

Results of Oral Human Abuse Potential Study

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

Oral Human Abuse Potential Study 067-EG-008

- Category 3 PK/PD Study
- Submitted under NDA 208-603
- Support development of EG-001 (Morphine Sulfate) ER Tablets

In this presentation product will be referred to as EG-001 tablets and not Arymo tablets.

Pharmacodynamic Measures

Drug Liking Visual Analog Scale (VAS) – 0-100-point Bipolar Scale (Primary Measure) (at-the-moment)

- Question: “Do you like the drug effect you are feeling now?”
- 0 = “Strong disliking” ; 50 = “Neither like nor dislike”; 100 = “Strong liking”

High VAS – 0–100-point Unipolar Scale (Secondary Measure) (at-the-moment)

- Question: “How high are you now?”
- 0 = “Not at All”; 100 = “Extremely”

Take Drug Again VAS - 0–100-point Bipolar Scale (Secondary Measure)

- Question: “Would you want to take the drug you just received again, if given the opportunity?”
- 0 = “Definitely would not”; 50 = “Do not care”; 100 = “Definitely would”
- Given only at 12 and 24 hours, post-dosing.

Overall Drug Liking VAS – 0-100 point Bipolar Scale (Secondary Measure)

- Statement: “Overall, my liking for this drug is:”
- 0 = “Strong Disliking”, 50 = “Neither Like nor Dislike”, 100 = “Strong Liking”
- Given only at 12 and 24 hours post-dosing

Primary Endpoint and Statistical Model

- Pharmacodynamic Parameters included **E_{max}** (peak effect) and **T_{E_{max}}** (time to peak effect).
- The primary endpoint was E_{max} of Drug Liking VAS.
- Statistical analyses for pharmacodynamic measures were conducted by the FDA CDER Office of Biostatistics.
- Statistical tests were conducted using a mixed effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Analyses used a one-sided test at a significance level of 0.025.
- Responder analysis (percentage reduction) for Drug Liking utilized a binomial proportion test at a significance level of 0.025 to ensure that a majority of subjects were responders.
- Comparisons of Interest
 - MS Contin Manipulated (Positive Comparator) versus Placebo – Validation
 - MS Contin Manipulated versus EG-001 Manipulated

Pharmacokinetics

- For purposes of assessing pharmacokinetic/pharmacodynamic relationships (PK/PD), focus will be on pharmacokinetics of morphine in plasma
- Relative bioavailability analysis was generated by the Sponsor using least square mean ratio (test/reference) along with the corresponding 90% confidence intervals.

Relevant Pharmacokinetic Parameters:

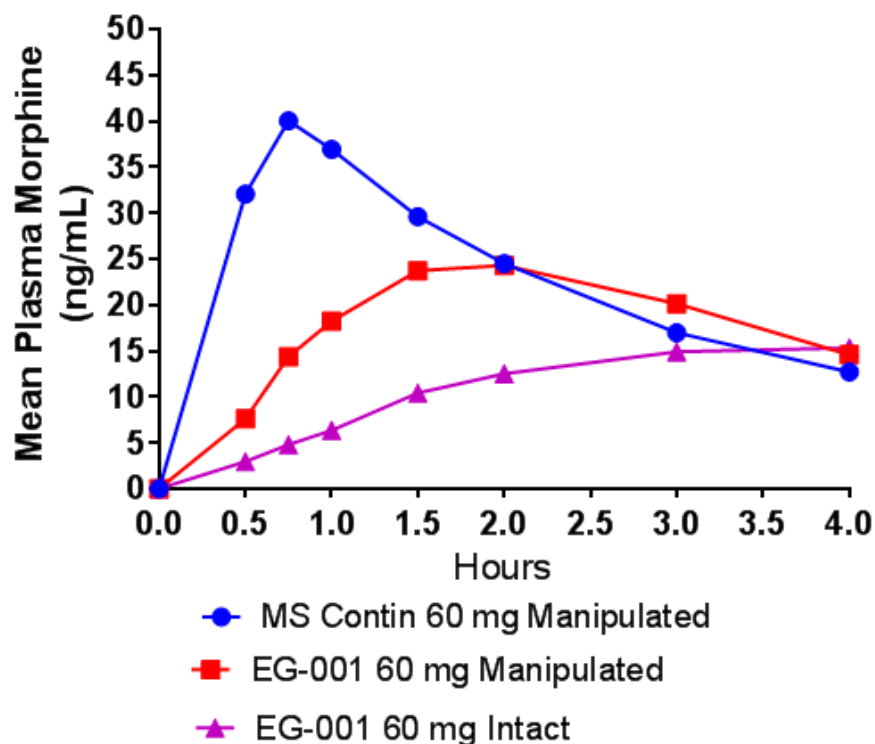
- C_{max} – Maximum observed plasma concentration of morphine
- T_{max} – Time at which C_{max} occurs

