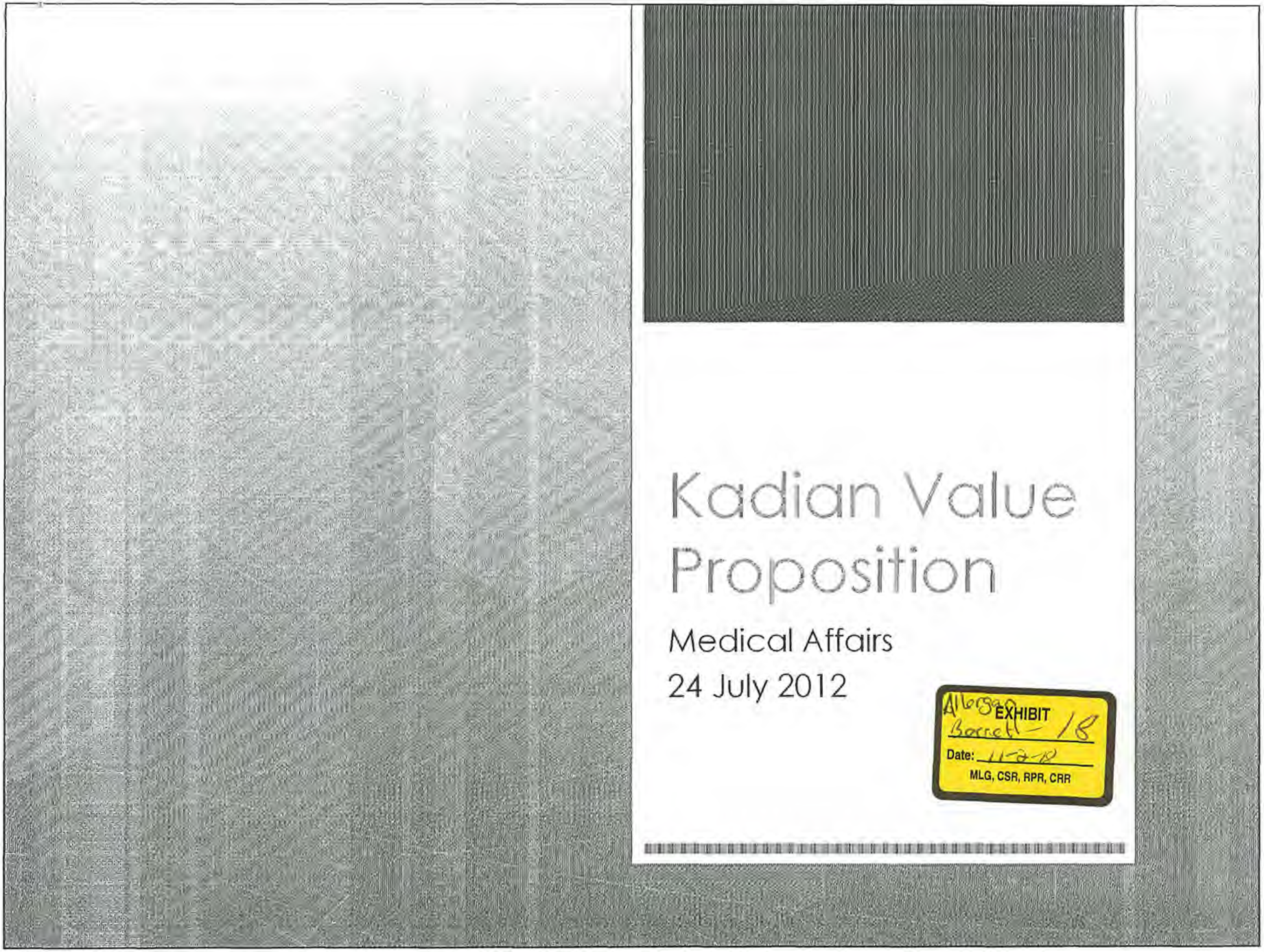
