

**OPANA® ER (OXYMORPHONE HYDROCHLORIDE)
EXTENDED-RELEASE TABLETS**

**JOINT MEETING OF THE ANESTHETIC AND
ANALGESIC DRUG PRODUCTS ADVISORY
COMMITTEE AND THE DRUG SAFETY AND RISK
MANAGEMENT ADVISORY COMMITTEE**

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**ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition or Explanation
ADF	Abuse-deterrent formulation
AE	Adverse event
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
ASI-MV	Addiction Severity Index-Multimedia Version
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
C _{max}	Maximum observed plasma drug concentration
CRF	Crush-resistant formulation
CYP450	Cytochrome P450
DA	Divided Attention
E _{max}	Maximum effect
ER	Extended release
FDA	Food and Drug Administration
GEE	Generalized estimation equations
HCl	Hydrochloride
IR	Immediate release
LA	Long acting
MedDRA	Medical Dictionary for Regulatory Activities
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New drug application
ORF	Reformulated OxyContin
PEO	Polyethylene oxide
PVRM	Pharmacovigilance and Risk Management
Q	Quarter
RADARS	Researched Abuse Diversion and Addiction Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
ROA	Route(s) of administration
TMA	Thrombotic microangiopathy
T _{max}	Time to maximum observed plasma drug concentration

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Abbreviation	Definition or Explanation
TTP	Thrombotic thrombocytopenic purpura
UGT	Uridine diphosphate glucuronosyltransferase
VAS	Visual analog scale(s)

1. EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) has convened a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to review pre- and post-market data and benefit/risk for OPANA® ER (oxymorphone hydrochloride) Extended-Release Tablets and overall abuse patterns with immediate-release (IR) and extended-release (ER) oxymorphone. Endo Pharmaceuticals Inc. (hereafter Endo) is the first Sponsor to present postmarketing epidemiology data for a crush-resistant formulation (CRF) of an opioid analgesic product, specifically for OPANA ER. The obtained epidemiology data to date show a changed abuse pattern for OPANA ER.

The development of abuse-deterrent formulations (ADFs) is part of a multifactorial effort to reduce the risk of abuse and diversion.⁽¹⁾ The original formulation of OPANA ER was approved in 2006. Based on abuse patterns, observed both, for original OPANA ER and other opioid products, reformulated OPANA ER was designed to resist crushing, with the intention of reducing both overall abuse and abuse of the product via intranasal administration, which was identified as the primary route of abuse for original OPANA ER. At the same time reformulated OPANA ER was designed to have properties to resist other forms of abuse.

The development of reformulated OPANA ER with abuse-deterrent properties was initiated prior to issuance of FDA guidance for the evaluation and labeling of abuse-deterrent opioids.

Reformulated OPANA ER was approved in December 2011 without ADF labeling, as a single-entity oxymorphone HCl tablet with an approved indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Non-crush-resistant versions of generic oxymorphone ER were introduced into the market initially in 2011 in low-dose strengths (7.5 mg and 15 mg only) with the additional strengths introduced in early 2013.

Throughout the reformulation development, FDA provided significant input, particularly in the design of the study to evaluate human abuse liability (Category 3) and postmarketing epidemiology (Category 4). In accordance with FDA guidance,⁽²⁾ the abuse-deterrent properties of OPANA ER were tested in Category 1 in vitro manipulation studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies. Endo initiated Category 4 studies to evaluate the impact of reformulated OPANA ER in a “real world setting.”⁽²⁾

1.1. Efficacy and Safety of OPANA ER in Patients with Chronic Pain

The efficacy of OPANA ER, approved in 2006, has been demonstrated in randomized, placebo-controlled, double-blind trials in opioid-inexperienced and opioid-experienced patients with moderate to severe pain including low back pain. Those trials showed statistically significant separation between OPANA ER and placebo in pain intensity measurements, which were sustained over the course of the double-blind periods.⁽³⁾

The most frequent adverse events (AEs; ≥2%) from the placebo-controlled trials are those typical for opioid analgesics as summarized in [Table 1](#).

Table 1: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence ≥2% in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets

MedDRA Preferred Term	Oxymorphone HCl ER Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (excl vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	<1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

1.2. Unmet Need in the Treatment of Pain Requiring Around-the-Clock Opioid Treatment

Both IR and ER opioid therapies are indispensable treatments for patients with acute and chronic pain, respectively. Opioids are an important component of modern pain management,(2) and ER/long-acting (LA) opioids are typically used for around-the-clock, maintenance treatment of chronic pain for which alternative therapies are inadequate. Their use has been endorsed by professional societies and is an integral part of European and US guidelines for the treatment of chronic pain.(4-6)

Multiple opioid therapeutic options are available to clinicians and while this may appear unnecessary based on a perceived common molecular mechanism of action, it is often justified by the well-established fact that opioids display wide variations in pharmacological efficacy and tolerability, necessitating individualized treatment for patients.(7) The diversity in response is based on multiple factors such as age, gender, comorbidities, concomitant medications, renal and hepatic function, as well as genetic variations in receptor subtypes.(8) The phenomenon of tolerance, whereby increasing doses are necessary to sustain a pharmacological effect also necessitates multiple therapeutic options for patients.(9,10) The need to have multiple opioid analgesics and the technique of opioid rotation are critical elements in clinical practice to overcome these limitations.(11) It allows physicians prescribing options to employ opioid

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rotation to help manage the negative effects of opioids by limiting doses required to obtain pain relief with tolerable side effects. In fact, 2 or 3 opioid drugs may have to be selected before effective analgesia with tolerable side effects is achieved.(8,11)

Pharmacokinetic and Pharmacodynamic Differences Between Opioids

Wide variations in patient response to opioids are generally attributed to genetic differences in pharmacokinetics and pharmacodynamics. Polymorphic variants of human mu opioid receptors, as well as additional genetic variants in 2 cytochrome P450 (CYP450) isoenzymes that are key to the metabolic transformation of the majority of opioid drugs, contribute to the variability of efficacy and safety among individual patients (section 2.7).(12) Opioid metabolism is very complex and differs between individual opioid molecules based on age, sex and ethnicity, each of these factors undoubtedly contribute to the variability in patient response.

There are 2 major metabolic pathways for opioids: a) the CYP450 pathway that mediates phase-1 metabolism and b) the uridine diphosphate glucuronosyl transferase (UGT) pathway that is responsible for phase-2 glucuronide conjugation. Not all opioids utilize both of these pathways. The CYP450 family of enzymes, in particular the CYP3A4 and CYP2D6 isozymes, are major determinants of the metabolic fate of most opioids (including buprenorphine, codeine, fentanyl, hydrocodone, methadone, and oxycodone) ([Table 2](#)). Only 2 of the clinically used opioids (oxymorphone and hydromorphone) avoid CYP450-based metabolism and proceed directly to phase-2 transformation via the UGT pathway. There are also several genetic variants of UGT isozymes but 2 in particular, UGT2B7 and UGT1A3, play dominant roles in the biotransformation of opioids ([Table 2](#)).

Table 2: Metabolic Pathways of Common Opioids

Opioid	Phase I Metabolism	Phase II Metabolism
Codeine	CYP2D6	UGT2B7
	CYP3A	
Hydrocodone	CYP2D6	UGT1A3
	CYP3A	UGT2B2 Dihydromorphine ketone reductase
Oxycodone	CYP3A	UGT2B7
	CYP2D6	
Methadone	CYP3A	
	CYP2B6	
	CYP2D6	
	CYP2C9 ^a	
	CYP2C19 ^a	
Tramadol	CYP3A	
	CYP2D6	
Fentanyl	CYP3A	
Morphine	CYP3A	UGT2B7
Hydromorphone		UGT1A3
		UGT2B7
		Dihydromorphine ketone reductase
Oxymorphone		UGT2B7

^a Minor pathways/clinical significance unknown.

Adapted from Smith HS. *Mayo Clin Proc.* 2009;84(7):613-624 and Fredheim CM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. *Acta Anaesthesiol Scand.* 2008;62(7):879-889.

The fact that so many of the available opioid medications are subject to CYP450-based metabolism creates a potential for pharmacokinetic interactions with any concomitant medications (13) since CYP450-based metabolism is responsible for the clearance of many other drugs (section 2.7).

1.2.1. Need for Multiple Opioid Options

The availability of multiple opioid medications provides necessary alternatives to physicians - enabling them to employ opioid rotation (8,11) to help manage the negative effects of opioids by limiting doses required to maintain adequate pain relief while minimizing side effects.

As discussed above, opioid rotation may be warranted if there are pharmacokinetic interactions between concomitant medications. Although there are very few prospective studies that have addressed the impact of drug-drug interactions with opioids, it is estimated that in a managed care setting about 30% of all patients taking opioids metabolized by CYP450 were also exposed to other CYP450 substrates (section 2.7)(14) – perhaps not surprising given that it is also estimated that the average chronic pain patient takes about 10 medications, many of which are substrates for, or inducers of CYP450 enzymes and thus have the potential to influence the metabolism and

clearance of an adjunct opioid medication.(13) More importantly, pharmacokinetic interactions have potential pharmacodynamic consequences, these may range from increased opioid exposure and toxicity to increased elimination and loss of analgesic efficacy. Therefore, opioids that are not subject to CYP450 metabolism (eg, oxymorphone) are less prone to drug-drug interactions and offer important treatment options to clinicians faced with managing chronic pain in a patient population with comorbidities requiring multiple concomitant medications.

Beyond the concern of pharmacokinetic-based drug-drug interactions there are suggestions that inter-patient variability in opioid pharmacodynamics, potentially attributed to genomic variations in opioid receptor structure/function, exist. This is an evolving science and as yet there are no guidelines for assessing the optimal opioid for a given patient's receptor genotype, yet clinical practice tends to employ a more empirical approach and pharmacological heterogeneity is supported by the observation that 2 or 3 opioid drugs may have to be selected before effective analgesia with tolerable side effects is achieved.(11) As an example of the heterogeneity of response to 2 seemingly similar drugs, a double-blind, placebo-controlled single dose 5-period crossover study of oral OPANA ER and OxyContin was conducted to compare drug-liking and cognitive effects. OPANA ER was associated with fewer positive, negative, balance, sedative or other subjective effects, a lower incidence of euphoric mood events, less miosis and less cognitive psychomotor impairment compared to equianalgesic doses of OxyContin (EN3202-402; data on file).

1.3. Need for Multifactorial Actions to Deter Abuse

While the utility of prescription opioids in the treatment of pain patients has been demonstrated, the abuse of opioids is a significant public health concern in the United States.

The abuse of prescription opioids and the potential consequences, such as addiction, overdose and death, pose a serious and growing public health risk. In fact, drug overdose is the leading cause of accidental death in the United States, with 52,404 lethal drug overdoses of all kinds in 2015. Of these, 33,091 overdose deaths were related to opioids (prescription and illicit opioids).(15)

“In response to this crisis, the FDA has developed a comprehensive action plan to take concrete steps toward reducing the impact of opioid abuse on American families and communities.”(1) In parallel, states have begun to implement legislation and monitoring.(16) One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.(2)

Formulations with abuse-deterrent properties have been developed to decrease manipulation by people who abuse drugs. In order to counteract the first step of manipulation, many abuse-deterrent products rely on hardness as a physical barrier to resist particle size reduction and therefore deter abuse.(17)

Balancing the benefits of prescription opioid analgesics against their abuse liability can be challenging for prescribing physicians. Thus, the development of formulations with abuse-deterrent properties could be an important step towards potentially reducing abuse and diversion of these medications.

1.4. Abuse-Deterrent Evaluation of OPANA ER

Reformulated OPANA ER, incorporating INTAC® technology, was designed to have increased tablet hardness using a polymer (polyethylene oxide [PEO]). Several approved opioids are currently utilizing PEO in their abuse- deterrent formulations, such as OxyContin® (oxycodone), Arymo™ ER (morphine), and Hysingla® ER (hydrocodone). INTAC technology utilizes a proprietary manufacturing process that applies heat and pressure to the formulation. Tablets with INTAC technology resist crushing because they exhibit a very high breaking strength, and form a viscous gel when exposed to an aqueous medium. The physicochemical barrier properties of the tablet are intended to reduce the likelihood of manipulation associated with abuse through unintended routes of administration (ROA), especially crushing it and subsequent intranasal administration, which was determined to be the primary route of abuse for original OPANA ER based on postmarketing surveillance data.

1.4.1. In Vitro Studies (Category 1) (Section 4.1)

Endo performed Category 1 (in vitro) studies that were designed to evaluate the ability of the product to be manipulated, as well as experiments to evaluate the potential for abuse via oral, nasal, and intravenous routes including extraction studies. These studies were filed in the original new drug application (NDA).

Subsequent to the approval of reformulated OPANA ER and approval of the ADF of OxyContin (oxycodone HCl extended-release tablets, referred to as OxyContin ADF throughout this document), additional studies were performed comparing the in vitro properties of the 2 products. Furthermore, after approval of 2 generic tablet formulations additional in vitro studies comparing reformulated OPANA ER to these generic formulations were performed

The results of in vitro studies comparing reformulated OPANA ER to OxyContin ADF and generic oxymorphone ER tablets show that

- Both reformulated OPANA ER and OxyContin ADF utilize similar approaches to abuse deterrence and yield formulations possessing similar crush resistance and gelling properties.
- Both reformulated OPANA ER and OxyContin ADF are crush resistant as both contain PEO and utilize heat in their respective manufacturing processes.
- Based on the results generated for both formulations, reformulated OPANA ER and OxyContin ADF have similar physicochemical properties and provide similar physical/chemical barriers to abuse by intranasal administration and injection.
- Simulated oral ingestion studies for reformulated OPANA ER and OxyContin ADF in a variety of solvents yield similar extraction results as expected based on similar formulations, manufacturing processes and solubilities. Percentage extracted and dissolved increase with more aggressive manipulation techniques which lead to smaller particles and larger surface area.
- Both reformulated OPANA ER and OxyContin ADF require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-crush-resistant oxymorphone ER formulations.

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- Generic products on the market are easily manipulated to small particle sizes with simple tools whereas reformulated OPANA ER is crush resistant and difficult to reduce to particles that can be administered intranasally.
- Generic oxymorphone ER tablets are easily crushed, dissolved, and extracted for injection.
- Generic oxymorphone ER tablets behave similarly to IR tablets. Once crushed generic oxymorphone ER does not provide any barrier to potential misuse and abuse whereas reformulated OPANA ER is crush resistant and provides a barrier to misuse and abuse.

These findings demonstrate that crush-resistant reformulated OPANA ER, while not abuse proof does provide a barrier to misuse and abuse. Its physicochemical properties are similar to OxyContin ADF and require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-crush-resistant generic oxymorphone ER formulations.

1.4.2. Pharmacokinetic Studies (Category 2) (Section 4.2)

The pharmacokinetic profile of reformulated OPANA ER was evaluated in a Category 2/3 study (EN3288-114), when administered intact or manipulated for intranasal administration. This study was conducted in subjects who use opioids recreationally and evaluated the primary route of abuse, intranasal administration. Amongst other parameters, the rate of rise of drug concentration (abuse quotient [AQ] = C_{max}/T_{max}) was assessed because it is thought to quantify the differential abuse potential among drugs, formulations, and ROA.

In study EN3288-114, manipulated, reformulated OPANA ER for intranasal administration was compared with oxymorphone HCl powder, which represents the manipulated form of non-abuse-deterrent OPANA ER, ie, the crushable non-abuse-deterrent oxymorphone formulations currently on the market. While oxymorphone levels rose rapidly following intranasal administration of oxymorphone HCl powder, manipulated, reformulated OPANA ER showed a lower C_{max} and delayed T_{max} . C_{max} was approximately 58% lower for manipulated, reformulated OPANA ER than for oxymorphone powder, and T_{max} was longer for manipulated, reformulated OPANA ER compared with oxymorphone power (1.5 hours vs 0.25 hours, respectively). The abuse quotient was 1.43 ng/mL/h after manipulated, reformulated OPANA ER compared to 19.20 ng/mL/h after oxymorphone powder was administered intranasally. The approximately 13-fold lower abuse quotient demonstrates that the abuse-deterrent properties of reformulated OPANA ER limit the rate and extent of rise of drug concentration following intranasal administration of the manipulated product.

In study EN3288-108 reformulated OPANA ER maintained ER properties when manipulated with various tools and ingested orally; these manipulations did not increase peak plasma exposure to the level of an IR tablet.

1.4.3. Human Abuse Liability Study (Category 3) (Section 4.3)

Human abuse potential was evaluated in recreational opioid abusers in the Category 2/3 study EN3288-114. The study incorporated study design characteristics and data analysis methods that were consistent with Agency recommendations for the evaluation of abuse deterrent opioids (section IV, parts B and C of the FDA guidance).(2) These included using matched placebo and

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positive control and use of a qualification phase of the study, which assured that the treatment phase included only subjects who were experienced, recreational opioid users with intranasal administration and who were able to distinguish between active drug and placebo. Based on the results of pilot study EN3288-113, the dose of manipulated, reformulated OPANA ER and oxymorphone powder used in this study was 7.5 mg. Pharmacodynamic assessments were subjective measures of drug liking, good drug effect, bad drug effects, sedative effects, and pupillometry, that were quantified using visual analog scales (VAS) and numerical rating scales (NRS). The primary endpoint was the E_{max} of the VAS for Drug Liking “at this moment” during the treatment phase between, manipulated, reformulated OPANA ER ADF and oxymorphone powder.

Statistically significant reductions in peak Drug Liking “at this moment” were observed following intranasal administration of reformulated manipulated OPANA ER compared with oxymorphone HCl powder. The mean ($\pm SD$) E_{max} for Drug Liking of reformulated OPANA ER 7.5-mg manipulated tablet was 70.3 ± 16.20 mm, compared to 87.8 ± 10.33 mm for oxymorphone HCl powder 7.5 mg.

The results of this human abuse potential study suggest that reformulated OPANA ER may have lower abuse potential via the intranasal ROA. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that reformulated OPANA ER has physicochemical properties that are expected to reduce abuse via the intranasal route when manipulated.

1.4.4. Postmarketing Epidemiology (Category 4) Studies (Section 4.4)

Three (3) postmarketing epidemiology studies (2 primary and 1 secondary study) were conducted in order to assess the change in the prevalence and routes of abuse of reformulated OPANA ER in a “real-world” setting. These studies were based on protocols developed in collaboration with partner organizations skilled in observational studies of drug abuse. All protocols were submitted to the FDA for review. These postmarketing studies provide the best available data on which to assess the impact of OPANA ER on abuse patterns. However, they have limitations:

NAVIPPRO®	
Strengths	Limitations
<p>Designed for active data collection; not dependent upon passive, retrospective, and often anecdotal data characteristic of other, commonly used data streams.</p> <p>ASI-MV Connect® system yields data in near real time: the majority of participating treatment sites (85%) uploads data within the same day. Data are uploaded within 2 weeks for 95% of sites.</p> <p>ASI-MV uses a methodology for questioning respondents about use/abuse of particular prescription medications that is similar to methods employed by the National Survey on Drug Abuse and Health (NSDUH) survey</p> <p>Data for numerators and denominators are obtained with geographic specificity.</p>	<p>Lack of national representativeness</p> <p>The network is a private business and relies on contractual business arrangements with substance abuse treatment facilities to install and use the ASI-MV Connect software.</p> <p>Treatment centers within the ASI-MV Connect system are not randomly recruited to join the network</p> <p>Treatment centers are “dropping in” and “dropping out” of the network as a result of gain of business or loss of business, respectively.</p> <p>Data are collected at the patient 3-digit ZIP Code level. Dataset contains at least 1 case in nearly 92% of all 3-digit ZIP Codes. However, “representation” may be by a single individual in a 3-digit ZIP Code.</p>

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NAVIPPRO®	
Strengths	Limitations
Numerator data are product specific allowing for the isolation of the effect of OPANA ER from other opioids and other oxymorphone products.	The set of individuals seeking treatment may be of limited representativeness for the entire population of individuals who misuse or abuse controlled substances. Data are self-reported, which is subject to recall bias Potential for potential for misclassification or misidentification
RADARS®	
Strengths	Limitations
Extensive national coverage (90.2%) of 2010 US population Data for numerators and denominators are obtained with geographic specificity. Numerator data are product specific allowing for the isolation of the effect of OPANA ER from other opioids and other oxymorphone products. Data are quality reviewed against case notes to ensure proper product identification, reason for exposure, ROA, and medical outcome.	Poison centers collect data on spontaneous reports which are subject to reporting bias. Not all persons ingesting a prescription opioid and experiencing an adverse effect will call a poison center. In this sense, the rates obtained are likely underestimates of the true rates of adverse effects. Callers to poison centers may report use of a branded product even though the exposure involved a generic version. Route of administration can be missing in the reports.

The studies used ongoing passive surveillance systems that collect data from 2 different partners: the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) and the Researched Abuse Diversion and Addiction Related Surveillance (RADARS®) System.

1. NAVIPPRO utilizes data from their Addiction Severity Index-Multimedia Version (ASI-MV), a proprietary data stream that collects data on substances used and abused by individuals entering treatment for substance use disorders at addiction treatment centers.
2. RADARS Poison Center Program collects intentional abuse data from participating poison control centers participating across the country. Such data consists of calls to poison centers reporting adverse drug-using experiences and usually requesting assistance.
3. RADARS Drug Diversion Program collects diversion information from municipal police departments (47%), multi-jurisdictional drug task forces (26%), county sheriff's departments (17%), regulatory agencies such as medical and pharmacy boards (5%), and other (5%) of events related to law enforcement activities or actions related to drugs of abuse.

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Table 3: Study Design and Prespecified Primary Comparisons

Study Title	Study Design/Comparisons
NAVIPPRO: “Post-Marketing Epidemiology Study to Assess Abuse of OPANA® ER Among Adults Assessed for Substance Abuse Treatment” (Primary Study)	<p>This protocol is aimed at evaluating whether OPANA ER ADF reduces or limits abuse following principles and recommendations outlined in the Agency’s guidance).</p> <p>Prespecified Primary Comparisons:</p> <ul style="list-style-type: none"> • All routes of abuse associated with tampering (eg, snorting and injection) of reformulated OPANA ER in the post-period compared to original OPANA ER in the pre-period within the ASI-MV population of adults assessed for substance abuse treatment. • Individual routes of administration (ie, oral, intranasal, injection) of reformulated OPANA ER in the post-period compared to original OPANA ER in the pre-period within the ASI-MV population of adults assessed for substance abuse treatment • All routes of abuse associated with tampering (eg, snorting and injection) of reformulated OPANA ER compared to non-crush-resistant generic oxymorphone ER in the post-period within the ASI-MV population of adults assessed for substance abuse treatment. • Individual routes of administration (ie, oral, intranasal, injection) of reformulated OPANA ER compared to non-crush-resistant generic oxymorphone ER in the post-period within the ASI-MV population of adults assessed for substance abuse treatment.
RADARS: “Proposed Analysis of Reformulated OPANA® ER using the RADARS® Poison Center Program” (Primary Study)	<p>This protocol examined differences in rates of intentional abuse mentions before and after introduction of reformulated OPANA ER.</p> <p>Comparisons:</p> <ul style="list-style-type: none"> • Rates of OPANA ER mentions by intentional abuse of reformulated OPANA ER compared to original OPANA ER. • Rates of OPANA ER mentions by intentional abuse using reformulated OPANA ER through routes other than swallowing the tablet whole compared to original OPANA ER. • Rates of OPANA ER mentions by intentional abuse resulting in a major medical outcome or a death of reformulated OPANA ER compared to original OPANA ER. • Rates of OPANA ER mentions resulting in overdoses (the total of intentional exposures, therapeutic errors, and unintentional general exposures) of reformulated OPANA ER compared to original OPANA ER.
RADARS: “Proposed Analysis of Reformulated OPANA® ER using the RADARS® Drug Diversion Program” (Secondary Study)	<p>This protocol examined differences in rates of diversion mentions before and after introduction of reformulated OPANA ER.</p> <p>Comparison:</p> <ul style="list-style-type: none"> • Rates of OPANA ER drug diversion mentions of reformulated OPANA ER compared to original OPANA ER.

1.4.4.1. Methodology for Postmarketing Epidemiology Studies

Time Periods

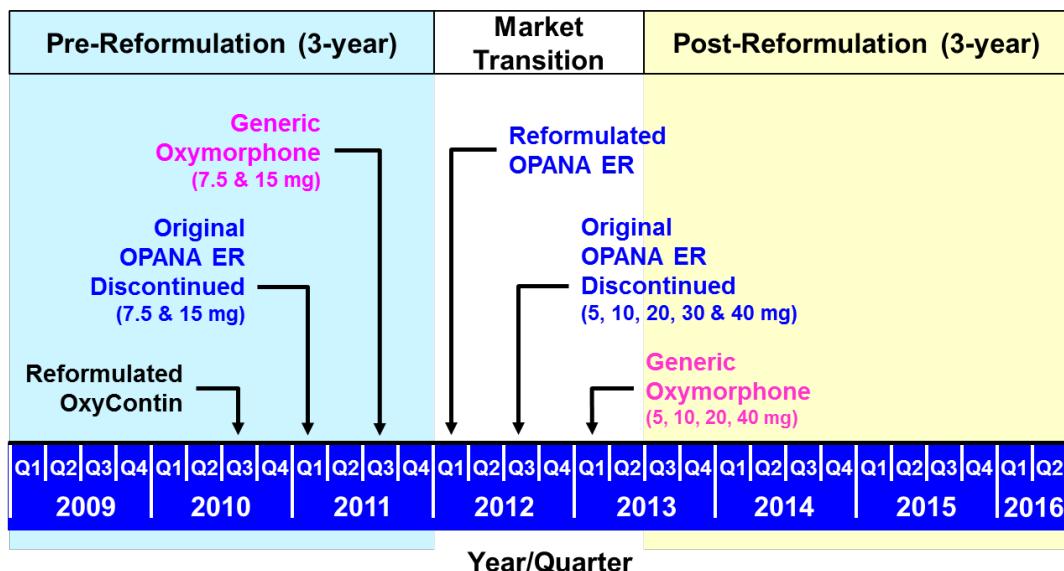
The studies are observational in nature and each are characterized by unique strengths and limitations (section 4.4.1.5 for NAVIPPRO; section 4.5.2 for RADARS). Each is a pre-post design, using a baseline pre-period of January 2009 through December 2011, during which original OPANA ER was on the market. Reformulated OPANA ER was introduced to the market in February 2012. However, the post-reformulation period is defined as the time from July 2013 through June 2016. The period from January 2012 through June 2013 is defined as the transition period. The FDA recommended that because of the high degree of instability of the market during that time, it would not be possible to understand adequately the effect of the reformulation, and, therefore, this period should not be included in the formal data analyses. The time period after the availability of reformulated OxyContin to the beginning of the transition period (Q3 2010 - Q4 2011) was part of a prespecified sensitivity analysis in both primary epidemiology studies to better understand the changing environment during the pre-reformulation period.

Details with regard to the prespecified analyses are provided in [Appendix 4](#).

1.4.4.2. Change in Opioid Product Availability During Epidemiology Studies

It is important to note that the opioid environment changed between 2010 and 2013, which directly affected OPANA ER abuse patterns. First, OxyContin was reformulated with a hard ADF in August 2010 during the pre-period. Secondly, low-dose strengths of generic ER oxymorphone, without ADF properties, became available in July 2011 – prior to availability of reformulated OPANA ER. The remaining full line of generic oxymorphone ER tablet strengths became available in early 2013 ([Figure 1](#)). These oxymorphone generics were approved as bioequivalent to the original non-PEO formulation of OPANA ER. The availability of these non-ADFs, and the corresponding abuse patterns, should provide a contrast to the abuse patterns seen for reformulated OxyContin and reformulated OPANA ER.

Figure 1: Time Periods of Data Utilized in the Category 4 NAVIPPRO Study and Changing Landscape



1.4.4.3. Key Results from Epidemiology Studies

The NAVIPPRO postmarketing epidemiology study evaluating abuse patterns of reformulated OPANA ER demonstrated that:

- The overall prevalence of abuse (all states and by alternate ROA) was higher in the post-period compared to the pre-period (pre-period 0.73; post-period 0.89 per 100 ASI-MV assessments).
 - Intranasal abuse was lower in the post-period compared to the pre-period (pre-period 0.61; post-period 0.23 per 100 ASI-MV assessments).
 - Intravenous abuse was higher in the post-period compared to the pre-period (pre-period 0.13; post-period 0.68 per 100 ASI-MV assessments).
- The prevalence of abuse for alternate ROA for non-crush-resistant generic oxymorphone ER was higher compared to reformulated OPANA ER in the post-period (0.89 for OPANA ER; 1.59 generic oxymorphone ER per 100 ASI-MV assessments).
 - The prevalences of abuse by alternate ROA for non-crush-resistant generic oxymorphone ER was higher for alternate ROA compared to reformulated OPANA ER,
 - For intravenous abuse the rates were similar (0.68 for OPANA ER; 0.66 for generic oxymorphone ER per 100 ASI-MV assessments).
- Data from the state of Tennessee have a disproportionate impact on the data for the entire NAVIPPRO reporting network and therefore appear to influence the results due to the fact that:

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- Tennessee contributes about 75% of abuse reports for OPANA ER to the overall abuse reports in the network in the post-period.
- Thus, it is necessary to look at the data both within Tennessee and within all other states in the NAVIPPRO network.
 - Outside of Tennessee, the rate of abuse for OPANA ER via intranasal administration was lower and via injection remained stable in the post-period compared to the pre-period (pre-period 0.65; post-period 0.06 for intranasal administration per 100 ASI-MV assessments; and pre-period 0.17; post-period 0.16 for intravenous administration per 100 ASI-MV assessments).
 - Within Tennessee, the prevalence of abuse for OPANA ER via intranasal administration was lower and the prevalence of abuse via injection was higher in the post-period (pre-period 9.87; post-period 1.47 for intranasal administration per 100 ASI-MV assessments; and pre-period 1.78; post-period 4.53 for intravenous administration per 100 ASI-MV assessments).
 - For comparator opioids, the prevalence of abuse via intravenous injection in Tennessee was higher in the pre-period and remained high in the post-period compared to states outside of Tennessee.
 - Part of this change may be explained by a shift in the patient population to more severely affected individuals in the post-period as evidenced by a higher proportion of in-patient treatment and prior history of injection abuse in the sample during the post-period compared to the pre-period.

