug Interactions (7)]*.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use of ULTRAM with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. A decrease in M1 exposure in patients who have developed physical dependence to tramadol, may result in signs and symptoms of opioid withdrawal and reduced efficacy. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in tramadol plasma levels and an increase in active metabolite M1 levels, which could increase or prolong adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression.

Follow patients receiving ULTRAM and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when ULTRAM is used in conjunction with inhibitors of CYP2D6 *[see Drug Interactions (7)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of ULTRAM with cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events including seizures and serotonin syndrome, and may cause potentially fatal respiratory depression.

The concomitant use of ULTRAM with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower tramadol levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving ULTRAM and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when ULTRAM is used in conjunction with inhibitors and inducers of CYP3A4 *[see Drug Interactions (7)]*.

5.7 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ULTRAM with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ULTRAM is used with benzodiazepines or other CNS depressants (including alcohol and illicit

drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7); and Patient Counseling Information (17)]*.

5.8 Serotonin Syndrome Risk

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, particularly during concomitant use with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue ULTRAM if serotonin syndrome is suspected.

5.9 Increased Risk of Seizure

Seizures have been reported in patients receiving ULTRAM within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses of ULTRAM above the recommended range.

Concomitant use of ULTRAM increases the seizure risk in patients taking *[see Drug Interactions (7)]*:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.),
- Other opioids,
- MAO inhibitors *[see Warnings and Precautions (5.8); Drug Interactions (7)]*.
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of seizure may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and

drug withdrawal, CNS infections). In ULTRAM overdose, naloxone administration may increase the risk of seizure.

5.10 Suicide Risk

- Do not prescribe ULTRAM for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed *[see Drug Abuse and Dependence (9)]*.

- Prescribe ULTRAM with caution for patients with a history of misuse and/or are currently taking CNS-active drugs including tranquilizers or antidepressant drugs, alcohol in excess, and patients who suffer from emotional disturbance or depression *[see Drug Interactions (7)]*.

- Inform patients not to exceed the recommended dose and to limit their intake of alcohol *[see Dosage and Administration (2), Warnings and Precautions (5.7)]*.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of ULTRAM in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

ULTRAM -treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ULTRAM *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating ULTRAM and when ULTRAM is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.7); Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.13 Severe Hypotension

ULTRAM may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ULTRAM. In patients with circulatory shock, ULTRAM may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ULTRAM in patients with circulatory shock.

5.14 Risks of use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ULTRAM may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ULTRAM.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ULTRAM in patients with impaired consciousness or coma.

5.15 Risks of Use in Patients with Gastrointestinal Conditions

ULTRAM is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus *[see Contraindications (4)]*.

The tramadol in ULTRAM may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.16 Anaphylaxis and Other Hypersensitivity Reactions

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with ULTRAM. When these events do occur it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of hypersensitivity reactions to tramadol and other opioids may be at increased risk and therefore should not receive ULTRAM *[see Contraindications (4)]*. If anaphylaxis or other hypersensitivity occurs, stop administration of ULTRAM immediately, discontinue ULTRAM permanently, and do not rechallenge with any formulation of tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. *[see Contraindications (4); Patient Counselling Information (17)]*.

5.17 Withdrawal

Do not abruptly discontinue ULTRAM in a patient physically dependent on opioids. When discontinuing ULTRAM in a physically dependent patient, gradually taper the dosage. Rapid tapering of tramadol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.5), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including ULTRAM. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.18 Driving and Operating Machinery

ULTRAM may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ULTRAM and know how they will react to the medication *[see Patient Counselling Information (17)]*.

