



AVENUE THERAPEUTICS, INC. | NASDAQ: ATXI

Forward Looking Statements

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Value Proposition

1. Potential acquisition agreement with InvaGen could deliver substantial value to shareholders upon 2nd stage closing*
 - Shareholders may also have upside from Contingent Value Rights (CVRs) based on IV tramadol sales under the InvaGen deal, if 2nd stage closing takes place
2. Strong IP position on our proprietary dosing regimen expected to protect exclusivity in the U.S. into the mid 2030's

****As of May 1, 2021, InvaGen retains an option to complete the second stage closing or terminate the Stock Purchase and Merger Agreement until October 31, 2021.***



Regulatory Status

- On February 12, 2021, we resubmitted our New Drug Application (NDA) for IV tramadol.
 - The resubmission included revised language relating to the proposed product label and a report relating to terminal sterilization validation.
- The NDA resubmission follows the receipt of official minutes from a Type A meeting with the FDA, which was conducted following a Complete Response Letter issued by the FDA in October 2020.
- PDUFA goal date was April 12, 2021. The FDA is still reviewing the NDA resubmission.



Why IV Tramadol?

Uniquely Positioned to Address a Clear and Significant Need for New Therapies for Post-operative Pain Amidst Opioid Crisis

- Dual MOA delivers opioid efficacy with less abuse potential and risk of dependence
- **If approved, IV Tramadol will be the only intravenous Schedule IV opioid in the U.S.**
- Provides convenient bridge to widely prescribed oral tramadol, which has established efficacy and safety
- Fills in the gap in acute care space between IV acetaminophen/NSAIDs and conventional narcotics

Broad Applicability with Potential to Replace Conventional Narcotics in Wide Range of Patients

- A new option for patients with contraindications to NSAIDs, those who can't tolerate strong narcotics, and those unwilling to take strong narcotics, etc.



Unique Dual Mechanism of Action Among IV Analgesics

IV TRAMADOL



Schedule IV versus Conventional Narcotics (Schedule II)

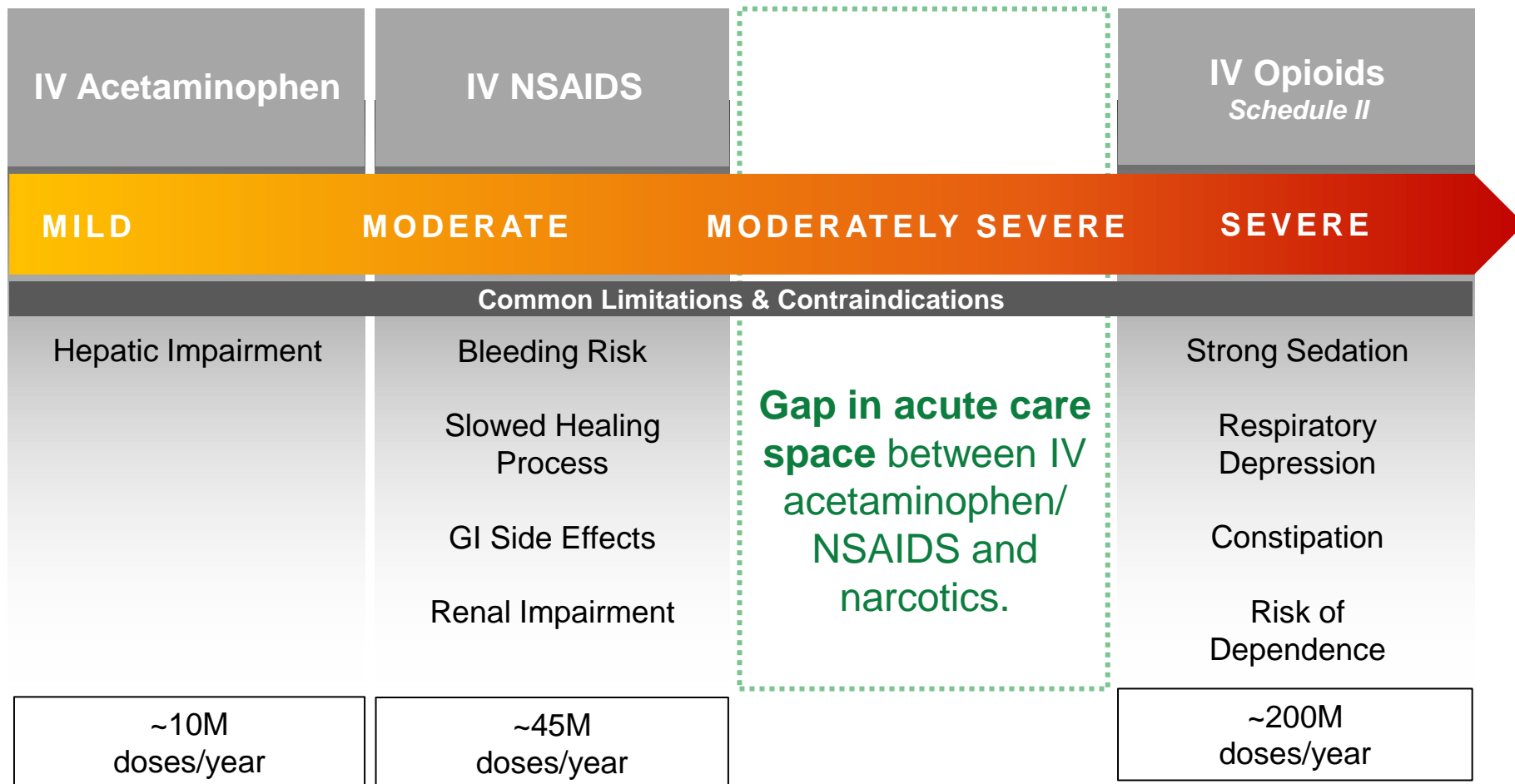
Note: Schedule IV means a low potential for abuse and low risk of dependence. Schedule II drugs have a high potential for abuse, with use potentially leading to severe psychological or physical dependence.