The RADARS Poison Center data demonstrated that:

- Rates of intentional abuse exposures, major medical outcome and death, and overdose exposure for original OPANA ER were higher following the introduction of reformulated OxyContin ADF in August 2010 (0.0192, 0.0061, and 0.0491, respectively per 100,000 population). Higher rates were also observed in both oral and non-oral ROA among intentional abuse exposures (0.0088 and 0.0080, respectively per 100,000 population).
- After the introduction of the reformulated OPANA ER, rates of abuse, major medical outcomes and deaths, and overdose were lower (0.0060, 0.0019, and 0.00198, respectively per 100,000 population). This was observed for both population and drug utilization rates. Rates via oral and non-oral ROA were lower (0.0022 and 0.0029, respectively per 100,000 population). Similar changes were observed for drug utilization denominated rates (per 100,000 tablets dispensed).
- Broken out by state, intentional abuse exposure mentions were lower in all states except Tennessee (0.0183 versus 0.0049 events per 100,000 population) and remained stable in Tennessee compared to the peak of abuse in Q4 2011 (0.0530 versus 0.0497 events per 100,000 population). The rate of abuse in Tennessee is about 10 times higher than in any other state.

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The **RADARS** Drug Diversion data demonstrated that:

- Rate of drug diversion of OPANA ER per 100,000 population was 75% lower in the post-period compared to the pre-period.

1.5. Benefit/Risk Assessment

Reformulated OPANA ER demonstrates a favorable benefit-risk profile for people with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

OPANA ER demonstrated efficacy in moderate to severe chronic pain in non-malignant and malignant conditions (18) and in patients with suboptimal response to their prior opioid therapy. Both opioid-inexperienced subjects and opioid-experienced subjects with moderate to severe chronic low back pain were able to initiate treatment with a low dose of OPANA ER, gradually titrating to a maintenance dose that provided appropriate pain relief with tolerable side effects, and continuing treatment on their maintenance dose while maintaining the same pain relief for at least 12 weeks compared to placebo.

The AE profile in the placebo-controlled clinical trials is consistent with the class of opioid analgesics. Nausea, constipation, dizziness, somnolence, and vomiting are the most common AEs that occurred at a higher frequency on OPANA ER than on placebo.

Effective chronic pain management necessitates the availability of a variety of opioids due to a highly variable patient response in pharmacological efficacy and tolerability to members of the same class of analgesics. Therefore, opioid rotation is a critical element in therapy to overcome these limitations which are based on multiple factors such as age, gender, comorbidities, concomitant medications, renal and hepatic function, as well as genetic variations in receptor subtypes.

Oxymorphone, in particular, has important pharmacokinetic characteristics as it is metabolized by the UGT pathway and therefore represents a treatment choice for patients who previously did not tolerate an opioid metabolized by CYP450 due to either problematic metabolism (on a genetic basis) or drug-drug interactions.

Oxymorphone is further characterized by the extremely low level of active metabolites, which may have a potential to complicate treatment with other opioids.

The diversion and abuse of prescription opioid analgesic products poses serious public health and safety risks. FDA, other US government agencies/legislators, academia, and industry have identified the need for development of abuse-deterrent opioid formulations that can hinder the ability to extract extremely high concentrations of medication and deter abuse and diversion.

The findings of the Category 1 studies demonstrate that crush-resistant reformulated OPANA ER, while not abuse proof does provide a barrier to misuse and abuse. Its physicochemical properties are similar to OxyContin ADF and require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-crush-resistant generic oxymorphone ER formulations. Results of the Category 2 studies showed that reformulated OPANA ER has an approximately 13-fold lower abuse quotient compared to oxymorphone powder and that the abuse-deterrent properties of reformulated OPANA ER limit the rate and

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extent of rise of drug concentration following intranasal administration of the manipulated product.

The Category 3 study showed a statistically significant reduction in peak “Drug Liking at this moment” following intranasal administration of reformulated manipulated OPANA ER compared with oxymorphone HCl powder. Based on these observations, the results of this human abuse potential study suggest that reformulated OPANA ER may have lower abuse potential via the intranasal ROA. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that reformulated OPANA ER has physicochemical properties that are expected to reduce abuse via the intranasal route when manipulated. Results of three Category 4 observational studies demonstrated:

For NAVIPPRO data from addiction treatment centers:

- Abuse of original OPANA ER was increasing during the pre-period and continued to increase after the introduction of a reformulated version of OxyContin in August 2010.
- During the post-period, following the introduction of reformulated OPANA ER, the prevalence of abuse by alternate ROA was higher although intranasal abuse was lower. The effect on abuse by alternate ROA was driven by an apparent increase in intravenous abuse.
- However, the results for abuse by alternate ROA are explained by a high degree of data heterogeneity with Tennessee being an outlier:
 - Within Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period, but intravenous abuse was higher.
 - Outside of Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period and intravenous abuse remained stable at levels reached in 2011.
- Not only did Tennessee provide the majority of abuse reports during the post-period, but intravenous abuse was higher in this state for many opioid products both during the pre-period and the post-period and the higher level of intravenous abuse for OPANA ER was similar to or less than the levels for other opioids in both time periods.
- During the post-period, abuse by alternate ROA and intranasal abuse of generic oxymorphone ER was higher than for OPANA ER and intravenous abuse was similar.

For RADARS poison center data:

- Abuse of original OPANA ER was increasing during the pre-period and increased even more after the introduction of a reformulated version of OxyContin in August 2010.
- During the post-period, following the introduction of reformulated OPANA ER, overall abuse, abuse by oral and non-oral routes, major medical outcomes and death, and overdoses were lower compared to the pre-period.

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For RADARS drug diversion data:

- Rate of drug diversion of OPANA ER was lower in the post-period compared to the pre-period.

Thus, the introduction of reformulated OPANA ER was associated with a favorable change in the abuse profile in most of the United States. In Tennessee, where intravenous abuse is prevalent, such abuse of OPANA ER rose, but to levels similar to or less than those of other intravenously abused opioid products in that state. Still, observational studies can only show associations, not causal relationships. With the available epidemiology sources for assessing opioid abuse, there are important methodological limitations related to regional heterogeneity, changes in sampling over time, and overall changes in background abuse ecology.

In conclusion, the totality of the evidence demonstrates a favorable benefit-risk profile for OPANA ER in the intended population which is not altered by the Category 4 data in the unintended population. Endo is prepared to work with the FDA, Inflexxion, RADARS, and other interested partners in improving Category 4 data collection and analysis.

2. UNMET MEDICAL NEED IN TREATMENT OF PAIN REQUIRING AROUND-THE-CLOCK OPIOID TREATMENT

Summary

- The efficacy and safety of OPANA ER, approved in 2006, has been demonstrated in randomized, placebo-controlled, double-blind trials in opioid-inexperienced and opioid-experienced patients with moderate to severe pain including low back pain.
- Opioids are an important component of modern pain management; ER opioids are utilized for the management of chronic pain for which alternative therapies are inadequate.
- Effective chronic pain management necessitates the availability of a variety of opioids due to a highly variable patient response in pharmacological efficacy and tolerability.
- Opioid rotation is a critical element in therapy to overcome these limitations which are based on multiple factors such as age, gender, comorbidities, concomitant medications, renal and hepatic function, as well as genetic variations in receptor subtypes.
- Oxymorphone has important pharmacokinetic characteristics as it is metabolized by the UGT pathway and therefore has little potential for metabolically based drug-drug interactions.

2.1. Background on Chronic Pain

Chronic pain is defined by the International Association for the Study of Pain as “pain that persists beyond normal tissue healing time, which is assumed to be 3 months.” Epidemiological studies have confirmed that musculoskeletal pain, especially joint and back pain, is the most common type of pain, and most people with chronic pain have multiple sites of pain. Chronic pain has a profound impact on quality of life potentially leading to depression, sleep disturbance and fatigue, decrements in physical and cognitive functioning, and changes in mood, personality, and social relationships.⁽¹⁹⁾ The risk of death by suicide among chronic pain sufferers is at least doubles relative to control groups and the lifetime prevalence of suicide attempt is in the range of 5% to 14% in those with chronic pain.⁽²⁰⁾ Taken together, these data suggest a suboptimal quality of life among individuals with chronic pain resulting in a significant public health problem affecting our national morbidity, mortality, and disability rates.

2.2. Medical Use of Extended-Release Opioid Products

Opioid analgesics are an indispensable component of pain management.⁽²⁾ The use of opioids for chronic non-malignant pain has been endorsed by numerous professional societies in particular for the treatment of chronic moderate to severe pain.⁽⁴⁻⁶⁾

While there are many available analgesic therapies, the unmet need for effective chronic pain treatment remains high due to high variability with regard to efficacy and tolerability of existing

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therapies.^(7,8) Both IR and ER opioid therapies are indispensable treatments to provide for patients presenting with acute and chronic pain, respectively. ER/LA opioids are typically used for around-the-clock, maintenance treatment of chronic pain. Further, due to the fact that opioids display wide variations in pharmacological efficacy and tolerability, the need to have multiple opioid analgesics and the technique of opioid rotation are critical elements in therapy to overcome these limitations.⁽⁸⁾

2.3. Efficacy of OPANA ER

OPANA ER demonstrated efficacy in moderate to severe chronic pain in non-malignant and malignant indications⁽¹⁸⁾ and in patients with suboptimal response to their prior opioid therapy.

The results of the 2 pivotal studies conducted with original OPANA ER demonstrated that both, opioid inexperienced subjects and opioid experienced subjects with moderate to severe chronic low back pain, were able to initiate treatment with a low dose of OPANA ER, gradually titrating to a maintenance dose that provided adequate pain relief and tolerability, and continuing treatment on their maintenance dose while maintaining the same pain relief and tolerability for at least 12 weeks compared to placebo. No new efficacy studies for reformulated OPANA ER were required.

2.3.1. Pivotal 12-Week Study in Opioid-Inexperienced Patients and Opioid-Experienced Patients with Low Back Pain

2.3.1.1. Study Design

The pivotal studies of OPANA ER, as presented in the label, were double-blind, placebo-controlled, randomized withdrawal studies in opioid-inexperienced and opioid experienced patients with chronic low back pain, who were suboptimally responsive to their prior non-opioid therapy or stabilized on their prior opioid therapy, respectively. Patients entered a 4-week, open-label dose titration phase. Opioid-inexperienced patients initiated therapy with 2 days of treatment with OPANA ER tablets 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5 to 10 mg every 12 hours every 3 to 7 days. Opioid-experienced patients were dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. Once titrated to a stable dose, patients entered the 12-week double-blind treatment withdrawal period, where they were randomized to remain on treatment or switch to placebo.

Patients assessed their average pain intensity using a 100-mm VAS. The 100-mm VAS was bounded on the left by “no pain” and on the right by “the worst pain imaginable.”

2.3.1.2. Statistical Analysis

All statistical tests were 2-sided with a significance level of $\alpha = 0.05$, unless otherwise stated. Efficacy analyses were conducted on the All Treated Patients (Double-blind Treatment Period) and the modified Intent-to-Treat (mITT) populations, which excluded patients with major protocol violations

The primary efficacy endpoint was the change from baseline in average pain intensity (VAS) to the final visit (day 84). Analysis of covariance (ANCOVA) was performed with treatment and

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center as effects, and screening and baseline average pain intensity as covariates. Least squares (LS) mean and 95% confidence interval (CI) of the treatment difference were calculated.

For patients who discontinued from the study early, the following methods of imputation for missing values were used:

- For patients who discontinued due to an AE, the screening pain score prior to the open-label titration period (entry score, which was the worst case) was carried forward to the final visit
- For patients who discontinued due to opioid withdrawal symptoms in the placebo group, the baseline pain score prior to randomization (after the open-label titration period, which was the best case) was carried forward to the final visit
- For patients who discontinued due to all other reasons there was no clinical concern about treatment, therefore, the last observation was carried forward to the final visit.

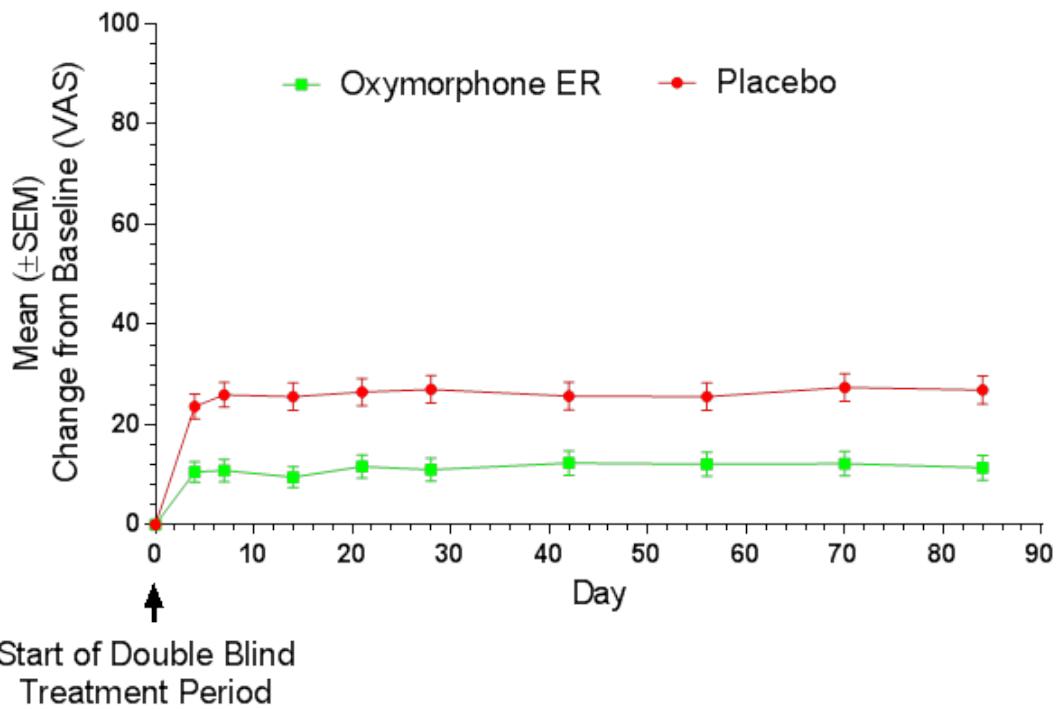
2.3.1.3. Results

2.3.1.4. Pivotal 12-Week Study in Opioid-Inexperienced Patients

Of the patients who were able to stabilize within the open-label titration period, the mean \pm SD VAS score at screening was 69.4 ± 11.8 mm and at baseline (beginning of double-blind period) were 18.5 ± 11.2 mm and 19.3 ± 11.3 mm for the OPANA ER and placebo groups, respectively. Sixty-three percent (63%) of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of OPANA ER tablets. The mean \pm SD stabilized doses were 39.2 ± 26.4 mg and 40.9 ± 25.3 mg for the OPANA ER tablets and placebo groups, respectively; total daily doses ranged from 10 to 140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of OPANA 5-mg IR tablets every 4 to 6 hours as supplemental analgesia; thereafter, the number of OPANA tablets was limited to 2 tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Sixty-eight percent (68%) of patients treated with OPANA ER tablets completed the 12-week treatment compared to 47% of patients treated with placebo.

OPANA ER tablets provided statistically significant better analgesia compared to placebo. The analgesic effect of OPANA ER tablets was maintained throughout the double-blind treatment period in 89% of patients who completed the study. These patients reported a decrease, no change, or a ≤ 10 mm increase in VAS score from day 7 until the end of the study. The mean change from baseline is shown in [Figure 2](#).

Figure 2: Mean Change from Baseline in Average Pain Intensity (VAS) by Visit – All Opioid-Inexperienced Treated Subjects (Double-blind Treatment Period) – Randomized Withdrawal Study Design



SEM=Standard error of the mean; VAS=Visual analog scale

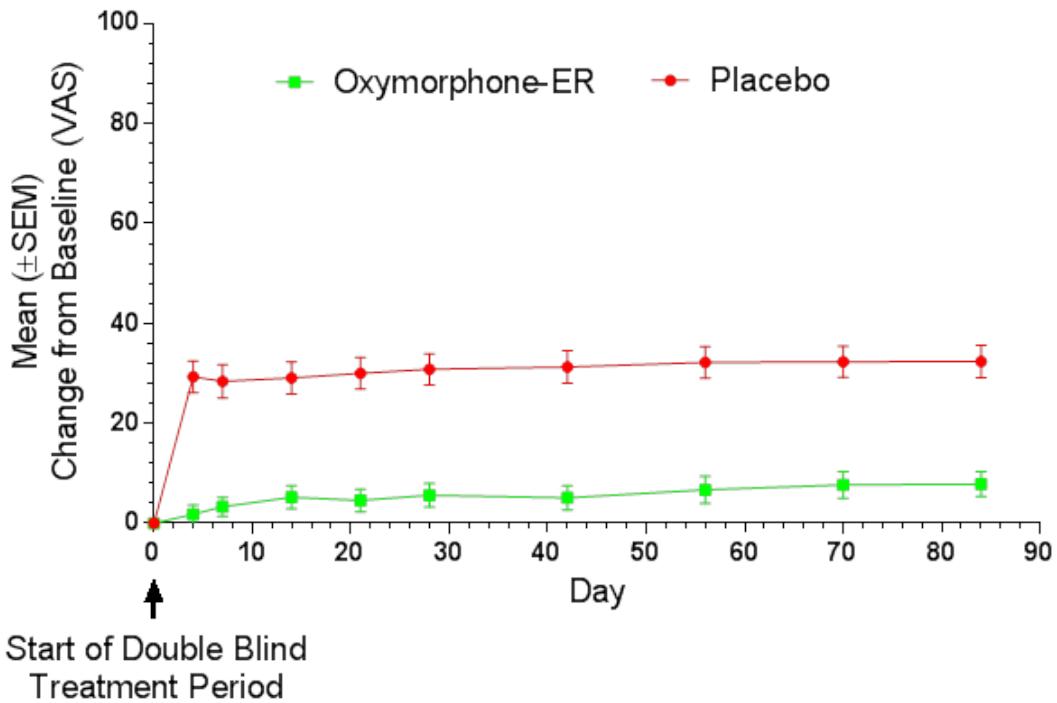
Note: Average pain intensity VAS scores ranged from 0 mm = “no pain” to 100 mm = “worst pain imaginable.”

2.3.1.5. Pivotal 12-Week Study in Opioid-Experienced Patients

Of the patients who were able to stabilize within the open-label titration period, the mean \pm SD VAS score at screening was 69.5 ± 17.0 mm and at baseline (beginning of double-blind period) were 23.9 ± 12.1 mm and 22.2 ± 10.8 mm for the OPANA ER and placebo groups, respectively. Stabilized patients entered a 12-week double-blind treatment phase with placebo or their stabilized dose of OPANA ER tablets. The mean \pm SD stabilized doses were 80.9 ± 59.3 mg and 93.3 ± 61.3 mg for the OPANA ER tablets and placebo groups, respectively; total daily doses ranged from 20 to 260 mg. During the first 4 days of double-blind treatment, patients were allowed an unlimited number of OPANA 5-mg IR tablets, every 4 to 6 hours as supplemental analgesia; thereafter the number of OPANA tablets was limited to 2 tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Fifty-seven percent (57%) of patients were titrated to a stabilized dose within approximately 4 weeks of OPANA ER tablets dose titration. Seventy percent (70%) of patients treated with OPANA ER tablets and 26% of patients treated with placebo completed the 12-week treatment.

OPANA ER tablets provided statistically significant better analgesia compared to placebo. The analgesic effect of OPANA ER tablets was maintained throughout the double-blind treatment period in 80% of patients who completed the study. These patients reported a decrease, no change, or a ≤ 10 mm increase in VAS score from day 7 until the end of the study (Figure 3).

Figure 3: Mean Change from Baseline in Average Pain Intensity (VAS) by Visit – All Opioid-Experienced Treated Subjects (Double-blind Treatment Period) – Randomized Withdrawal Study Design



SEM=Standard error of the mean; VAS=Visual analog scale

Note: Average pain intensity VAS scores ranged from 0 mm = “no pain” to 100 mm = “worst pain imaginable.”

2.4. Safety Profile of OPANA ER

2.4.1. Clinical Trials

The safety of oxymorphone HCl ER tablets was evaluated in a total of 2011 patients in open-label and controlled clinical trials as outlined in the current, approved label. The clinical trials enrolled of patients with moderate to severe chronic non-malignant pain, cancer pain, and postsurgical pain.

[Table 4](#) and [Table 5](#) list the most frequently occurring adverse reactions (in at least 5% of patients) from the 2 placebo-controlled trials in patients with low back pain. Adverse events with an incidence of $\geq 2\%$ in all placebo-controlled trials are presented in [Table 6](#).

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Table 4: Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-label Titration Period and Double-blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Inexperienced Patients with Low Back Pain)

MedDRA Preferred Term	Open-label Titration Period	Double-blind Treatment Period	
	Oxymorphone HCl ER Tablets (N = 325)	Oxymorphone HCl ER Tablets (N = 105)	Placebo (N = 100)
Constipation	26%	7%	1%
Somnolence	19%	2%	0%
Nausea	18%	11%	9%
Dizziness	11%	5%	3%
Headache	11%	4%	2%
Pruritus	7%	3%	1%

Table 5: Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-label Titration Period and Double-blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Experienced Patients with Low Back Pain)

MedDRA Preferred Term	Open-label Titration Period	Double-blind Treatment Period	
	Oxymorphone HCl ER Tablets (N = 250)	Oxymorphone HCl ER Tablets (N = 70)	Placebo (N = 72)
Nausea	20%	3%	1%
Constipation	12%	6%	1%
Headache	12%	3%	0%
Somnolence	11%	3%	0%
Vomiting	9%	0%	1%
Pruritus	8%	0%	0%
Dizziness	6%	0%	0%

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Table 6: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence $\geq 2\%$ in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets

MedDRA Preferred Term	Oxymorphone HCl ER Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (excl vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	<1%
Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

The common ($\geq 1\%$ to $<10\%$) adverse drug reactions reported at least once by patients treated with oxymorphone HCl ER tablets in the clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) system organ class and not represented in [Table 4](#) were:

- Eye disorders: vision blurred
- Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia
- General disorders and administration site conditions: dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema
- Nervous system disorders: insomnia
- Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression
- Respiratory, thoracic and mediastinal disorders: dyspnea
- Vascular disorders: flushing and hypertension

Other less common adverse reactions known with opioid treatment that were seen $<1\%$ in the oxymorphone HCl ER tablet trials include the following: bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, abdominal distention, ileus, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system

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depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, clamminess, dermatitis, and hypotension.

All of these AEs are typical for the class of opioid analgesic medications.

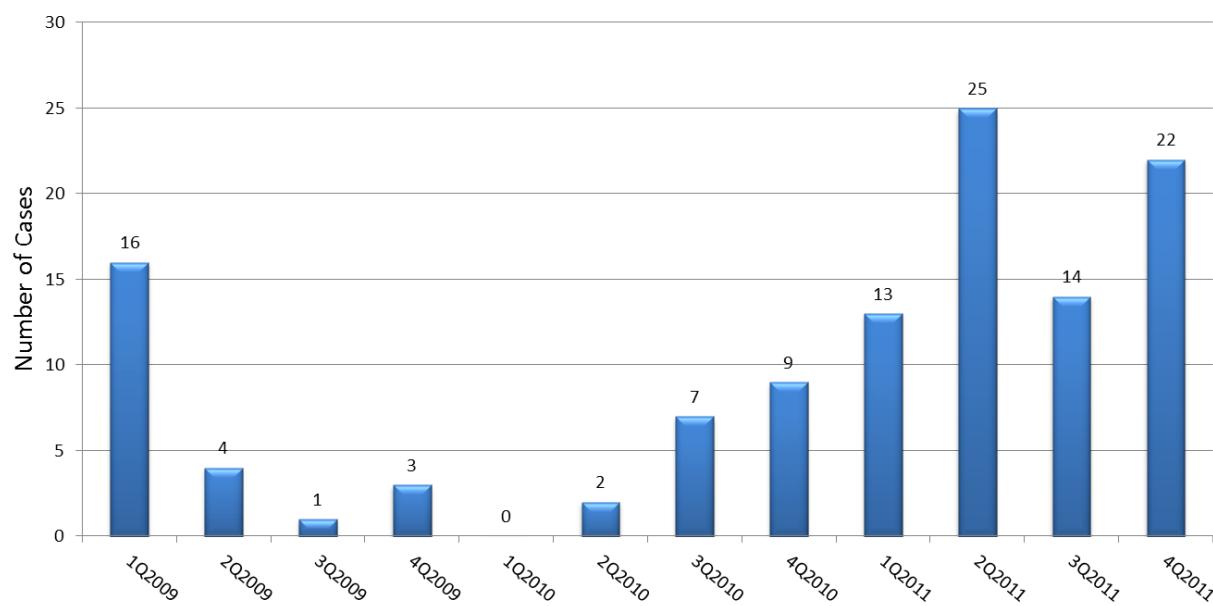
2.4.2. Postmarketing Data

2.4.2.1. Reported Cases of Drug Abuse

Endo monitors all postmarketing reports of AEs through its Pharmacovigilance & Risk Management (PVRM) department. PVRM has reviewed all cases of drug abuse reported to the company for OPANA ER corresponding to the 2 time periods of the NAVIPPRO and RADARS epidemiological studies. The baseline pre-period is considered to be January 1, 2009 through December 31, 2011 and the post-period is from July 1, 2013 to June 30, 2016. All cases are from the United States and have been coded using MedDRA Version 19.0. All terms coding to the preferred term of “drug abuse” or “drug abuser” are included in this analysis.

During the baseline pre-period a total of 116 reports of Drug Abuse were reported to Endo’s PVRM department for original OPANA ER. The distribution of these cases over time is shown in Figure 4.

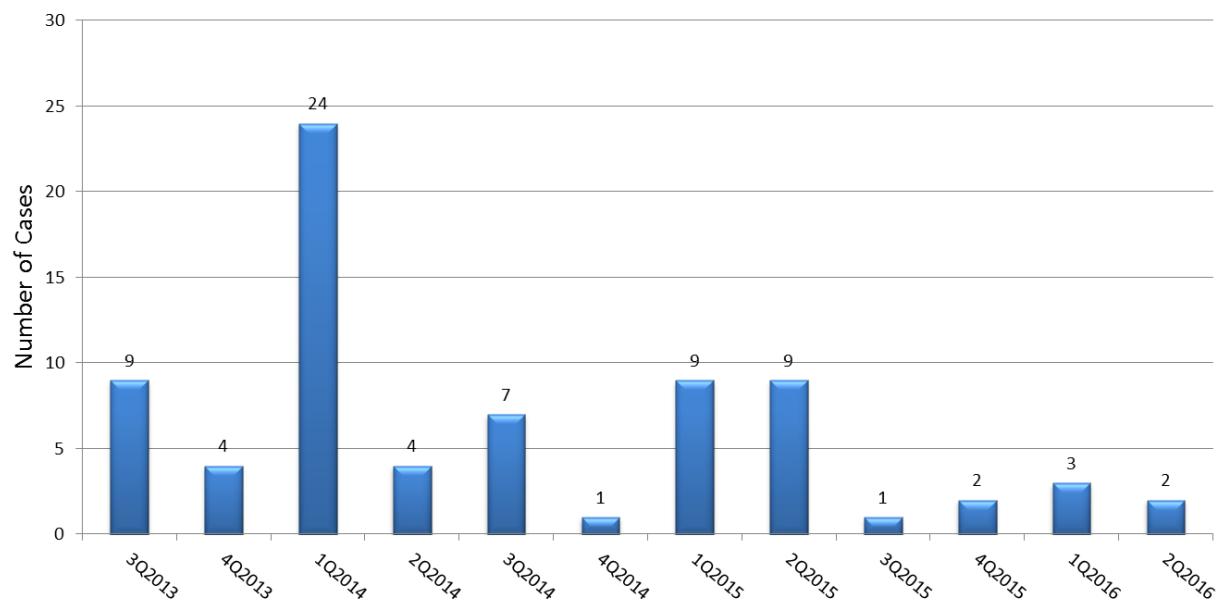
Figure 4: Distribution of Original OPANA ER Drug Abuse Cases by Quarter During Pre-period (1Q2009 – 4Q2011)



Reports of cases of drug abuse were relatively low in 2009 and the first half of 2010. However, beginning in 3Q2010 receipt of such cases increased and of the 116 reports, 74 (64%) were received in the 4 quarters of 2011. Thus, approximately 2/3 of the cases were received in the last 1/3 of the pre-period.

The post-period covers reports of cases of drug abuse for reformulated OPANA ER and is shown in [Figure 5](#).

Figure 5: Distribution of Reformulated OPANA ER Drug Abuse Cases by Quarter During Post-period (3Q2013 – 2Q2016)



During the post-period a total of 75 reports of drug abuse were received by Endo's PVRM department. Except for 1Q2014, the number of reports received for reformulated OPANA ER on a quarterly basis was lower than or similar to the reports received during the last 6 quarters of the baseline pre-period with original OPANA ER. During 1Q2014, 2 literature reports of cases of thrombotic microangiopathy (TMA; see section 2.4.2.2) were received by PVRM. Of the 24 cases received that quarter, 17 came from those 2 literature reports. All of those cases actually occurred earlier in 2013 and 2012. Generally, cases are attributed to the date when they are received, which is frequently when they occurred, particularly with spontaneously reported cases. However, for literature cases, this convention of attributing the case to the date the literature article was received, results in "spikes" such as this one, which is not related to when the cases actually occurred.

The remaining 7 cases for that quarter were spontaneously reported. Nonetheless, the last 4 quarters of the post-period show very few postmarketing cases of OPANA ER drug abuse being reported to the company.

In summary, a review of cases received by Endo's PVRM department shows that receipt of reports of drug abuse was higher during the baseline pre-period with original OPANA ER compared to the post-period with reformulated OPANA ER. As with all spontaneously reported postmarketing data, incomplete reporting is always a limiting factor.

2.4.2.2. Thrombotic Microangiopathy Associated with Intravenous Administration of Polyethylene Oxide

In August 2012 a nephrologist in northeast Tennessee reported to Endo and the Tennessee Department of Health (TDOH) 5 cases of a thrombotic thrombocytopenic purpuric-like (TTP) disorder in individuals who had extracted the ingredients of reformulated OPANA ER and

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injected them intravenously. Additional cases were reported from the same immediate geographic area and from other regions in central to eastern Tennessee. These patients reported initially were often ill with confounding conditions such as sepsis and endocarditis and often were treated with plasmapheresis. Endo promptly reported all of these cases to the FDA and a posting was made on the FDA website on October 11, 2012. Subsequently the TDOH and the Centers for Disease Control and Prevention (CDC) published an epidemiologic investigation in January 2013 of the outbreak in northeast Tennessee (21) that included a total of 15 cases of the disorder of whom 14 admitted to injecting reformulated OPANA ER. A subsequent publication from North Carolina presented a series of cases with spontaneous recovery where plasmapheresis was not necessary as long as injection of the material ceased.(22) The active ingredient, oxymorphone HCl, was not implicated because intravenous OPANA, initially approved by the FDA in 1959, is available as a safe and effective analgesic in the United States. Endo promptly reported all cases to the FDA and subsequently an update to the US Prescribing Information describing this risk occurred in April 2014 where the events are described as “thrombotic microangiopathy” (TMA), a medical synonym for this condition.

