AVENUE THERAPEUTICS, INC. | NASDAQ: ATXI | MAY 2019

Forward Looking Statements

Statements in this presentation that are not descriptions of historical facts are forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995. We have attempted to identify forward-looking statements by terminology including “anticipates,” “believes,” “can,” “continue,” “could,” “estimates,” “expects,” “intends,” “may,” “plans,” “potential,” “predicts,” “should,” or “will” or the negative of these terms or other comparable terminology. Forward-looking statements are based on management’s current expectations and are subject to risks and uncertainties that could negatively affect our business, operating results, financial condition and stock price. Factors that could cause actual results to differ materially from those currently anticipated are risks relating to: our growth strategy; results of research and development activities; uncertainties relating to preclinical and clinical testing; our dependence on third party suppliers; our ability to obtain, perform under and maintain financing and strategic agreements and relationships; our ability to attract, integrate, and retain key personnel; the early stage of products under development; our need for substantial funds; government regulation; patent and intellectual property matters; competition; as well as other risks described in the “Risk Factors” section of our Annual Report on Form 10-K for the year ended December 31, 2017 (“Form 10-K”) and other periodic reports filed from time to time with the Securities and Exchange Commission. We expressly disclaim any obligation or undertaking to update or revise any statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances after the date of this presentation. You should read carefully our “Special Cautionary Notice Regarding Forward-looking Statements” and the factors described in the “Risk Factors” sections of our Form 10-K and other periodic reports to better understand the risks and uncertainties inherent in our business.

Value Proposition

1. Two-stage acquisition agreement with InvaGen minimizes dilution and provides substantial upside to shareholders

2. IV tramadol has a substantial market opportunity and can sell hundreds of millions of dollars or more in the U.S.

3. Strong IP position on our proprietary dosing regimen expected to protect exclusivity in the U.S. into the late 2030's

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, elderly patients at risk for respiratory depression, obese patients with sleep apnea, and those who can't tolerate strong narcotic, etc.

Unique Dual Mechanism of Action Among IV Analgesics

IV TRAMADOL

OPIOID AGONIST

Blocking pain signal transmission at both the spinal and brain levels

Opioid Efficacy with Less Abuse Potential

INHIBITOR OF NOREPINEPHRINE & SEROTONIN RE-UPTAKE

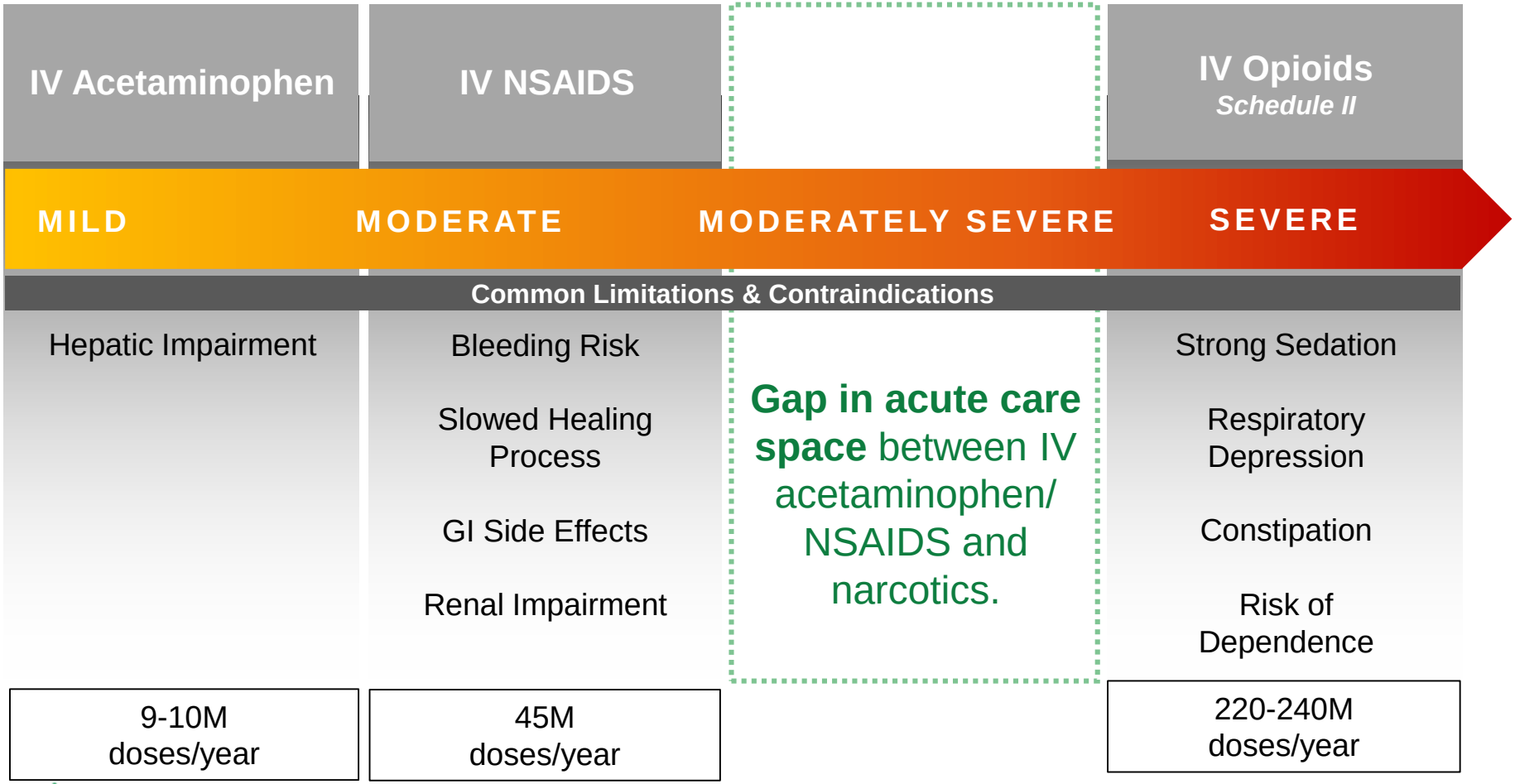
Blocking pain signal transmission at the spinal level