Source: <https://www.dea.gov/druginfo/ds.shtml>



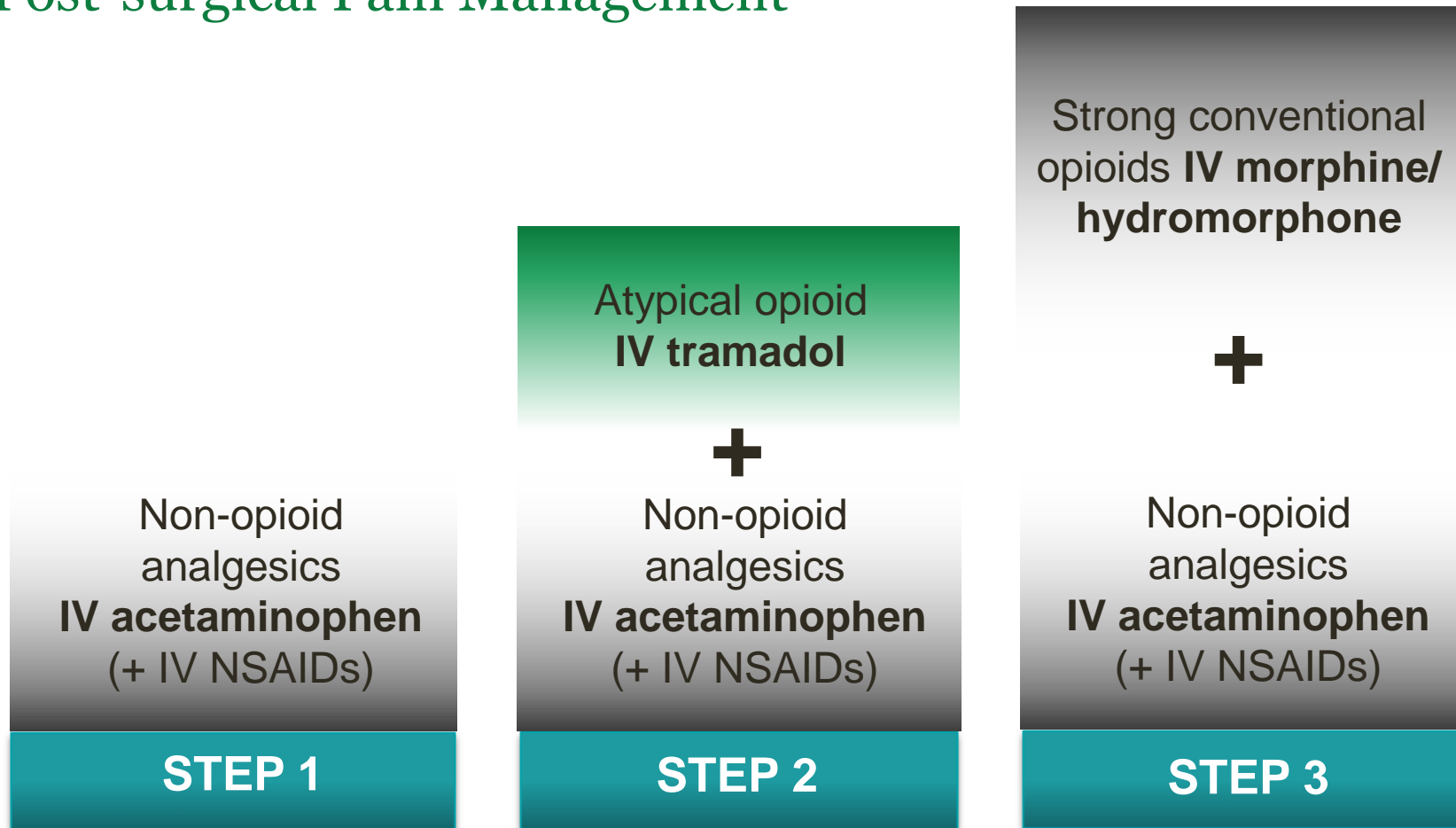
What is the Unmet Need in Post-op Pain Care?