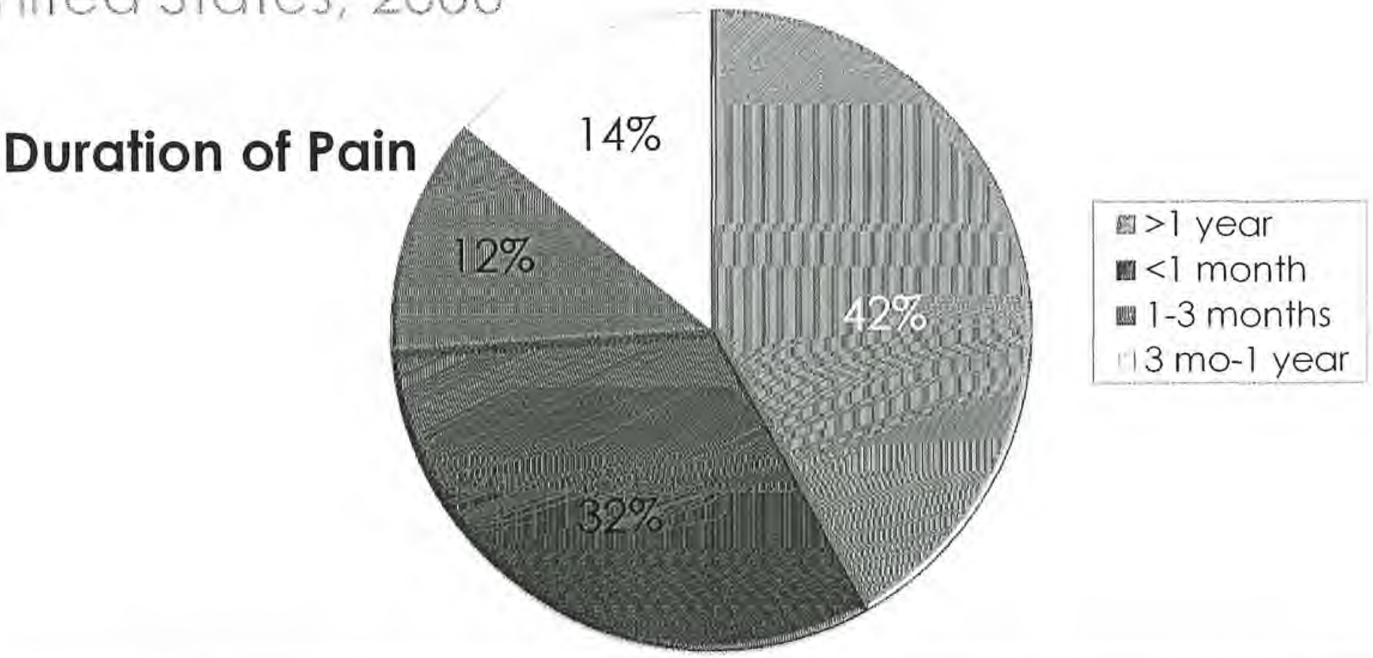