In reviewing the inactive ingredients of reformulated OPANA ER, the single biggest difference compared to original OPANA ER is the use of PEO. This excipient provides the extended-release characteristics of reformulation and also has the property of becoming a hard plastic-like substance under certain manufacturing conditions of heat and pressure. This results in the proprietary INTAC formulation, which resists crushing. PEO is used in a number of drug formulations and is listed in the FDA’s database of inactive ingredients for oral administration. Of note, PEO has never been tested or listed for use in pharmaceutical products by any other ROA. After the first cases of TMA were reported, a literature search of the toxicology of PEO was conducted. This literature review disclosed a single report in Russian of animal experiments with PEO at the time that it was being considered for use as a volume expander in shock states such as blood loss.(23) In these rat experiments dose-dependent reversible hemolytic anemia, neutrophilia, lymphopenia and thrombocytopenia were observed after.

Subsequently, an interested research-oriented investigator with experience in hematologic disorders in the Center for Biologics Evaluation and Research (CBER) at the FDA approached Endo to collaborate on a series of in vitro and animal experiments to investigate the effects of the parenteral administration of the OPANA ER excipients. Given prior descriptions of a “TTP-like” state developing in patients who had adulterated and intravenously delivered extracts of OPANA ER tablets, isolated in vitro experiments were first carried out which showed that neither PEO nor the entire inert ingredient have an effect on the expression or function of ADAMTS13—the plasma protease implicated in the development of TTP (data on file). However, guinea pigs intravenously administered the solubilized excipients showed evidence of microangiopathic hemolytic anemia, thrombocytopenia, and glomerular and tubular renal damage. This was associated with high levels of intravascular hemoglobin accumulation. The pathology seen in such animals was dose-dependent, with intravascular hemolysis alone elicited after single injections of the solubilized excipients, and end-organ injury only occurring in animals administered repeated doses. These outcomes were generated independent of an effect to ADAMTS13 and were ultimately attributable to the impact of PEO, the main constituent of the excipient mixture, in the microvasculature.(24)

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Importantly, this property of PEO is independent of the actual drug that is administered intravenously. There are now 2 reports in the literature of the same TMA syndrome reported with intravenous administration of reformulated OxyContin, a product that also uses PEO in its formulation.^(25,26) Thus intravenous administration of ER products with PEO, opioid or otherwise, may put an individual at risk for TMA.

2.5. Comparison of OPANA ER to Oxycodone ER

Oxymorphone is a mu opioid agonist whose principal therapeutic action is analgesia. In addition to analgesia, other pharmacologic effects include euphoria, anxiolysis, and feelings of relaxation. Orally administered oxymorphone is approximately 2-fold more potent than oxycodone in analgesic efficacy.

Although OPANA ER is associated with typical opioid-related effects, anecdotal reports from patients and prescribing physicians have suggested that OPANA ER may be associated with less euphoria, “buzz”, and other positive subjective effects compared to an ER formulation of oxycodone (OxyContin). Therefore, the purpose of this randomized, double-blind, placebo-controlled crossover study was to evaluate the subjective and objective effects of oxymorphone ER compared to oxycodone ER in healthy, non-dependent recreationally opioid users.

2.5.1. Study Design

Study EN3202-402 was designed as a 5-period, 10-sequence crossover study, that evaluated the subjective and objective effects of single doses of oxymorphone ER compared to oxycodone ER in healthy non-dependent recreational opioid users. Subjects attended a randomized, double-blind qualification phase, in which they received hydromorphone 8 mg and matching placebo in a randomized crossover manner. Each dose in the qualification phase was separated by approximately 24 hours. The pharmacologic qualification ensured that subjects were able to discriminate the positive subjective effects of opioids compared to placebo. A washout interval of at least 72 hours between drug administrations separated the qualification and treatment phases. During the treatment phase, subjects received single oral doses of each of the following treatments in a randomized, double-blind, crossover manner: placebo, oxymorphone ER 15 mg, oxymorphone ER 30 mg, oxycodone ER 30 mg, and oxycodone ER 60 mg. The low and high doses were chosen to be approximately equianalgesic. Drug administration occurred on day 1 of each treatment period followed for up to 24 hours post-dose by pharmacodynamic, pharmacokinetic, and safety assessments, including VASs, Addiction Research Center Inventory (ARCI) scales, Subjective Drug Value (SDV), pupillometry, and the Divided Attention (DA) test. Drug administration in each treatment period was separated by a washout interval of at least 7 days (maximum of 21 days).

2.5.2. Statistical Analysis

2.5.2.1. Data Summary

Raw scores were summarized at each time point using descriptive statistics (N, mean, standard deviation, median, and range) by treatment based on the Per-protocol population.

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The derived endpoints for all pharmacodynamic measures were summarized by treatment using descriptive statistics (N, mean, standard deviation, median, range and 95% CI) for all subjects in the Per-protocol population.

2.5.2.2. Data Analysis

Statistical data analysis of pharmacodynamic endpoints was done using a mixed effect ANCOVA model. The model included treatment, period, treatment sequence, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as a covariate where applicable, and subject nested within sequence as a random effect. The mixed effect model was based on the Per-Protocol population. The following contrasts were tested in the mixed effect model for all those pharmacodynamic endpoints:

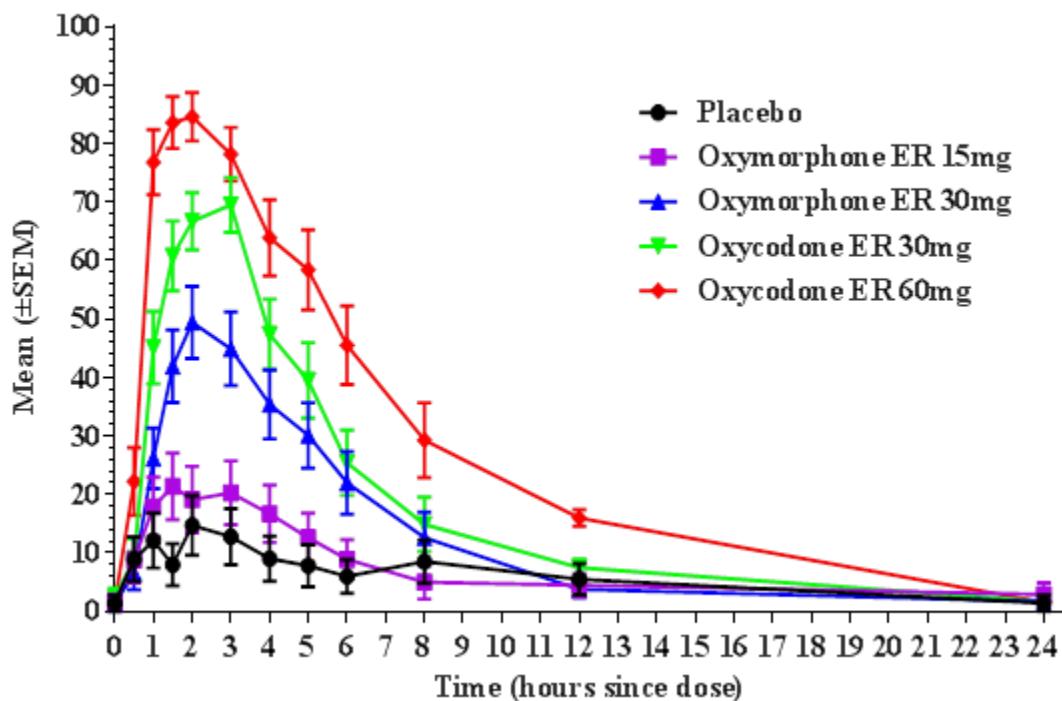
- Oxymorphone ER 30 mg vs oxycodone ER 60 mg
- Oxymorphone ER 15 mg vs oxycodone ER 30 mg
- Oxymorphone ER 15 mg vs oxymorphone ER 30 mg
- Oxycodone CR 30 mg vs oxycodone ER 60 mg
- Each dose of oxymorphone ER vs placebo
- Each dose of oxycodone ER vs placebo (study validity)

Due to the exploratory nature of this study, no Type I error adjustment for multiple endpoints or multiple comparisons was performed.

2.5.3. Results

On most subjective endpoints, including measures of balance, positive, negative, sedative and other subjective effects, oxymorphone ER 30 mg showed significantly less effect than oxycodone ER 60 mg and oxymorphone ER 15 mg showed significantly less effect than oxycodone ER 30 mg. Oxymorphone ER 15 mg was not significantly different from placebo on the majority of subjective endpoints, although oxymorphone ER 30 mg and both oxycodone ER doses showed significantly greater effects compared to placebo ([Figure 6](#)). The comparisons with placebo demonstrate the sensitivity of the measures and overall validity of the study for detecting abuse-related opioid effects. In addition, within and across types of measures, the subjective effects showed a large degree of consistency further indicating the reliability of the data. Finally, AEs of interest, such as euphoric mood, showed a pattern of effects consistent with the subjective measures (eg, 24.3% and 52.6% for oxymorphone ER 15 mg and 30 mg versus 67.5% and 92.5% for oxycodone ER 30 mg and 60 mg, respectively).

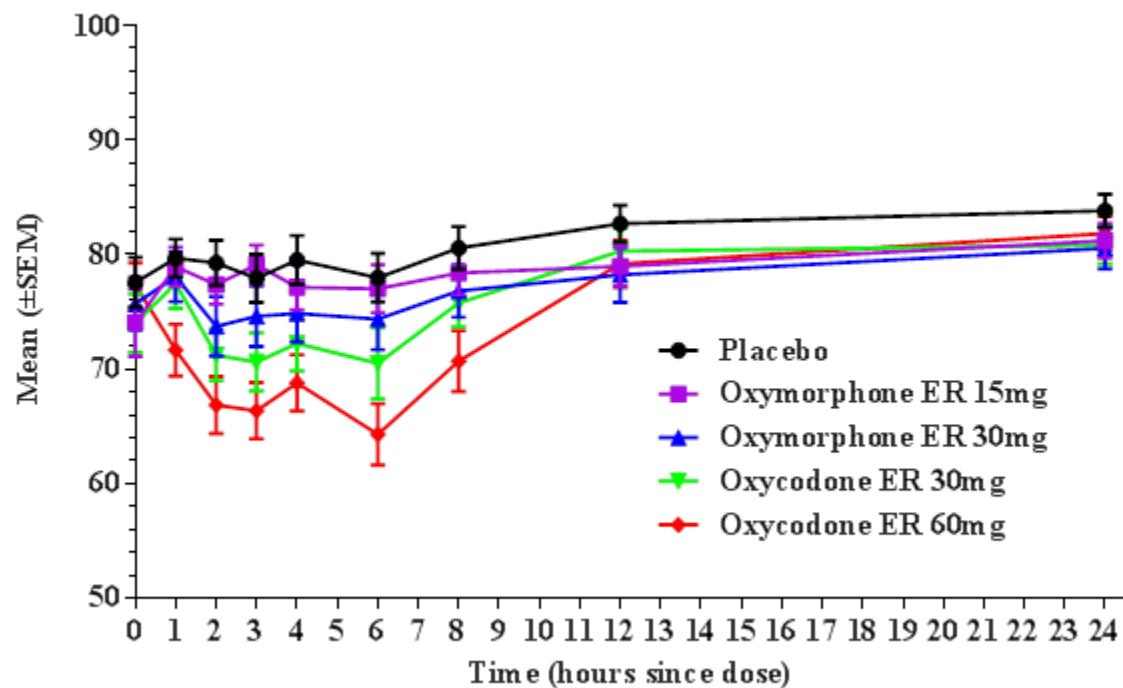
Figure 6: High VAS Scores Over Time



High VAS item: "I am feeling high", where values can range from 0 (Definitely not) to 100 (Definitely so).
SEM=Standard error of the mean; VAS=Visual analog scale

Oxymorphone ER (15 mg and 30 mg) also showed fewer cognitive and motor impairing effects compared to oxycodone ER, especially at the 60-mg dose. The DA test (Figure 7) showed significant and consistent effects of oxycodone ER 60 mg compared to placebo and oxymorphone ER 30 mg.

Figure 7: Divided Attention Driving Test Percentage Over Road (%) Over Time



SEM=Standard error of the mean

In summary, OPANA ER was associated with fewer positive, negative, balance, sedative or other subjective effects, a lower incidence of euphoric mood events, less miosis and less cognitive psychomotor impairment compared to equianalgesic doses of oxycodone ER.

2.6. Opioid Rotation

Among clinicians it is widely recognized that people with chronic cancer and non-cancer pain will require changes in their opioid regimen over the course of months or years. Cherny et al demonstrated that cancer patients over the course of their illness will require 4 to 6 changes in drug or ROA on average,(27) and similar findings have been noted over the course of chronic non-cancer pain as well.(11,28,29) Thus, in the ongoing attempt to achieve the best possible balance of analgesia to toxicity, it frequently becomes necessary to switch amongst mu opioids, capitalizing on incomplete cross tolerance and many other factors to restore a favorable clinical picture. For example, a patient with chronic pain may have a worsening in their depression and require the addition of an antidepressant medication that affects the metabolism of their pain medication and worsens their ongoing or breakthrough pain and/or worsens their opioid side effects. In such situations the use of a medication that doesn't compete for the same metabolic pathway may restore them to a better balance of analgesia to toxicity.

Changes in concomitant medications and thereby the metabolism of a patient's opioid medication is one of many reasons that patients may require rotation of their opioid therapy. There are at least 3 subclasses within the opioid class,(30) and because of many individual differences in patients, changes within and amongst these subclasses are called for over time – these individual differences include but are not limited to genetics, age, gender, comorbid

conditions and renal/hepatic function. Smith and Peppin have attempted to bring order and logic to these switches recognizing how crucial they have become in an era when overcoming suboptimal analgesia solely through ongoing dose escalation is no longer recommended in clinical guidelines.⁽⁸⁾ Thus, opioid rotation to a more suitable opioid for a particular individual can also help to lower their opioid dose, thereby lowering their risk of overdose and can have an impact on the amount of drug available for diversion and abuse as well. Clinicians grapple with state laws and other mandates to lower the mean morphine sulfate equivalents (MMSE) utilized for the treatment of chronic pain, particularly in the treatment of their patients who have suffered with chronic pain for protracted periods of time and opioid rotation has become even more crucial in the present regulatory context than it might have been just a decade or so ago.

In summary, given the vast number of factors at play, an opioid armamentarium with multiple options is needed to help optimize the treatment of as many patients as possible.

2.7. Genetic Polymorphisms of the Mu Opioid Receptor and Opioid Metabolism

Genetic polymorphism in key CYP450 isozymes impacts inter-patient responsiveness to opioid therapeutics. The fact that the analgesic profile for codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol is variable and not predictable can be explained, in part, by CYP2D6 variability.⁽³¹⁾ The Human Genome Project has identified 57 genes coding for various CYP450 enzymes with the largest phenotypic variability being associated with the CYP2D6 isozyme.⁽³²⁾

Within the CYP2D6 genetic variants, 4 metabolic phenotypic subtypes have been characterized. Clinical genetics defines normal metabolizers as extensive metabolizers, whereas other variants are defined as either ultra-rapid, poor or intermediate metabolizers. Approximately 15% of the US population are non-extensive metabolizers at CYP2D6. Genetic polymorphism is likely to confer significant pharmacodynamic consequences for opioid-based therapies. For example, poor pain control may result in a patient that is unable to metabolize an opioid pro-drug medication (eg, codeine, tramadol) into the pharmacologically-active analgesic metabolite. Phenotypic ultra-rapid metabolizers may require more frequent dosing than ‘extensive metabolizers’ in order to maintain analgesia and the need for higher doses carries additional risks for adverse outcomes. On the contrary, poor metabolizers present additional complexity, as they may require higher doses of prodrug medications or lower doses of non-prodrug opioids. Intermediate metabolizers can be treated much as extensive metabolizers but the addition of medications that are inducers or inhibitors of CYP2D6 can change the clinical outcome dramatically.

The clinical implications of phenotypic differences in opioid metabolism are further compounded by the fact that chronic pain is often associated with comorbid conditions that also require additional pharmacotherapy with drugs that are also likely to be subject to CYP450-based elimination. Major depression is one of the more common comorbidities with which people with chronic pain struggle and antidepressant medications, many of which are potent CYP2D6 substrates, are extremely commonly prescribed to these populations.⁽³³⁻³⁶⁾ The potential adverse consequences of such polypharmacy are of considerable importance in the context of drug-drug interactions and the fact that OPANA ER is not impacted by CYP450 metabolism offers important options for the prescribing physician managing such complex clinical presentations.

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As shown in Table 7, oxymorphone and hydromorphone are the only opioids that are primarily metabolized by the UGT pathway. Though ethnic genetic polymorphisms encoding UGT2B7 have also been identified, they have not been associated with significant phenotypic differences in enzyme activity.(37) As a consequence, oxymorphone has no known pharmacokinetic-based drug-drug interactions and, therefore, represents an important treatment option for patients taking multiple concomitant medications.

Table 7: Metabolic Pathways of Common Opioids

Opioid	Phase I Metabolism	Phase II Metabolism
Codeine	CYP2D6	UGT2B7
	CYP3A	
Hydrocodone	CYP2D6	UGT1A3
	CYP3A	UGT2B2
		Dihydromorphone ketone reductase
Oxycodone	CYP3A	UGT2B7
	CYP2D6	
Methadone	CYP3A	
	CYP2B6	
	CYP2D6	
	CYP2C9 ^a	
	CYP2C19 ^a	
Tramadol	CYP3A	
	CYP2D6	
Fentanyl	CYP3A	
Morphine	CYP3A	UGT2B7
Hydromorphone		UGT1A3
		UGT2B7
		Dihydromorphone ketone reductase
Oxymorphone		UGT2B7

^a Minor pathways/clinical significance unknown.

Adapted from Smith HS. *Mayo Clin Proc.* 2009;84(7):613-624 and Fredheim CM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. *Acta Anaesthesiol Scand.* 2008;62(7):879-889.

The discussion on metabolism has, thus far, focused largely on the potential for drug-drug interactions, but differences in the products of opioid metabolism are also worthy of mention. Oxymorphone is conjugated to glucuronic acid by UGT2B7 to form oxymorphone-3-glucuronide (OXM-3-G) and, to a much lesser extent, the parent drug is reduced to 6-hydroxy-oxymorphone (6-OH-OXM). Neither of these metabolites are likely to complicate treatment, OXM-3-G is not known to have any analgesic or other activity and 6 OH-OXM, though active as an analgesic, makes up less than 1% of the administered dose. Morphine is also extensively conjugated by UGT2B7 to morphine-3-glucuronide (M-3-G; 90%) and morphine-6-glucuronide (M-6-G; 10%). M-3-G has no intrinsic pain relieving effects but, in contrast to OXM-3-G, M-3-G is a potent neuroexcitant.(38) M-6-G has been reported to be an active metabolite.(38)

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In summary, OPANA ER may offer distinct benefits for patients who are taking multiple medications or who have previously taken an opioid metabolized by CYP450, due to the low potential for drug-drug interaction and the benign metabolite profile.

3. OVERVIEW OF OPANA ER FORMULATION AND DEVELOPMENT PROGRAM

Summary

- Endo conducted a comprehensive evaluation of the abuse-deterrent properties of reformulated OPANA ER, which is consistent with FDA's Final Guidance, "Abuse Deterrent Opioids – Evaluation and Labeling". This included Category 1 in vitro studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies as well as Category 4 postmarketing epidemiology studies.

3.1. Abuse of Opioid Products

While there is a demonstrated therapeutic need for prescription opioids, in general, and oxymorphone in particular for pain patients, their abuse continues to be a significant public health concern in the United States.⁽³⁹⁾

The risks of abuse of prescription opioids and the potential consequences, such as addiction, overdose and death, pose a serious and growing public health risk. Drug overdose is the leading cause of accidental death in the United States, with 52,404 lethal drug overdoses of all kinds in 2015, thereof 33,091 overdose deaths were related to opioids (illicit and prescription opioids).⁽¹⁵⁾

3.2. Need for ADF Technologies

The White House, Congress, and the FDA acknowledged the significant unmet medical need for more ADFs for opioid products, and for ER products in particular, that provide greater safety against abuse.⁽⁴⁰⁾

Endo initiated the development of a formulation of OPANA ER with abuse-deterrent properties in 2007. Since original OPANA ER was approved in 2006, the most common route of abuse, intranasal administration, could be identified based on postmarketing surveillance data. Reformulated OPANA ER was approved without ADF labeling in December 2011 prior to issuance of a draft FDA guidance in 2013. Reformulated OPANA ER tablets were designed with a proprietary ER technology that increases tablet hardness using a PEO that resists reduction in particle size and gels in an aqueous solution, thereby providing barriers to abuse.

3.3. Product Characteristics

The formulation of OPANA ER incorporating INTAC technology, was designed to have increased tablet hardness using a polymer (PEO). This new technology utilizes a proprietary manufacturing process that applies heat and pressure to the formulation. Tablets with INTAC technology resist crushing because they exhibit a very high breaking strength. In addition, they form a viscous gel when exposed to an aqueous medium (the phenomenon of hydrogelling).

These physicochemical barrier properties are intended to reduce the likelihood and increase the difficulty of manipulation associated with abuse through unintended ROA, especially crushing it

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and then abusing it via intranasal administration, which was determined to be the primary route of abuse for original OPANA ER. In addition, the resistance to solubilization conferred by gelling in aqueous media was incorporated.

3.4. Key FDA Milestones and Guidance During Development

The NDA for the original OPANA ER was approved by the FDA on June 22, 2006. Endo subsequently developed a new formulation of OPANA ER, designed to resist crushing, which was approved by the FDA on December 9, 2011 without any abuse-deterrence label claims, prior to issue of the FDA guidance “Abuse-Deterrent Opioids — Evaluation and Labeling” in 2013.

Prior to the original NDA submission for the reformulated OPANA ER only Category 1 and 2 studies were conducted. Subsequently, Endo submitted a labeling supplement (S-009) on February 15, 2013 which proposed the addition of labeling language describing in vitro and in vivo data in the DRUG ABUSE AND DEPENDENCE section of the Package Insert. A Complete Response letter was received on May 10, 2013. A Type A Meeting was also held on July 10, 2013 to discuss the Complete Response in light of the FDA draft guidelines issued in January 2013.

During the Type A meeting the Agency noted that, “The totality of the evidence is weighed in determining whether or not to include information in a label.” During the discussion, it was noted that the requested intranasal clinical abuse potential study would be adequate to address many of the concerns identified by the Agency during their review of Endo’s data.

Subsequently, Endo engaged with FDA in discussions with regard to the design of the intranasal abuse liability study and of 3 postmarketing epidemiology studies to assess the impact of the reformulation in a “real-world setting.” FDA guidance with respect to the postmarketing epidemiology protocols was included in the final protocols.

Endo submitted the results of the intranasal clinical abuse liability study as well as interim postmarketing epidemiology study in a complete response submission on January 29, 2016. In response to an information request on July 11, 2016, an error in the RADARS data was identified. Subsequently Endo withdrew S-009 on August 11, 2016. On October 20, 2016, a Type A Meeting was held to discuss the postmarketing epidemiology data. Final 3-year data were submitted in late 2016.

3.5. Overview of Abuse-Deterrence Evaluation

Reformulated OPANA ER was developed and evaluated in a manner consistent with recommendations described in FDA’s draft and then final guidance on the evaluation and labeling of abuse-deterrent opioids and with specific feedback from FDA throughout the development program.

Endo conducted a comprehensive evaluation of the abuse-deterrent properties of reformulated OPANA ER, which is consistent with FDA’s Final Guidance, “Abuse Deterrent Opioids – Evaluation and Labeling”. This included Category 1 in vitro manipulation studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies as well as Category 4 postmarketing epidemiology studies. [Table 8](#)

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provides a list of the core studies conducted to assess the abuse-deterrent properties of OPANA ER.

Table 8: Core Abuse-Deterrent Studies for OPANA ER

Study Title (Number, as applicable)	FDA Guidance Category ^a
In vitro studies simulating preparation for abuse by nasal, injection, and oral route	Category 1
EN3288-114 Insufflation study	Category 2/3
EN3288-108 Oral ingestion of manipulated, reformulated OPANA ER	Category 2
NAVIPPRO addiction treatment center data	Category 4
RADARS poison control center data	Category 4
RADARS drug diversion data	Category 4

^a FDA Guidance for Industry, “Abuse-Deterrent Opioids—Evaluation and Labeling,” April 2015.

4. OPANA ER ABUSE-DETERRENT DEVELOPMENT PROGRAM

Summary

- **Category 1 (Laboratory Manipulation and Extraction)**
 - Both reformulated OPANA ER and OxyContin ADF utilize similar approaches to abuse deterrence and yield formulations possessing similar crush resistance and gelling properties.
 - Both reformulated OPANA ER and OxyContin ADF are crush resistant as both contain PEO and utilize heat in their respective manufacturing processes.
 - Based on the results generated for both formulations, reformulated OPANA ER and OxyContin ADF have similar physicochemical properties and provide similar physical/chemical barriers to abuse by nasal insufflation and injection.
 - Simulated oral ingestion studies for reformulated OPANA ER and OxyContin ADF in a variety of solvents yield similar extraction results as expected based on similar formulations, manufacturing processes and solubilities. Percentage extracted and dissolved increase with more aggressive manipulation techniques which lead to smaller particles and larger surface area.
 - Both reformulated OPANA ER and OxyContin ADF require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-crush-resistant oxymorphone ER formulations.
 - Generic oxymorphone ER products on the market are easily manipulated to small particle sizes with simple tools whereas reformulated OPANA ER is crush resistant and difficult to reduce to particles that can be readily snorted.
 - Generic oxymorphone ER tablets are easily crushed, dissolved, and extracted for injection.
 - Generic oxymorphone ER tablets behave similar to IR tablets once crushed generic oxymorphone ER does not provide any barrier to potential misuse and abuse whereas reformulated OPANA ER is crush resistant and provides a barrier to misuse and abuse.
- **Category 2 (Pharmacokinetics)**
 - Reformulated OPANA ER maintained ER properties when manipulated with various tools and ingested orally; these manipulations did not increase peak plasma levels to the level of an IR tablet.
 - Reformulated OPANA ER, manipulated for intranasal administration, demonstrated an approximately 58% lower C_{max} than for oxymorphone powder, and a longer T_{max} (1.5 hours vs 0.25 hours, respectively). The abuse quotient was 13-fold lower for manipulated reformulated OPANA ER compared to

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oxymorphone powder, which represents the non-crush resistant oxymorphone formulations currently on the market.

- **Category 3 (Human Abuse Liability)**

- A human abuse liability study demonstrated significant reductions in “Drug linking” following intranasal administration of reformulated, manipulated OPANA ER compared to oxymorphone powder. Similar reductions were seen in the key secondary endpoints of High VAS and Good effects VAS.

- **Category 4 (Postmarketing Epidemiology Studies)**

- Three (3) postmarketing epidemiology studies from 2 different data partners (NAVIPPRO; RADARS) evaluated abuse patterns of OPANA ER in the post-reformulation period (post-period) compared to the pre-reformulation period (pre-period) and also compared reformulated OPANA ER to non-crush resistant generic oxymorphone ER concurrently available in the post-period.
 - The pre-period is characterized by increased abuse of original OPANA ER, which continued to increase further after the introduction of OxyContin ER ADF.

Based on the available data in the NAVIPPRO system from addiction-treatment centers:

- During the post-period, following the introduction of reformulated OPANA ER, the prevalence of abuse by alternate ROA was higher although intranasal abuse was lower. The effect on abuse by alternate ROA was driven by an apparent increase in intravenous abuse.
 - However, the results for the nation as a whole are explained by a high degree of data heterogeneity with Tennessee being an outlier.
 - Within Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period, but intravenous abuse was higher.
 - Outside of Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period and intravenous abuse remained stable at levels observed at the end of the pre-period in 2011.
 - Not only did Tennessee provide the majority of abuse reports during the post-period, but intravenous abuse was higher in this state for many opioid products both during the pre-period and the post-period and the higher level of intravenous abuse for OPANA ER was similar to or less than the levels for other opioids in both time periods.
 - During the post-period, abuse by alternate ROA and intranasal abuse of generic oxymorphone ER were higher than for OPANA ER and intravenous abuse was similar.

Based on the RADARS poison center data:

- Intentional abuse exposures, major medical outcome and death rates, and overdose exposure for OPANA ER were higher following the introduction of

reformulated OxyContin in August 2010 in the pre-period. Increases were also observed in both oral and non-oral ROA among intentional abuse exposures following the introduction of reformulated OxyContin during the pre-period.

- In the post-period, after the introduction of the reformulated OPANA ER, rates of intentional abuse, abuse by oral and non-oral routes, major medical outcomes and deaths, and overdose, were lower compared to the pre-period.

Based on the RADARS drug diversion data:

- Rate of drug diversion of OPANA ER were lower in the post-period compared to the pre-period.

4.1. In Vitro Studies (Category 1)

The original NDA for reformulated OPANA ER (NDA 201655) was submitted on July 7, 2010 and subsequently approved on December 9, 2011. Original OPANA ER was readily crushable into powder and its main route of abuse was intranasal administration based on postmarketing safety surveillance information. The original formulation could be easily crushed with simple tools in a few seconds whereas reformulated OPANA ER is unaffected or only deformed by simple tools and specialty tools are necessary to reduce its particle size.

In the NDA, the in vitro studies that were designed to evaluate the ability of the product to be manipulated, as well as the experiments to evaluate the potential for abuse via oral, nasal, and intravenous routes including extraction studies were discussed in detail. During development, Endo consulted FDA regarding design of physicochemical testing. About 20 tools were utilized to manipulate reformulated OPANA ER and a broad range of solvents (different pH and polarities) were used to determine extractability. These tools and solvents were representative of manipulation methods used by people who abuse opioid drugs and were aligned with industry practice for testing abuse deterrent properties of formulations.

Reformulated OPANA ER was designed with the dual intent of maintaining the extended release properties of the original formulation and making the tablet hard so that it resists crushing. The key ingredient in the formulation is PEO. The PEO formulation together with heat used in the manufacturing process yields crush-resistant tablets. PEO also has the property of gelling in aqueous solutions.

[Appendix 3](#) presents the dissolution of reformulated OPANA ER with and without alcohol. The results indicate that dose dumping does not occur. It is noted that the in vitro dissolution is significantly decreased and this formulation is not susceptible to alcohol induced dose dumping.

Subsequent to approval of reformulated OPANA ER and approval of OxyContin ADF, additional studies were performed comparing the in vitro properties of the 2 products. The combination of PEO and hot melt extrusion (HME) used in the manufacture of reformulated OPANA ER forms a very strong matrix system yielding thermoplastic-like tablets that resist breakage and pulverization into small particles or powder. OxyContin ADF uses a similar approach in its ADF involving PEO and thermo-curing process to heat fuse the PEO before and after curing. Based on these similarities, it was expected that many of the in vitro tests would yield similar results for the 2 products and indeed that was the case as presented in section [4.1.1](#).