Current Post-Op Pain Management Paradigm



Potential Paradigm: Simplified IV “Analgesic Ladder” Post-2020

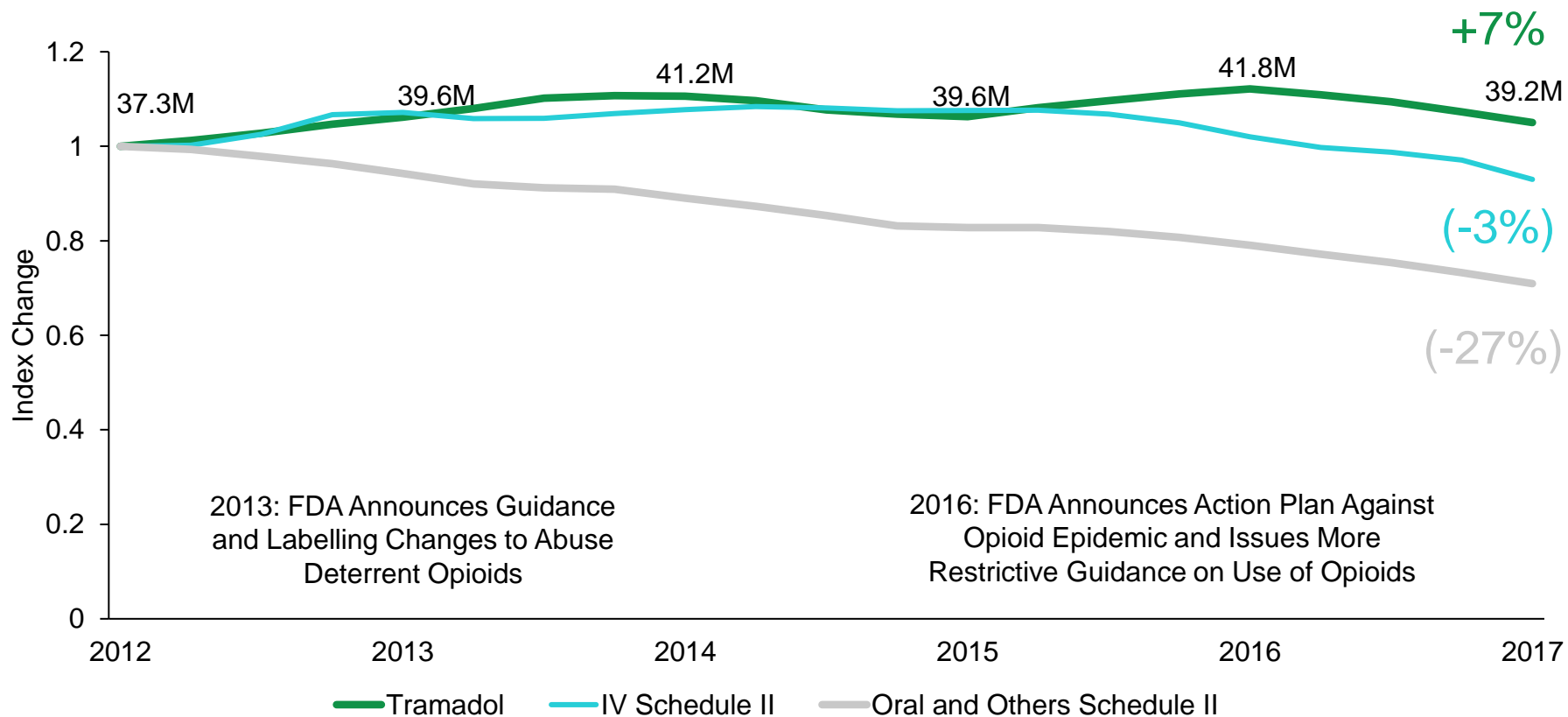
Systemic Pharmacotherapy to Remain the Mainstay of Post-surgical Pain Management



Oral Tramadol is Widely Prescribed in the U.S.