5.19 Hyponatremia

Hyponatremia (serum sodium < 135 mmol/L) has been reported with the use of tramadol, and many cases are severe (sodium level < 120 mmol/L). Most cases of hyponatremia occurred in females over the age of 65 and within the first week of therapy. In some reports, hyponatremia resulted from the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Monitor for signs and symptoms of hyponatremia (e.g., confusion, disorientation), during treatment with ULTRAM, especially during initiation of therapy. If signs and symptoms of hyponatremia are present, initiate appropriate treatment (e.g., fluid restriction) and discontinue ULTRAM *[see Dosage and Administration: Safe Reduction or Discontinuation of ULTRAM (2.5)]*.

5.20 Hypoglycemia

Cases of tramadol-associated hypoglycemia have been reported, some resulting in hospitalization. In most cases, patients had predisposing risk factors (e.g. diabetes). If hypoglycemia is suspected, monitor blood glucose levels and consider drug discontinuation as appropriate *[see Dosage and Administration: Safe Reduction or Discontinuation of ULTRAM (2.5)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*

- Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Suicide *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.13)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.15)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.16)]*
- Withdrawal *[see Warnings and Precautions (5.17)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ULTRAM was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 1 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to ULTRAM administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM and the active control groups, TYLENOL with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM groups.

Table 1: Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N=427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Dizziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"[1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1] "CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations

Incidence 1% to Less than 5% Possibly Causally Related

The following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.

Cardiovascular: Vasodilation.

Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Gastrointestinal: Abdominal pain, Anorexia, Flatulence.

Musculoskeletal: Hypertonia.

Skin: Rash.

Special Senses: Visual disturbance.

Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence Less than 1%, Possibly Causally Related

The following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials of tramadol and/or reported in postmarketing experience with tramadol-containing products.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).

Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.

Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure, Tremor.

Respiratory: Dyspnea.

Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.

Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder.

Other Adverse Experiences, Causal Relationship Unknown

A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or reported in postmarketing experience. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.

Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.

Central Nervous System: Migraine.

Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.

Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.

Sensory: Cataracts, Deafness, Tinnitus.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ULTRAM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

QT prolongation/torsade de pointes: Cases of QT prolongation and/or *torsade de pointes* have been reported with tramadol use. Many of these cases were reported in patients taking another

drug labeled for QT prolongation, in patients with a risk factor for QT prolongation (e.g., hypokalemia), or in the overdose setting.

Eye disorders – mydriasis

Metabolism and nutrition disorders – Hyponatremia: Cases of severe hyponatremia and/or SIADH have been reported in patients taking tramadol, most often in females over the age of 65, and within the first week of therapy *[see Warnings and Precautions (5.19)]*.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients *[see Warnings and Precautions (5.20)]*.

Nervous system disorders – movement disorder, speech disorder

Psychiatric disorders – delirium

7 DRUG INTERACTIONS

Table 2: Clinically Significant Drug Interactions with ULTRAM

Inhibitors of CYP2D6	
Clinical Impact:	The concomitant use of ULTRAM and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of ULTRAM is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping a CYP2D6 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase. This could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, such as potentially fatal respiratory depression *[see Clinical Pharmacology (12.3)]*.
Intervention:	If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome. If a CYP2D6 inhibitor is discontinued, consider lowering ULTRAM dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine and bupropion
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of ULTRAM and CYP3A4 inhibitors can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of ULTRAM is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to tramadol.
Intervention:	If concomitant use is necessary, consider dosage reduction of ULTRAM until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals.

	If a CYP3A4 inhibitor is discontinued, consider increasing the ULTRAM dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of ULTRAM and CYP3A4 inducers can decrease the plasma concentration of tramadol *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause seizures, serotonin syndrome, and/or potentially fatal respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the ULTRAM dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ULTRAM dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of ULTRAM and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.7)]*. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3, 5.7)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, and alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ULTRAM immediately if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.9)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	Do not use ULTRAM in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of ULTRAM and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ULTRAM and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.3, 5.7)]*.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when ULTRAM is used concomitantly with anticholinergic drugs.
Digoxin	
Clinical Impact:	Postmarketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
Intervention:	Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Warfarin	
Clinical Impact:	Postmarketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with ULTRAM in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome can present as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during postmarketing.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. ULTRAM is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including ULTRAM, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Data

Animal Data

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m^2 basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental

or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.

Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg 1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).

8.2 Lactation

Risk Summary

ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, *O*-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding *[see Clinical Pharmacology (12)]*. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM *[see Warnings and Precautions (5.4)]*.

Clinical Considerations

If infants are exposed to ULTRAM through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Data

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

8.4 Pediatric Use

The safety and effectiveness of ULTRAM in pediatric patients have not been established.

Life-threatening respiratory depression and death have occurred in children who received tramadol *[see Warnings and Precautions (5.4)]*. In some of the reported cases, these events followed tonsillectomy and/or adenoidectomy, and one of the children had evidence of being an ultra-rapid metabolizer of tramadol (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6). Children with sleep apnea may be particularly sensitive to the respiratory depressant effects of tramadol. Because of the risk of life-threatening respiratory depression and death:

- ULTRAM is contraindicated for all children younger than 12 years of age *[see Contraindications (4)]*.
- ULTRAM is contraindicated for postoperative management in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy *[see Contraindications (4)]*.

Avoid the use of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol unless the benefits outweigh the risks. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression.

8.5 Geriatric Use

A total of 455 elderly (65 years of age or older) subjects were exposed to ULTRAM in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ULTRAM slowly in geriatric patients starting at the low end of the dosing range and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.12)]*.

Tramadol is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Renal and Hepatic Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosing reduction is recommended *[see Dosage and Administration (2.3)]*. Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver. In patients with severe hepatic impairment, dosing reduction is recommended *[see Dosage and Administration (2.3)]*.

With the prolonged half-life in these conditions, achievement of steady-state is delayed, so that it may take several days for elevated plasma concentrations to develop.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ULTRAM (tramadol hydrochloride) contain tramadol, a Schedule IV controlled substance.

9.2 Abuse

ULTRAM contains tramadol, a substance with a high potential for abuse similar to other opioids. ULTRAM can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially harmful, consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent

tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

ULTRAM, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of ULTRAM

ULTRAM is intended for oral use only. Abuse of ULTRAM poses a risk of overdose and death. The risk is increased with concurrent abuse of ULTRAM with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of drugs to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue ULTRAM in a patient physically dependent on opioids. Rapid tapering of ULTRAM in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing ULTRAM, gradually taper the dosage using a patient-specific plan that considers the following: the dose of ULTRAM the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.5), Warnings and Precautions (5.17)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with ULTRAM can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Deaths due to overdose have been reported with abuse and misuse of tramadol *[see Warnings and Precautions (5.1); Drug Abuse and Dependence (9.2)]*. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or serious arrhythmias will require advanced life-supporting measures.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

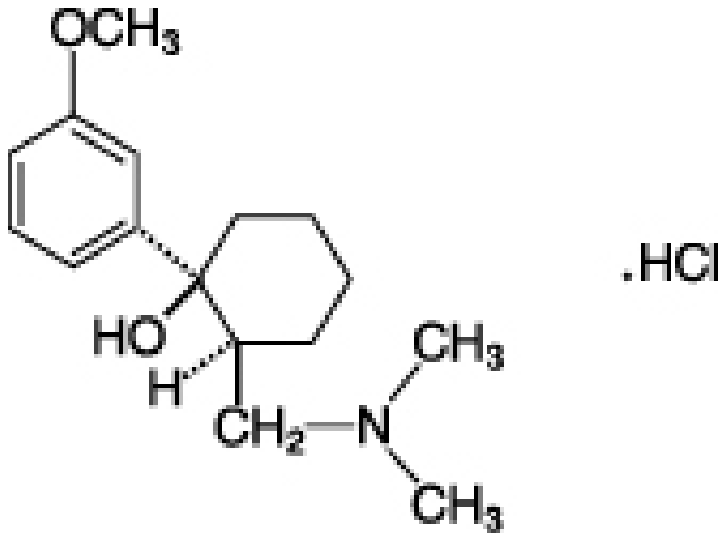
While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of ULTRAM could be suppressed with barbiturates or benzodiazepines but were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