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



Many Patients Could Benefit from IV Tramadol

Contra-indicated for NSAIDS

Obese Patients with Sleep Apnea

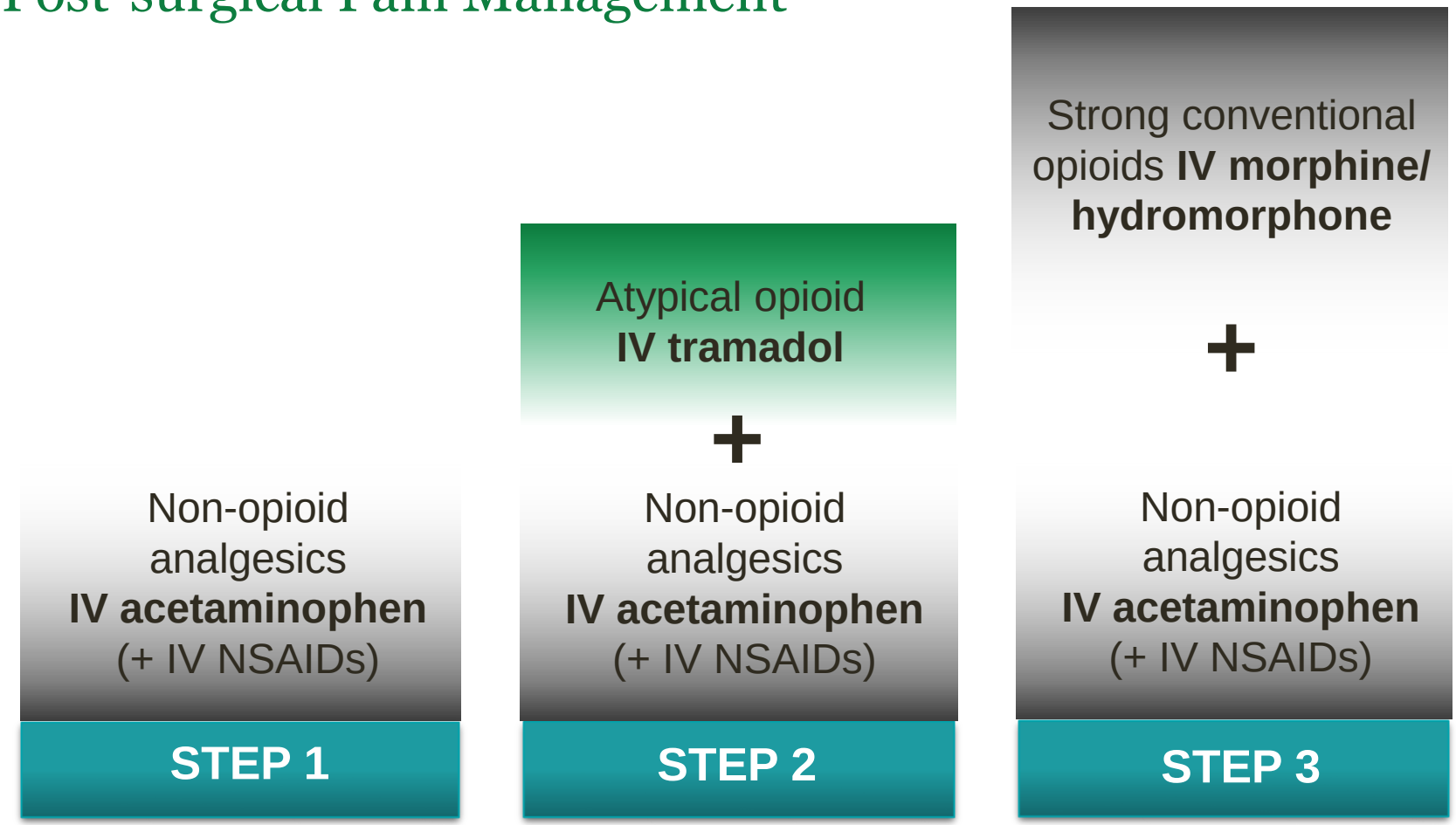
For the rest of the patients: Why use a conventional (Schedule II) opioid when IV tramadol might be adequate?