Oral Tramadol Usage Has Increased During the Opioid Crisis
Schedule II Usage Has Decreased Significantly, Less so in the IV Setting

~5 Year Period^{1,2}



Source: Symphony Health Solutions; Note: 1. Decline shown as of 9/30/2017 2. Constraints at Pfizer's McPherson site have affected IV product supply since November 2017



IV Tramadol Favorably Suited for Multi-modal Pain Management

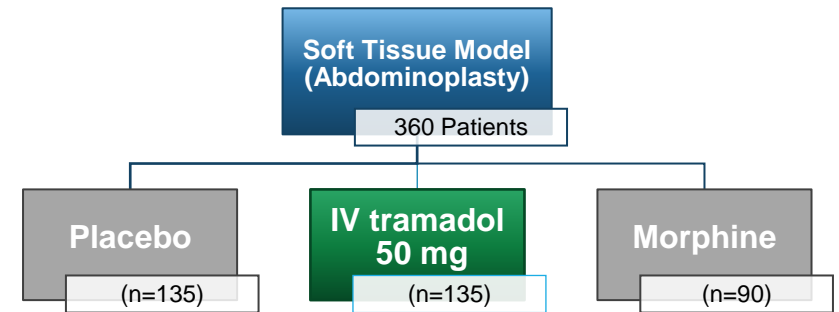
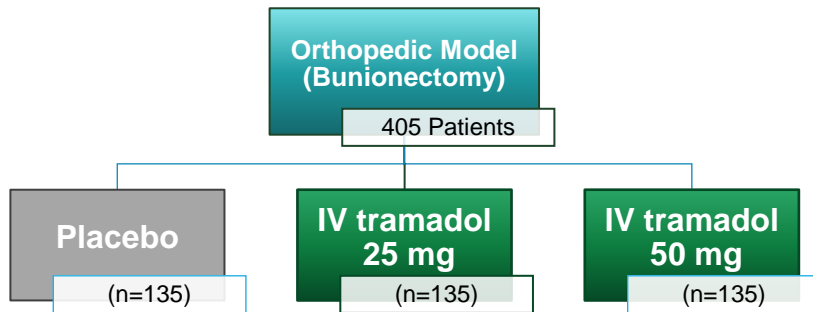
Future Post-Op Pain Management Paradigm

IV Acetaminophen	IV NSAIDS	IV Tramadol <i>Schedule IV</i>	IV Opioids <i>Schedule II</i>
MILD	MODERATE	MODERATELY SEVERE	SEVERE
Common Limitations & Contraindications			
Hepatic Impairment	Bleeding Risk Slowed Healing Process GI Side Effects Renal Impairment	Nausea/Dizziness History of Seizure Concomitant use of Serotonergic Drugs	Strong Sedation Respiratory Depression Constipation Risk of Dependence
		Effective pain relief in place of Schedule II intravenous narcotics	

IV Tramadol to avoid use of conventional opioid; Step-down therapy to oral Tramadol



2 Phase 3 Trials – Completed in 2Q2019



PRIMARY ENDPOINT

Sum of Pain Intensity Differences (SPID) through 48 hours post first dose

PRIMARY ENDPOINT

Sum of Pain Intensity Differences (SPID) through 24 hours post first dose

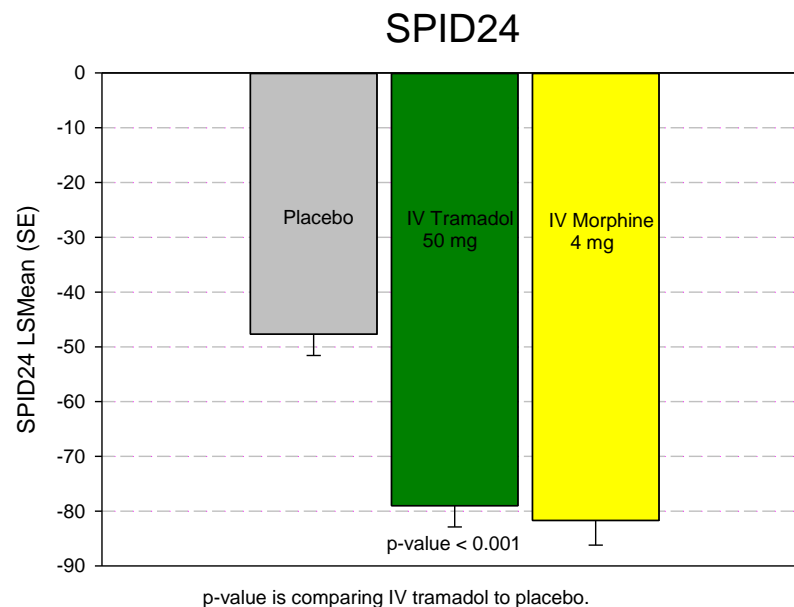
Safety Study
(n=250)