Because the duration of opioid reversal is expected to be less than the duration of action of tramadol in ULTRAM, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

ULTRAM® (tramadol hydrochloride) tablets, for oral use, are an opioid agonist. The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The structural formula is:



The molecular weight of tramadol hydrochloride is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. ULTRAM tablets contain 50 mg of tramadol hydrochloride (equivalent to 43.9 mg of tramadol) and are white in color. Inactive ingredients in the tablet are pregelatinized corn starch, modified starch (corn), hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and carnauba wax.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULTRAM contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound *[see Clinical Pharmacology (12.2)]*.

Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Tramadol produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Tramadol administration may produce a constellation of symptoms including nausea and vomiting, dizziness, and somnolence.

Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Tramadol produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

The effect of oral tramadol on the QTcF interval was evaluated in a double-blind, randomized, four-way crossover, placebo- and positive- (moxifloxacin) controlled study in 68 adult male and female healthy subjects. At a 600 mg/day dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTcF interval.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Warnings and Precautions (5.11); Adverse Reactions (6)]*.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may

influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioid agonists. The minimum effective analgesic concentration of tramadol 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)]*.

Concentration–Adverse Reaction Relationships

There is a relationship between increasing tramadol plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

The analgesic activity of ULTRAM is due to both parent drug and the M1 metabolite *[see Clinical Pharmacology (12.1, 12.2)]*. Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption

The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~ 10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with four times per day dosing. There is no evidence of self-induction (see Figure 1 and Table 3 below).

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given four times per day.