Cannot Tolerate Strong Narcotics

Elderly at Risk for Respiratory Depression

Future Paradigm: Simplified IV "Analgesic Ladder" Post-2020

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

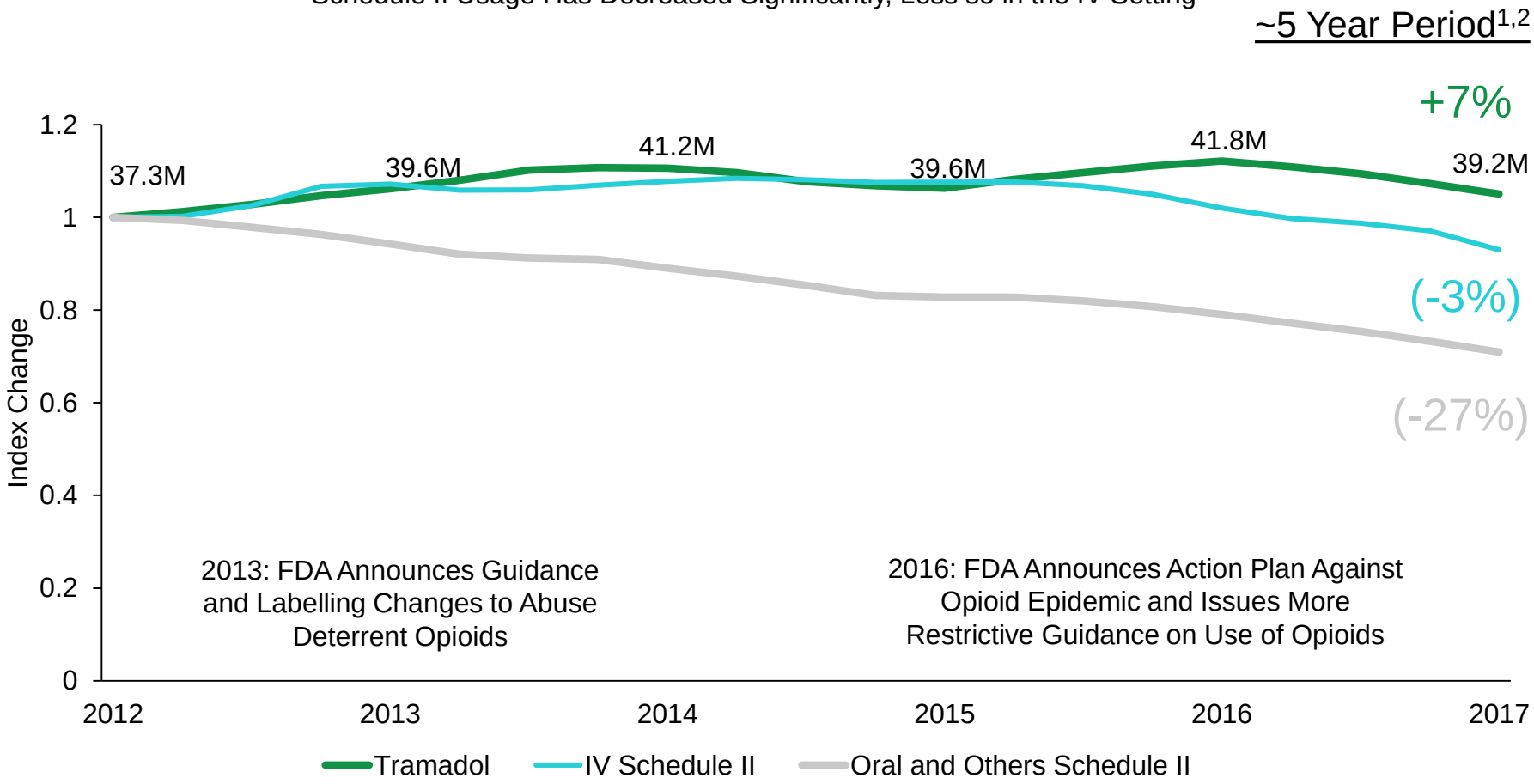


Source: Can Fam Physician. 2010 Jun; 56(6): 514–517; Avenue research

Oral Tramadol is Widely Prescribed in the U.S.

Oral Tramadol Usage Has Increased During the Opioid Crisis

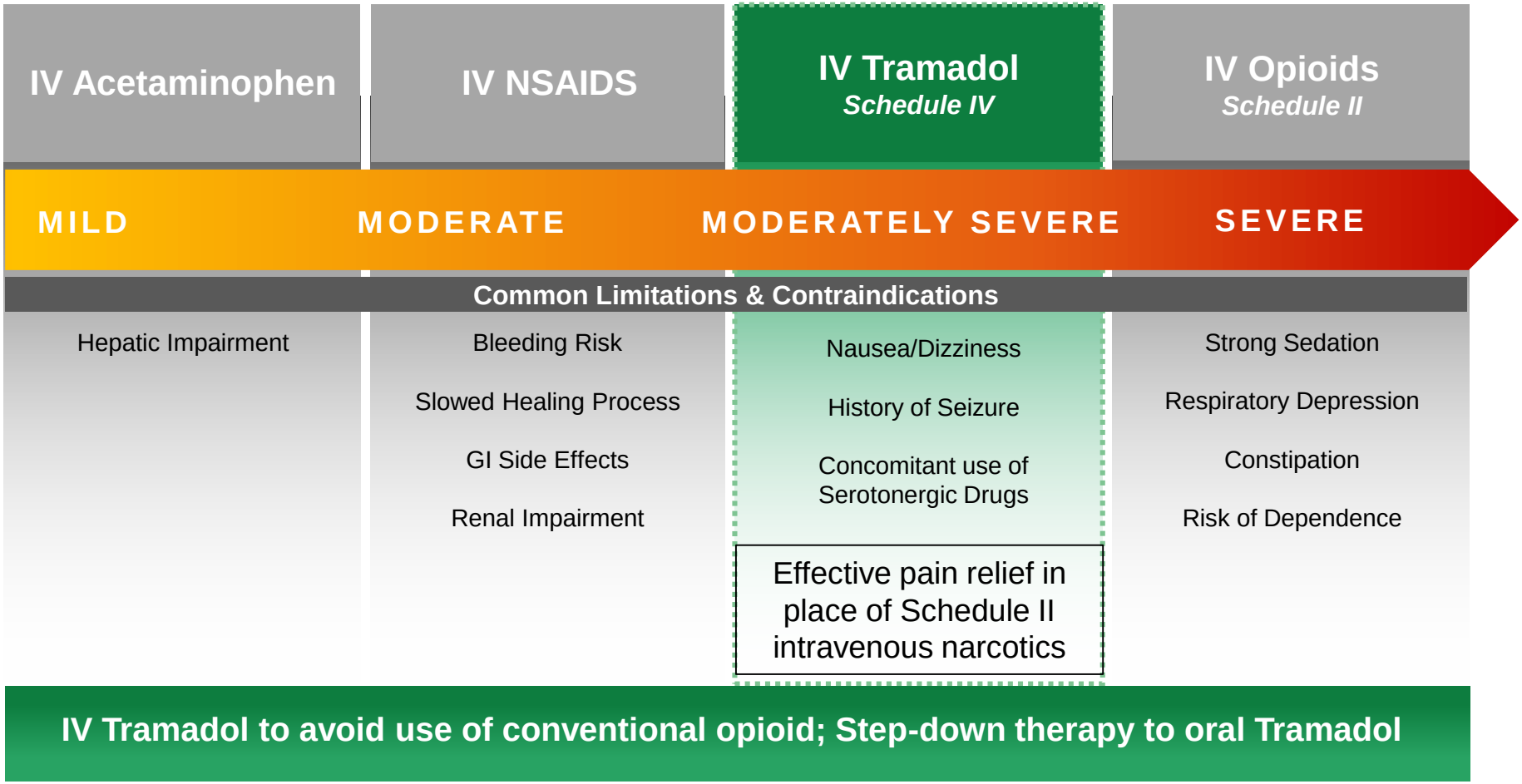
Schedule II Usage Has Decreased Significantly, Less so in the IV Setting