Abdominoplasty Study Results

IV Tramadol 50 mg Achieved Primary Endpoint and All Key Secondary Endpoints in this soft-tissue model

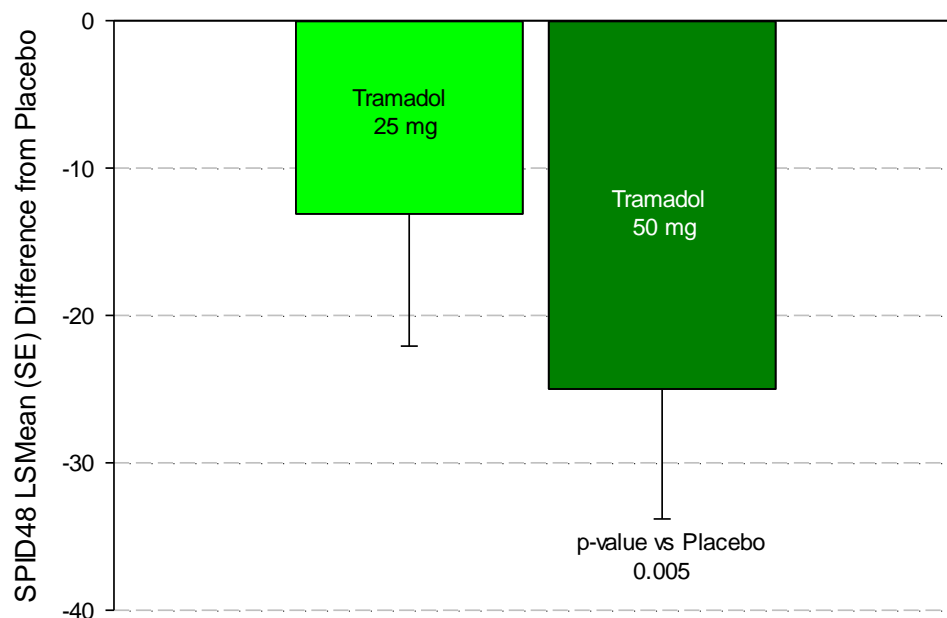
- $P < 0.001$ for the primary endpoint of SPID24 (Sum of Pain Intensity Difference over 24 hours)
- Key secondary endpoints included:
 - PGA
 - SPID48
 - Total consumption of rescue medicine
- Similar efficacy benefit to IV morphine 4 mg, a standard-of-care IV opioid



Bunionectomy Study Results

IV Tramadol 50 mg Achieved Primary Endpoint and All Key Secondary Endpoints in this orthopedic model

- P=0.005 for the primary endpoint of SPID48 (Sum of Pain Intensity Difference over 48 hours)
- Key secondary endpoints included:
 - SPID24
 - Total consumption of rescue medicine
 - Patient Global Assessment (PGA)
- Rapid onset of efficacy
 - Statistically significant pain reduction seen as early as 30 minutes after dosing