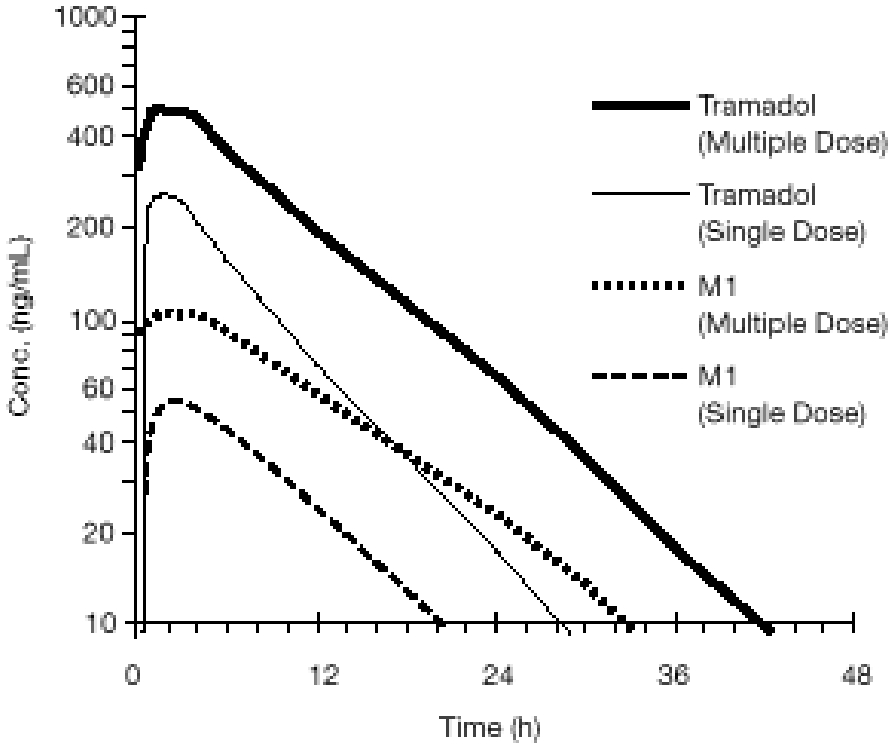


Table 3: Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/Dosage Regimen[a]	Parent Drug/ Metabolite	Peak Conc.(ng/mL)	Time to Peak (hrs)	Clearance/F[b] (mL/min/Kg)	$t_{1/2}$ (hrs)
Healthy Adults,	Tramadol	592 (30)	2.3 (61)	5.90 (25)[c]	6.7 (15)
100 mg qid, MD p.o.	M1	110 (29)	2.4 (46)		7.0 (14)
Healthy Adults,	Tramadol	308 (25)	1.6 (63)	8.50 (31)[c]	5.6 (20)
100 mg SD p.o.	M1	55.0 (36)	3.0 (51)		6.7 (16)
Geriatric, (>75 yrs)	Tramadol	208 (31)[d]	2.1 (19)[d]	6.89 (25)[c]	7.0 (23)[d]
50 mg SD p.o.	M1				
Hepatic Impaired,	Tramadol	217 (11)	1.9 (16)	4.23 (56)[c]	13.3 (11)
50 mg SD p.o.	M1	19.4 (12)	9.8 (20)		18.5 (15)
Renal Impaired,	Tramadol	[c]	[c]	4.23 (54)[c]	10.6 (31)
CLcr10-30 mL/min	M1	[c]	[c]		11.5 (40)
100 mg SD i.v.					
Renal Impaired,	Tramadol	[c]	[c]	3.73 (17)[c]	11.0 (29)
CLcr<5 mL/min	M1	[c]	[c]		16.9 (18)
100 mg SD i.v.					

[a] SD = Single dose, MD = Multiple dose, p.o.= Oral administration, i.v.= Intravenous administration, q.i.d. = Four times daily

[b] F represents the oral bioavailability of tramadol

[c] Not applicable

[d] Not measured

Food Effects

Oral administration of ULTRAM with food does not significantly affect its rate or extent of absorption, therefore, ULTRAM can be administered without regard to food.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean (%CV) apparent total clearance of tramadol after a single 100 mg oral dose is 8.50 (31) mL/min/kg. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Metabolism

Tramadol is extensively metabolized after oral administration by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. One metabolite (*O*-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response *[Warnings and Precautions (5.4); Drug Interactions (7)]*.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers”, while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of serotonin re-uptake inhibitors and MAO inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*.

Excretion

Tramadol metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites.

Special Populations

Hepatic Impairment

Metabolism of tramadol and M1 is reduced in patients with severe hepatic impairment based on a study in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). In patients with severe hepatic impairment, adjustment of the dosing regimen is recommended *[see Dosage and Administration (2)]*.

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended *[see Dosage and Administration (2)]*. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Age: Geriatric

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years *[see Dosage and Administration (2.3)]*.

Sex

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

Poor / Extensive Metabolizers, CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6, a polymorphic enzyme. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450 metabolizing enzyme system. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies with IR tablets in healthy subjects, concentrations of

tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A slight, but statistically significant, increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.36 times the MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water, 0.73 times the MRHD.

Mutagenesis

Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the *in vitro* bacterial reverse mutation assay using *Salmonella* and *E. coli* (Ames), the mouse lymphoma assay in the absence of metabolic activation, the *in vitro* chromosomal aberration assay, or the *in vivo* micronucleus assay in bone marrow.

Impairment of Fertility

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.2 and 1.8 times the maximum recommended human daily dose based on body surface area, respectively.

14 CLINICAL STUDIES

ULTRAM has been given in single oral doses of 50, 75 and 100 mg to patients with pain following surgical procedures and pain following oral surgery (extraction of impacted molars).

In single-dose models of pain following oral surgery, pain relief was demonstrated in some patients at doses of 50 mg and 75 mg. A dose of 100 mg ULTRAM tended to provide analgesia superior to codeine sulfate 60 mg, but it was not as effective as the combination of aspirin 650 mg with codeine phosphate 60 mg.