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Following the approval of 2 generic tablet formulations of OPANA ER, additional studies were performed. The generic tablets are non-crush resistant and therefore it was expected that they would not perform to the same standard in vitro as reformulated OPANA ER, which was designed to be crush resistant. This was indeed the case as detailed in section [4.1.2](#).

All of these studies referenced above were completed before the issuance of the FDA guidance for industry “Abuse-Deterrent Opioids – Evaluation and Labeling,” April 2015, and many before the draft of this guidance in January 2013; however, in general the completed testing is aligned with the final guidance.

Per FDA’s request, additional laboratory studies were conducted on intact and crushed reformulated OPANA ER and generic oxymorphone ER tablets to determine syringeability and extractability in 2 solvents following a variety of pretreatment conditions (P3, P4, P5, P6, P7, and P8). Particle size was tested after pretreatment and manipulation. In addition, large volume extraction in solvent ‘a’ was performed on the 2 generic oxymorphone ER tablets. A summary of these studies is provided in section [4.1.2](#).

Samples were tested via high performance liquid chromatography (HPLC) analysis to determine active pharmaceutical ingredient (API) concentration using either the approved oxymorphone assay method, or oxycodone assay method, as per United States Pharmacopeia (USP) monograph. Dissolution experiments were performed using the approved dissolution method for OPANA ER and in the oxycodone USP monograph. For generic oxymorphone ER tablets, OPANA ER methods were utilized.

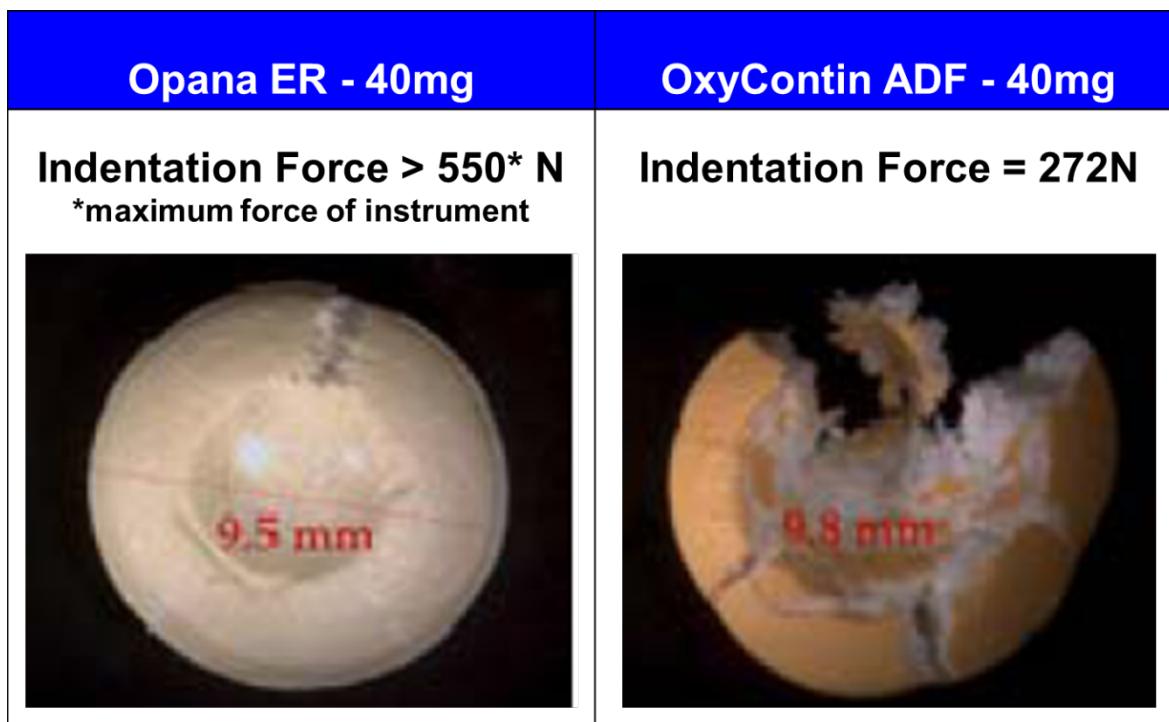
4.1.1. Reformulated OPANA ER vs OxyContin ADF

Physicochemical properties of reformulated OPANA ER and OxyContin ADF were compared. The testing included physical appearance after manipulation, particle size determination, dissolution, extraction into various solvents, and preparation for intravenous injection. Similar results were obtained for the 2 products as presented in greater detail in Appendix 1, [Table 1-1](#). Representative tests are summarized below.

Tablet Hardness

Several common tools were studied to determine their effect on crushability of the tablets. Simple tools did not affect either tablet and the capacity of the typical USP force tester was exceeded. Therefore, more specialized tools were studied including tool G ([Figure 8](#)). The results for this tool, which measures the breaking force needed to crack the tablet indicate that reformulated OPANA ER is more resistant to this type of manipulation than OxyContin ADF.

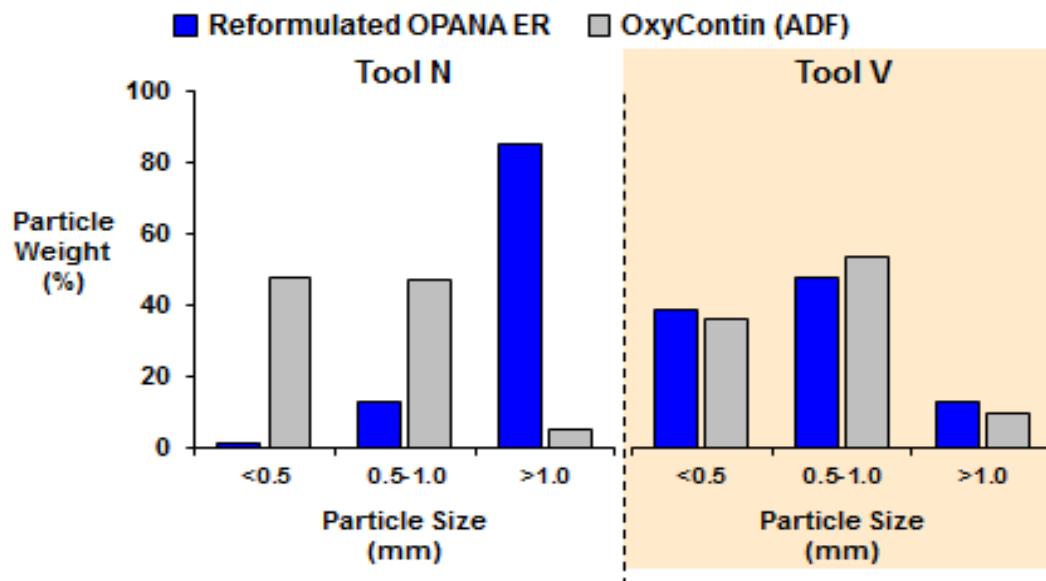
Figure 8: Tablet Hardness



Particle Size – Simulate Nasal Abuse

Testing with tools N and V was used to study particle size reduction of both tablets. While both tablets were resistant to particle size reduction, reformulated OPANA ER was more resistant than OxyContin ADF to manipulation by tool N ([Figure 9](#)), OxyContin ADF had larger percent of particles less than 1.0 mm than reformulated OPANA ER; similar particle size results were obtained for both products manipulated using tool V ([Figure 9](#)).

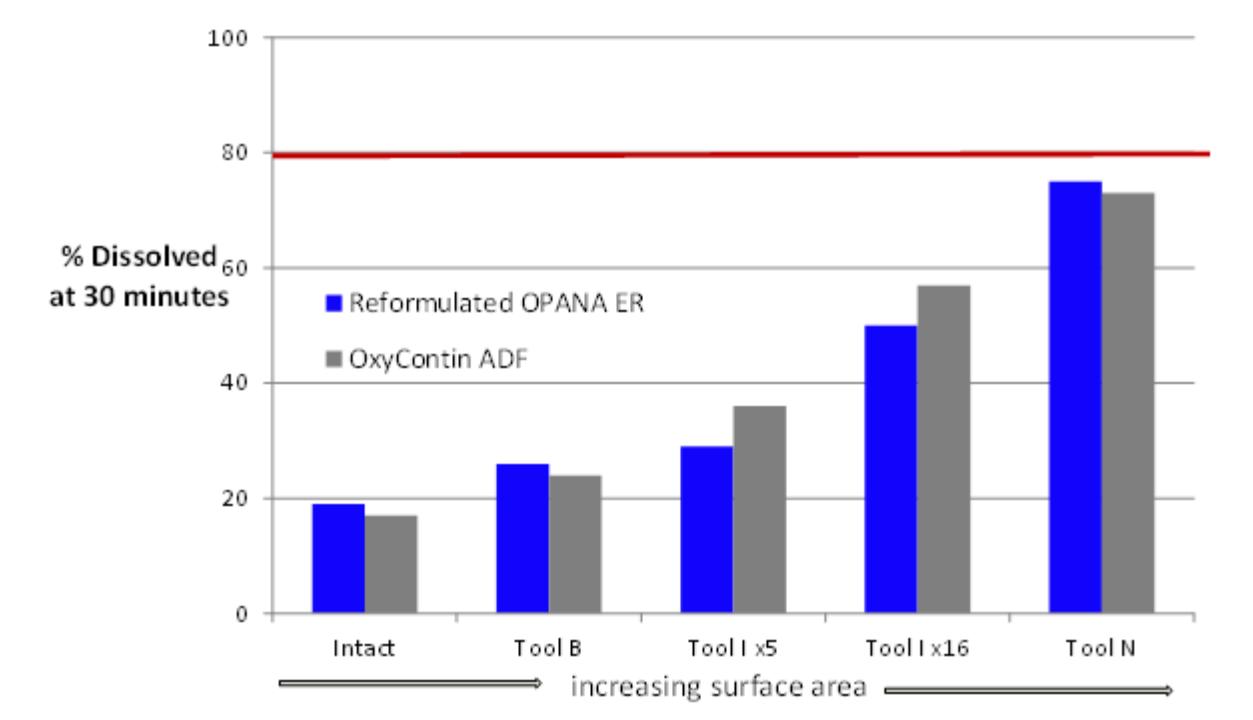
Figure 9: Reformulated OPANA ER and OxyContin ADF Resist Particle Size Reduction



Dissolution – Simple Aqueous Extraction for Oral Ingestion

Dissolution testing was performed on intact and manipulated reformulated OPANA ER and OxyContin ADF tablets. The results confirm that both products behave similarly when manipulated with various tools. The data clearly demonstrate that the rate of release is proportional to surface area as more aggressive tools yielded smaller particle sizes (Figure 10).

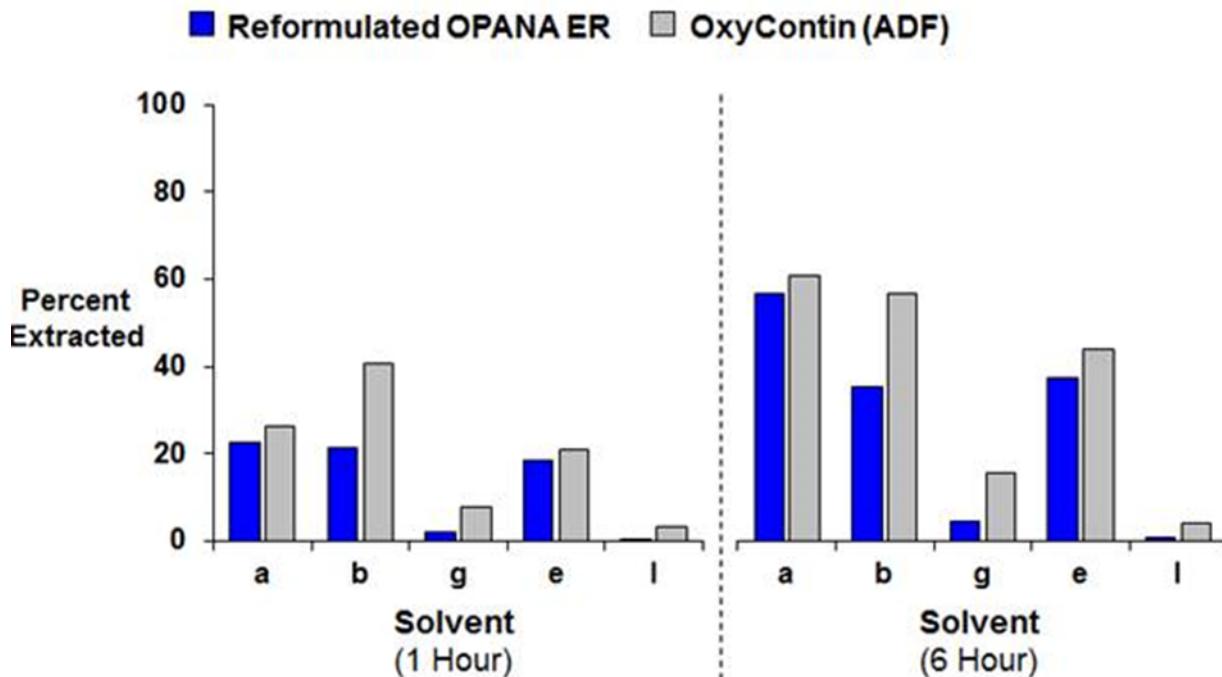
Figure 10: Simulated Oral Ingestion – Reformulated OPANA ER vs OxyContin ADF (Dissolution at 30 Minutes)



Extraction – Advanced Solvents Simulating Oral Ingestion

The extraction results for reformulated OPANA ER and OxyContin ADF tablets, both manipulated with tool B at temperature T1, in a variety of solvents were similar ([Figure 11](#)). The results at 6 hours are higher than 1 hour as expected since dissolution over a period of time is required for the product to work as intended.

Figure 11: Similar Extraction Results in Advanced Solvents Simulating Oral Ingestion



Syringeability/Extractability - Simulate Intravenous Injection

Reformulated OPANA ER and OxyContin ADF were evaluated for extraction into solvent 'a' using 3 different methods. For each method, a different tool was utilized to provide a range of materials for testing (different surface area). Both products gelled when placed in solvent 'a'. In each case, the results are similar between reformulated OPANA ER and OxyContin ADF (Table 9).

Table 9: Similar Extraction for Reformulated OPANA ER and OxyContin ADF

Manipulation Tool	Solvent 'a' (mL)	% API Extracted	
		Reformulated OPANA ER	OxyContin (ADF)
Tool V	3 mL	Not syringeable	Not syringeable
Tool B	5 mL	26% - 40%	42% - 46%
Tool I	2 mL, 5 times	39%	36%

API=Active pharmaceutical ingredient

Conclusion

In summary, reformulated OPANA ER and OxyContin ADF utilize similar approaches to abuse deterrence and yield formulations possessing similar crush resistance and gelling properties. Both products require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-CRFs. Both products yield similar particle size distribution after manipulation, similar extraction results in common solvents associated with oral abuse and

similar extraction results for various experiments designed to evaluate syringeability and extractability.

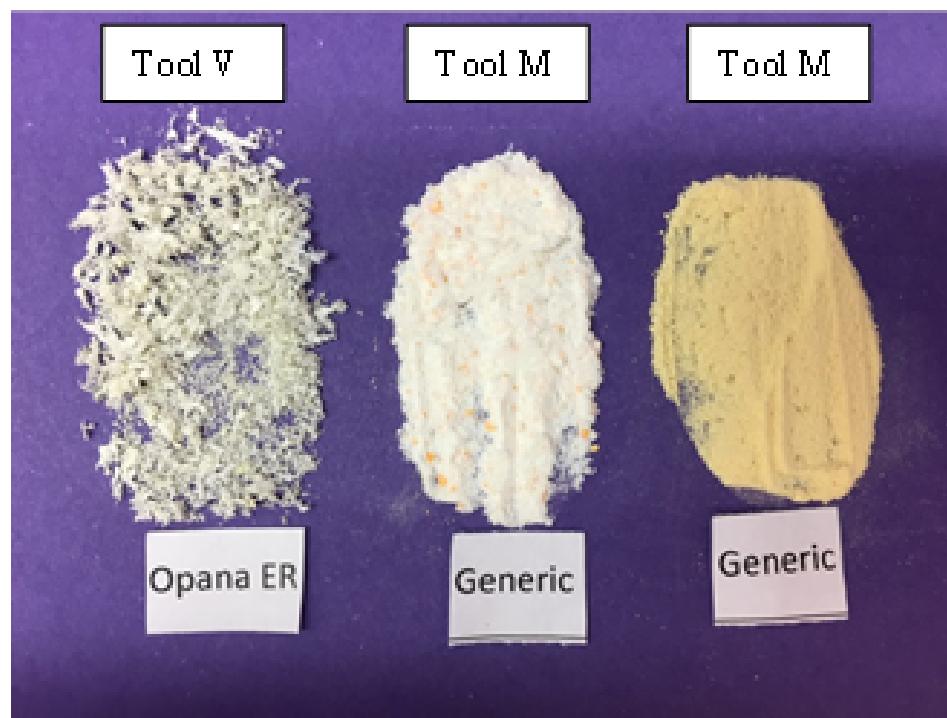
4.1.2. Reformulated OPANA ER vs Generic Oxymorphone ER

The 2 approved generic tablet formulations of OPANA ER were developed to be bioequivalent to the original OPANA ER and are not crush resistant. Studies to compare the physicochemical properties of the crush resistant reformulated OPANA ER with the 2 generic oxymorphone ER products were performed. Experiments were divided into several categories: physical manipulations, amount released via dissolution, particle size distribution and evaluation of the preparation for injection. A summary of data is presented in Appendix 2, [Table 2-1](#).

Appearance After Manipulation

Figure 12 shows the resulting appearance and particle size after manipulation of generic oxymorphone ER with a simple tool (tool M) and of reformulated OPANA ER with a more advanced and destructive tool (tool V). When crushing generic oxymorphone ER tablets with tool M, powder was generated in a few seconds. In contrast, it took about 30 minutes to generate particles of reformulated OPANA ER with tool V.

Figure 12: Representative Appearance After Manipulation

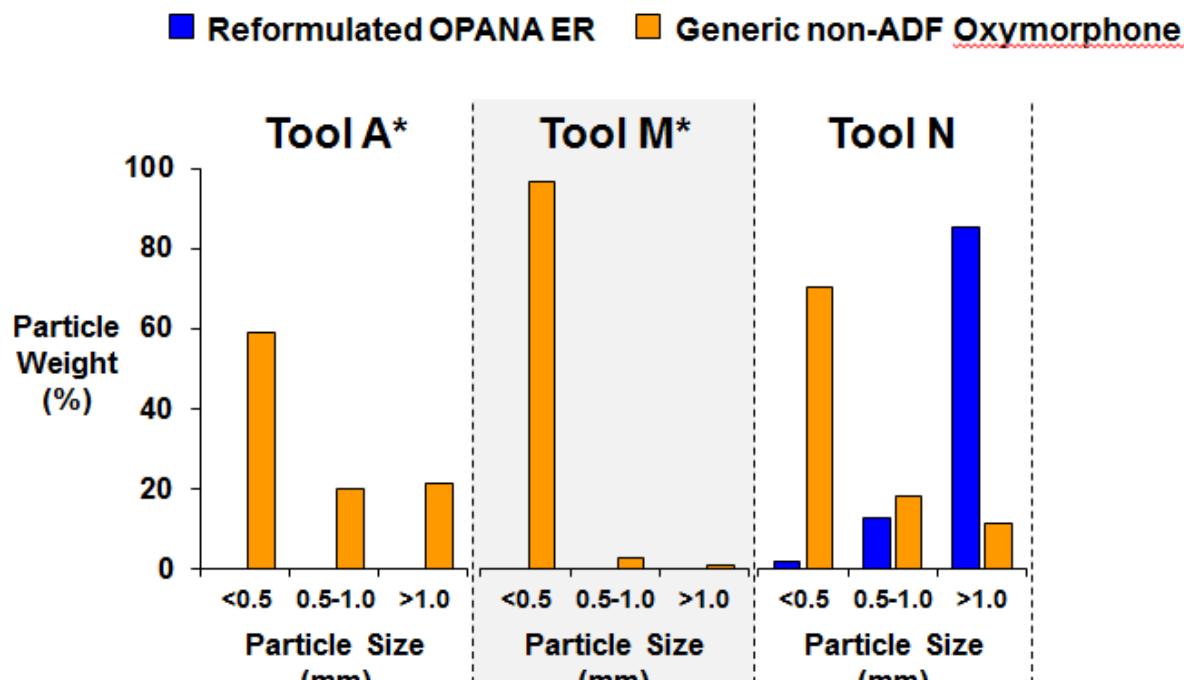


Particle Size – Simulate Nasal Abuse

[Figure 13](#) shows the distribution of particle sizes following manipulation with 3 tools. Reformulated OPANA ER is not affected by tool A and tool M, therefore there were no particles to measure for size distribution. Reformulated OPANA ER resisted manipulation even with specialized manipulation techniques like tool N, resulting in larger particle sizes, ie, more than 80% of particles greater than 1 mm. In contrast, non-crush-resistant generic oxymorphone ER

was easily crushable to powder less than 0.5 mm. Using tool M more than 95% of the particles were less than 0.5 mm.

Figure 13: Particle Size Comparison of Reformulated OPANA ER and Generic Oxymorphone ER



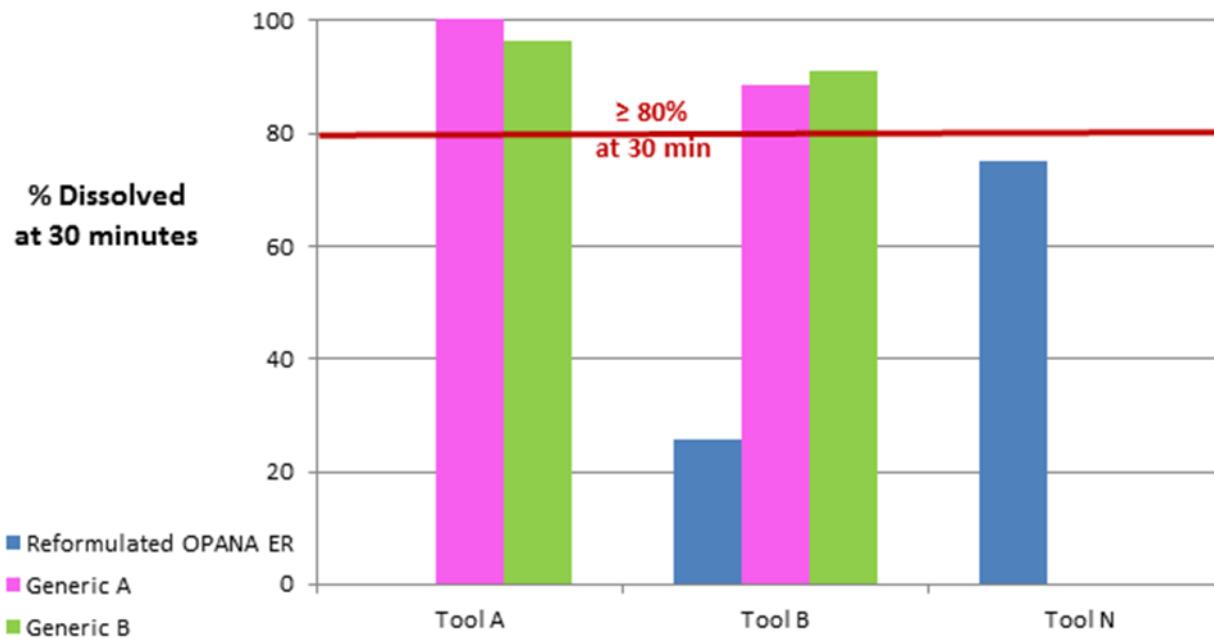
* No particles generated for Reformulated OPANA ER

Dissolution – Simple Aqueous Extraction for Oral Ingestion

Dissolution testing of generic oxymorphone ER products manipulated with tool A and tool B yielded a much faster release, ie, immediate-release results (Figure 14). Data from 30 minute time point is shown as this time is important in light of FDA's recent March 2016 draft guidance "Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products," which suggests that $\geq 80\%$ drug release at 30 minutes is a criterion for no abuse deterrence when simulating oral abuse after manipulation.

Using the same common tool B, reformulated OPANA ER dissolution results were unaffected. A more destructive tool such as tool N is needed for reformulated OPANA ER to generate higher release. Since generic products are easily crushable, destructive tool N was not used.

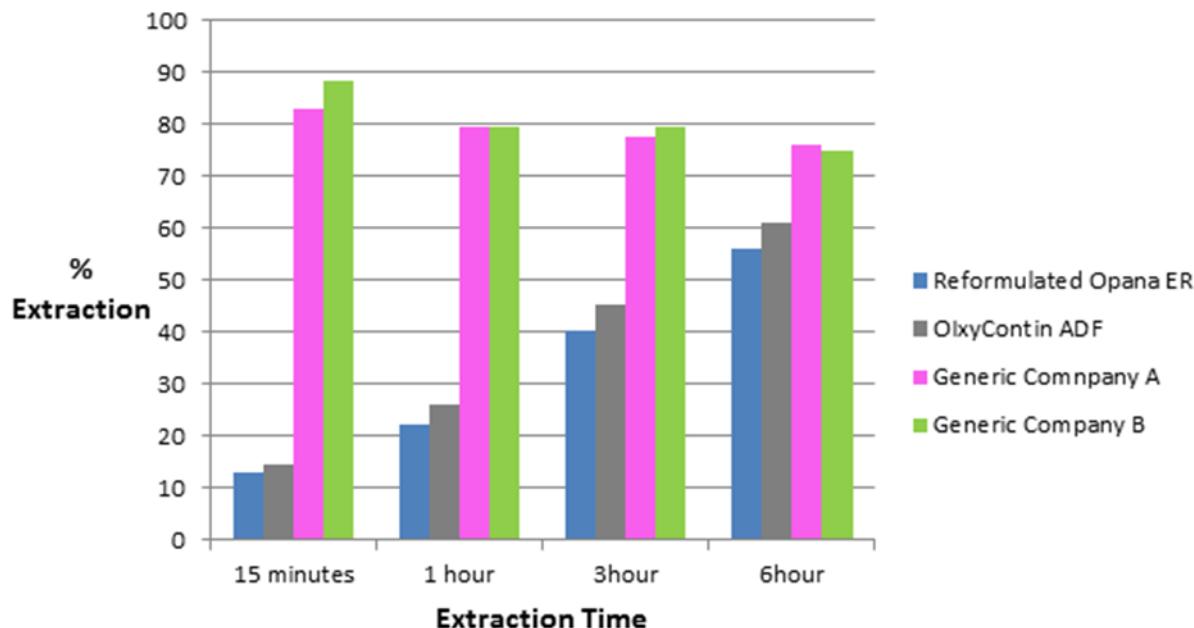
Figure 14: Simulate Oral Ingestion



Extraction – Aqueous Extraction Simulating Oral Ingestion

After manipulation with tool B, an extraction in 30 mL solvent 'a' at temperature T1 was performed on both generic tablets and compared to the results for reformulated OPANA ER as well as OxyContin ADF. The results (Figure 15) for the generic tablets show that >80% of the API was dissolved after 15 minutes of agitation indicating an immediate release of the active ingredient. Thus, both generic oxymorphone ER products are considered to have no abuse deterrence. In contrast, reformulated OPANA ER and OxyContin ADF maintain their extended release properties showing a gradual release of the API into solvent 'a' over time.

Figure 15: Large Volume Extraction in Solvent ‘a’



Syringeability/Extractability – Simulate Intravenous Injection

Reformulated OPANA ER and generic oxymorphone ER were evaluated for extraction into solvent ‘a’ using 3 different methods. For each method, a different tool was utilized to provide a range of materials for testing. Reformulated OPANA ER gelled more and thus was harder to syringe. In contrast, more liquid can be drawn into a syringe for generic oxymorphone ER (Table 10).

Table 10: Extraction for Reformulated OPANA ER and Generic Oxymorphone ER

Manipulation Tool	Solvent ‘a’ (mL)	% API Extracted		
		Reformulated OPANA ER	Generic Company A	Generic Company B
Tool V	3 mL	Not syringeable	Not tested ^a	Not tested ^a
Tool A	5 mL	Not tested ^b	79%	Not tested ^c
Tool B	5 mL	26% - 40%	66% - 74%	61% - 80%

^a Destructive tool V not needed for generics as they can be crushed with simple tool A.

^b Simple tool A not effective for reformulated OPANA ER.

^c Unnecessary to test.

API=Active pharmaceutical ingredient

With Pretreatment

Per FDA’s recommendation, additional laboratory studies were conducted on intact and crushed reformulated OPANA ER and generic oxymorphone ER tablets to determine syringeability, extractions from various sample manipulations and particle size analysis following pretreatment with heat. [Table 11](#) summarizes the parameters for the experiments.

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Table 11: Particle Size and Extraction Studies

Pretreatment	Particle Size Analysis	Solvent 'a'			Solvent 'e'		
		2 mL	5 mL	10 mL	2 mL	5 mL	10 mL
P3	A,B,C	A,B,C	A,B,C	A,B,C	A	A,B	A,B
P4	A		A	A	A	A	A
P5	B,C	A,B,C	B,C	B			
P6	A	A	A,B	A,B	A	A,B	A,B
P7			A	A			
P8			A	A		A	A

A=Reformulated OPANA ER; B=Generic from company B; C=Generic from company A

Pretreatment did not have an effect on the medium particle size range as shown in Appendix 2, [Table 2-2](#).