Agenda

- Disease Overview/Treatment Guidelines
- Clinical Program
- MOA/unique formulation
- PK/PD
- Efficacy/Safety
- LT Efficacy/Safety
- Dosing flexibility

Duration of Pain

National Center for Health Statistics. Health, United States, 2006[1]



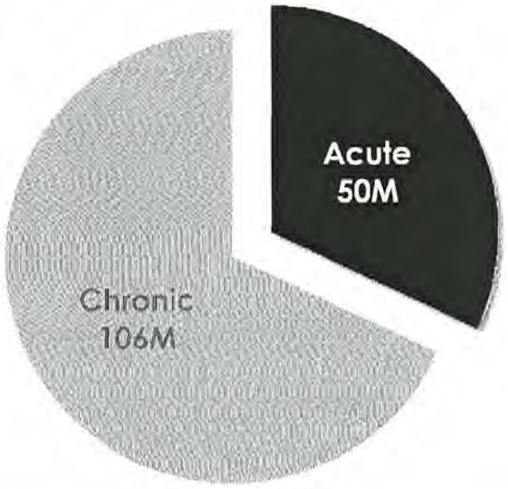
An estimated 42% of Americans ≥20 years old reported a problem of chronic pain that persisted for more than one year in duration...

1National Center for Health Statistics. Health, United States, 2006, Special Feature on Pain With Chartbook on Trends in the Health of Americans. Hyattsville, MD. Available at http://www.cdc.gov/nchs/data/hus/hus06.pdf.

Prevalence

It is estimated that more than 100 million people in the US suffer with chronic pain.1

Breakdown of Pain Prevalence by Type[2]



Post-operative pain is the most common form of acute pain, accounting for 42 million acute pain cases annually.[1]

1. The Pain Market Outlook to 2011. Cowen and Company. Therapeutic Outlook, Pain Management. 2006. 2. American Pain Foundation: Pain Facts and Stats.

Transition of Acute Postoperative Pain to Persistent Pain

Unresolved Acute[1]

- Reported by approximately 50% of patients
- Associated with significant physiological, emotional, mental, and economic consequences

Chronic Postsurgical[2]

- Reported by about 30% of patients after specific types of major surgery
- RCTs needed to determine which anesthetic interventions reduce risk

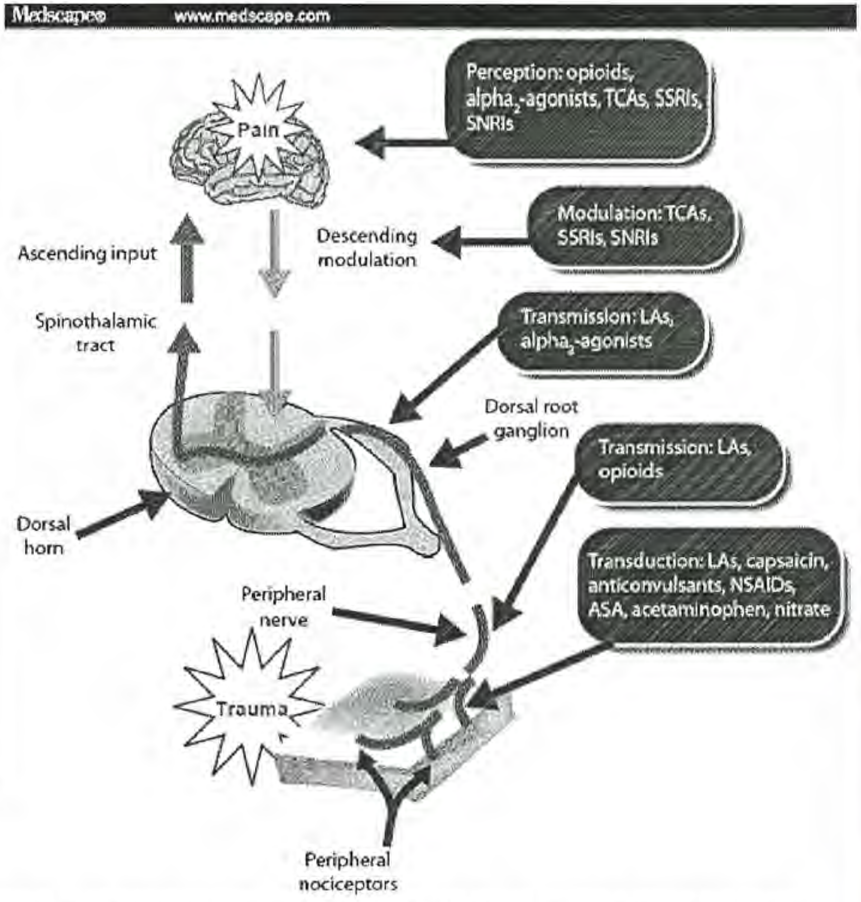
The etiology and treatment of pain produced by surgery is different than clinical pain conditions such as rheumatoid arthritis[3]

Abbreviation: RCT = randomized controlled trial

Source: 1. Polomano RC, et al. *J Perianesth Nurs*. 2008;23(1 Suppl):S4-S14.; 2. De Kock M. *Anesthesiology*. 2009;111(3):461-463.; 3. Brennan TJ. *Pain*. 2011;152(3 Suppl):S33-S40.