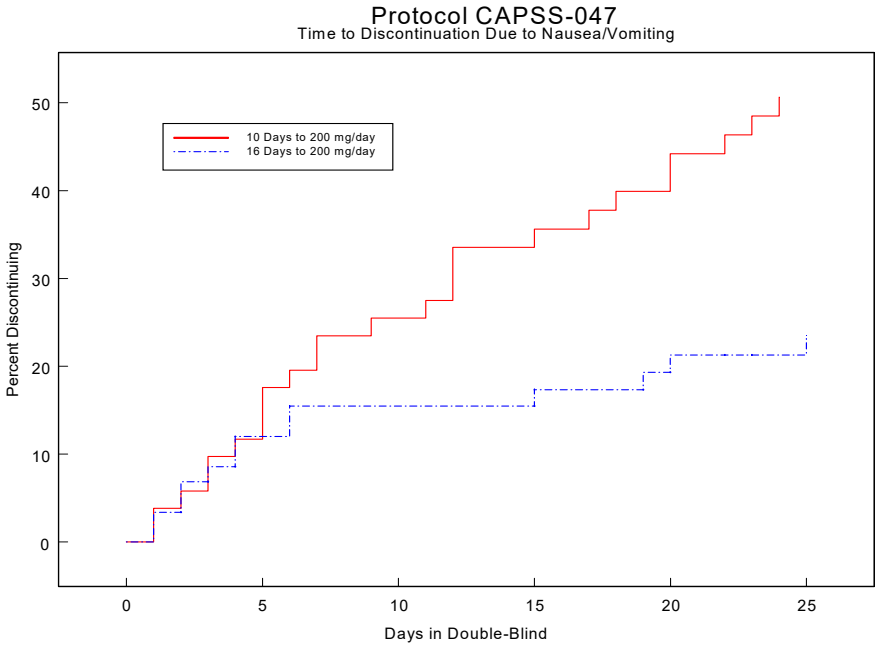
ULTRAM has been studied in three long-term controlled trials involving a total of 820 patients, with 530 patients receiving ULTRAM. Patients with a variety of chronic painful conditions were studied in double-blind trials of one to three months duration. Average daily doses of approximately 250 mg of ULTRAM in divided doses were generally comparable to five doses of acetaminophen 300 mg with codeine phosphate 30 mg (TYLENOL with Codeine #3) daily, five doses of aspirin 325 mg with codeine phosphate 30 mg daily, or two to three doses of acetaminophen 500 mg with oxycodone hydrochloride 5 mg (TYLOX) daily.

Titration Trials

In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM dose of 200 mg (50 mg four times per day), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates.

A 16-day titration schedule, starting with 25 mg every morning and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg four times per day), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg four times per day), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

Figure 2:



16 HOW SUPPLIED/STORAGE AND HANDLING

ULTRAM® (tramadol hydrochloride) 50 mg tablets are white, capsule-shaped, coated, with a functional score. The tablets are imprinted “ULTRAM” on one side and “06 59” on the scored side.

Bottle of 100 tablets: NDC 50458-659-60

Dispense in a tight container. Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].

Store ULTRAM securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store ULTRAM securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.17), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving ULTRAM unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that medicine take-back options are the preferred way to safely dispose of most types of unneeded medicines. If no take back programs or Drug Enforcement Administration (DEA)-registered collectors are available, instruct patients to dispose of ULTRAM by following these four steps:

- Mix ULTRAM (do not crush) with an unpalatable substance such as dirt, cat litter, or used coffee grounds;
- Place the mixture in a container such as a sealed plastic bag;
- Throw the container in the household trash;
- Delete all personal information on the prescription label of the empty bottle.