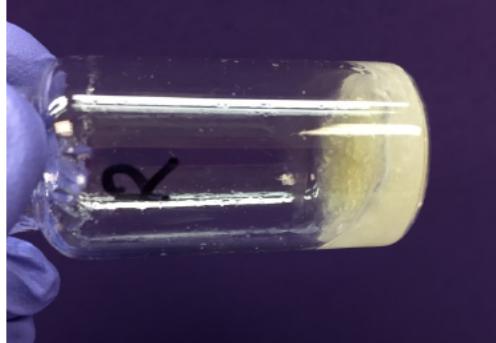
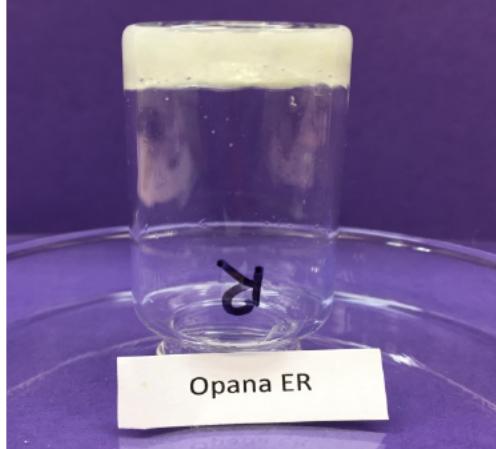
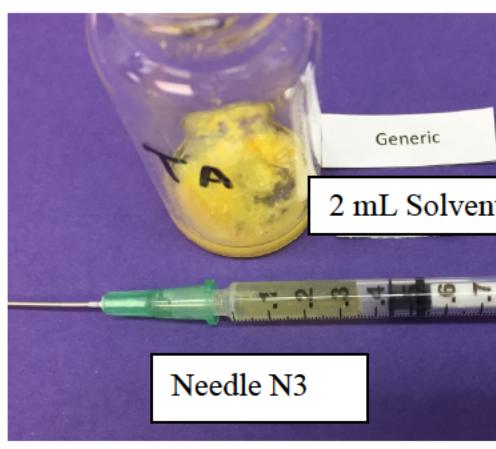
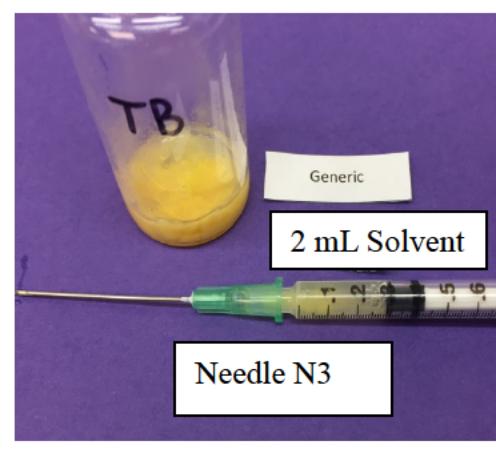
The results of the syringeability/extractability experiments for reformulated OPANA ER and generic oxymorphone ER tablets are presented in:

- Reformulated OPANA ER Tablets – 5 mL (Appendix 2, [Table 2-3](#)) and 10 mL (Appendix 2, [Table 2-4](#))
- Generic oxymorphone ER tablets from company B – 5 mL (Appendix 2, [Table 2-5](#)) and 10 mL (Appendix 2, [Table 2-6](#))
- Generic oxymorphone ER tablets from company A – 5 mL (Appendix 2, [Table 2-7](#)) and 10 mL (Appendix 2, [Table 2-8](#))

Note that 2-mL extractions did not yield any filterable or syringeable solutions; none for reformulated OPANA ER and less than 0.5 mL of generic tablets were syringeable – see [Figure 16](#). The overall results indicate that the most likely factors to affect syringeability and extractability were solvent volume and needle size. The greater the solvent volume, the more API extracted. In terms of the syringe needle size, the experiments proceeded systematically from the smallest size (^{(b)(4)}) to the largest size (^{(b)(4)}).

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Figure 16: Extraction in 2 mL of Solvent 'a' for Reformulated OPANA ER and Generic Oxymorphone ER Products

Reformulated OPANA ER	Generic Company A	Generic Company B
		
		
Not Syringeable	0.35 mL Syringeable	0.30 mL Syringeable

Conclusion

Overall, the data indicate that reformulated OPANA ER is crush resistant and provides physical/chemical barriers to abuse whereas the generic formulations are easily manipulated for oral ingestion, intranasal administration and intravenous injection.

4.2. Pharmacokinetics Studies (Category 2)

The goal of the pharmacokinetic studies was to understand the in vivo properties of the manipulated formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of a comparator drug.

The pharmacokinetic evaluation involved study EN3288-114 (pivotal intranasal administration study) that assessed pharmacodynamics and pharmacokinetics of oxymorphone HCl powder (non-abuse deterrent comparator) and manipulated reformulated OPANA ER by intranasal administration in subjects who abuse opioids recreationally. The abuse liability component of these studies is discussed in section 4.3 (Category 3, Clinical Abuse Liability Studies). In addition, study EN3288-108 was conducted to investigate the effect of selected methods of tampering used by recreational and experienced abusers (tool B, tool I, and tool N) and their effect on the relative bioavailability and pharmacokinetics when ingested orally. This study was conducted in healthy subjects.

4.2.1. EN3288-114

4.2.1.1. Study Design

Study EN3288-114 was designed to evaluate the subjective effects and pharmacokinetics of reformulated OPANA ER manipulated and administered intranasally compared with oxymorphone HCl powder and administered at the dose determined to be pharmacodynamically active and tolerated. The applicable dose was determined in a prior dose-escalation study (EN3288-113). Study EN3288-114 utilized a randomized, double-blind, single-dose, placebo-controlled, 4-period, crossover design in healthy, non-dependent subjects who recreationally administer opioids intranasally.

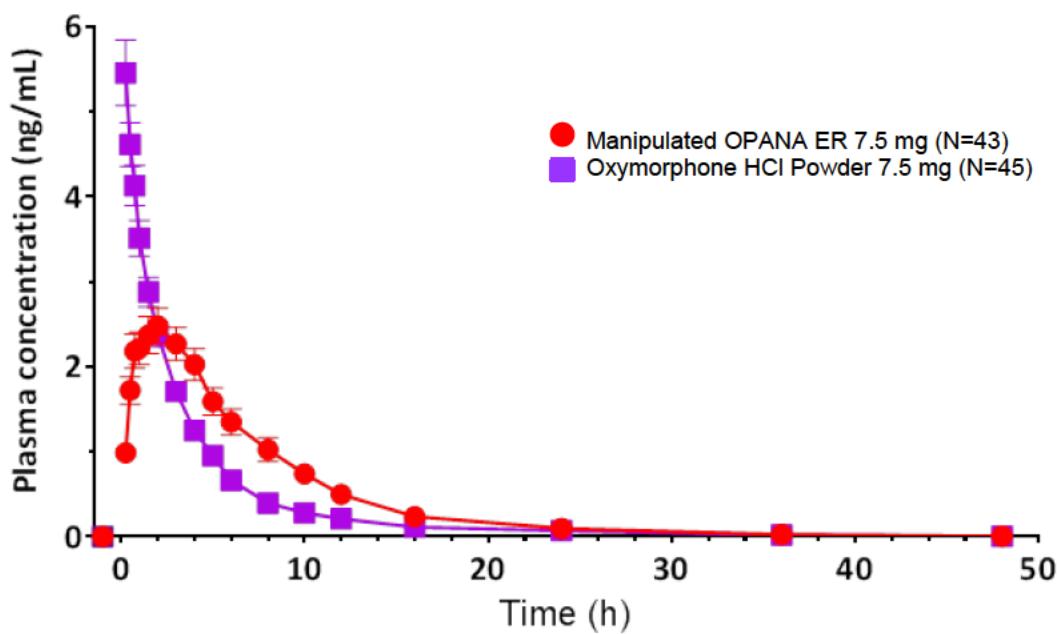
In order to qualify for the study, each subject participated in a screening visit and a qualification phase. Prior to receipt of the first dose in the qualification phase, each subject had a naloxone challenge test to determine if he/she was physically dependent on opioids. In the qualification phase, subjects received oxymorphone HCl powder 7.5 mg and placebo intranasally in a randomized, double-blind, crossover manner to ensure that he/she could discriminate between active drug and placebo, and could tolerate oxymorphone HCl powder 7.5 mg. In the treatment phase of the study, subjects were administered intranasally a reformulated OPANA ER 7.5-mg tablet manipulated using a tool V, reformulated OPANA ER placebo tablet manipulated using tool V, oxymorphone HCl powder 7.5 mg, and oxymorphone HCl placebo powder. Each dose was separated by at least a 4-day washout period. Pharmacodynamic measurements were obtained through 24 hours, and blood samples for pharmacokinetics were obtained through 48 hours postdose.

4.2.1.2. Results

Pharmacokinetic data were available from 43 subjects who administered the reformulated OPANA ER 7.5 mg manipulated tablet intranasally, and from 45 subjects who administered oxymorphone HCl powder 7.5 mg intranasally. The median percentage of each treatment actually administered in the treatment phase ranged from 96% to 97%.

Systemic oxymorphone absorption from the intranasally administered, reformulated OPANA ER 7.5-mg manipulated tablet was slower than from intranasally administered oxymorphone HCl powder 7.5 mg, resulting in a 58% lower maximum concentration (C_{max}) and equivalent extent of systemic exposure (AUC_{0-t}). Systemic absorption of the insufflated oxymorphone HCl powder 7.5 mg was rapid, with maximum concentrations (6.03 ± 2.33 ng/mL) observed at median T_{max} of 0.25 hours. In contrast, systemic absorption of oxymorphone from the reformulated OPANA ER manipulated tablet 7.5 mg was slower, with significantly lower maximum concentrations (2.84 ± 1.46 ng/mL) and longer T_{max} of 1.5 hours (C_{max} ratio of LS means, 0.42; 90% CI, 0.37-0.49). There was no significant difference in extent of systemic exposure (AUC_{0-t}). The abuse quotient (oxymorphone C_{max}/T_{max}) was 13 times lower for the manipulated tablet than for the powder (1.43 vs 19.20 ng/mL/h).

Figure 17: Oxymorphone Plasma Concentrations (Mean \pm SE) Versus Time After Single Intranasal Doses of Manipulated OPANA ER 7.5 mg and Oxymorphone HCl Powder 7.5 mg



The extent of systemic exposure to oxymorphone did not differ from equal doses (7.5 mg) of the 2 intranasally administered dosage forms; reformulated OPANA ER 7.5 mg manipulated tablet, and oxymorphone HCl powder 7.5 mg. AUC_{0-t} were 20.59 ± 12.64 and 16.38 ± 5.70 ng \cdot h/mL, respectively (ratio of LS means, 1.02; 90% CI, 0.83-1.24); and $AUC_{0-\infty}$ were 20.91 ± 12.97 and 16.516 ± 5.77 ng \cdot h/mL, respectively (ratio of LS means, 1.05; 90% CI, 0.85-1.29).

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In conclusion, study EN3288-114 found that:

- Oxymorphone absorption from the intranasally administered, reformulated OPANA ER 7.5 mg manipulated tablet was slower than from intranasally administered oxymorphone HCl powder 7.5 mg, resulting in 58% lower maximum concentrations and equivalent extent of systemic exposure.
- The abuse quotient (oxymorphone C_{max}/T_{max}) was 13 times lower for the manipulated tablet than for the powder.

4.2.2. EN3288-108

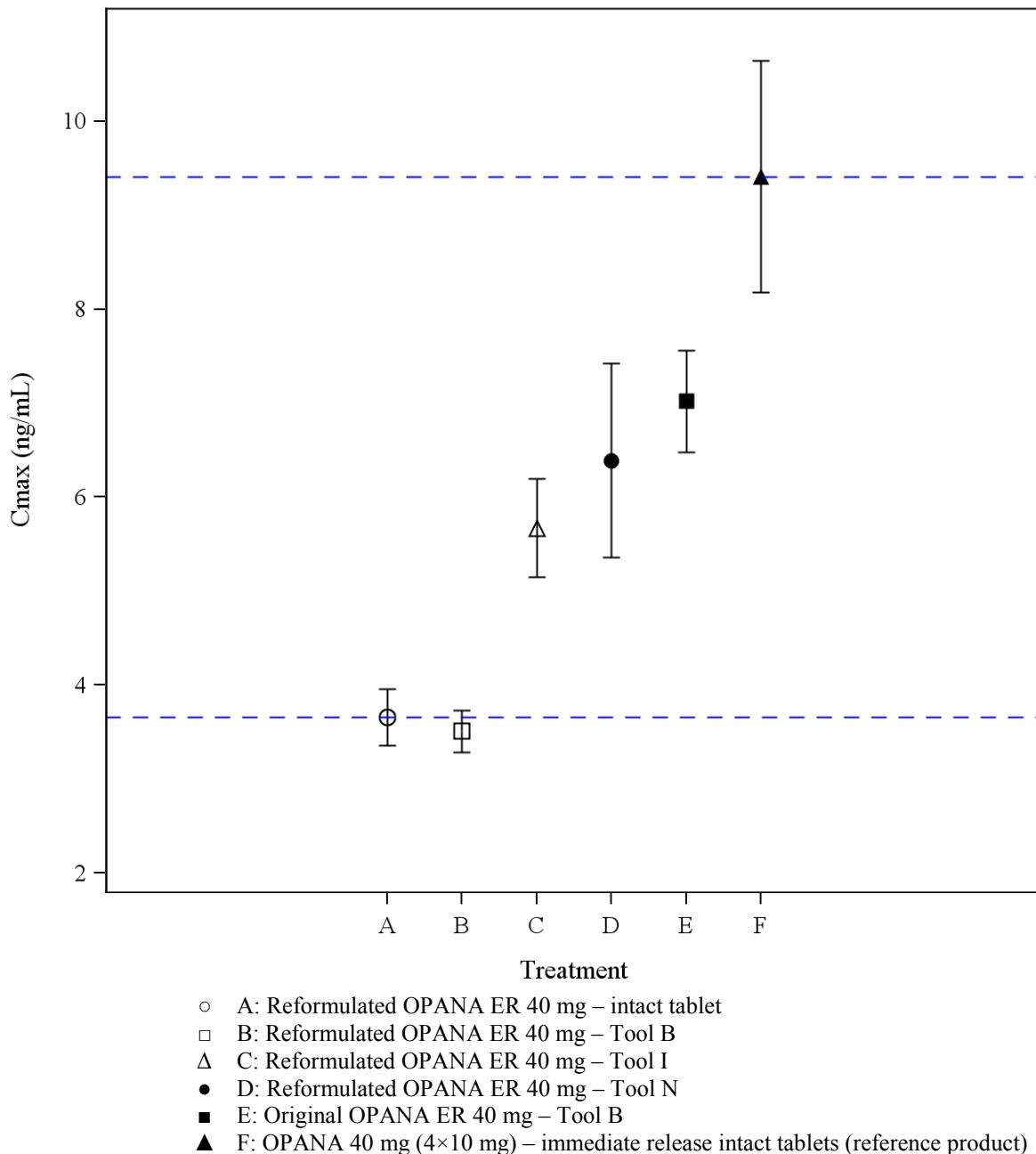
4.2.2.1. Study Design

In study EN3288-108 systemic exposure after oral administration to oxymorphone from reformulated OPANA ER 40 mg was examined after 3 methods of tampering: with tool B, tool I, and tool N. In addition, original OPANA ER 40 mg was administered after tampering with tool B. The results were compared to systemic exposure to oxymorphone from reformulated OPANA ER 40 mg intact and the IR formulation OPANA 4×10 mg administered as intact tablets. Systemic exposure to oxymorphone after tampering with reformulated OPANA ER 40 mg and original OPANA ER 40 mg with tool B was also compared.

4.2.2.2. Results

Tampering with reformulated OPANA ER to various degrees using the 3 methods did not have an effect on systemic exposure to oxymorphone. The extent of systemic exposure to oxymorphone (AUC) was similar for intact reformulated OPANA ER and all tampered products when compared to OPANA IR. The effects of 1 method of tampering (with tool B) upon the 2 ER formulations were compared, and again the extent of systemic exposure was similar. However, C_{max} was 49% lower for reformulated OPANA ER tampered with tool B than for original OPANA ER tampered with tool B indicating that the ER properties of reformulated OPANA ER were more resistant to tampering by this method than was original OPANA ER.

Figure 18: Mean (\pm SE) Oxymorphone C_{max} After Single Oral Doses of Intact and Tampered Reformulated OPANA ER 40 mg, Tampered Original OPANA ER 40 mg, and Intact OPANA 10 mg (4 \times 10 mg) Tablets Administered to Fasted Healthy Subjects (N=29)



The results demonstrated that both, reformulated OPANA ER and original OPANA ER retained some ER properties compared to the IR formulation despite the tampering methods used. The extent of the effects of various tampering methods can be ranked according to observed C_{max} and T_{max} , where C_{max} and T_{max} observed after administration of the IR formulation (intact OPANA 4 \times 10 mg) (9.41 ± 6.626 ng/mL at 0.5 hours) represent the potential greatest effect of tampering, and C_{max} and T_{max} observed after intact reformulated OPANA ER 40 mg tablets ($3.66 \pm$

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1.616 ng/mL at 5.0 hours) represents the least potential effect of tampering. Thus, from most affected to least affected, the treatments are ranked: Original OPANA ER 40 mg tampered with tool B > reformulated OPANA ER 40 mg tampered with tool N > reformulated OPANA ER 40 mg tampered with tool I > reformulated OPANA ER 40 mg tampered with tool B. The established ranking regarding the greatest effect of tampering also confirmed the results of the in vitro test battery and demonstrated the dependence of the rate of drug release upon the surface area of the tablet matrix.

C_{max} after ingestion of reformulated OPANA ER tampered with tool B was equivalent to C_{max} after ingestion of reformulated OPANA ER intact tablets (3.51 ± 1.201 ng/mL versus 3.66 ± 1.616 ng/mL, respectively). Tampering with tool I and tool N increased C_{max} by 51% and 56%, respectively.

After reformulated OPANA ER was tampered with tool B, C_{max} was 49% lower than that observed after original OPANA ER tampered with tool B, demonstrating the relative tamper resistance of reformulated OPANA ER compared to original OPANA ER.

The pharmacokinetic results from study EN3288-108 (oral administration of manipulated reformulated OPANA ER) confirm that some extended-release properties are maintained despite the manipulation of the tablet, as demonstrated by a lower C_{max} and slower absorption.

4.3. Human Abuse Liability Study (Category 3)

Endo conducted an intranasal insufflation study among people who recreationally abuse opioids in order to understand the intranasal abuse potential of reformulated OPANA ER. The study was designed to evaluate the subjective effects of OPANA ER ADF manipulated and administered intranasally compared with oxymorphone HCl powder administered intranasally.

Protocol design and statistical analysis for study EN3288-114 were reviewed by FDA (Advice/Information Request; March 17, 2014). A Type C meeting was held on June 15, 2015 where the Agency confirmed that study EN3288-114 met the criteria for a Category 3 study.

As determined by Category 1 studies tool V produced the smallest particle size and greatest release of drug product. Therefore, this method was chosen for study drug preparation for the insufflation studies.

4.3.1. EN3288-114

4.3.1.1. Study Design

In study EN3288-114, manipulated, reformulated OPANA ER and oxymorphone HCl powder were administered by insufflation to non-dependent recreational intranasal prescription opioid users in order to compare the subjective effects, to characterize the systemic oxymorphone exposure, and to evaluate the safety. Further details on study design are described in section 4.2.1.1.

4.3.1.2. Statistical Analysis

The prespecified primary endpoint was the E_{max} of VAS for Drug Liking “at this moment” during the treatment phase consistent with FDA guidelines.⁽²⁾ The primary comparison was

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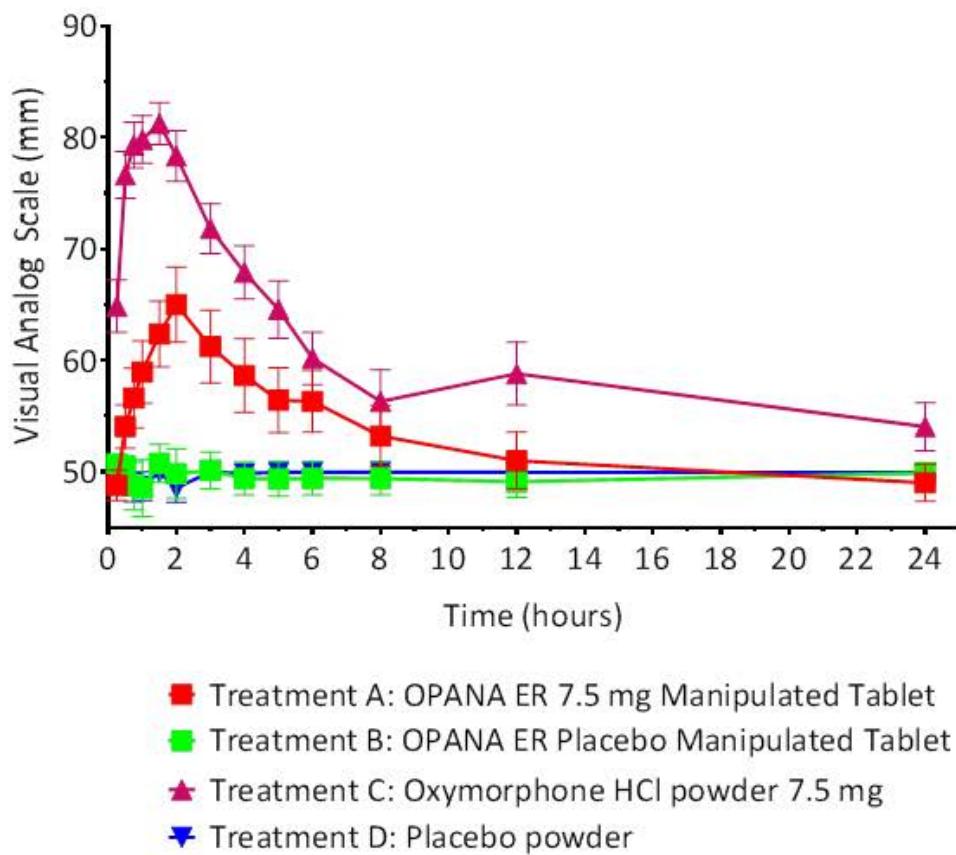
reformulated OPANA ER-manipulated vs oxymorphone HCl powder. The key secondary endpoints were E_{max} of VAS for Good Drug Effects, High, and Take Drug Again. If there was a statistically significant difference between reformulated OPANA ER-manipulated and oxymorphone HCl powder for the primary endpoint, then the key secondary endpoints would be compared between reformulated OPANA ER-manipulated and oxymorphone HCl powder using Hochberg's method. A linear mixed effects model was fitted to each pharmacodynamic parameter including the primary endpoint. The model had treatment, period, and sequence as fixed effects, and subject nested in the sequence as a random effect. For each parameter, LS means for each treatment and 95% CIs for each treatment differences were computed, along with the p values of all treatment differences. Parameters that did not have a normal distribution were to be analyzed non-parametrically.

4.3.1.3. Results

Pharmacodynamic data were available from 43 subjects administered insufflated, reformulated OPANA ER 7.5 mg manipulated tablet, and 45 subjects administered insufflated oxymorphone HCl powder 7.5 mg. The median percentage of each treatment actually insufflated in the treatment phase ranged from 96% to 97%.

The primary endpoint of the study, difference in Drug Liking "at this moment" E_{max} between manipulated, reformulated OPANA ER 7.5 mg and oxymorphone HCl powder 7.5 mg, was successfully met ([Figure 19](#)). A reduction in the subjective effects of insufflated, reformulated OPANA ER 7.5-mg manipulated tablet compared to oxymorphone HCl powder 7.5 mg was demonstrated. Based on a nonparametric analysis, the median difference for E_{max} for Drug Liking was 15.5 mm (interquartile range, 33.0 mm; $p<0.0001$). A parametric analysis was also conducted for comparative purposes. The mean ($\pm SD$) E_{max} for Drug Liking of reformulated OPANA ER 7.5-mg manipulated tablet was 70.3 ± 16.20 mm, compared to 87.8 ± 10.33 mm for oxymorphone HCl powder 7.5 mg. The LS means (70.67 and 87.82 mm, respectively) differed by 17.15 mm; 95% CI, 12.53-21.77 mm by parametric analysis ($p<0.0001$) ([Table 12](#)).

**Figure 19: Time Course of Drug Liking by Treatment (Mean±SE) – Study EN3288-114
Pharmacodynamic Population (N=38)**



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Table 12: Summary Parameters for Subjective Effects Measures: Primary Endpoint and Key Secondary Endpoints - Pharmacodynamic Population (N=38) [Mean±SD or Median (Range)]

Effect/Parameter	OPANA ER Manipulated Tablet 7.5 mg (N=38)	OPANA ER Placebo Manipulated Tablet (N=38)	Oxymorphone HCl Powder 7.5 mg (N=38)	Placebo Powder (N=38)
Primary Endpoint				
Drug Liking VAS				
E _{max} (mm)	70.3±16.20	53.3±8.69	87.8±10.33	50.3±0.65
E _{max} ^a (mm)	70.5 (50-97)	50.0 (50-88)	89.0 (62-100)	50.0 (50-53)
tE _{max} ^a (h)	1.9 (0-8)	0.2 (-0-8)	0.9 (0-12)	0.2 (0-24)
Key Secondary Endpoints				
Take Drug Again VAS^b				
Maximum Response	59.8±24.40	48.7±17.26	81.7±17.55	53.8±15.25
Average Response	56.5±23.88	47.1±16.46	78.3±19.00	50.4±11.85
High VAS				
E _{max} (mm)	45.3±37.06	9.2±21.03	83.0±16.60	2.5±8.85
Good Effects VAS				
E _{max} (mm)	45.8±36.35	10.8±22.17	81.3±18.58	4.7±12.71

^a Median (range).

^b Maximum and average of 2 observations.

Table 13: Parametric and Nonparametric Analyses of Primary Endpoint - E_{max} (mm) of Drug Liking

Effect/Parameter	Comparison	LS Means Difference	95% CI	P Value
Parametric Analysis of Primary Endpoint E _{max} (mm)	C-A	17.15	12.53;21.77	<0.0001
	C-D	37.40	32.78;42.00	<0.0001
	A-B	17.14	12.52;21.75	<0.0001
	B-D	3.10	-1.51;7.72	0.186
			Interquartile Range	
Nonparametric Analysis of Primary Endpoint E _{max} (mm)	C-A	15.5	33.0	<.0001

A = OPANA ER manipulated tablet 7.5 mg; B = OPANA ER placebo manipulated tablet; C = Oxymorphone HCl powder 7.5 mg, D = Placebo powder

No statistically significant differences in the subjective effects of insufflated, reformulated, matching OPANA ER placebo manipulated tablets and oxymorphone HCl placebo powder were observed.

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In conclusion, study EN3288-114 found that:

- This was a valid study of the comparison of subjective effects of insufflated reformulated OPANA ER 7.5-mg manipulated tablet compared to insufflated oxymorphone HCl 7.5 mg powder.
- Drug Liking was significantly reduced for insufflated, reformulated OPANA ER 7.5-mg manipulated tablet compared to insufflated oxymorphone HCl 7.5 mg powder.
- Take Drug Again, High VAS, and Good Effects VAS were significantly reduced for insufflated, reformulated OPANA ER 7.5-mg manipulated tablet compared to insufflated oxymorphone HCl 7.5 mg powder.
- No statistically significant differences in the subjective effects of insufflated, reformulated matching OPANA ER placebo manipulated tablets and placebo powder were observed

4.4. Category 4 (Postmarketing Epidemiology Studies)

In order to determine whether reformulated OPANA ER resulted in a meaningful reduction in abuse, misuse, and related clinical outcomes, Endo initiated 3 postmarketing Category 4 studies (2 primary and 1 secondary study) using ongoing passive surveillance systems that collect data from 2 different data partners (NAVIPPRO and RADARS). The 3 postmarketing epidemiology protocols were submitted to FDA for review and feedback was incorporated prior to study conduct. The 3 studies were as follows:

- Primary epidemiological study - NAVIPPRO: “Post Marketing Epidemiology Study to Assess Abuse of OPANA® ER Among Adults Assessed for Substance Abuse Treatment”
- Primary epidemiological study - RADARS: “Analysis of Reformulated OPANA® ER using the RADARS® Poison Center Program” which examined differences in rates of intentional abuse mentions before and after introduction of reformulated OPANA ER.
- Secondary epidemiological study - RADARS: “Analysis of Reformulated OPANA® ER using the RADARS® Drug Diversion Program” which examined differences in rates of diversion mentions before and after introduction of reformulated OPANA ER.

4.4.1. NAVIPPRO Addiction Treatment Centers Postmarket Epidemiology Study

This primary postmarketing epidemiology study to evaluate abuse patterns of reformulated OPANA ER among a sentinel population of adults assessed for substance use problems and treatment planning utilized data from the NAVIPPRO surveillance system for the period January 1, 2009 (Q1 2009) through June 30, 2016 (Q2 2016).

4.4.1.1. Objectives

The main objective was to characterize and assess changes in patterns of abuse of OPANA ER, including abuse by ROA, before and after introduction of reformulated OPANA ER.

Comparisons were:

- All routes of abuse associated with tampering (eg, snorting and injection) of reformulated OPANA ER in the post-period compared to original OPANA ER in the pre-period within the ASI-MV population of adults assessed for substance abuse treatment.
- Individual ROA (ie, oral, intranasal, injection) of reformulated OPANA ER in the post-period compared to original OPANA ER in the pre-period within the ASI-MV population of adults assessed for substance abuse treatment
- All routes of abuse associated with tampering (eg, snorting and injection) of reformulated OPANA ER compared to non-crush resistant generic oxymorphone ER in the post-period within the ASI-MV population of adults assessed for substance abuse treatment.
- Individual ROA (ie, oral, intranasal, injection) of reformulated OPANA ER compared to non-crush resistant generic oxymorphone ER in the post-period within the ASI-MV population of adults assessed for substance abuse treatment

A central theme of the study was the recognition that the landscape of prescription opioid abuse had changed over time and continued to change with the introduction of new products to the market including both opioid formulations with abuse-deterrent properties (eg, OxyContin ADF) and non-ADFs of oxymorphone ER. Therefore, a goal of the study was to examine abuse of reformulated OPANA ER in the broader context of the changing environment of prescription opioid abuse.

4.4.1.2. Study Design and Study Period

Analyses included comparisons across various time periods throughout more than 7 years in order to assess rates of abuse and patterns of abuse via different ROA in relation to historical patterns of abuse of non-abuse-deterrent OPANA ER formulation as well as to assess comparative patterns of abuse to currently available non-abuse-deterrent, generic oxymorphone ER formulations. These comparisons were made in the context of changes to the opioid marketplace that included the introduction of both formulations with abuse-deterrent properties and non-ADF opioids and changes in the severity and composition of the clientele being served by treatment centers providing data to NAVIPPRO.