Targets of Pain Management Drugs

- Multiple targets available for pain management
  - Inhibition of Prostaglandin synthesis
  - Na^+ and K^+ channels
  - Ca^{2+} and neurotransmitter release
  - Serotonin and norepinephrine reuptake
  - GABAergic inhibition
  - NMDA-receptor activation



Abbreviations: ASA = aspirin; LAs = local anesthetics; NMDA = N-Methyl-D-aspartic acid; NSAIDs = nonsteroidal anti-inflammatory drugs; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.
Source: Kehlet H, Dahl JB. *Anesth Analg*. 1993;77:1048-1056.

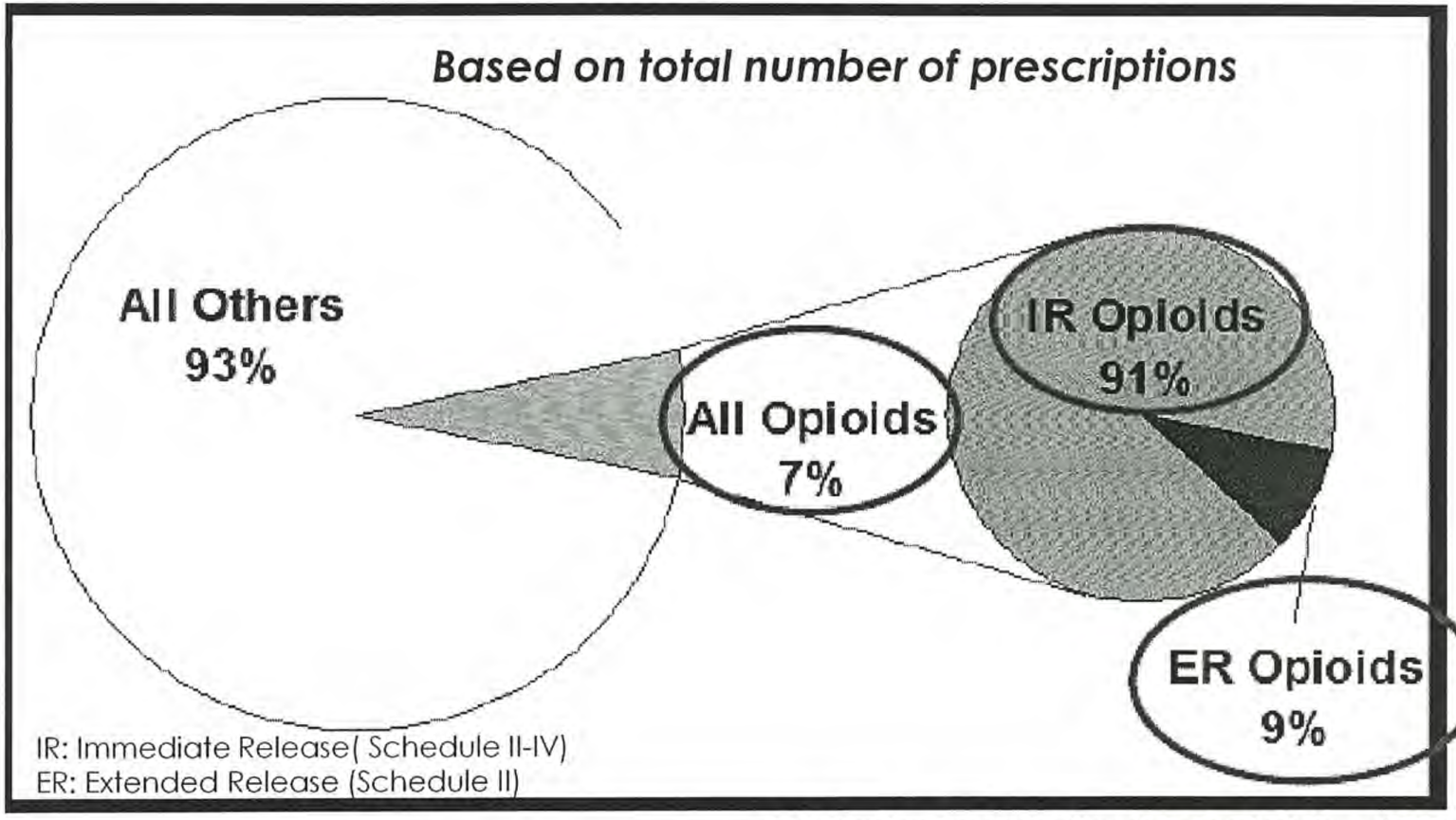
Need to replace or recreate graphic if slide used (or use reference's original illustration)
AH: I called medscape, got transferred 4 times and then left a vm for someone regarding graphics...