No Surprise in Safety Outcomes

IV Tramadol 50 mg was Well Tolerated in both studies

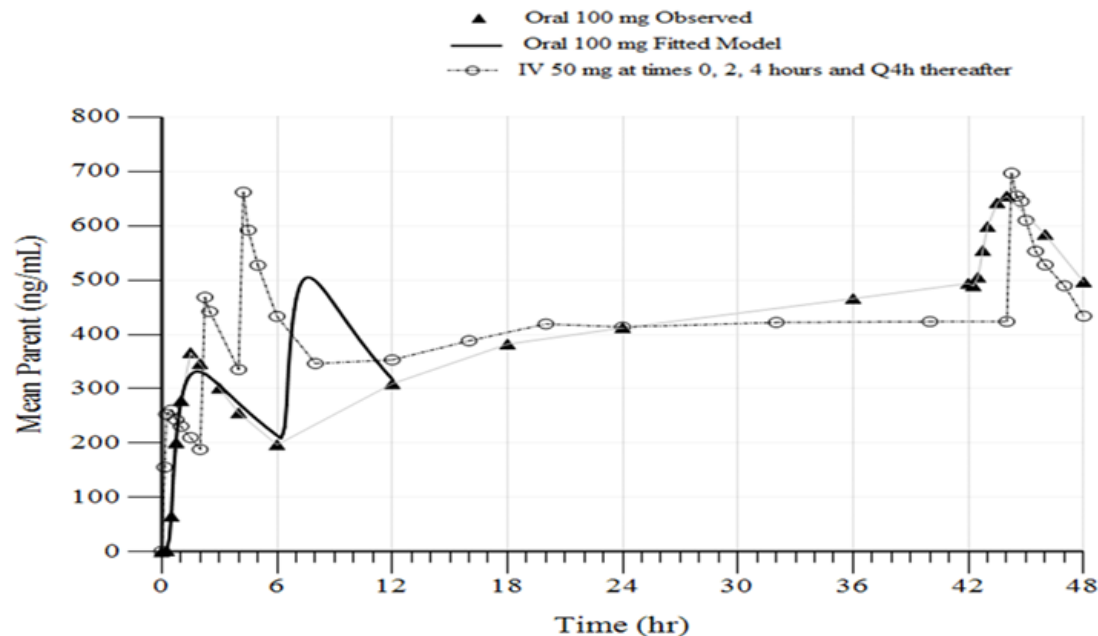
- There were no drug-related serious adverse events (SAEs)
- AE profile was consistent with known tramadol pharmacology
- The most common AEs (>10%) in the abdominoplasty study:

	Nausea (%)		Vomiting (%)		Headache (%)		Dizziness (%)	
	As reported	Placebo-adjusted	As reported	Placebo-adjusted	As reported	Placebo-adjusted	As reported	Placebo-adjusted
Placebo	37.0		6.7		14.8		6.7	
IV tramadol	69.7	32.7	38.7	32.0	18.3	3.5	12.7	6.0
IV morphine	78.5	41.5	45.2	38.5	23.7	8.9	18.3	11.6



Novel Dosing Regimen Maximizes Efficacy and Tolerability

- IV tramadol 50 mg is infused intravenously over 15 minutes at Hours 0, 2, 4, and once every 4 hours thereafter
- Similar C_{max} and AUC to that of 100 mg oral tramadol given every 6 hours at steady state



Strong Patent Portfolio

- U.S. Patents No. 8,895,622, No. 9,561,195, No. 9,566,253, No. 9,962,343, No. 10,406,122
 - Expire in 2032
- U.S. Patents No. 9,693,949, No. 9,968,551, No. 9,980,900, No. 10,624,842
 - Expire in 2036



Post-Surgical Pain Management is a Gateway to Opioid Dependence

Approximately 6% of patients who are prescribed an opioid become new persistent opioid users in the post-surgical setting

“In this population-based study of 36,177 surgical patients, the incidence of new persistent opioid use after surgical procedures was 5.9% to 6.5% and did not differ between major and minor surgical procedures.”⁽¹⁾

Regimens initiated with conventional narcotics have a significant association with opioid misuse

“After adjusting for covariates, other risk factors... including benzodiazepines ...as well as regimens initiated with hydromorphone... and oxycodone ...had a statistically significant association with opioid misuse.”⁽²⁾

(1) Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg.* 2017;152(6):e170504.

(2) Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naïve patients and association with overdose and misuse: retrospective cohort study. *BMJ.* 2018;Jan 17;360:j5790.



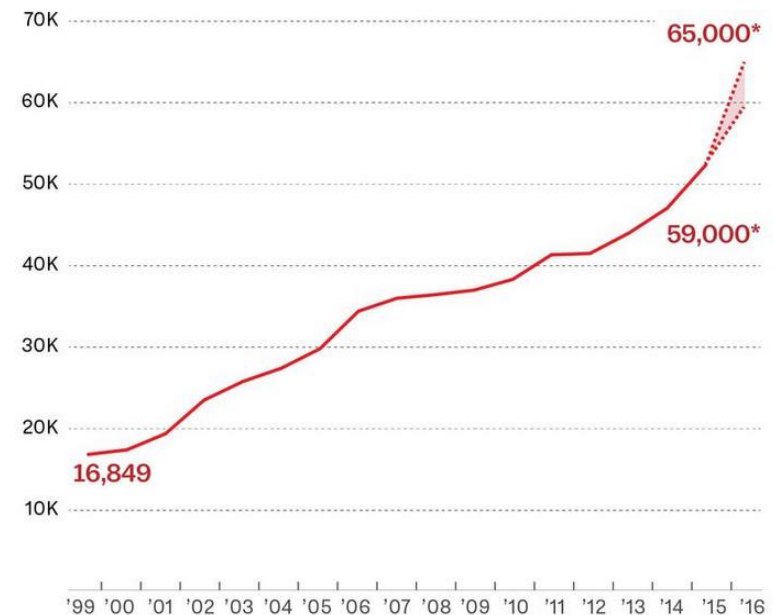
Opioid Crisis Puts Pressure on the Use of Conventional Narcotics