Oral Study 067-EG-008

- Single-center, randomized, double-blind, triple-dummy, 4-way, placebo-controlled, crossover study
- Primary objective : To compare the relative abuse potential of oral intact and oral manipulated formulations of EG-001 tablets vs. oral manipulated MS Contin.
- 38 subjects completed the study.
- Oral Treatments:
 - MS Contin 60 mg manipulated (positive comparator)
 - EG-001 60 mg manipulated
 - EG-001 60 mg intact
 - Placebo
- Methods of Manipulation for EG-001 and MS Contin were based on results of Category 1 studies.

Pharmacokinetics of Plasma Morphine

Mean Plasma Morphine Time Course Profile

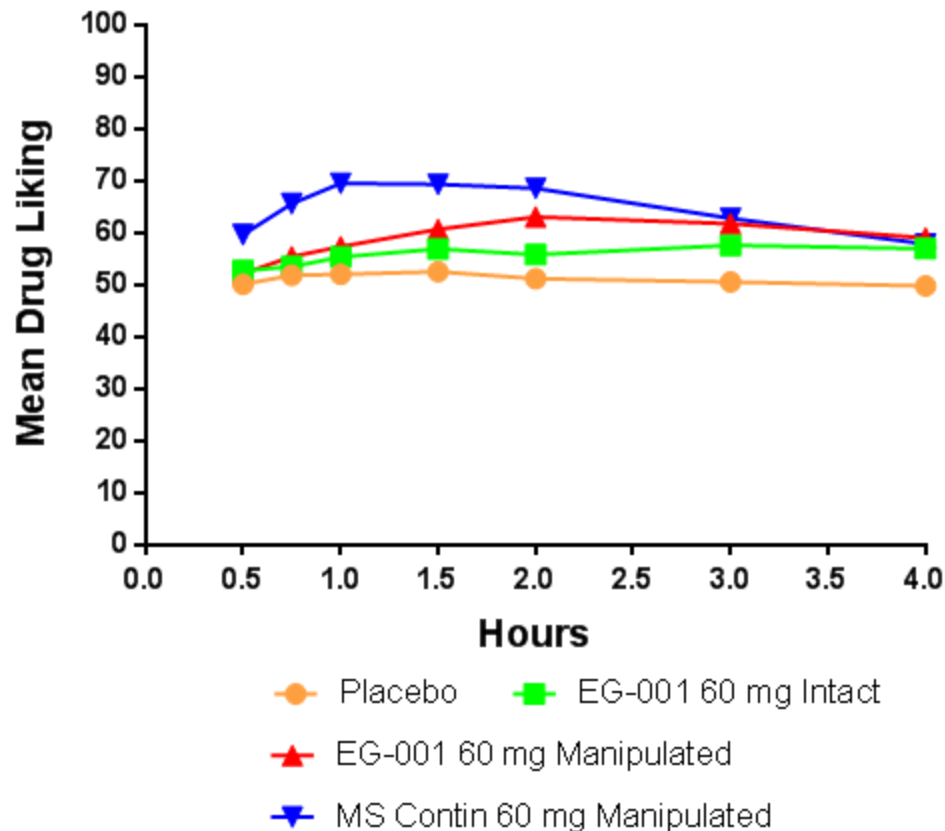


Mean C_{max} (ng/mL) for morphine:
 43.34 – MS Contin 60 mg Manipulated
 28.73 – EG-001 60 mg Manipulated
 17.81 – EG-001 60 mg Intact

Median T_{max} (Hours) for Morphine:
 0.88 – MS Contin Manipulated
 2.12 – EG-001 Manipulated
 4.12 – EG-001 Intact