National Dispensed Prescription Data: SDI, Vector One®: National (VONA)

- SDI's Vector One®: National (VONA) is a national-level projected prescription and patient-centric tracking service
  - Receives more than 2.0 Billion prescription claims per year, representing over 160 million unique patients
  - Sample includes 59,000 pharmacies throughout the US
- In total 257 million opioids prescriptions (TRx) delivered each year in US retails pharmacies
  - 91% (233.6 million) are Immediate Release formulation
    - 40% (93.5 million NRx) of Immediate Release are given to new patients
  - 9% (23.1 million) are Extended Release formulations
    - 28% (6.5 million NRx) of Extended Release formulations are for ne w patients

TRx: Total prescriptions; NRx: New prescriptions
Adapted from FDA Office of Surveilance and Epidemiology by L Governale, PharmD, MBA 22JULY2010. "Outpatient prescription opioid utilization in the US: Years 2000-2009."

Share Of Outpatient Opioid Prescription Market (2009)



SDI, Vector One®: National. Extracted June 2010

Adapted from FDA Office of Surveilance and Epidemiology by L Governale, PharmD, MBA 22JULY2010. "Outpatient prescription opioid utilization in the US: Years 2000-2009."

Types of Treatment

[redacted]

actavis
think smart medicine

Classes of Pain-Management Options[2]

Non-Opioids

NSAIDS

- Relieve mild to moderate pain and reduce fever and inflammation

Acetaminophen

- Relieves mild to moderate pain and treats fever, but does not reduce inflammation

Opioids

- Standard of care for treatment of moderate to severe pain associated with surgery or trauma, as well as chronic cancer and non-cancer pain
- Examples include codeine, hydrocodone, morphine oxycodone, and fentanyl

Adjuvant Analgesics

- Certain antidepressants, anticonvulsants, and corticosteroids have analgesic properties
- Mainly prescribed by pain specialists for the treatment of neuropathic pain

Non-Pharmacologic Treatments

- Psychosocial interventions
- Rehabilitation techniques Complementary and Alternative Medicine
- Injection and infusion therapies (e.g. nerve blocks)
- Implantable devices and surgical interventions

Sources: 1. American Pain Foundation: Pain Facts and Stats. 2. *Treatment Options: A Guide for People Living With Pain*, American Pain Foundation publication. Available at http://www.painfoundation.org/learn/publications/files/TreatmentOptions2006.pdf, accessed January 2012

Benefits Of Multimodal Analgesic Therapy

- Reduced doses of each analgesic
- Improved pain relief secondary to synergistic or additive effects of particular agents
- Side effects of individual medications may be reduced
- Outcomes of acute pain are improved

Pain is complex and multifactorial, thus appropriate management requires a "balanced" therapeutic approach

Source: Kehlet H, Dahl JB. *Anesth Analg*. 1993;77:1048-1056.

Benefits of Multimodal Analgesia

The effectiveness of multimodal strategies for postoperative pain management has been demonstrated with a variety of medications and therapeutic interventions. The rational use of combinations of analgesic medications, such as nonopioid analgesics, local anesthetic, and opioid analgesia, in addition to other therapeutic interventions can improve pain relief, reduce postoperative adverse effects, and improve functional postoperative recovery for patients.

Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77:1048-1056.