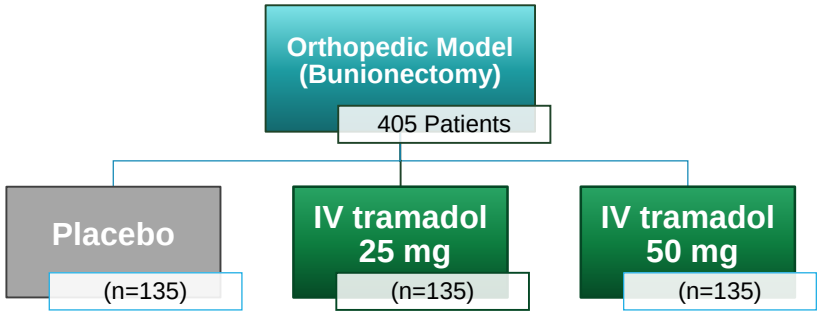
Source: Symphony Health Solutions; Note: 1. Decline shown as of 9/30/2017 2. Constraints at Pfizer's McPherson site have affected IV product supply since November 2017

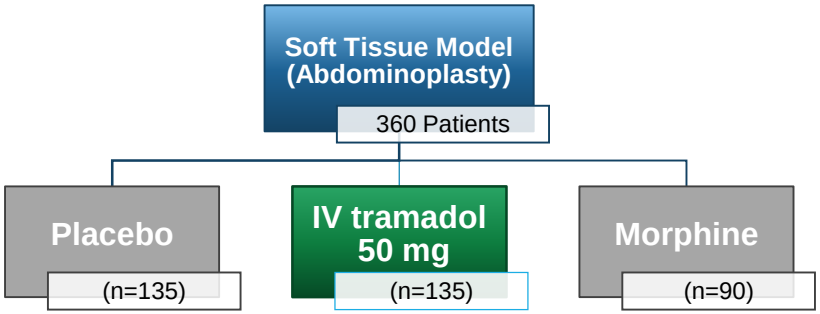
IV Tramadol Ideally Suited for Multi-modal Pain Management

Future Post-Op Pain Management Paradigm



Phase 3 Program Overview





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

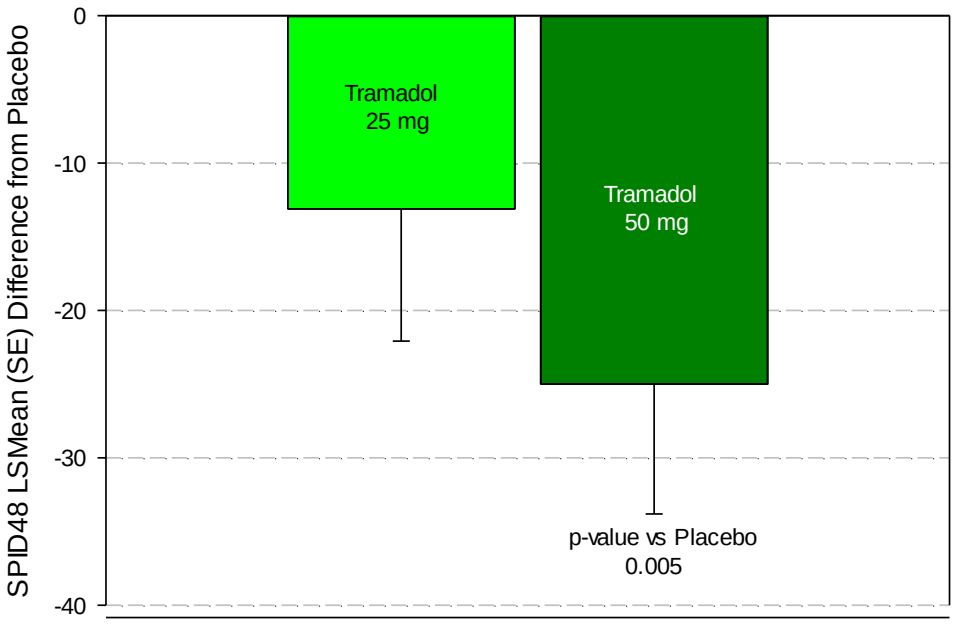
PRIMARY ENDPOINT
Sum of Pain Intensity Differences (SPID) through 24 hours post first dose

Safety Study
(n=250)