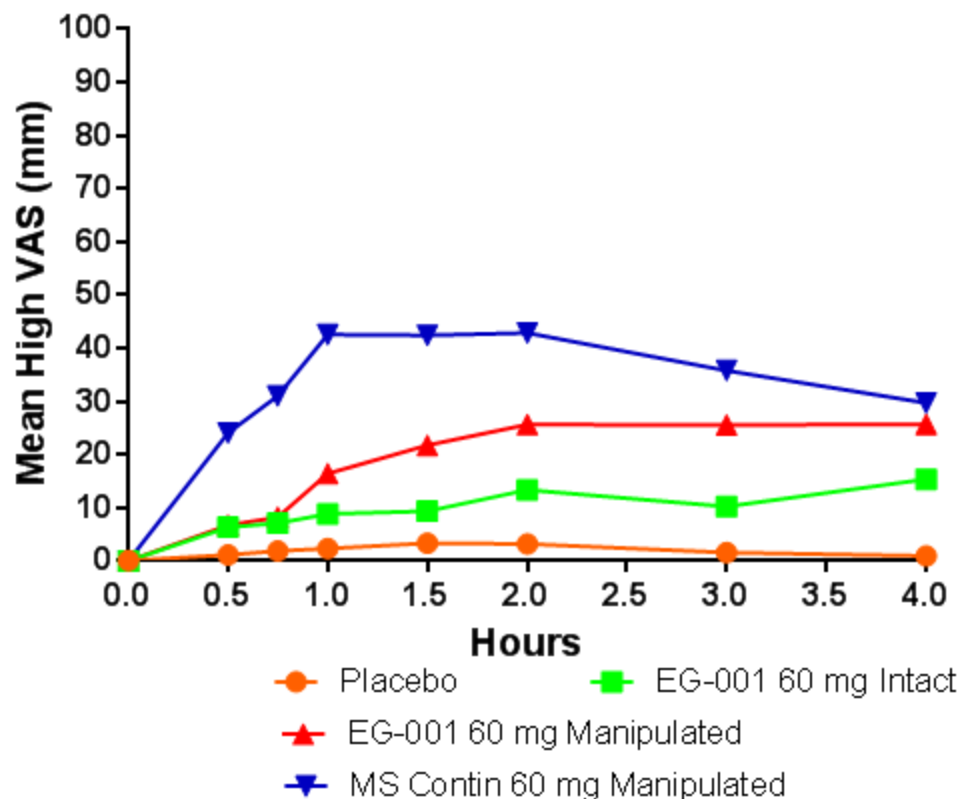
Based on the mean plasma morphine time course profile much of the rise in morphine occurs at:
 0.5 Hours – MS Contin Manipulated
 1.5 Hours – EG-001 Manipulated

Mean Drug Liking Time Course Profile



Median T_{Emax} (hrs):
 1.02 – MS Contin Manipulated
 1.99 – EG-001 Manipulated
 3.00 – EG-001 Oral

Mean High Time Course Profile



Much of the rise in mean High was achieved within 0.75 hours following MS Contin Manipulated and 1.5 hrs following EG-001 manipulated.

Median TEmax (Hours)
1.5 – MS Contin - Manipulated
3.0 – EG-001 Manipulated

E_{max}

| Oral Treatments | Mean (SE) E _{max} (mm) (n = 38) | | | |
|-----------------------------|--|----------------------|---------------------------------|-------------------------------------|
| | Drug Liking VAS (Primary) | High VAS (Secondary) | Take Drug Again VAS (Secondary) | Overall Drug Liking VAS (Secondary) |
| MS Contin 60 mg Manipulated | 73.3 (1.6) | 51.9 (3.8) | 70.1 (2.8) | 69.8 (2.5) |
| EG-001 60 mg Manipulated | 68.3 (2.0) | 38.8 (4.1) | 62.9 (3.2) | 65.1 (3.0) |
| EG-001 60 mg Intact | 63.2 (1.6) | 26.8 (4.0) | 54.8 (3.4) | 55.7 (3.2) |
| Placebo | 53.3 (1.3) | 5.3 (1.9) | 51.0 (1.6) | 52.2 (1.3) |

With regard to MS Contin 60 mg manipulated versus EG-001 60 mg manipulated there is a statistically significant difference in mean E_{max} for Drug Liking (p = 0.0192) and High (p = 0.0087), **but NOT** for Take Drug Again (p = 0.0483) or Overall Drug Liking (p = 0.1130).

What is the clinical relevance of a 5 mm difference in Drug Liking with respect to a potential abuse deterrent effect to oral abuse?