“IV to Oral” Tramadol is Positioned to Help Reduce Conventional Opioid Usage in the Postoperative Setting

- **Release of the CDC guidelines:**

“ When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.”
- **DEA has proposed a 20% reduction** in the manufacture of opioids for 2018
- **CVS/other pharmacies limiting opioid (new) prescriptions** to 7 days and the daily dosage (mg)

Drug overdose deaths



*Estimate based on preliminary data

SOURCE: National Institute on Drug Abuse, The New York Times



Physician Enthusiasm for IV Tramadol Product Profile

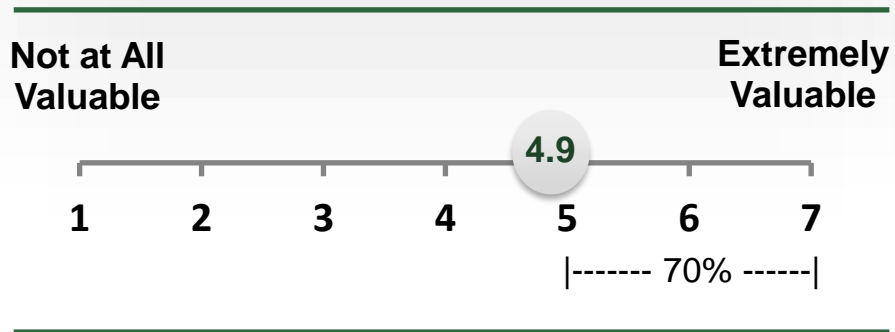
70% of physicians rated IV Tramadol “5 or higher” on the Value Scale (1-7)

- 80% of orthopedic surgeons and 76% of general surgeons rated IV Tramadol “5 or higher”

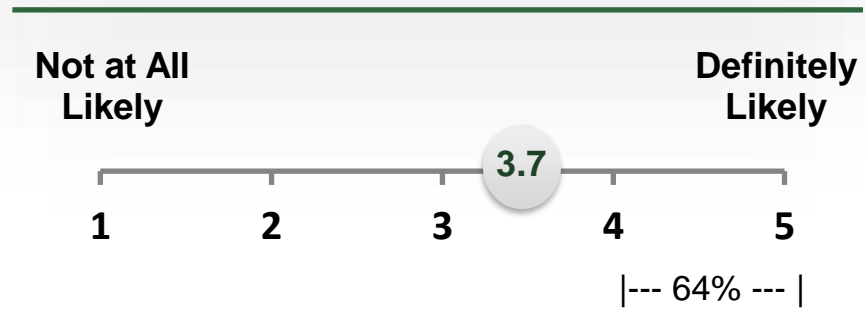
Strong interest in prescribing IV Tramadol

- Almost two-thirds (64%) were “*probably-definitely*” likely to prescribe;
- Orthopedic surgeons displayed the highest prescribing intent (74% - “*probably-definitely*”)