Positive Bunionectomy Study Results

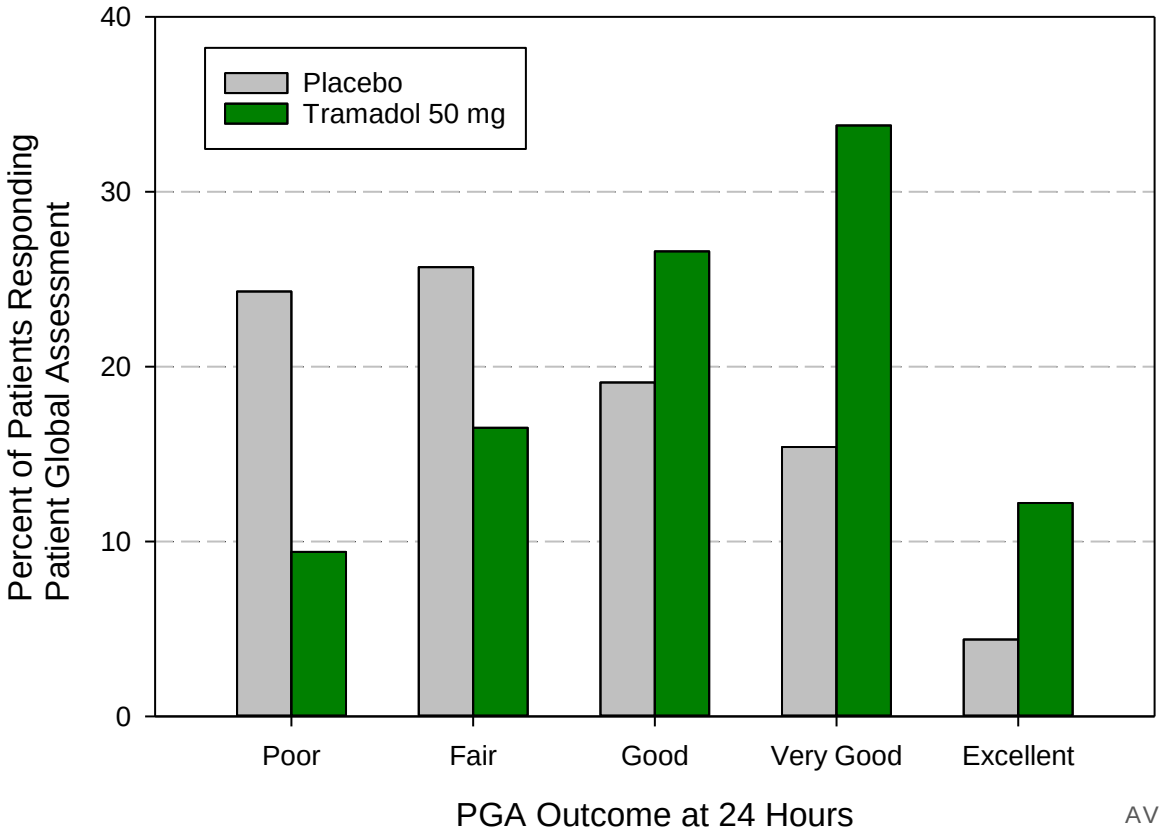
IV Tramadol 50 mg Achieves Primary Endpoint and All Key Secondary Endpoints

- 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, captures patients' perception of treatment
- Rapid onset of efficacy
  - Statistically significant pain reduction seen as early as 30 minutes after dosing



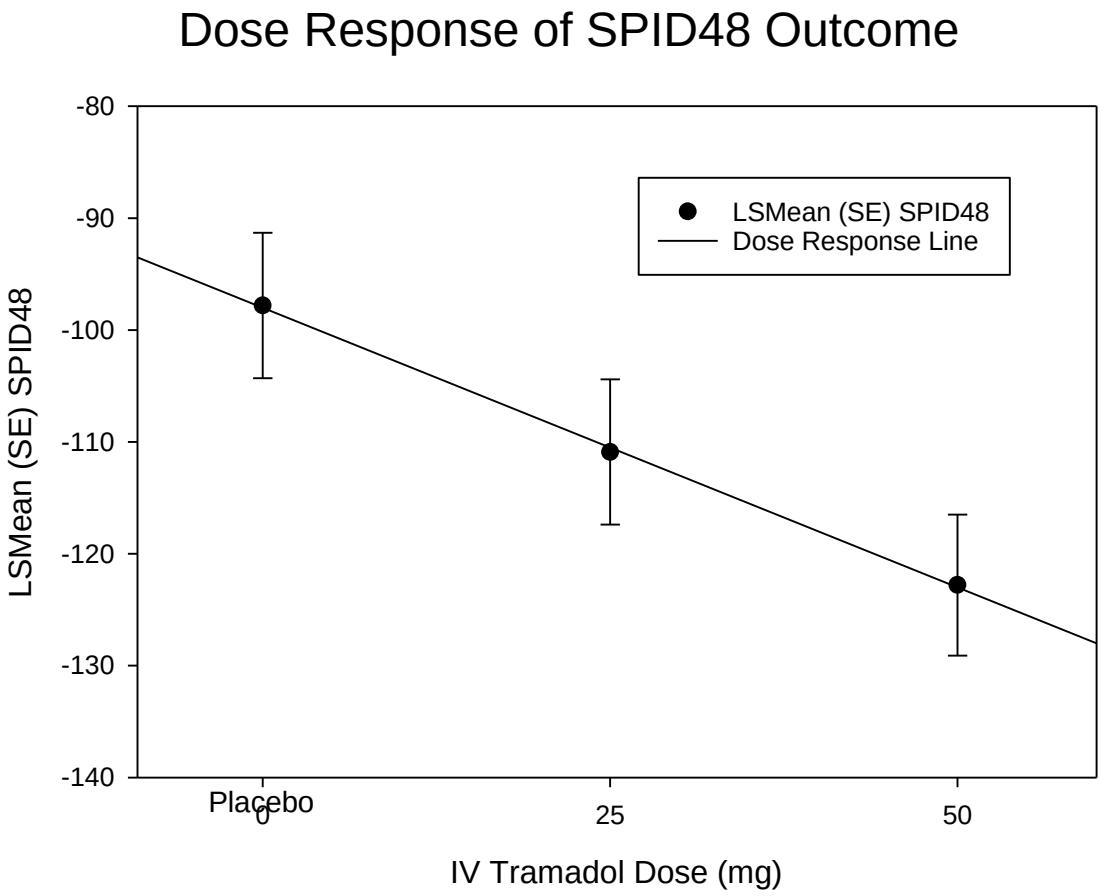
Favorable Patient Reported Outcome

The Patient Global Assessment (PGA), which captures patients' perception of the treatment, demonstrated statistically significant improvement over placebo.