As illustrated in [Figure 20](#), the study utilized data across 2 separate time periods:

- A **Baseline period** prior to the introduction of reformulated OPANA ER (January 1, 2009 through December 31, 2011; referred to as the **pre-period**)
- A defined market **transition period** of market change for oxymorphone products (January 1, 2012 through June 30, 2013; referred to as the transition period) was excluded from the analysis because the rapidly changing environment made it

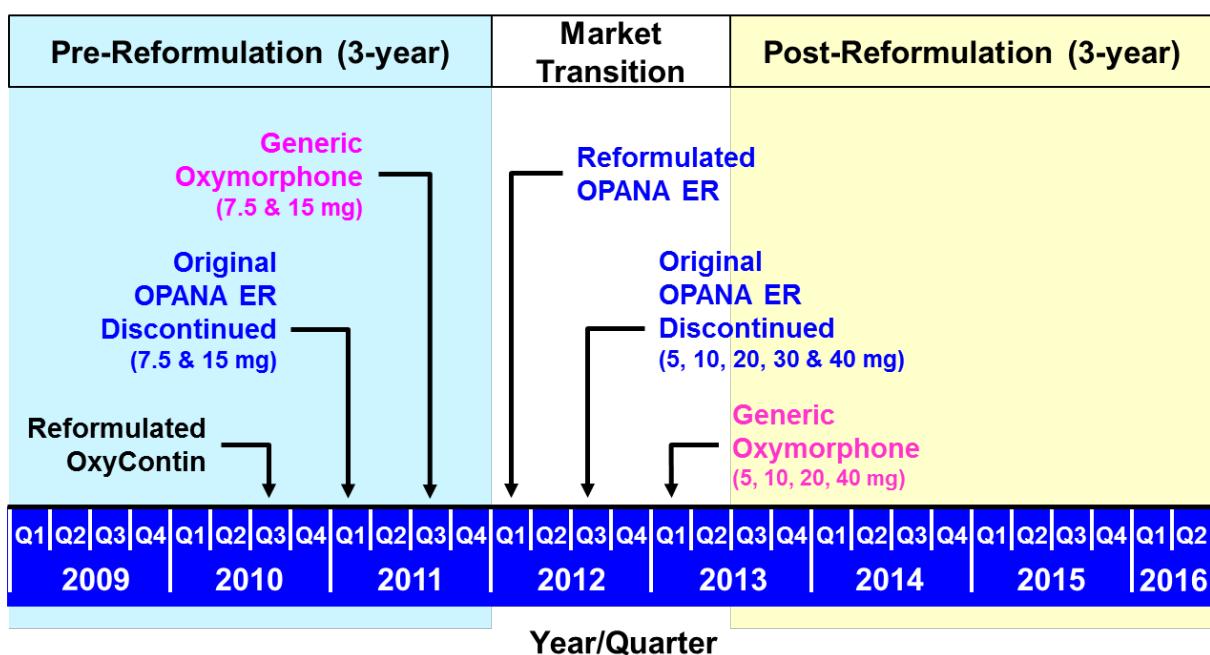
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impossible to interpret observational data during that time as agreed by the FDA and Sponsor.

- The period after introduction of reformulated OPANA ER (July 1, 2013 through June 30, 2016; referred to as the **post-period**).
- In addition, comparisons of the **Sensitivity pre-period** (July 2010 to December 2011) to the **post-period** (July 2013 to June 2016) were prespecified. The data for the sensitivity period are presented since the baseline period was not homogeneous due to the introduction of the ADF formulation of oxycodone ER (OxyContin ADF), which was subsequently temporally associated with a shift in the abuse pattern of OPANA ER and needs to be taken into consideration when interpreting the data.

Details with regard to the prespecified analysis are provided in [Appendix 4](#).

Figure 20: Time Periods of Data Utilized in the Category 4 NAVIPPRO Study and Changing Landscape



4.4.1.3. Data Sources

4.4.1.3.1. Addiction Severity Index - Multimedia Version (ASI-MV®)

The ASI-MV is a proprietary data stream of the NAVIPPRO system that collects data on substances used and abused by individuals in treatment for substance use disorders. Data are collected from adults within a network of substance abuse treatment centers and other assessment settings using a self-administered and structured computerized interview. Since data collection began, the ASI-MV contains assessments from substance abuse treatment sites in 44 states (including Washington, DC) in the United States. This computerized version of the Addiction Severity Index (ASI) interview was built upon a modified version of the ASI, which is a standard intake assessment tool designed for use on admission to drug and alcohol

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treatment (41) and has demonstrated reliability and validity.(42,43) The assessment asks questions related to patient demographics and drug-abuse experiences.

Specifically, the ASI is a structured clinical interview used to measure the severity of a range of problem areas typically associated with drug and alcohol abuse. The ASI-MV collects individual-level data across a series of domain areas, including medical, employment/support status, alcohol/drug use, legal, family/social status, and psychiatric status and includes product-specific questions on use and abuse of prescription medications. The ASI-MV has demonstrated good reliability (test-retest) along with discriminant validity, tested against other scales measuring the same domains, and criterion validity, tested against the standard, interviewer-administration of the ASI for both English and Spanish.(44,45)

Multimedia Aspect of the Scale

Although the brand name for both the original and reformulated OPANA ER is “OPANA ER,” the tablets for the 2 formulations are different in their physical appearance; the original OPANA ER tablets have an octagon shape while reformulated OPANA ER is a bi-concave shaped tablet which is curved in on both sides. To minimize misidentification of original and reformulated OPANA ER, the ASI-MV screen images include indicia and a description of the shape of each formulation. It is important to note that the screens used in the ASI-MV interview for respondents to indicate use of specific prescription medications are updated to reflect changes in the market place as new drugs are introduced. This feature of the ASI-MV allows for timely analysis of product-specific data that reflect current market trends. However, with each change to the ASI-MV screen there is the potential for response bias or possible misclassification due to misidentification of products that have similar appearance and the addition of images of new products and the removal of images for products no longer on the market. It is important to note that the ASI-MV screen for oxymorphone products has been updated since the interview began collecting data on use of abuse of original formulation OPANA ER so as to include images of new oxymorphone products (ie, OPANA ER and generic formulations of IR or ER oxymorphone) as they entered the market or the discontinuation of products no longer available on the market. Analyses conducted for this study include evaluation of quarterly trend in abuse over all quarters of the study period from the start of the baseline period to the completion of the 3-year follow-up period post-introduction of reformulated OPANA ER.

4.4.1.4. Planned Analysis

The primary analyses for this post-marketing epidemiology study included examination of patterns of abuse via alternate ROA for OPANA ER and opioid comparators included in the study. Assessment of abuse outcomes for overall abuse prevalence and abuse via either alternate or specific ROA included means analysis of the average level of past 30-day abuse comparing pre-period and post-period abuse estimates for the defined study periods as well as quarterly estimates of abuse and trend over time. All primary and secondary study analyses present the percent change in abuse for OPANA ER and comparators with associated 95% CIs and *p* values. There was no adjustment for multiplicity; therefore, no *p* values are presented.

For purposes of this study, abuse by alternate ROAs or routes of abuse associated with tampering is defined as abuse via any ROA not including the intended route for the medication (ie, swallowed whole). The routes include snort, inject, smoke, chewed then swallowed, drink in

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solution, and “other” route. Note that within the ASI-MV assessment, individuals can indicate abuse of a product via more than one ROA and therefore analyses are not mutually exclusive across categories of ROA.

For primary analyses, changes in abuse by ROA were measured in 2 ways. First, abuse was measured as the prevalence of past 30-day abuse of the product via either any alternate ROA or separately for individual specific ROAs among the study population (ie, adults assessed for substance abuse treatment within the ASI-MV) using the population denominator per 100 ASI-MV assessments. An additional analysis for abuse by ROA included review of abuse via alternate routes and route-specific abuse presented as prevalence rates per prescription volume (as abuse per 10,000 dosage units/tablets dispensed).

Data analysis for the study was conducted using log-binomial or Poisson regression models to estimate and contrast pre-period¹ and post-period route-specific (oral, snort, inject, any alternate ROA) and product (ie, OPANA ER and individual opioid study comparators) prevalence rates of past 30-day abuse. Except where noted, all analyses were performed at the individual-level data; that is, for each individual or subject included in the study sample, the outcome (ie, abuse or abuse via a specific route) is binary indicating whether or not the individual abuses a given drug (ie, either the target drug of interest or comparator opioid). Relative risks (probability of abuse during pre-period compared to probability of abuse in the post-period) and relative percent change in abuse for OPANA ER and comparator opioids are the effect sizes used in this study.

Additionally, analyses for ROA as prevalence rates included adjustment for prescription volume based on total dosage units (ie, tablets/pills) dispensed. The ROA models were also carried out using both pre-period specifications (ie, the 3-year pre-period prior to introduction of OPANA ER ADF (January 2009 through December 2011) and the 18-month period after introduction of OxyContin ADF but prior to introduction of reformulated OPANA ER (July 2010 through December 2011) – the sensitivity period. Sensitivity analyses were also conducted using analyses described above to examine route and administration and abuse of OPANA ER geographically using stratification of individuals from all sites within the ASI-MV from Tennessee and sites excluding Tennessee.

There were 2 types of dependencies in the data originally considered to incorporate into each model including: (1) within-subject correlation (random patient effect) and (2) within-ZIP code correlation (random ZIP code effect). Upon an empirical evaluation, it was determined that accounting for both of these dependencies required integrating over an inordinate number of random effects due to the large number of ASI-MV respondents and ZIP codes included in the dataset, rendering the models too computationally intensive using the current SAS 9.4/STAT 14.1 GLIMMIX procedure algorithms. To achieve convergence, the ZIP code random effect (within-ZIP code correlation) was removed from all models, and the random subject effect (within-subject correlation) was incorporated as an R-side random effect. It is generally advisable to account for the strongest dependency in the dataset to minimize the bias in the standard errors. Therefore, within-subject correlation was deemed more important to account for in the analytic models than incorporating within-ZIP code correlation because repeated measurements on the same individual would be expected to be more strongly correlated than

¹ Note that the study design included 2 separate pre-periods, a 3-year pre-period and an 18-month pre-period. Comparisons were made using the modeling approach described for each defined pre-period as separate analyses.

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measurements between people who reside in the same ZIP code. Moreover, these changes to the models allowed for the use of the highly efficient generalized estimation equations (GEE) method offered in the GENMOD procedure (SAS Institute Inc., 2015). Technical details regarding the GEE method are provided below.

A GEE belongs to a class of semiparametric regression techniques, and is used to estimate the parameters of a generalized linear model with a possible unknown correlation between outcomes. The GEE is commonly used in large epidemiological studies, because they can handle many types of unmeasured dependence between outcomes. The focus of the GEE is on estimating the average response over the population (ie, population-averaged effects). The GEE is usually used in conjunction with “robust standard error” or “sandwich variance” estimates. Parameter estimates from the GEE are valid even if the covariance structure is mis-specified, which makes the GEE a popular alternative to the likelihood-based generalized linear mixed model which is more sensitive to variance structure specification.

4.4.1.5. Strengths and Limitations

The ASI-MV system is a data stream that provides sentinel surveillance for potential drug abuse-related events by recording the use of controlled substances in individuals entering programs for addiction treatment. It acts as a surrogate since no direct outcomes of abuse-related actions such as overdose, withdrawal, or death are monitored through this system. The system provides important information about trends of abuse because the data are captured over time; however, the system also has distinct limitations based on the source of the data and how they are collected:

1. The lack of national representativeness is due to various aspects of the system:
 - a. The network is a private business and relies on contractual business arrangements between itself and substance abuse treatment facilities to install and use the ASI-MV Connect® software. This results in a network of centers dependent upon the success, scope, and pricing of their business model versus other ways of handling treatment intake that results in non-representative coverage across the United States. Some states (such as New Mexico or Tennessee) have greater coverage, while data from other states are represented from no or only a small number of participating treatment centers, resulting in under-representation of those geographies. Further, geographic differentiation might be even difficult within a state due to the unbalanced distribution of treatment centers within a particular state. Consequently, the system might miss pockets of relatively high or low abuse and therefore, might present a skewed picture of the extent and distribution of abuse in a state or a region within a state.
 - b. Since treatment centers within the ASI-MV Connect system are not randomly recruited to join the network, data collected from these treatment centers cannot and should not be generalized to all substance abuse treatment centers. Such limitations are inherent in this country’s substance abuse landscape, rendering any data stream for this population susceptible to some serious limitations based on this source of information.

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2. Linked to the fact that the network is a subscription service is the limitation of treatment centers “dropping in” and “dropping out” of the network as a result of gain of business or loss of business, respectively. In essence, each quarterly assessment represents a prevalence estimate of the network at that particular point in time. This could have the greatest impact on temporal trends as the data may reflect the alteration in the sample by the change in sites or population over time rather than in actual use of the implicated substances. The following hypothetical example illustrates this point.

Assume there are 20 treatment centers in a region during the baseline period recording 1,000 ASI-MV assessments. There are 100 mentions of drug A resulting in a prevalence of abuse of 10 events per 100 ASI-MVs. Those sites are stable and the same 20 treatment centers also participate in the post-period with the same number of ASI-MV assessments, the same number of mentions of drug A and the same prevalence of abuse of 10 mentions per 100 ASI-MVs.

However, a new cohort of 15 treatment centers subscribes to the software in the post-period. Thus, those centers contribute to information in the post-period but did not contribute information to the ASI-MV software during the pre-period. Those 15 centers record 1,000 ASI-MV assessments but treat sicker patients who mention drug A 300 times. This results in a post-period prevalence of abuse of 30 mentions per 100 ASI-MV assessments for those centers.

When the original sites and the new sites are combined there is now a post-period prevalence of abuse of drug A of 20 mentions per 100 ASI/MV assessments (2000 assessments and 400 mentions). When comparing the baseline period to the post-period, it appears that the prevalence has doubled (from 10 to 20 mentions per 100 ASI-MV assessments) when, in reality, what has changed is the sample. Since there is no baseline measure for the new cohort of centers that joined the network in the post-period, there is no way to account for this.

3. Data are collected at the patient 3-digit ZIP Code level, and the entire dataset contains at least 1 case in nearly 92% of all 3-digit ZIP Codes. However, this fact is misleading since such “representation” may be by a single individual in a 3-digit ZIP Code across all of the controlled substances monitored by the system (opioids, stimulants, anxiolytics, etc). Therefore, calculation of rates of abuse in the states or other geographical regions with few sites and/or few cases is limited and must be interpreted with caution. Further, individual sites within the network contribute data on varying schedules and with varying sample size.
4. The set of individuals seeking treatment may be of limited representativeness for the entire population of individuals who misuse or abuse controlled substances. This set consists of those persons who either have 1) made a decision to seek treatment for substance abuse, have access to a substance abuse facility, and the means to pay for such treatment; or 2) were placed in treatment involuntarily as a result of court-ordered actions. Thus, this database may have a socioeconomic bias against those who do not have access to such care, choose not to seek treatment, or cannot afford treatment. Furthermore, those individuals placed by the courts are likely to have committed criminal activities and cannot be considered representative of the larger population of substance

abusing individuals. It is unclear how prescription opioid abuse data collected at intake to substance abuse treatment centers relate to abuse in the community given how such patients find their way to treatment. Findings on a sample of adult substance abusers in treatment are not generalizable to children or adult abusers who are not seeking treatment.

5. Another possible limitation is that these data are self-reported, which is subject to recall bias, particularly since individuals are asked to reflect back on substances abused during the past 30 days. Given the known cognitive-impairing effects of these drugs, it is possible that memory is distorted and does not accurately reflect actual consumption over such a time frame. For example, more recent use may greatly outweigh use in the more distant past. Furthermore, the information cannot be independently validated since such use is often surreptitious and there may not be any corroborating evidence such as pill bottles or blood levels of these drugs. Traditionally, the reliability and validity of self-report from substance abuse clients has been questioned. This concern usually reflects the observed phenomena of “denial” and the consistent under-reporting of consumption in general population surveys. Some research and reviews support the reliability and validity of self-report of patients entering treatment.⁽⁴⁶⁻⁵⁰⁾ However, it should be acknowledged that a few studies have found self-reported use to under-report drug use.^(51,52) A further consideration is that individuals in this particular patient population have an acknowledged difficulty with substance abuse—a difficulty that has developed to the degree of desiring or necessitating treatment—and thus they may have less motivation to minimize or deny their drug use in comparison with people who are not in treatment.

Separate from the issue of the validity of self-reported substance use data in the treatment setting, is the matter of computer administration of the instrument. However, there is evidence that reporting via computer self-administration is as valid as reporting to a live interviewer. Where discrepancies exist, computer self-administration tends to elicit reports of more, rather than fewer, psychosocial and substance use problems.⁽⁵³⁾

6. The ASI-MV Connect assessment presents respondents with a “fake” prescription opioid product to gauge the extent to which respondents may be responding haphazardly or otherwise not reporting honestly. A few respondents (0.01% of all respondents) endorse use/abuse of this non-existent “drug.” These few respondents are removed prior to analyses as “unreliable reporters.”
7. The potential for misclassification or misidentification of individual drug products within the ASI-MV Connect interview is also a potential limitation. Possible misclassification of prescription opioids maybe as high as 20% among non-medical prescription opioid users and is dependent on multiple factors.⁽⁵⁴⁾ Among those are age, trust relationship with the drug source, context in which the drug was obtained and literacy level.

Despite its limitations, it is important to note several strengths of data collected from the ASI-MV Connect data stream. For example, this data stream is designed for active data collection, and as such, is not dependent upon passive, retrospective, and often anecdotal data characteristic of other commonly used data streams. Secondly, the ASI-MV Connect system yields data in near real time: the majority of participating treatment sites (85%) uploads data within the same day. Data are uploaded within 2 weeks for 95% of sites. While representative

data are always preferable, when available, the public health importance of near-real time data from a sentinel population of those most involved with substances, such as the ASI-MV Connect data, can potentially reflect use patterns of “early adopters.” Thus, the ASI-MV Connect could potentially provide information for estimating the impact of ADFs, with respect to emerging trends in drug abuse indicators. However, to date it is not clear if the detected changes in the treatment center abuse population translate into the broader community setting.

The ASI-MV uses a methodology for questioning respondents about use/abuse of particular prescription medications that is similar to methods employed by the National Survey on Drug Abuse and Health (NSDUH) survey.⁽⁵⁵⁾ NSDUH utilizes pictures of prescription products, names, slang and so forth as well as other widely accepted methodological practices for increasing the accuracy of self-reports, such as audio computer-assisted self-interviewing (as does the ASI-MV). Examinations of these NSDUH methods have shown that they reduce reporting bias in general populations.⁽⁵⁶⁾

4.4.1.6. Analytic Approach

There are some limitations to the data analytic approach worth noting. First, the statistical power of these analyses depends on the number of abuse cases captured by the ASI-MV data stream and this cannot be as easily addressed as in a clinical trial where the sample size is set in advance. Second, the alternate way in which product availability is measured (locally dispensed tablets) is limited by excluding other forms of legal dispensing (eg, mail order) as well as illicit interstate trafficking. Estimating the impact of supply in a particular region that results from such underground transportation of drugs is notoriously difficult. Thus, it is possible that in certain regions of the country the measure of availability will be compromised by this limitation and underestimate the denominator of these calculations.⁽⁵⁷⁾ Also, availability is measured at state level only for those states that contribute data to the ASI-MV Connect network of sites during the study period and as a result, is not as accurate as patient level availability data. Similarly, there may be other confounders (eg, product street price and heroin availability) for which data are not readily available.

4.4.1.7. Limits to Interpretation of Results

Interpretation of study results will depend on all of the limitations and strengths of the ASI-MV Connect network as well as external considerations such as changes in the opioid market with the introduction of new opioids, including ADFs, and their relative availability/market penetration; the implementation of the class-wide Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids which itself has the goal to reduce abuse and misuse of opioids; and secular trends in the availability and supply of illicit drugs (eg, heroin) which might blunt the abuse of prescription opioids, and the presence of generic formulations of ER oxymorphone. In summary, ASI-MV Connect provides an additional source of data on prescription drug abuse and should only be considered part of a spectrum of existing resources available for prescription drug abuse surveillance in the United States as well as interpreted in light of external conditions such as changes in the prescription opioid market.

4.4.1.8. Results

4.4.1.8.1. Abuse Rates in All States (Pre-period vs Post-period)

The following results focus on the changes from the Pre-period (January 2009 to December 2011) to the Post-period (July 2013 to June 2016).

The prevalence rates of past 30-day abuse via alternate routes of abuse were lower in the pre-period compared to the post-period. By ROA, oral abuse and abuse via intravenous injection were higher in the post-period, however abuse via intranasal administration was lower (Figure 21, Figure 22) independent of the denominator.

Figure 21: Prevalence Rates of Past 30-Day Abuse via Specific Routes of Administration for Original OPANA ER, and Reformulated OPANA ER per 100 ASI-MV Assessments, Pre-period vs Post-period

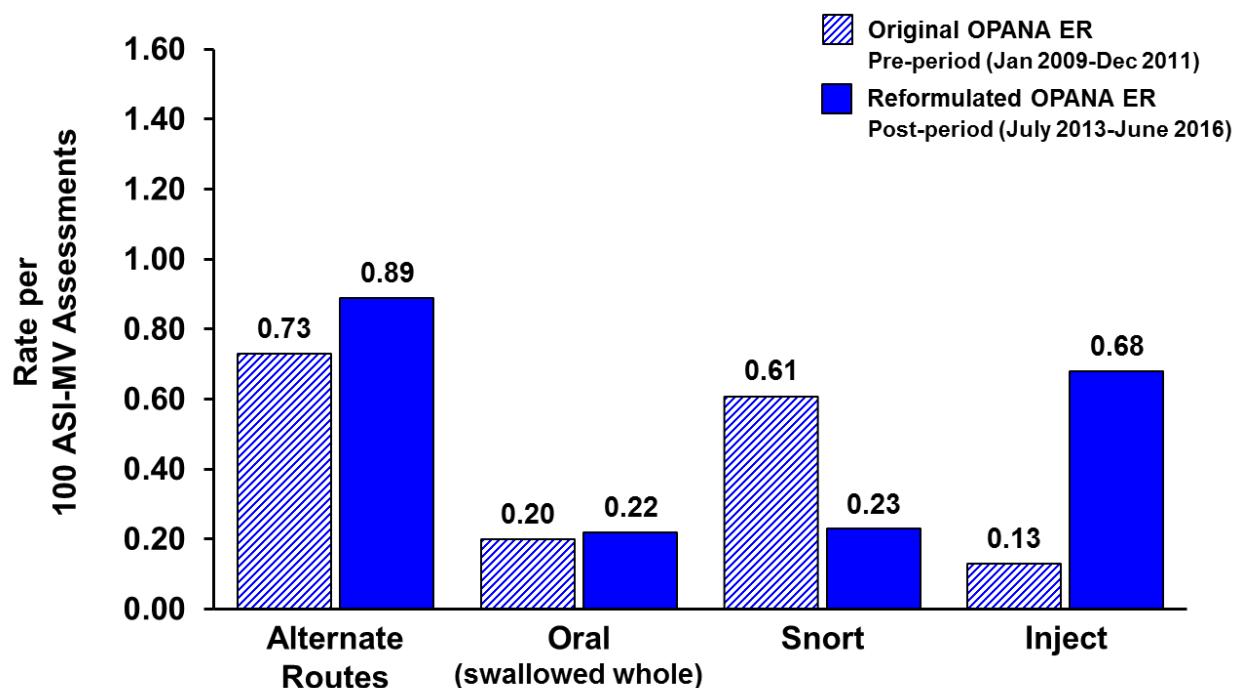
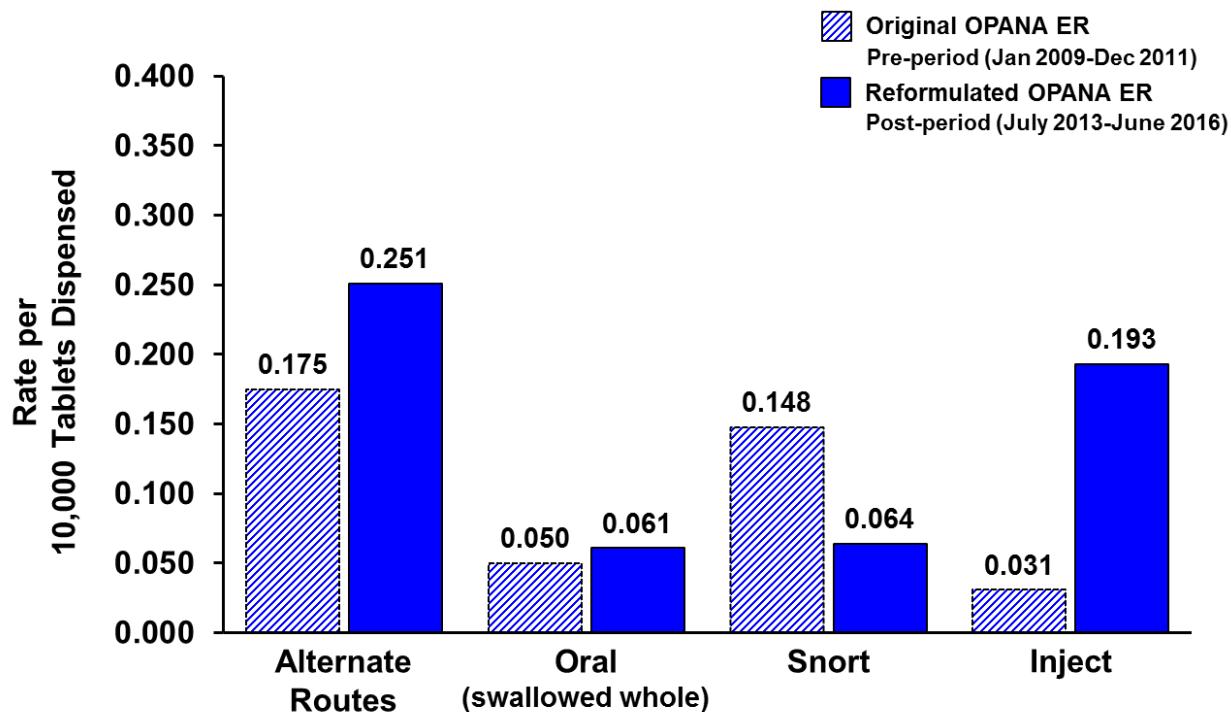


Figure 22: Prevalence Rates of Past 30-Day Abuse via Specific Routes of Administration for Original OPANA ER, and Reformulated OPANA ER per 10,000 Tablets, Pre-period vs Post-period



In the post-period the prevalence rates of past 30-day abuse by alternate routes was lower for reformulated OPANA ER compared to generic oxymorphone ER, independent of the denominator. For individual ROA, prevalence rates were higher for oral and intranasal abuse for generic oxymorphone ER compared to reformulated OPANA ER regardless of denominator. For intravenous abuse, prevalence rates were higher for OPANA ER using the population denominator (0.68 for OPANA ER; 0.66 for generic oxymorphone ER per 100 ASI-MV assessments) but lower using the tablet denominator (0.193 for OPANA ER; 0.282 for generic oxymorphone ER per 10,000 tablets) (Figure 23, Figure 24).

Figure 23: Prevalence Rates of Past 30-Day Abuse via Specific Routes for Reformulated OPANA ER and Oxymorphone ER (Generics) per 100 ASI-MV Assessments, Post-period

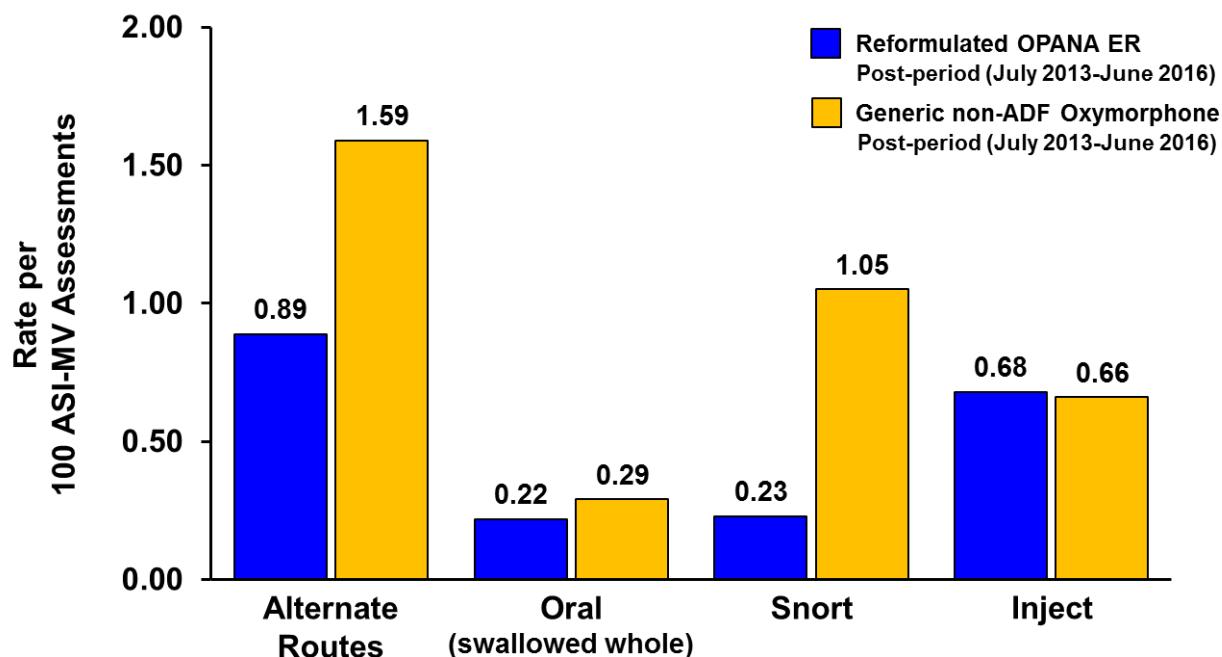
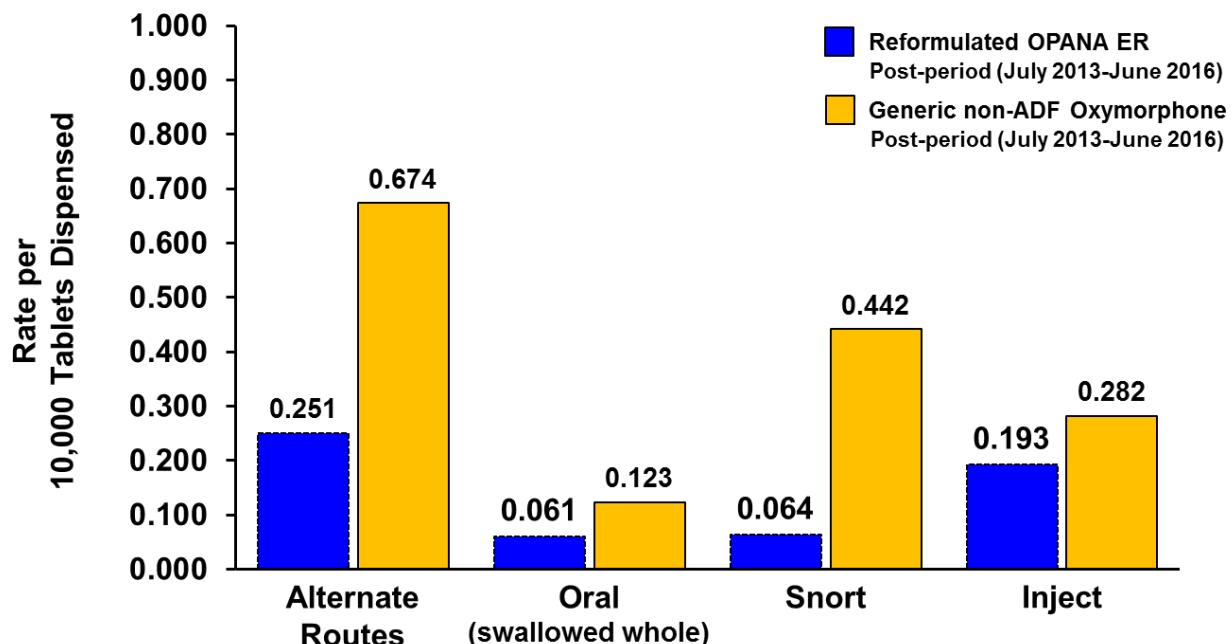


Figure 24: Prevalence Rates of Past 30-Day Abuse via Specific Routes of Administration for Reformulated OPANA ER and Oxymorphone ER (Generics) per 10,000 Tablets Dispensed, Post-period



4.4.1.9. Impact of Tennessee on Interpretation of Data

Close examination of the data revealed that among the ASI-MV participating substance abuse treatment sites, patients at ASI-MV sites in Tennessee appeared to have a disproportionately high number of cases of abuse of reformulated OPANA ER during the post-period versus all other states in the ASI-MV network (1250 cases versus 425 cases, respectively; Table 14). During the post-period, there were 10,432 prescription drug abusers in Tennessee versus 30,885 abusers in all other states in the network. Thus, within the ASI-MV network of sites, Tennessee contributes about 25% of prescription drug abusers, even though Tennessee represents 2% of the US population.