Value of IV Tramadol



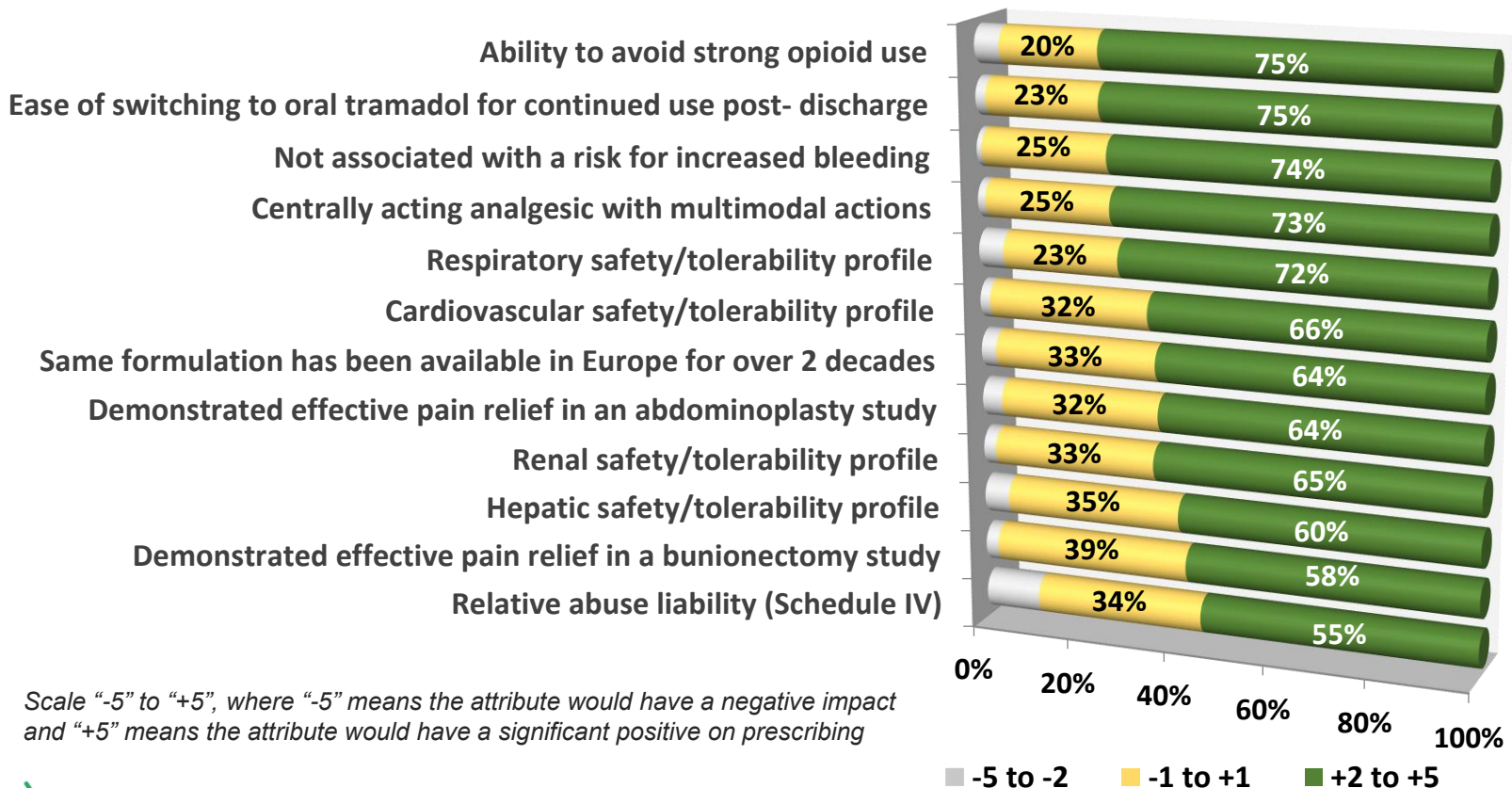
Likelihood of Prescribing IV Tramadol



Characteristics Supportive of IV Tramadol Usage

The potential for IV Tramadol to offer an alternative to use of strong opioids was viewed as the most significant enticement to prescribe

- A direct transition from an IV to oral formulation and potential safety benefits vs. both opioids and non-opioids would also be very meaningful to clinicians



Potential Acquisition Agreement signed with InvaGen (a Cipla subsidiary)

- At first stage closing in February 2019, InvaGen acquired 5.8M shares @\$6 per share for \$35M representing a 33.3% stake in Avenue on a fully diluted basis
- At second stage closing, InvaGen would purchase remaining shares for up to \$180M subject to certain terms disclosed in our public filings
 - InvaGen has the option to complete the second stage closing or terminate the agreement at any time from May 1, 2021 through October 31, 2021
 - Avenue may terminate the SPMA on November 1, 2021



Contingent Value Rights under InvaGen Agreement

- Each non-InvaGen shareholder at time of second stage closing would be entitled to one CVR for each share owned
- CVR payments are on annual IV tramadol net sales (product launch to 2028):
 - 10% of all gross profits if net sales >\$325M
 - 12.5% of all gross profits if net sales >\$400M
 - 15% of all gross profits if net sales >\$500M
- Beginning in 2029 if cumulative net sales of IV tramadol are at least \$1.5B and annual net sales are >\$100M, then annual payment of CVR is 20% of all gross profits





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