Inform patients that they can visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of ULTRAM, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share ULTRAM with others and to take steps to protect ULTRAM from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting ULTRAM or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.3)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with ULTRAM. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*.

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Advise caregivers that ULTRAM is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Advise caregivers of children ages 12 to 18 years of age receiving ULTRAM to monitor for signs of respiratory depression *[see Warnings and Precautions (5.4)]*.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ULTRAM is used with benzodiazepines, CNS depressants, including alcohol, or some illicit drugs and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.7); Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of

serotonin syndrome, and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.8)]*.

Seizures

Inform patients that ULTRAM may cause seizures with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol *[see Warnings and Precautions (5.9)]*.

MAOI Interaction

Inform patients not to take ULTRAM while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking ULTRAM *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Important Administration Instructions

- Instruct patients how to properly take ULTRAM. *[see Dosage and Administration (2)]*.
- Advise patients not to adjust the dose of ULTRAM without consulting with a physician or other healthcare professional.

Important Discontinuation Instructions

- In order to avoid developing withdrawal symptoms, instruct patients not to discontinue ULTRAM without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)]*.

Hypotension

Inform patients that ULTRAM may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.13)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in ULTRAM. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4); Warnings and Precautions (5.16); Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and that the patient should inform their healthcare provider if they have used opioids at any time during their pregnancy, especially near the time of birth. *[see Warnings and Precautions (5.5); Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that ULTRAM may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with ULTRAM *[see Warnings and Precautions (5.4); Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that ULTRAM may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.18)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Maximum single-dose and 24-hour dose

Advise patients not to exceed the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures and death *[see Dosage and Administration (2); Warnings and Precautions (5.3)]*.

Product of Switzerland

Manufactured by:

Janssen Ortho LLC
Gurabo, Puerto Rico 00778

Manufactured for:

Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

MEDICATION GUIDE
ULTRAM® [UHL-tram]
(tramadol hydrochloride)
Tablets, C-IV

ULTRAM is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used for the management pain in adults, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about ULTRAM:

- **Get emergency help or call 911 right away if you take too much ULTRAM (overdose).** When you first start taking ULTRAM, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking ULTRAM with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your ULTRAM. They could die from taking it. Selling or giving away ULTRAM is against the law.
- Store ULTRAM securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Important Information Guiding Use in Pediatric Patients:

- Do not give ULTRAM to a child younger than 12 years of age.
- Do not give ULTRAM to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
- Avoid giving ULTRAM to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take ULTRAM if you have:

- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or have narrowing of the stomach or intestines.
- An allergy to tramadol.
- Taken a Monoamine Oxidase Inhibitor, MAOI, (medicine used for depression) within the last 14 days.

Before taking ULTRAM, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant**. Prolonged use of ULTRAM during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized

and treated.

- **breastfeeding**. Not recommended; it may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ULTRAM with certain other medicines can cause serious side effects that could lead to death.

When taking ULTRAM:

- Do not change your dose. Take ULTRAM exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose as indicated by your healthcare provider. The maximum dosage is 1 or 2 tablets every 4 to 6 hours, as needed for pain relief. Do not take more than your prescribed dose and do not take more than 8 tablets per day. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking ULTRAM regularly, do not stop taking ULTRAM without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused ULTRAM by taking your drug to an authorized Drug Enforcement Administration (DEA)-registered collector or drug take-back program. If one is not available, you can dispose of ULTRAM by mixing the product with dirt, cat litter, or coffee grounds; placing the mixture in a sealed plastic bag, and throwing the bag in your trash.

While taking ULTRAM DO NOT:

- Drive or operate heavy machinery, until you know how ULTRAM affects you. ULTRAM can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ULTRAM may cause you to overdose and die.

The possible side effects of ULTRAM:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These are not all the possible side effects of ULTRAM. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov.

Manufactured by: Janssen Ortho LLC, Gurabo, Puerto Rico 00778. Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, New Jersey 08560, 1-800-526-7736

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 09/2021