Table 14: Number of Assessments, ASI-MV Sites and States Within Tennessee and Contribution from All States Excluding Tennessee

	Total Study Period (Jan 2009 – Jun 2016)	3-Year Pre-period (Jan 2009 – Dec 2011)	18-Month Sensitivity Pre-period ^a (July 2010 – Dec 2011)	Post-period (Jul 2013 – Jun 2016)
ASI-MV Sites Within Tennessee				
No. of assessments	31,024	4,695	2,982	20,964
No. of ASI-MV sites	53	26	20	38
Total prescription opioid abusers	15,268	2,102	1,480	10,432
Total Original OPANA ER past 30-day abuse cases	1,112	400	353	N/A
Total Reformulated OPANA ER past 30-day abuse cases	1,545 ^b	N/A	N/A	1,250
ASI-MV Sites Excluding Tennessee				
No. of assessments	428,216	201,771	100,403	147,114
No. of ASI-MV sites	1,031	661	569	605
No. of states	39	35	33	36
Total prescription opioid abusers	84,216	37,706	19,930	30,885
Total Original OPANA ER past 30-day abuse cases	1,723	1,170	867	N/A
Total Reformulated OPANA ER past 30-day abuse cases	604	N/A	N/A	425

Source: NAVIPPRO Report [Table 4]

^a The 18-month sensitivity pre-period from July 2010 through December 2011 was used for sensitivity analyses and represents a period of time after introduction of an ADF oxycodone ER (reformulated OxyContin) and prior to introduction of Reformulated OPANA ER.

^b The number of past 30-day abuse cases for Reformulated OPANA ER for the total study period includes the count of abuse cases from the post-period as well as the transition period (not displayed in this table).

Further, there is a distinct difference in the number of reports originating in Tennessee versus all other states in the network in the pre-period compared to the post-period. In Tennessee, total past

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30-day abuse cases for OPANA ER increased from 400 to 1250 while in all other states, total past 30-day reports decreased from 1170 to 425 for the 3-year pre-period to the post-period.

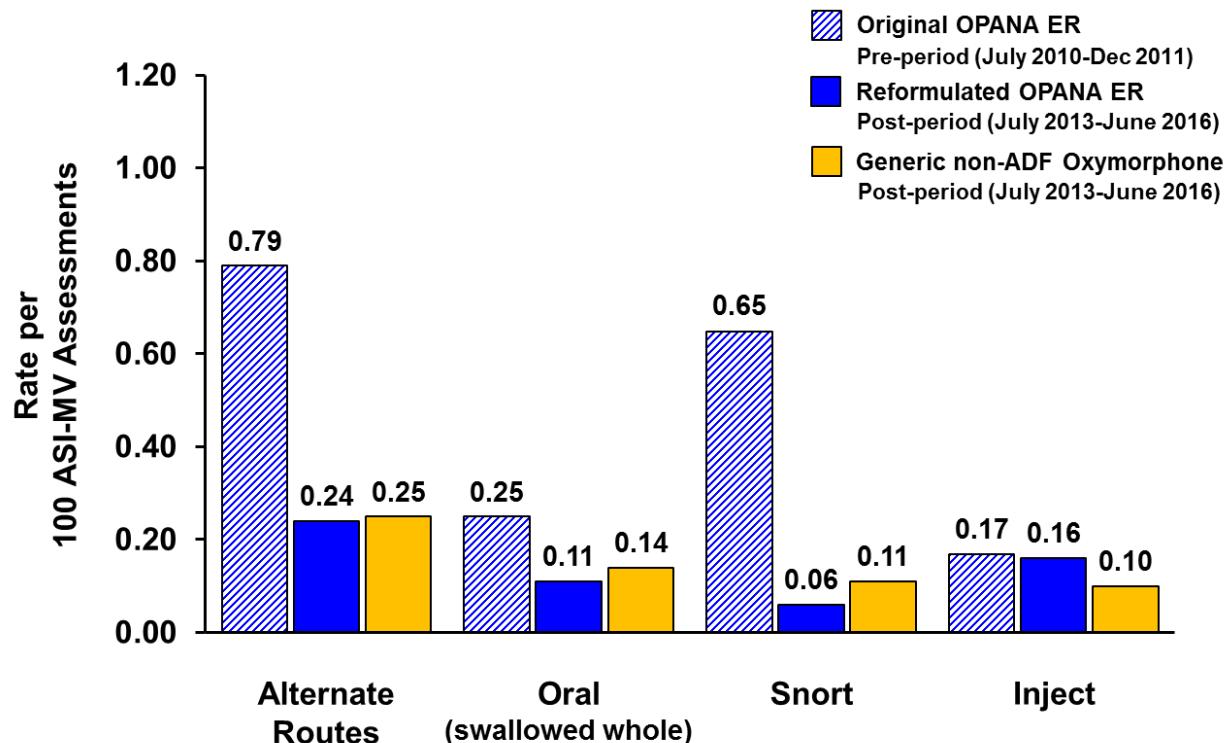
4.4.1.10. Abuse Rates in All States Except Tennessee

4.4.1.10.1. Abuse by Route of Administration: Sensitivity Pre-period Versus Post-period

In addition to the impact of Tennessee on the data, the baseline pre-period was not homogeneous due to the introduction of OxyContin ADF, which was temporally associated with a shift in the abuse pattern of OPANA ER. Therefore, the data for the prespecified sensitivity period are presented (July 2010 to December 2011) to demonstrate the shift in abuse during this time. The marked shift in the abuse pattern in the pre-period needs to be taken into consideration, when interpreting the data.

Overall, the rate of abuse of OPANA ER by alternate routes was higher in the Sensitivity Pre-period (July 2010 to December 2011) compared to the Post-period (July 2013 to June 2016) for the rate per 100 ASI-MV assessments (Figure 25). The rate of abuse for generic oxymorphone ER is similar or higher compared to reformulated OPANA ER, with the exception of intravenous abuse (0.16 per 100 ASI-MV assessments for OPANA ER versus 0.10 per 100 ASI-MV assessments for generic oxymorphone ER).

Figure 25: Prevalence Rates of Past 30-Day Abuse via Specific Routes of Administration for Original OPANA ER, Reformulated OPANA ER, and Generic oxymorphone ER per 100 ASI-MV Assessments, All States Except Tennessee, Sensitivity Pre-period vs Post-period

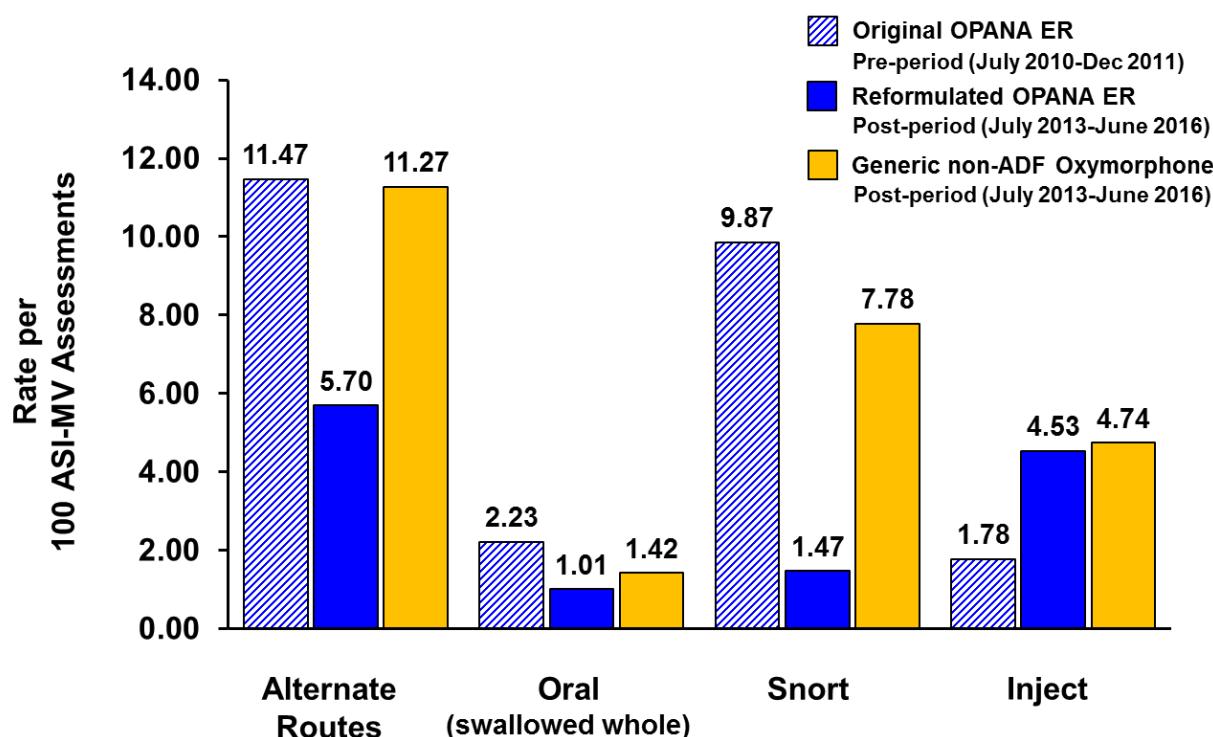


4.4.1.11. Abuse Rates for Tennessee Only

The prevalence rate of abuse by all alternate routes in Tennessee during the pre-period was higher compared to all other states (11.47 per 100 ASI-MV assessments in Tennessee vs 0.79 per 100 ASI-MV assessments in all other states) (Figure 26), suggesting that the rates of abuse in Tennessee are an anomaly.

Despite the higher rate of abuse in Tennessee, a similar pattern of reduction from the Sensitivity Pre-period to the Post-period for OPANA ER was seen for alternate routes, oral, and intranasal abuse. For intravenous abuse of OPANA ER, the prevalence was higher in the post-period. For generic oxymorphone ER, prevalence of abuse was higher than that for reformulated OPANA ER by all routes in Tennessee including intravenous abuse.

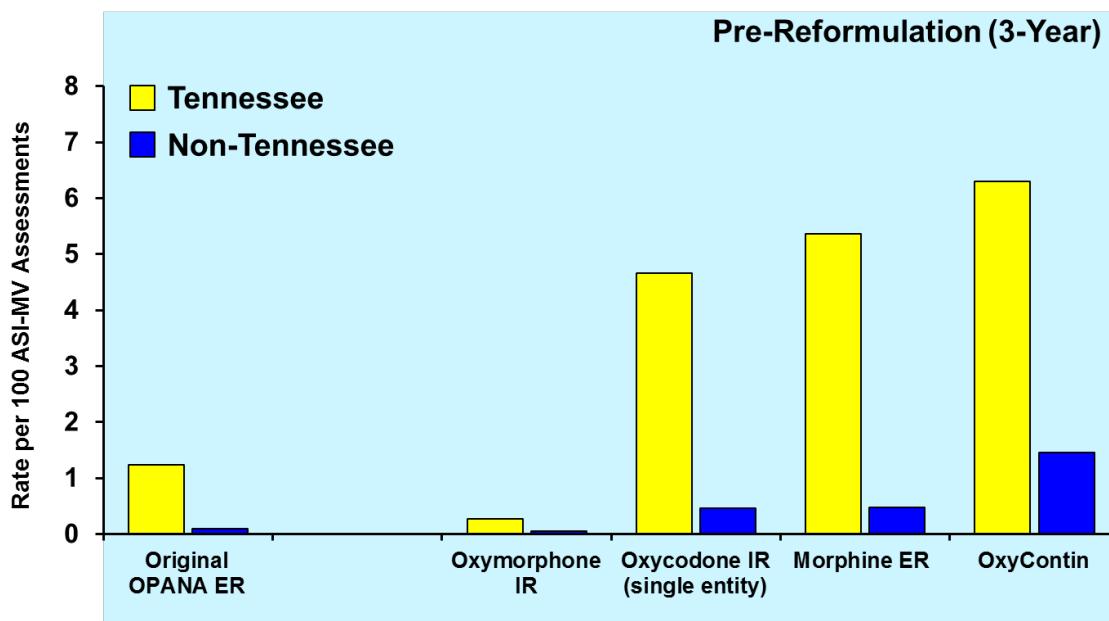
Figure 26: Prevalence Rates of Past 30-Day Abuse via Specific Routes of Administration for Original OPANA ER and Reformulated OPANA ER, per 100 ASI-MV Assessments, Tennessee Only, Sensitivity Pre-period vs Post-period



Even before the reformulation of OPANA ER, abuse by injection was high in Tennessee. Figure 27 shows the injection abuse rate in Tennessee for 5 different opioids monitored by the NAVIPPRO system during the year and a half immediately before the reformulation of OPANA ER. Injection rates for oxycodone IR, morphine ER, and OxyContin were all higher than for OPANA ER.

The contrast between Tennessee and all other states outside of Tennessee is even more evident when looking at the data for all other states for the same time period. The high rate of intravenous injection in Tennessee is in contrast to the remaining states in the network. It goes beyond OPANA ER and pre-dates the introduction of reformulated OPANA ER.

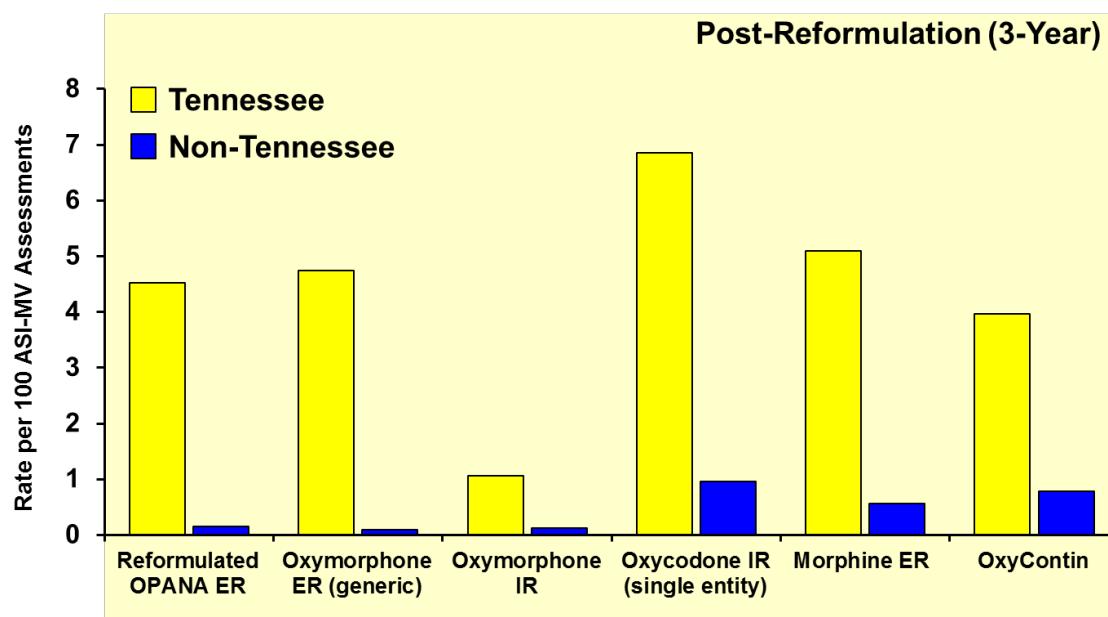
Figure 27: Rate of Injection Abuse in Tennessee Prior to the Reformulation of OPANA ER



After the reformulation of OPANA ER, injection rates are still high during the post-period ([Figure 28](#)). Injection rates for generic oxymorphone ER, oxycodone IR, and morphine ER are all higher than that for OPANA ER ([Figure 28](#)).

Looking at all states outside of Tennessee, the pattern is the same as previously. Oxycodone IR, morphine ER, and oxycodone ER are injected at a higher rate than OPANA ER outside of Tennessee during the post-period. Secondly, for any given drug, the injection rate is far lower outside of Tennessee than in that state.

Figure 28: Rate of Injection Abuse in Tennessee Following the Reformulation of OPANA ER



Clearly, prescription drug abuse in Tennessee follows a different pattern than in other regions. This tendency towards greater intravenous abuse in Tennessee has been documented in the NAVIPPRO system as far back as 2008, independent of the abuse of OPANA ER.⁽⁵⁸⁾ and before the reformulation of OPANA ER

This difference in Tennessee may also reflect a changing drug abuse ecology in the state with a trend towards more problematic abuse overall. Review of substance abuse characteristics among abusers of reformulated OPANA ER within Tennessee indicates a level of severity in abuse that may be greater than that observed in other states within the ASI-MV network and has changed over time.

Since the introduction of reformulated OPANA ER, 90% of abusers of reformulated OPANA ER in Tennessee were assessed as part of residential or inpatient settings compared to 67% during the pre-period. This increase in the use of a residential/inpatient setting is higher than in other states in the ASI-MV network. Additionally, more than 80% of abusers of reformulated OPANA ER in Tennessee had a history of injection of any prescription opioid upon entering treatment, which is higher when compared with other regions in the United States (Table 15). This suggests that the observed rates of intravenous abuse of OPANA ER in Tennessee may be influenced by a change in the underlying population of individuals coming into treatment or by a shift in the sample over time related to changes in the types of centers that subscribe to the ASI-MV. As an example of this latter point, during the post-period, 38 centers in Tennessee contributed abuse reports of OPANA ER to the ASI-MV network compared to 26 centers during the pre-period.

Table 15: Demographic Differences Between Tennessee and All Other States

	Tennessee		All Other States Except Tennessee	
	Pre-Reformulated OPANA ER (%) (n = 400)	Post-Reformulated OPANA ER (%) (n = 1,250)	Pre-Reformulated OPANA ER (%) (n = 1,170)	Post-Reformulated OPANA ER (%) (n = 425)
Modality				
Residential/Inpatient	67.0	88.5	29.0	40.5
Outpatient/Non-Methadone	17.5	7.6	44.2	20.0
Methadone/LAAM	1.0	0.0	7.2	6.1
Corrections	1.8	0.1	14.3	20.0
Other	12.8	3.8	5.4	13.4
Missing	0.0	0.0	0.0	0.0
History of injection of any drugs*				
Number of drugs injected (at least 1 drug)	50.0	83.2	52.8	75.3

*Any drugs within the ASI-MV dataset, not mutually exclusive.

4.4.2. Conclusions

The NAVIPPRO postmarketing epidemiology study evaluating abuse patterns of reformulated OPANA ER demonstrated the following findings:

- The rate of abuse by alternate routes of administration of OPANA ER across all states in the NAVIPPRO network was higher in the post-period compared to the pre-period.
 - By individual ROA, intranasal administration was lower and intravenous injection was higher.
- The rate of abuse by alternate routes of administration across all states in the NAVIPPRO network for non-crush-resistant generic oxymorphone ER was higher compared to reformulated OPANA ER in the post-period.
 - The rates of abuse by individual ROA for non-crush-resistant generic oxymorphone ER were higher for intranasal administration and similar for intravenous injection compared to reformulated OPANA ER.
- However, data from Tennessee have a disproportionate impact on the data for the entire NAVIPPRO reporting network and therefore appear to influence the reporting due to the fact that:
 - Tennessee contributes about 75% of abuse reports for OPANA ER to the overall abuse reports in the network during the post-period.
- By ROA the rate of abuse for OPANA ER via intranasal administration was lower and via injection remained stable in all states in the NAVIPPRO network except Tennessee. For Tennessee only, the rate of abuse via intranasal administration was lower and the rate of abuse via injection was higher.

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- For comparator opioids, the rate of abuse via intravenous injection in Tennessee was higher in the pre-period and remained high in the post-period compared to states outside of Tennessee.
 - Part of this change may be explained by a shift in the patient population to more severely affected individuals in the post-period or by a change in sampling over time based on a change in treatment centers included in the sample.

4.5. RADARS Poison Center Program

4.5.1. Design

The primary postmarketing epidemiology study of OPANA ER intentional abuse exposure mentions to poison centers participating in the RADARS System Poison Center had the objectives of determining if:

- Rates of OPANA ER intentional abuse case mentions declined following the introduction of reformulated OPANA ER in 1Q 2012.
- Rates of OPANA ER mentions of use through non-oral ROA by intentional abuse exposure cases declined following the introduction of reformulated OPANA ER in 1Q 2012 and, if so, this decline was different from declines in mentions of OPANA ER use through oral ROA by intentional abuse exposures.
- The rate of intentional abuse exposure cases reported to Poison Centers that resulted in a major outcome or death declined following introduction of reformulated OPANA ER.
- Rates of OPANA ER mentions resulting in overdose declined following the introduction of reformulated OPANA ER

The analyses were conducted using a comparison of means modeling approach that contrasts the following 3 time periods:

- Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER (pre-CRF): January 2009 to September 2010 (1Q 2009-3Q 2010, where 4Q 2010 is the first full quarter following release of reformulated OxyContin [ORF] in August 2010). This period takes the launch of reformulated OxyContin into consideration.
- Post-ORF/pre- reformulated OPANA ER (Pre-CRF): October 2010 through December 2011 (4Q 2010-4Q 2011). This is the period after ORF was introduced but prior to the reformulation of OPANA ER. This period aligns closely with the sensitivity period previously presented for the NAVIPPRO data.
- Post-ORF/post- reformulated OPANA ER (Post-CRF): This period includes quarters after the reformulation of OPANA ER and after various generic ER oxymorphone products were introduced. This period includes July 2013 through June 2016 (3Q 2013-2Q 2016), which aligns with the post-period in the NAVIPPRO data set.

A transition period defined as January 2012 through June 2013 (1Q 2012-2Q 2013) was excluded from the analysis per FDA request since several changes occurred in the oxymorphone

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market in 2012 through mid-year 2013. These changes included the introduction of reformulated OPANA ER in February 2012 in addition to the introduction of generic versions.

4.5.1.1. Methods

This protocol examined differences in product mentions before and after introduction of reformulated OPANA ER using 2 different denominators as follows:

- **Population data** based on information made available from the 2010 US Census. Each population rate was calculated by dividing the sum of the cases by the sum of the population across 3-digit ZIP codes covered by the Drug Diversion Program. This value was scaled per 100,000 population.
- **Units dispensed** at the 3-digit ZIP code level for OPANA ER and all comparator groups. For a given year-quarter, the total dosage units in the 3-digit ZIP codes covered by the RADARS System Programs for the entire analysis period was computed and these numbers used as the denominators to calculate product availability rates. All rates were scaled per 100,000 dosage units dispensed.

4.5.1.1.1. Definitions

Intentional Abuse Exposures were defined as “an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect.”

Route of administration by intentional abuse exposure cases: If it was reported that a case “took” a drug, then the intended ROA was assigned. Due to low mention counts for injection and inhalation use of OPANA ER in the Poison Center Program, ROA was classified as oral (swallowing whole) or non-oral (injection, inhalation, chewed prior to swallowing) for these analyses. Non-oral was assigned when there was sufficient data to make that determination during case review.

Major Medical Outcomes and Deaths: Deaths from cases where an inquiry was initially placed at a regional poison center, regardless of reason for exposure, were summarized. As deaths are sparse in the Poison Center Program, deaths and major medical outcomes were combined. Major medical outcomes are defined in the National Poison Data System as “The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.”

Overdose was defined as the total of intentional exposures, therapeutic errors, and unintentional general exposures.

4.5.1.2. Planned Analyses

Planned analyses examined changes in Poison Center mentions of OPANA ER per population, and dosage units dispensed. The OPANA ER drug category included reports of both the original OPANA ER and reformulated OPANA ER. Changes in OPANA ER between time periods were compared to 2 other opioid groups: ER morphine and single-entity (SE) IR oxymorphone. ER morphine included branded (eg, MS Contin[®], EMBEDA[®]) and generic ER morphine tablets and capsules. Other formulations (eg, solutions) were not included. ER morphine was included as a

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comparator because it displays similar proportions of unintended route use among treatment center samples as OPANA ER. ER morphine is also an ER opioid formulation with a stable number of prescriptions during the analysis period. Any secular changes in the abuse of ER opioids would be identified with this comparator. SE IR oxymorphone included branded (eg, OPANA) and generic IR oxymorphone products according to protocol. This comparator was used because it contains the same active ingredient as OPANA ER but in an IR formulation. Note that rate per dosage units dispensed may show wide variability due to the inclusion of different formulations. Data for the comparators are shown in [Appendix 5](#).

The primary analysis used a cohort of 43 poison centers that contributed data through every quarter of the study. A sensitivity analysis was conducted for all analyses and included data from all participating poison centers.

Details with regard to prespecified analyses are provided in [Appendix 4](#).

Modeling

Briefly, data was analyzed for the individual objectives using Poisson regression analyses and is presented with the following approach:

- Comparison of Means Model: the mean rate of the outcome variable (unique product mentions by exposure cases defined above) was compared to the mean rate of the outcome variable in other time periods.

The outcome variable is regressed on an indicator variable representing the 3 time periods, the 3 drug groups, and a drug group by time period effect. Data are presented as the percentage change. The percentage change is calculated by subtracting the rate ratio by 1 and multiplying this value by 100. The drug group by time period effect represents the difference in the change in rates from the reference period. In analyses of ROA, an indicator variable for ROA substitutes for the drug group variable.

A drug group-specific dispersion parameter is included to allow variances to differ across drug groups. In models comparing ROA, the dispersion parameter is ROA specific.

4.5.2. Strengths and Limitations

The strengths of the RADARS System Poison Center Program include extensive national coverage (90.2%) of 2010 US population. Data for numerators and denominators are obtained with geographic specificity. The RADARS system data are available within 3 months of data capture allowing for rapid recognition of trends. Numerator data are product specific allowing for the isolation of the effect of OPANA ER from other opioids and other oxymorphone products. Data are quality reviewed against case notes to ensure proper product identification, reason for exposure, ROA, and medical outcome. Changes in rates over time have been shown to be sensitive indicators of product formulation changes.

A limitation of the research methods is that poison centers collect data on spontaneous reports which are subject to reporting bias. Not all persons ingesting a prescription opioid and experiencing an adverse effect will call a poison center. In this sense, the rates obtained are likely underestimates of the true rates of adverse effects. However, there is no reason to expect that this bias will differ over time, thus making the trend data valuable.

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These data do have notable limitations. Poison centers collect only a fraction of all product exposures. In fact, the greatest source of loss of information is likely from cases that are taken directly to emergency facilities for treatment. In those instances, since professional case management is available, there is no need to consult a poison center and such information about an ingestion would not be captured by the RADARS system. In addition, information on product specific ROA is missing in more than 20% of OPANA ER abuse exposures. Finally, ROA was not reviewed by trained poison center staff until 2010. These factors reduce the power of these analyses and limit the ability to determine if changes are clinically meaningful. Another limitation is that callers to poison centers may report use of a branded product even though the exposure involved a generic version. Given the utilization of generic ER oxymorphone products increased following the reformulation of OPANA ER, the OPANA ER rates in the post-ORF/post-CRF period could be inflated due to misclassification of generic products as branded.

4.5.3. Results

Similar to the results presented for NAVIPPRO, the focus of the results should be on the data from the post-reformulation period for both OPANA ER and OxyContin (the Post-ORF/Post-CRF period of July 2013-June 2016) compared to the period after reformulation of OxyContin but prior to reformulation of OPANA ER (the Post-ORF/Pre-CRF period of October 2010 through December 2011), which aligns closely with the sensitivity pre-period (July 2010 to December 2011) presented for the NAVIPPRO data. The data for the sensitivity period are presented since the baseline period was not homogeneous due to the introduction of the ADF formulation of OxyContin ER, which was temporally associated with a shift in the abuse pattern of OPANA ER which needs to be taken into consideration when interpreting the data.

Of note, comparison data for oxymorphone IR are not presented because abuse, overdose, major medical outcome, and death case mentions are low for these comparators. Therefore changes should be interpreted with caution. Further, the analysis only included mentions of OPANA ER, and not generic oxymorphone ER.