Responder Analysis for Emax of Drug Liking: EG-001 Manipulated Versus MS Contin Manipulated (N = 38 Subjects)

| | Number of Subjects | Percent (%) | p-value (Proportion Test) |
|--------------------------------|--------------------|-------------|---------------------------|
| Percent Reduction at least 0% | 27 | 71.05 | 0.0047 |
| Percent Reduction at least 5% | 25 | 65.79 | 0.0258 |
| Percent Reduction at least 10% | 21 | 55.26 | 0.2582 |
| Percent Reduction at least 20% | 15 | 39.47 | 0.9028 |
| Percent Reduction at least 30% | 14 | 36.84 | 0.9476 |
| Percent Reduction at least 40% | 9 | 23.68 | 0.9994 |
| Percent Reduction at least 50% | 9 | 23.68 | 0.9994 |

Proportion test: for null hypothesis that 50% or fewer subjects are responders at a 2.5% significance level.

Result: Majority of subjects did not demonstrate a 5% or greater reduction in Emax of Drug Liking following EG-001 manipulated compared to MS Contin manipulated.

Summary

1. Oral EG-001 60 mg manipulated produced an “at-the-moment” Emax of Drug Liking that was statistically significantly lower than that produced by oral MS Contin 60 mg manipulated. The difference in Emax for these two treatments was 5 mm, raising the question of clinical significance with respect to abuse deterrent effects.
2. Oral EG-001 60 mg manipulated produced an “at-the-moment” mean Emax of High that was significantly lower than that produced by MS Contin 60 mg manipulated.
3. As revealed by the Take Drug Again assessment, subjects, upon reflection of the treatment experiences at 12 and 24 hours post-dosing, demonstrated a similar degree of willingness to take oral MS Contin 60 mg manipulated or EG-001 60 mg manipulated again, if given the opportunity to do so.

Summary

4. As revealed by the Overall Drug Liking assessment, subjects, upon reflection of the treatment experiences at 12 and 24 hours post-dosing, noted a similar degree of Drug Liking experience associated with taking either MS Contin 60 mg manipulated or EG-001 60 mg manipulated.
5. The number of subjects reporting a 5% or greater reduction in Emax of Drug Liking following EG-001 Manipulated compared to MS Contin Manipulated was borderline statistically not significant ($p \geq 0.0258$). So the majority of subjects did not have at least at 5% reduction in Emax of Drug Liking following EG-001 manipulated compare to following MS Contin manipulated.

Drug Utilization Patterns for Morphine ER and Other ER/LA Opioid Analgesics 2011-2015

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Committee

Outline

- Sales Distribution
- Prescription Utilization
- Prescriber Specialty
- Limitations
- Summary

Extended Release (ER)/ Long Acting (LA) Opioid Analgesics

- **Oral-dosage Forms:**
 - Morphine
 - Oxycodone
 - Methadone
 - Oxymorphone
 - Tapentadol
 - Hydromorphone
 - Hydrocodone
- **Transdermal Delivery (TD) Systems:**
 - Fentanyl
 - Buprenorphine