Statistically Significant Dose Response

A clear dose response confirms that the 50 mg dose will move forward.



No Surprise in Safety Outcomes

IV Tramadol 50 mg Was Well Tolerated

- There were no drug-related serious adverse events (SAEs)
- The most common (≥5%) adverse events in the trial where IV tramadol 50 mg differed from placebo were nausea, vomiting, dizziness and somnolence.
  - Most of these adverse events were mild or moderate (Grade 1 or 2) with only 4 (3%) patients experiencing a Grade 3 event (vomiting) and no Grade 4 events in the IV tramadol 50 mg group
  - One patient in the 50 mg IV tramadol arm discontinued from the study due to adverse events.
- IV Tramadol 50 mg patients were able to complete the study and receive all their treatment doses
  - Only 2 (1.4%) IV Tramadol 50 mg patients discontinued the study, versus 16 (11.8%) placebo patients
  - 98.6% of IV Tramadol 50 mg patients received their full course of infusions during the study

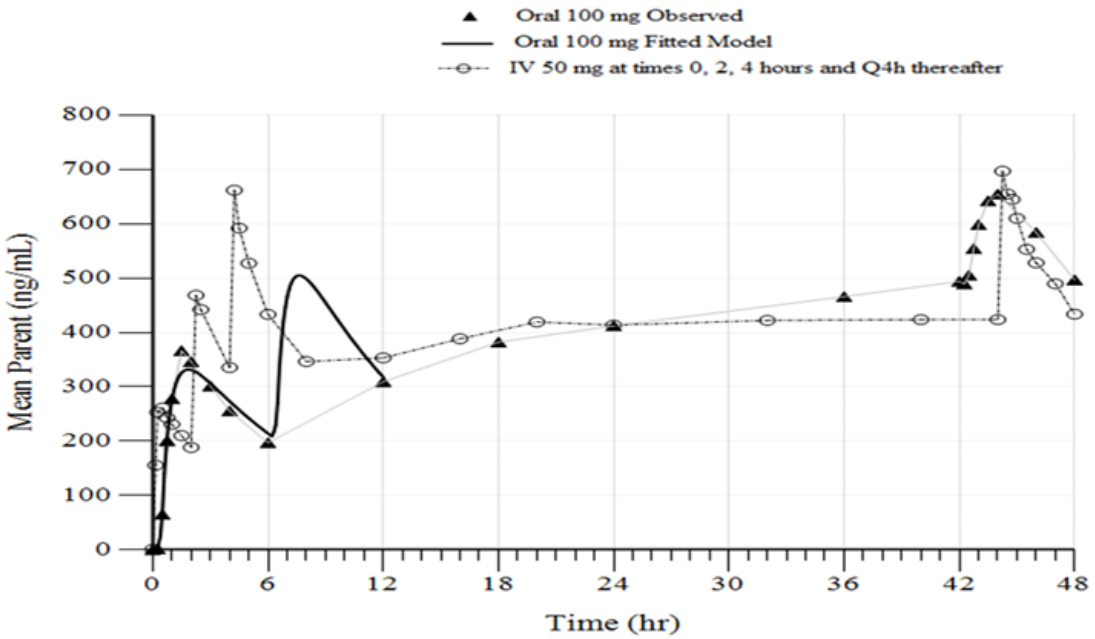
2nd Phase 3 – Soft Tissue Model

6-month enrollment timeline

- Approximately 360 patients will be randomized in this Phase 3, double-blind, three-arm (IV tramadol 50 mg, placebo, IV morphine) study in a 3:3:2 ratio
  - The primary measure of efficacy is SPID 24
  - Key secondary endpoints are: PGA 24, SPID 48, and Rescue med consumption (through 24 hours)
  - As a centrally acting analgesic, IV tramadol should perform similarly in this study as in the orthopedic model on the efficacy side
- The purpose of the morphine arm is to compare tolerability of IV tramadol to standard-of-care on opioid-related adverse events (ORAE)
  - Key comparisons include: Respiratory impairment, vomiting, severe nausea, etc.
  - Goal is to confirm European literature that IV tramadol does not cause as much respiratory events as conventional narcotics

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
  - Expire in 2032

- U.S. Patents No. 9,693,949, No. 9,968,551, No. 9,980,900
  - Expire in 2036

Third party patent strength opinion available upon request

Post-Surgical Pain Management is a Gateway to Opioid Dependence

Approximately 6% of patients 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]

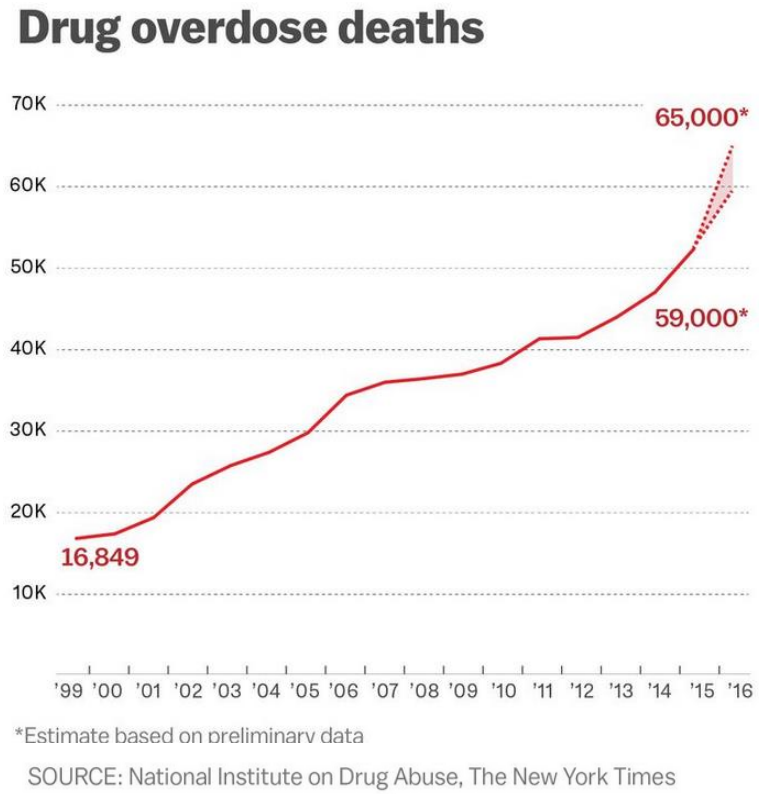
(1) *Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504.*