Treatment Guideline Recommendations

Clinical Program

- X Well-Controlled Clinical Trials
- Y Open-Label
- Z LT studies
- Demographics
- Overall PT exposure
- Estimated exposures or scripts since launch

Clinical Trial Program

PIVOTAL

- CDD-14556 (US) PIVOTAL: R, DB, double-dummy, parallel, moderate to severe cancer pain, n=172, 152 complete; Kadian QD, BID vs MScontin QID
- MOR-9/92 (AU) PIVOTAL: R, DB, double-dummy, 2-period x-over, moderate to severe cancer pain, n=29, 25 complete; Kadian QD, BID vs MScontin QID

Supportive

- MOBES-8/90 (AU): R, DB, double-dummy, 2-period x-over with 12w OL extension, moderate to severe cancer pain, n=27, 24 completed, 20 enter OL, 10 complete OL
- MOR-2/92 (US, incomplete): R, DB, double-dummy, balanced incomplete Block 2 2period x-over, moderate to severe chronic cancer, n=19, 16 completed 6 evaluable
- MOB-1/90 (AU): R, OL, 3-period x-over, moderate to severe cancer pain, n=50, 24 completed
- MOR-5/92: OL, randomized parallel switch, n=49, 37 completed

Clinical Trial Program

Long-term safety

- MOS-1/901 (AU): OL, long-term safety/efficacy. 12w OL extension to MOB-1/90: n=19, 9 completed
- MOS-2/91 + 3/91 (AU): OL, long-term safety/efficacy. 9m OL extension to MOB-1/90 and MOBES-8.90: n=29, 8 completed
- MOR-3/92 (AU): OL, long-term safety/efficacy. 12m OL extension to MOS-2/91 and MOS-3/91: n=7, 1 completed

Efficacy Parameters

- Primary efficacy parameters amount of rescue medication taken during final 24h of each 7 day period
- Time to first remedication – time between morning dose of study med and next dose of active irrespective of whether rescue or regularly-scheduled
- Elapsed time to rescue – number of hours from morning dose to first dose of rescue medication
- Total amount of rescue medication taken in 24h of final day
-
- Secondary: VASm 4-point VRS for pain control, 5-point VRS for intensity, 4-point VRS for sleep, 4-point VRS for global assessment, 4-point VRS for investigator PGA
-

Agenda

- Clinical Program
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MOA

- Kadian (morphine sulfate) is an opioid agonist
  - Relatively selective for the mu receptor
  - May interact with other opioid receptors at higher doses
- Morphine as a full agonist; analgesia produced by binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, ventro-medical medulla and the spinal cord.
- Other widely diverse effects of morphine including dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility and altered circulatory dynamics

Unique Formulation

[need additional information about the pellets…]

- Polymer-coated sustained-release pellets release morphine at a significantly more slowly than oral morphine solution
  - ~50% of oral morphine reaches systemic circulation in 30 min vs 8 hours with an equivalent dose of Kadian
  - ~20-40% Kadian reaches the systemic circulation
- Kadian can be sprinkled on applesauce for patients who have difficultly swallowing
- Kadian can be administered via a 16 French gastrostomy tube

Agenda

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PK

- Single dose PK of KADIAN are linear over the dosage range of 30-100mg
- At steady state (2 days), KADIAN will have a significantly lower C_{max} and a higher C_{min} than equivalent doses of oral morphine solution and some other extended-release preparations
- KADIAN (QD) had similar C_{max} and higher C_{min} at steady state in clinical usage, when compared to BID extended-release morphine tablets, given at an equivalent total daily dosage
- KADIAN can be administered without regard to meals
- KADIAN *in vivo* testing showed there was not an increase in drug release in the presence of alcohol. However, KADIAN may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs that cause CNS depression.

Agenda

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Efficacy: Pain intensity scores using Visual Analog Scales (VAS)

- Mean VAS pain intensity scores remained consistent during QD dosing…
  - Figure 3 from ISE
  - [need study description for baseline bain]
- Secondary efficacy measures:
  - Sleep
  - Global impression of change

Safety

- Total exposures
- Most common AEs
- SAEs
- LT safety studies
- Post Marketing experience.

Dosing Flexibility

- 12 dosing strengths
  - Provides lowest solid oral dosage form of morphine
  - Allows for dose titration up or down
  - BID or QD dosing option
  - No ceiling effect of KADIAN
- Administration options
  - Ability to sprinkle for patients with difficulty swallowing
  - Administration via gastrostomy tube (16 French)
- Other considerations
  - Can be administered without regards to meals
  - KADIAN *in vivo* testing showed there was not an increase in drug release in the presence of alcohol (dose dumping). However patients should be advised against the consumption of alcohol, illicit drugs or other opioid medications that depress the CNS