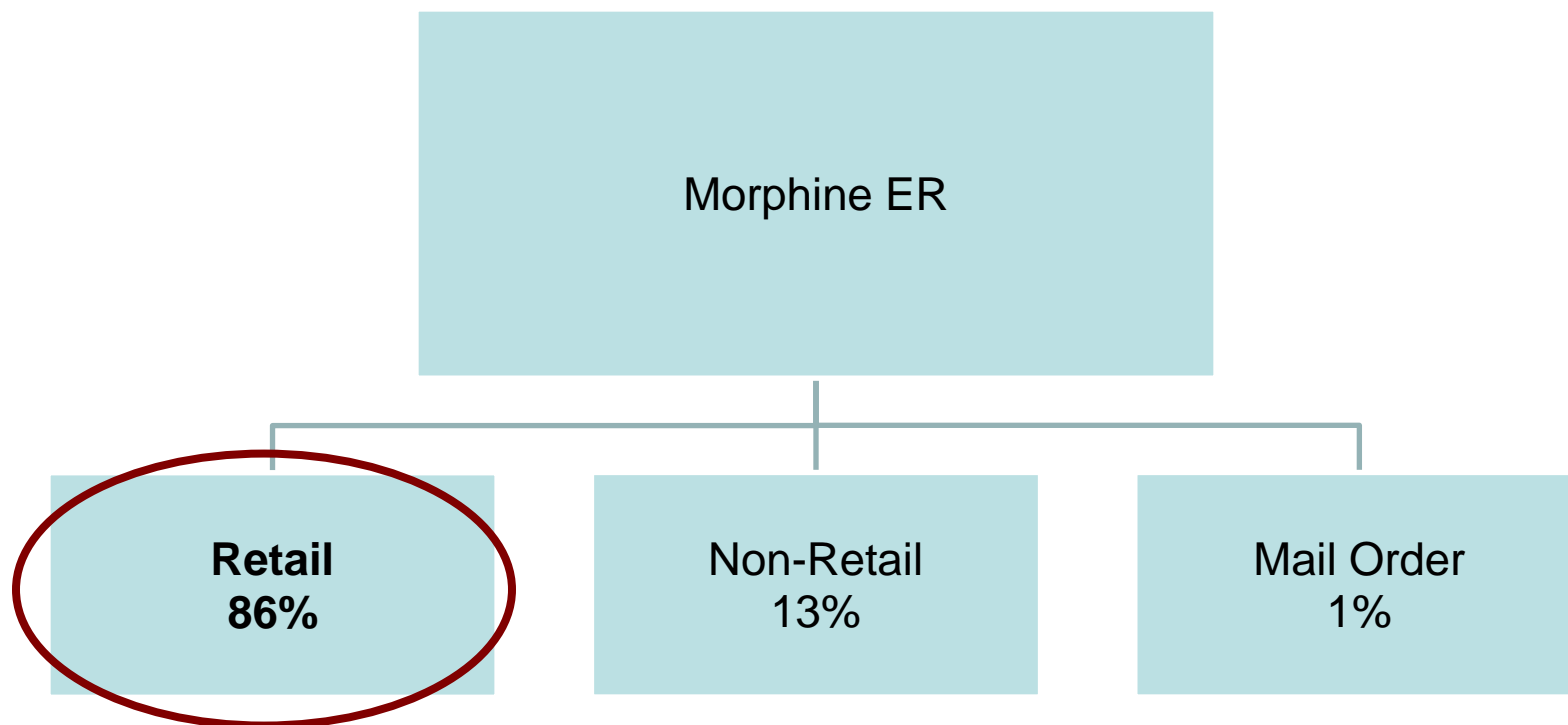
Sales Distribution Data

- IMS National Sales Perspectives Database™
- Captures sales of drug products from manufacturers to all retail and non-retail settings
 - Retail chain pharmacies, mail-order pharmacies, hospitals, etc.
- Data are nationally projected
- Does not represent actual patient use