(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)



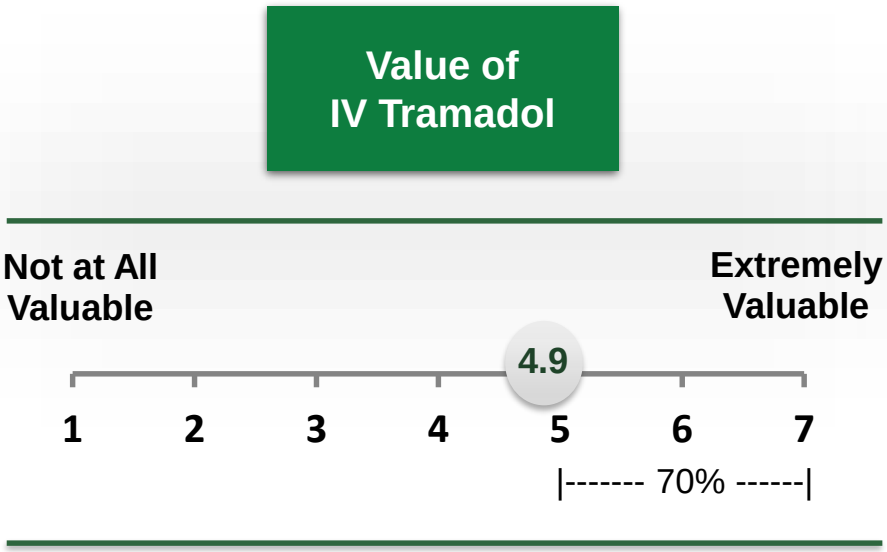
Physician Excitement for IV Tramadol Product Profile

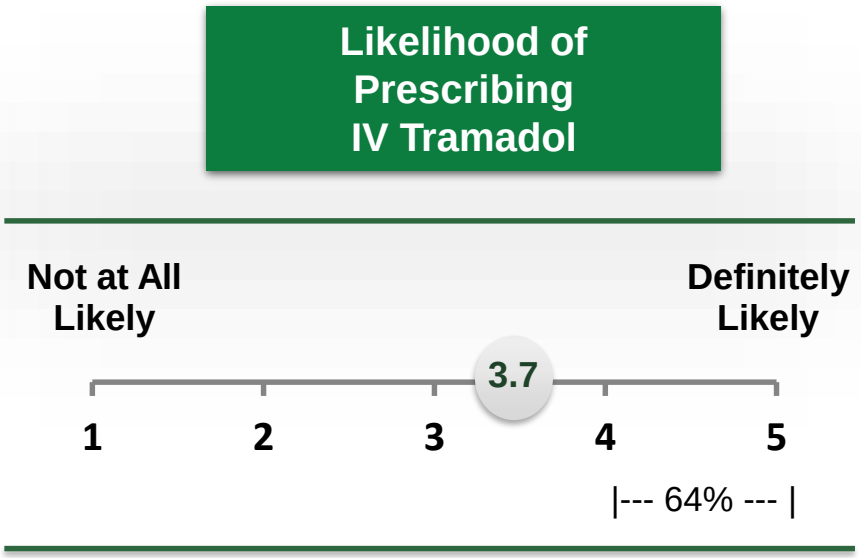
70% of physicians rated IV Tramadol "5 or higher" on the Value Scale (1-7)

- 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*")