Sales Distribution Data

Year 2015

IMS Health, IMS National Sales Perspective™, Extracted June 2016



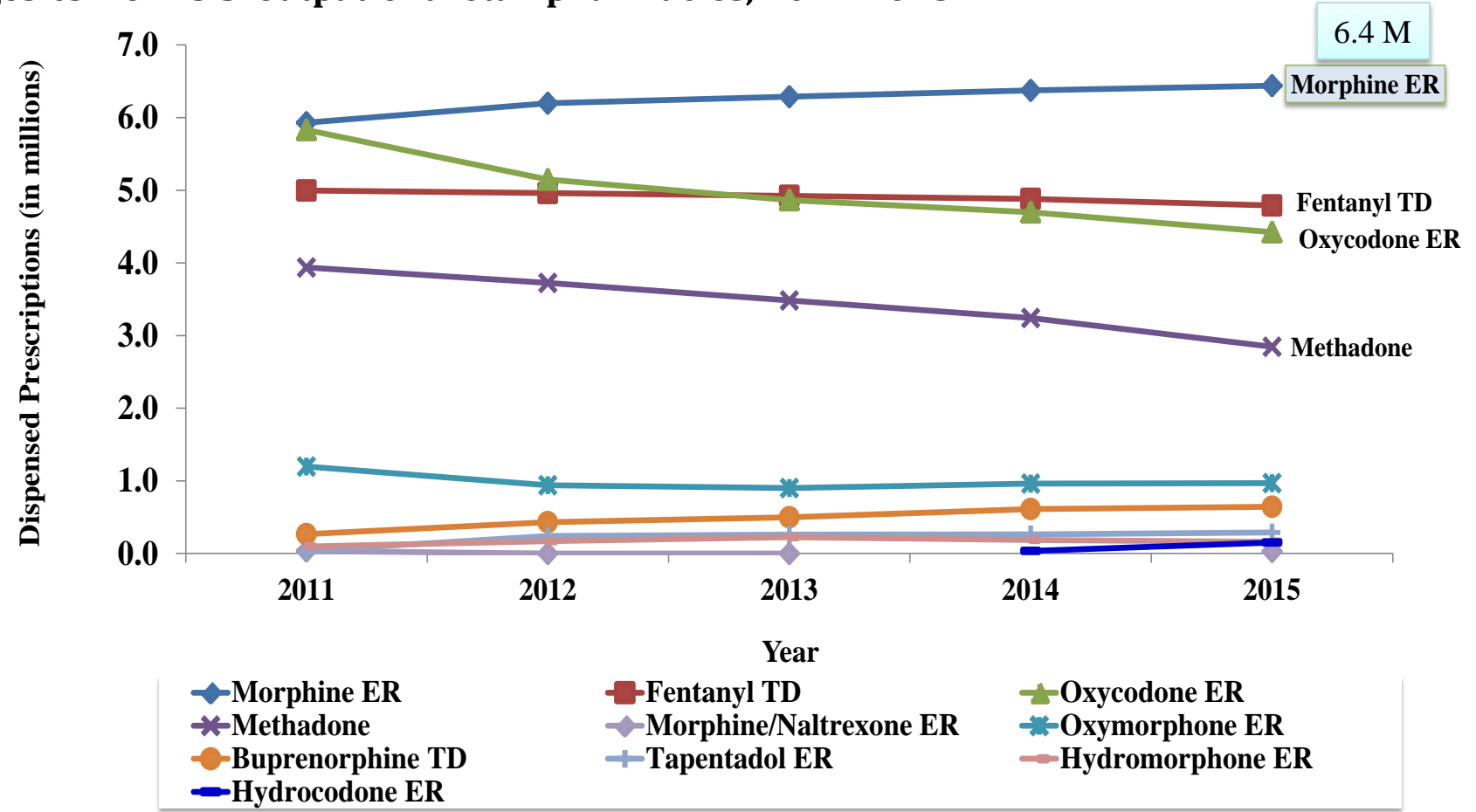
Database Descriptions

Prescription Utilization and Prescriber Specialty Data :

- IMS Health, National Prescription Audit™ (NPA) Database
- Measures dispensing of prescriptions out of retail pharmacies into the hands of consumers
- Data can be stratified by prescriber specialty

Prescription Drug Utilization:

Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015



Source: IMS, National Prescription Audits (NPA) Data extracted March 2016. File: NPA 2016-950 Rx morphine ERLA AC June 2016.xlsx
 **No data for years 2011, 2012, and 2013 for hydrocodone products: Zohydro ER approved in 10/2013 and Hysingla ER approved 11/2014

Top Prescriber Specialty: 2015

Top 10 prescriber specialties by the nationally estimated number of prescriptions dispensed for morphine ER from U.S. outpatient retail pharmacies

| PRESCRIBER SPECIALTY | Prescriptions (N) | Share (%) |
|--|--------------------------|------------------|
| Morphine ER Total Prescriptions | 6,441,121 | 100.0% |
| Family Practice/General Practice/Osteopathy | 1,706,226 | 26.5% |
| Anesthesiology | 863,681 | 13.4% |
| Nurse Practitioner | 811,374 | 12.6% |
| Internal Medicine | 709,509 | 11.0% |
| Physician Assistant | 619,726 | 9.6% |
| Physical Medicine/Rehabilitation | 524,352 | 8.1% |
| Pain Medicine | 362,184 | 5.6% |
| Oncology | 217,555 | 3.4% |
| Neurology | 96,472 | 1.5% |
| Orthopedic Surgery | 67,299 | 1.0% |
| All Other Specialties | 462,743 | 7.2% |

Source: IMS, National Prescription Audit (NPA). Year 2015. Extracted June-2016. File: NPA 2016-950 specialty morphine ERLA AC June 2016.xlsx

Limitations:

- Only outpatient retail pharmacy use was assessed
- Top specialties captured as reported by the prescription data

Summary:

Morphine ER

- Steady utilization from 2011-2015
- Most frequently dispensed ER/LA opioid with 6.4 million prescriptions
- One-quarter of prescriptions written by family practice/general practice/osteopathy



Back-Up Slides Shown

The *in vitro* data demonstrate that TRADENAME has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that TRADENAME has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of TRADENAME by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of TRADENAME on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

TRADENAME contains “opioid”, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxycodone. TRADENAME can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.