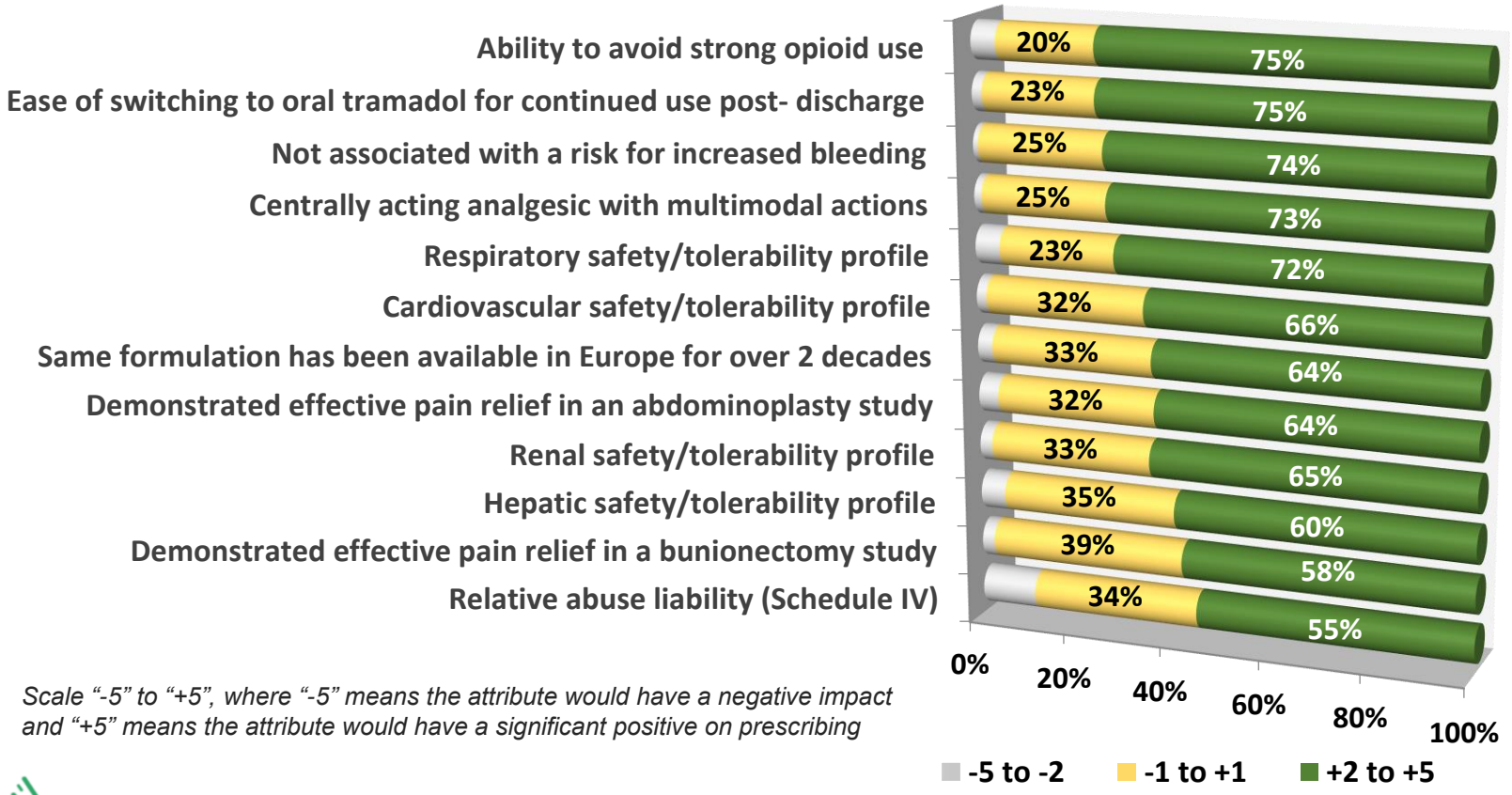


Characterizing the Acceptance of IV Tramadol in the Treatment of Acute (post-surgical) Pain. Internet survey - n=201 practitioners (orthopedic surgeons; general surgeons, anesthesiologists; and emergency medicine physicians)

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



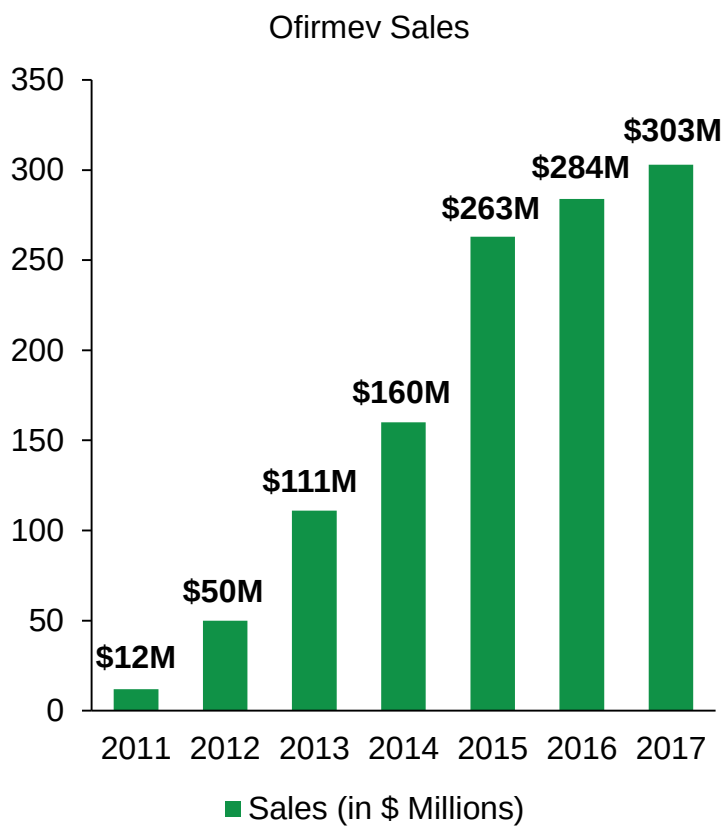
Scale "-5" to "+5", where "-5" means the attribute would have a negative impact and "+5" means the attribute would have a significant positive on prescribing

Characterizing the Acceptance of IV Tramadol in the Treatment of Acute (post-surgical) Pain. Internet survey - n=201 practitioners (orthopedic surgeons; general surgeons, anesthesiologists; and emergency medicine physicians)

A Success Story – IV Acetaminophen

Cadence Pharmaceuticals - OFIRMEV®

- Licensed drug from Bristol-Myers Squibb in 2006 – upfront fee of $25 million and $15 million milestone upon FDA approval
- FDA approval in November 2010 and launched in January 2011
- Acquired in February 2014 for $1.3 billion by Mallinckrodt
- Currently accounts for ~30% of the total dollar market on approximately 3 to 4% of the unit volume of the U.S. analgesics market
- Expected authorized generic launch in December 2020



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 to purchase remaining shares for up to $180M subject to certain terms disclosed in the 8-k and proxy

- In event of second stage closing, Avenue shareholders also to receive contingent value rights based on annual net sales and gross profits of IV Tramadol

Upcoming Milestones

Initiated Phase III abdominoplasty study	2H 2018	✓
InvaGen agreement-Stage 1 Closing	1Q 2019	✓
Topline data from Phase III abdominoplasty study	Mid- 2019	
Complete Safety study	Mid- 2019	
Submit NDA	Year-end 2019	

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