4.5.3.1. Intentional Abuse Exposure

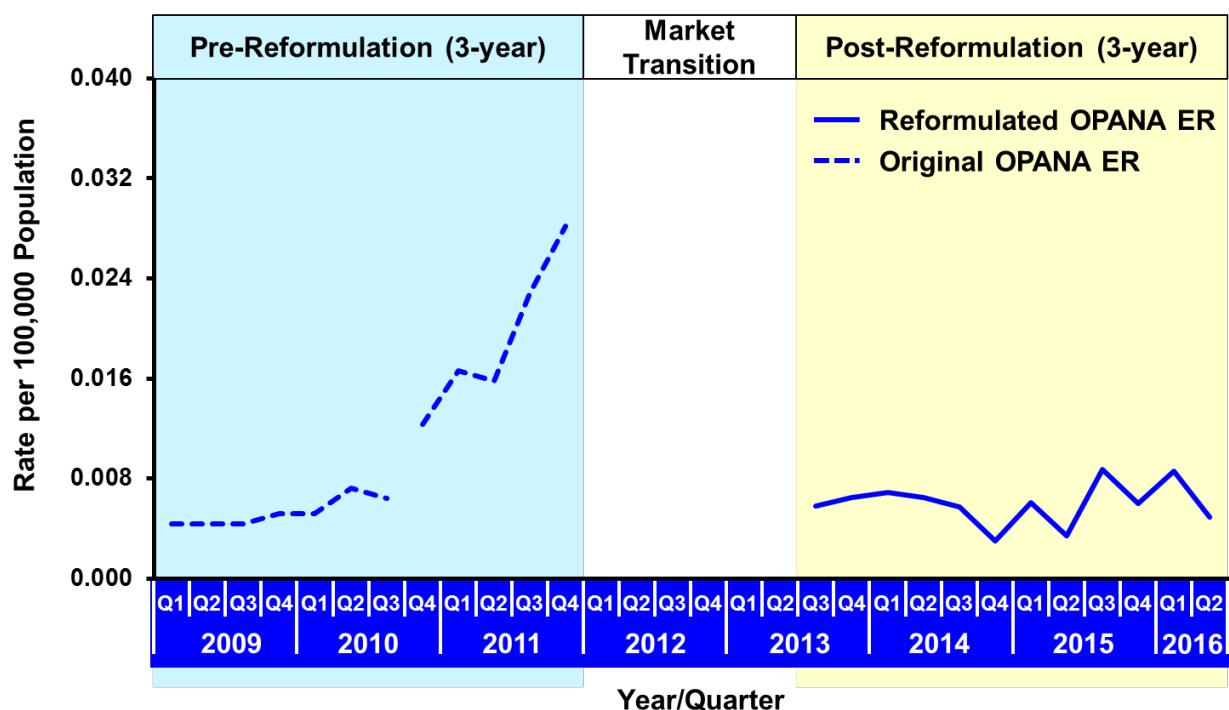
4.5.3.1.1. Intentional Abuse Exposure Rate Changes

Following the introduction of reformulated OPANA ER (ie, in the Post-ORF/Post-CRF time period), the intentional abuse exposure rate was 0.0060 per 100,000 population compared to 0.0192 per 100,000 population during the Post-ORF/Pre-CRF time period ([Figure 29](#)). [Table 16](#) displays the intentional abuse exposure rate per 100,000 population by time period using the comparison of means model. Results of the analysis by rate per 100,000 dosing units dispensed were consistent with these findings. The rate was 0.1979 per 100,000 tablets during the Post-ORF/Post-CRF period compared to 0.3356 per 100,000 tablets during the Post-ORF/Pre-CRF time period. ([Figure 30, Table 17](#)).

Data for the comparators ER Morphine and SE IR oxymorphone are presented in Appendix 5 ([Table 5-1](#) per 100,000 population and in [Table 5-2](#) per 100,000 dosing units dispensed).

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Figure 29: Quarterly Intentional Abuse Exposure Rate of OPANA ER per 100,000 Population, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.1.1.1]

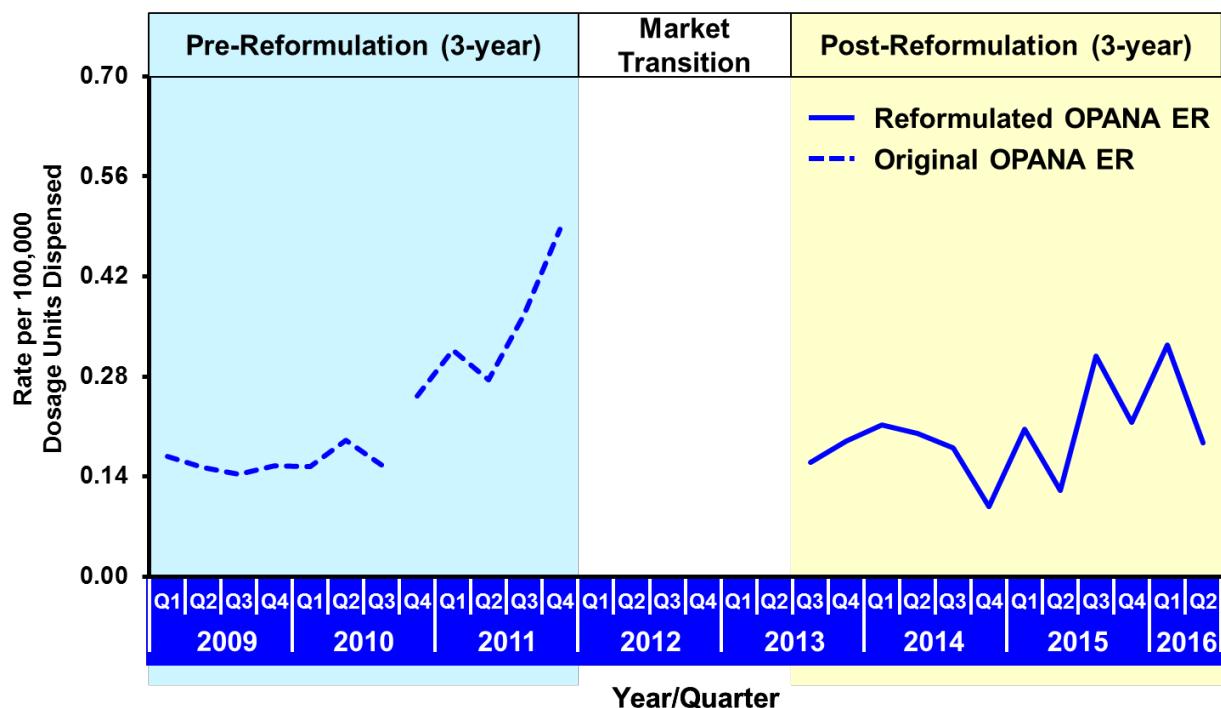
Table 16: Intentional Abuse Exposure Rate of OPANA ER per 100,000 Population, Percent Change, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage Change (95% CI)
Pre-ORF/Pre-CRF	0.0053 (0.0040, 0.0070)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	12.7% (-19.5%, 57.9%)
Post-ORF/Pre-CRF	0.0192 (0.0161, 0.0227)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	260.0% (160.2%, 398.2%)
Post-ORF/Post-CRF	0.0060 (0.0049, 0.0073)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-68.7% (-75.8%, -59.5%)

Source: RADARS Poison Center Program Report [Table 4.1.1.1]

CRF=Crush-resistant formulation; ORF=Reformulated OxyContin

Figure 30: Quarterly Intentional Abuse Exposure Rate of OPANA ER per 100,000 Dosing Units, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.1.1.3]

Table 17: Intentional Abuse Exposure Rate of OPANA ER per 100,000 Dosing Units Dispensed, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage Change (95% CI)
Pre-ORF/Pre-CRF	0.1604 (0.1268, 0.2029)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	23.4% (-7.3%, 64.4%)
Post-ORF/Pre-CRF	0.3356 (0.2902, 0.3881)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	109.3% (58.7%, 175.9%)
Post-ORF/Post-CRF	0.1979 (0.1679, 0.2333)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-41.0% (-52.6%, -26.5%)

Source: RADARS Poison Center Program Report [Table 4.1.1.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

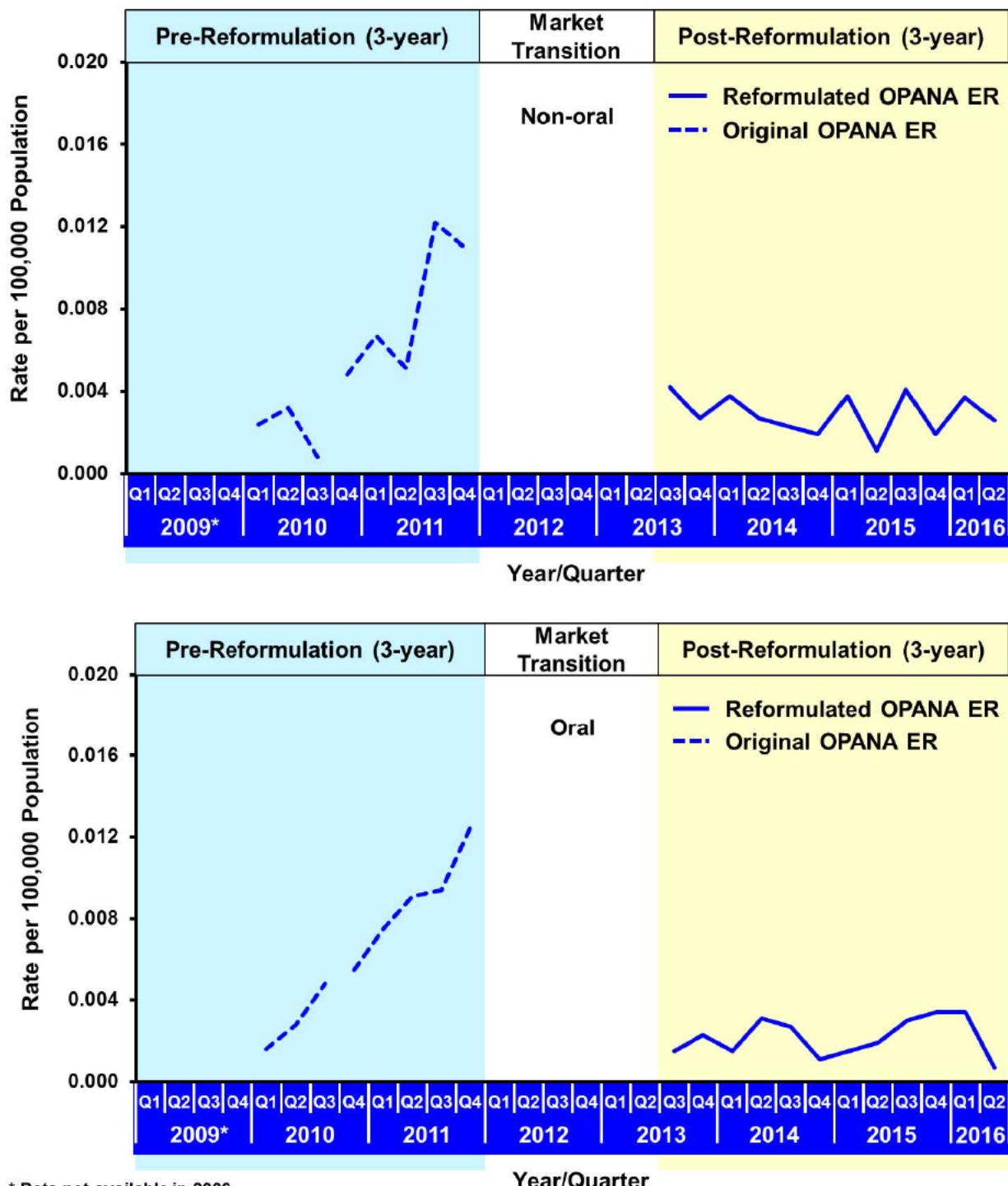
4.5.3.1.2. Intentional Abuse Case Exposure by Route of Administration (Oral vs Non-Oral)

The mean OPANA ER oral ROA abuse rate in the Post-ORF/Post-CRF period was lower (0.0029 per 100,000 population) compared to the mean Post-ORF/Pre-CRF rate (0.0088 per 100,000 population) (Figure 31, Table 18) and for the rate per 100,000 dosing units dispensed (0.0719 versus 0.1547 per 100,000 dosing units) (Figure 32, Table 19).

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Similarly, the mean OPANA ER non-oral ROA abuse rate in the Post-ORF/Post-CRF period was lower (0.0029 per 100,000 population) compared to the mean Post-ORF/Pre-CRF rate for the per population rate (0.0080 per 100,000 population) ([Table 18](#)) and for the rate per 100,000 dosing units dispensed (0.0958 versus 0.1395 per 100,000 dosing units) ([Figure 32](#), [Table 19](#)).

Figure 31: Intentional Abuse Exposure Mentions of OPANA ER by Route of Administration (Non-oral and Oral) per 100,000 Population, January 2010 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.2.1.1]

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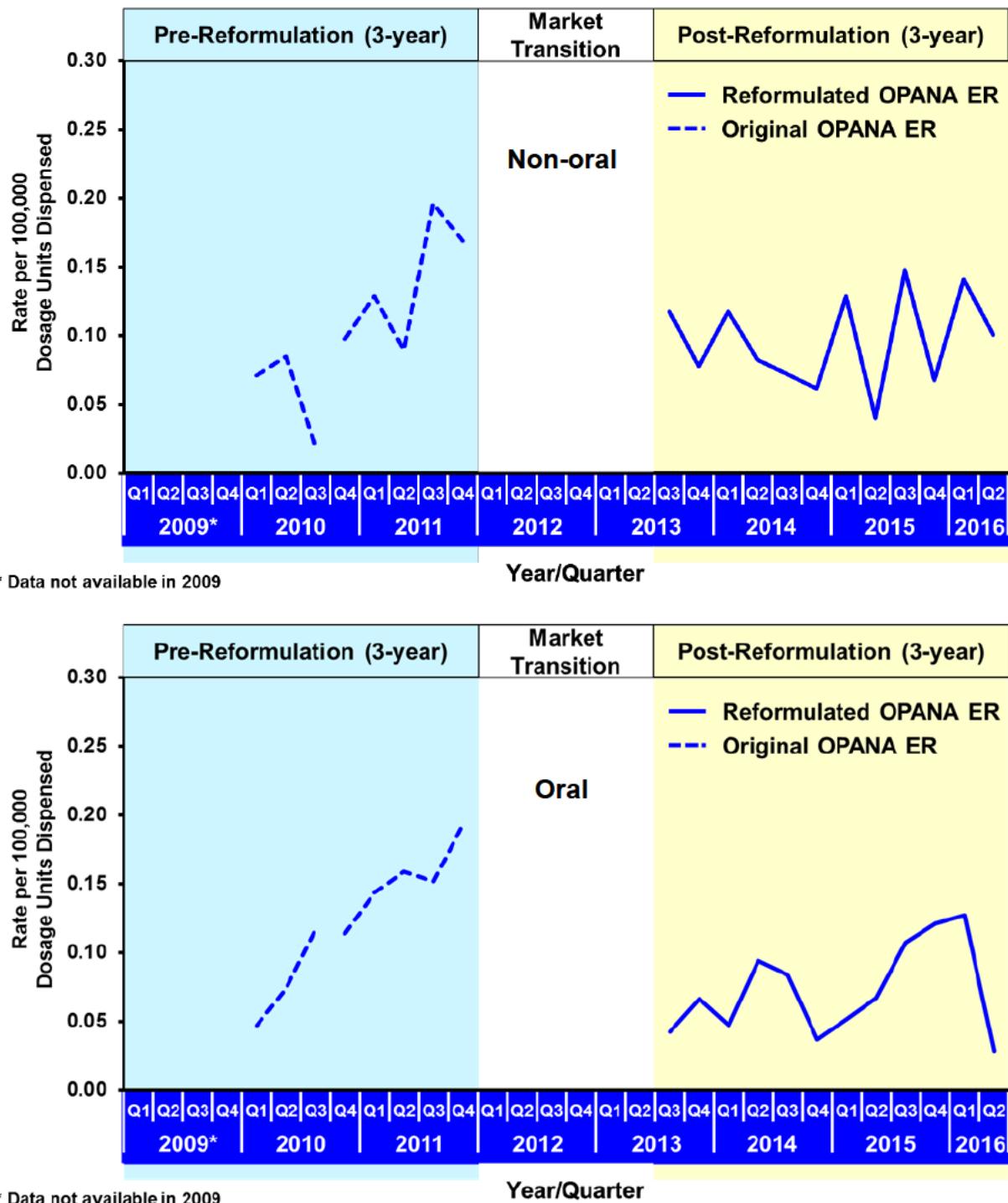
Table 18: Intentional Abuse Exposure Mentions of OPANA ER by Route of Administration per 100,000 Population, Percent Change, January 2010 to June 2016 – Comparison of Means Model

Route	Period	Estimate (95% CI)	Comparison	Percent Change (95% CI)
Non-oral	Pre-ORF/ Pre-CRF	0.0021 (0.0011,0.0040)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	36.6% (-31.5%, 172.7%)
	Post-ORF/ Pre-CRF	0.0080 (0.0062,0.0103)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	274.5% (88.5%, 644.0%)
	Post-ORF/ Post-CRF	0.0029 (0.0022,0.0038)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-63.5% (-74.7%,-47.3%)
Oral	Pre-ORF/ Pre-CRF	0.0031 (0.0019,0.0049)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-28.7% (-58.8%, 23.3%)
	Post-ORF/ Pre-CRF	0.0088 (0.0071,0.0109)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	188.9% (71.6%, 386.5%)
	Post-ORF/ Post-CRF	0.0022 (0.0017,0.0029)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-75.3% (-82.6%,-65.0%)

Source: RADARS Poison Center Program Report [Table 4.2.1.1]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

Figure 32: Intentional Abuse Exposure Mentions of OPANA ER by Route of Administration (Non-oral and Oral) per 100,000 Dosing Units, January 2010 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.2.1.3]

Table 19: Intentional Abuse Exposure Mentions of OPANA ER by Route of Administration per 100,000 Dosing Units Dispensed, Percent Change, January 2010 to June 2016 – Comparison of Means Model

Route	Period	Estimate (95% CI)	Comparison	Percent Change (95% CI)
Non-oral	Pre-ORF/ Pre-CRF	0.0568 (0.0320,0.1009)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	68.8% (-9.4%, 214.5%)
	Post-ORF/ Pre-CRF	0.1395 (0.1110,0.1753)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	145.6% (32.3%, 355.9%)
	Post-ORF/ Post-CRF	0.0958 (0.0754,0.1218)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-31.3% (-50.7%,-4.3%)
Oral	Pre-ORF/ Pre-CRF	0.0816 (0.0530,0.1257)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-12.0% (-46.5%, 44.9%)
	Post-ORF/ Pre-CRF	0.1547 (0.1272,0.1881)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	89.5% (18.0%, 204.3%)
	Post-ORF/ Post-CRF	0.0719 (0.0560,0.0922)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-53.5% (-66.1%,-36.2%)

Source: RADARS Poison Center Program Report [Table 4.2.1.3]

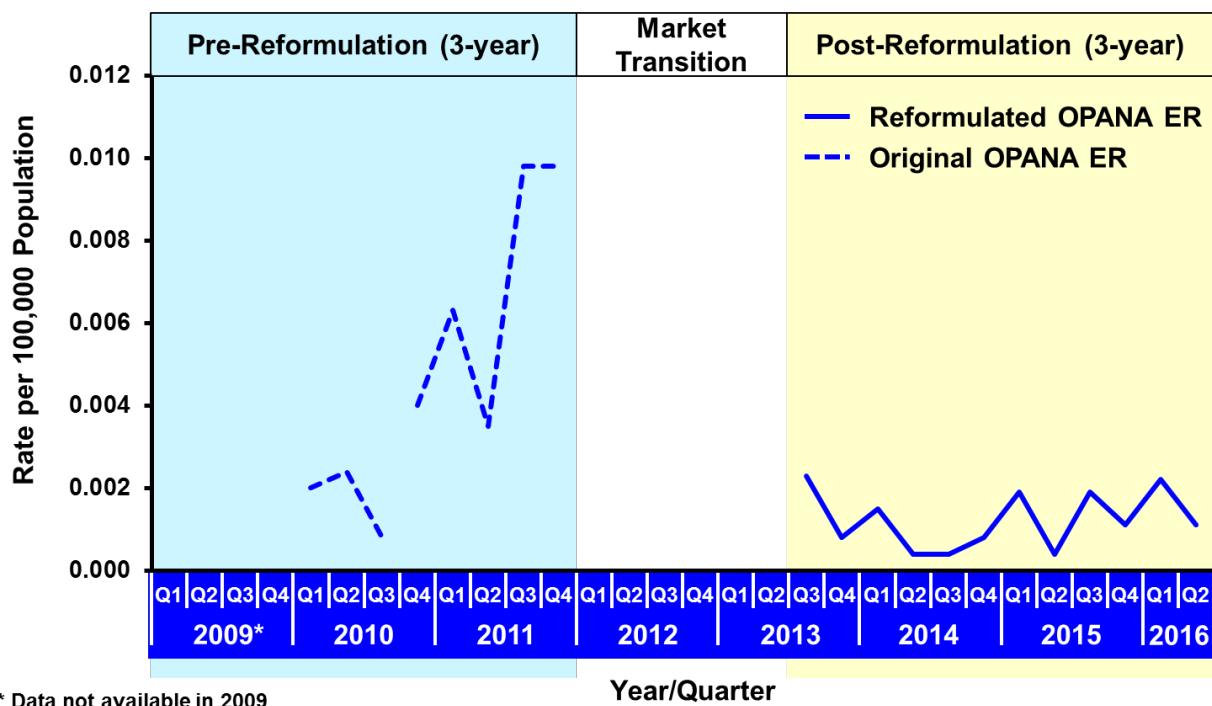
CRF=Crush resistant formulation; ORF=Reformulated OxyContin

4.5.3.1.3. Intentional Abuse Case Exposure by Inhalation and Injection

Looking with more detail at the non-oral ROA, abuse by inhalation mentions was high at the end of the post-ORF/pre-CRF period, but was lower during the post-ORF/post-CRF period. This is demonstrated for the 2 denominators of population ([Figure 33](#) and [Table 20](#)) and dosing units dispensed ([Figure 34](#)).

Overall, injection mentions were generally low at all time points both during the post-ORF/pre-CRF period and the post-ORF/post-CRF period (between 3 and 6 mentions per quarter). The population rates are shown in [Figure 35](#) and [Table 22](#). Because of a marked decline in dosing units dispensed, the temporal pattern of intravenous mentions when denominated by tablets dispensed shows an increase in the Post-ORF/Post-CRF period but could represent unstable values because of the low mentions.

Figure 33: OPANA ER Intentional Abuse Exposure Mentions via Inhalation per 100,000 Population - Quarterly Rates from January 2010 through June 2016



* Data not available in 2009

Source: RADARS Poison Center Program Report Information Amendment 1 [Figure 3.1.3.1]

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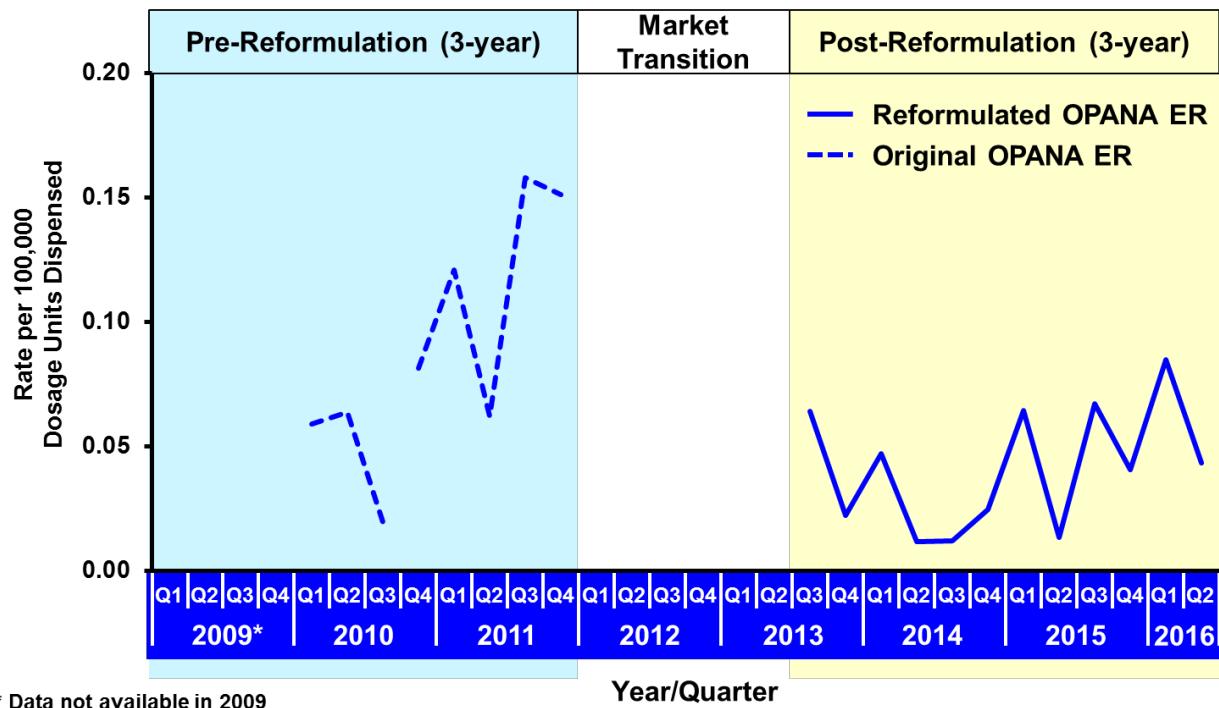
Table 20: OPANA ER Intentional Abuse Exposure Mentions via Inhalation per 100,000 Population - Quarterly Rates from January 2010 through June 2016

Period	Number of Centers Participating	Year-Quarter	Number of Mentions	Population Covered	Population Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	1Q2010	5	250,171,020.40	0.0020 (0.0006,0.0047)
	43	2Q2010	6	250,846,976.00	0.0024 (0.0009,0.0052)
	43	3Q2010	2	251,554,728.71	0.0008 (0.0001,0.0029)
Post-ORF/Pre-CRF	43	4Q2010	10	252,262,481.43	0.0040 (0.0019,0.0073)
	43	1Q2011	16	252,970,234.14	0.0063 (0.0036,0.0103)
	43	2Q2011	9	253,677,986.85	0.0035 (0.0016,0.0067)
	43	3Q2011	25	254,385,739.56	0.0098 (0.0064,0.0145)
	43	4Q2011	25	255,093,492.28	0.0098 (0.0063,0.0145)
Post-ORF/Post-CRF	43	3Q2013	6	260,047,761.26	0.0023 (0.0008,0.0050)
	43	4Q2013	2	260,755,513.98	0.0008 (0.0001,0.0028)
	43	1Q2014	4	261,463,266.69	0.0015 (0.0004,0.0039)
	43	2Q2014	1	262,171,019.40	0.0004 (0.0000,0.0021)
	43	3Q2014	1	262,878,772.11	0.0004 (0.0000,0.0021)
	43	4Q2014	2	263,586,524.83	0.0008 (0.0001,0.0027)
	43	1Q2015	5	264,294,277.54	0.0019 (0.0006,0.0044)
	43	2Q2015	1	265,002,030.25	0.0004 (0.0000,0.0021)
	43	3Q2015	5	265,709,782.96	0.0019 (0.0006,0.0044)
	43	4Q2015	3	266,417,535.68	0.0011 (0.0002,0.0033)
	43	1Q2016	6	267,125,288.39	0.0022 (0.0008,0.0049)
	43	2Q2016	3	267,833,041.10	0.0011 (0.0002,0.0033)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 3.1.3.1.]
CRF=Crush resistant formulation; ORF=Reformulated OxyContin

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Figure 34: OPANA ER Intentional Abuse Exposure Mentions via Inhalation per 100,000 Dosing Units - Quarterly Rates from January 2010 through June 2016



Source: RADARS Poison Center Program Report Information Amendment 1 [Figure 3.1.3.3]

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Table 21: OPANA ER Intentional Abuse Exposure Mentions via Inhalation per 100,000 Dosage Units Dispensed - Quarterly Rates from January 2010 through June 2016

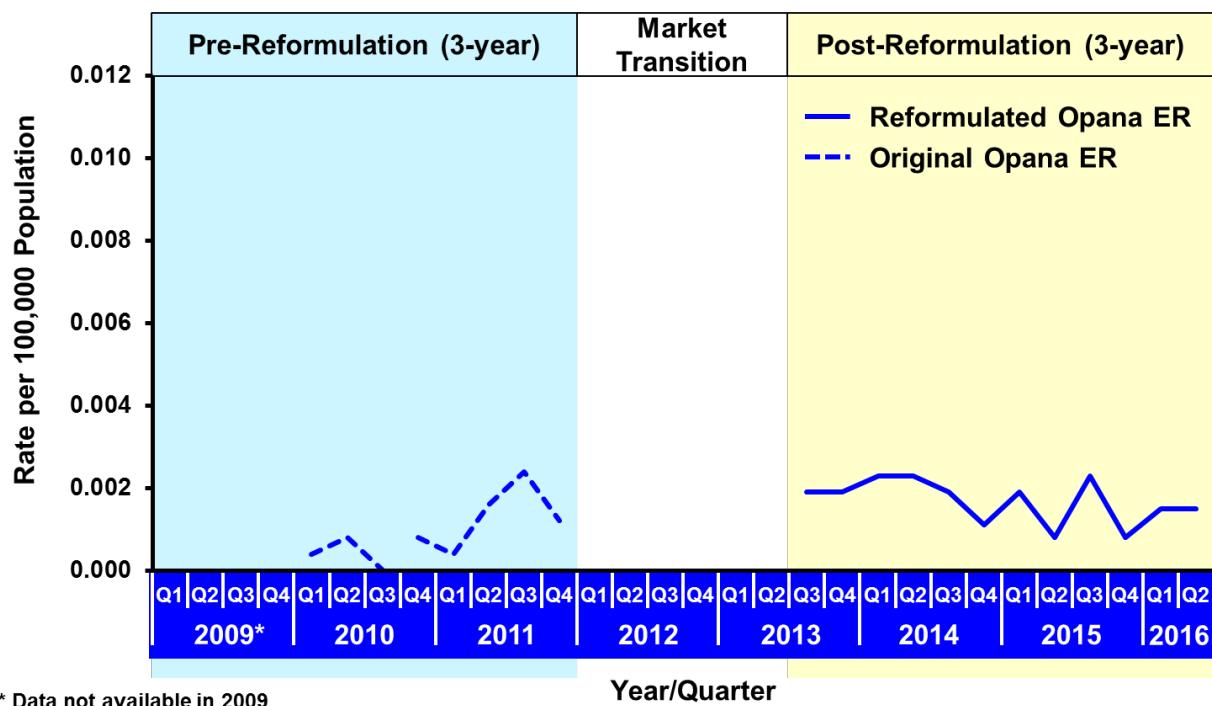
Period	Number of Centers Participating	Year-Quarter	Number of Mentions	Dosage Units Dispensed Covered	Dosage Units Dispensed per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	1Q2010	5	8,471,197.86	0.0590 (0.0192,0.1377)
	43	2Q2010	6	9,422,800.27	0.0637 (0.0234,0.1386)
	43	3Q2010	2	10,277,231.57	0.0195 (0.0024,0.0703)
Post-ORF/Pre-CRF	43	4Q2010	10	12,280,431.16	0.0814 (0.0390,0.1498)
	43	1Q2011	16	13,228,628.80	0.1209 (0.0691,0.1964)
	43	2Q2011	9	14,505,052.19	0.0620 (0.0284,0.1178)
	43	3Q2011	25	15,827,574.66	0.1580 (0.1022,0.2332)
	43	4Q2011	25	16,560,848.65	0.1510 (0.0977,0.2228)
Post-ORF/Post-CRF	43	3Q2013	6	9,370,992.54	0.0640 (0.0235,0.1394)
	43	4Q2013	2	8,990,973.90	0.0222 (0.0027,0.0804)
	43	1Q2014	4	8,502,778.12	0.0470 (0.0128,0.1204)
	43	2Q2014	1	8,495,817.31	0.0118 (0.0003,0.0656)
	43	3Q2014	1	8,332,029.11	0.0120 (0.0003,0.0669)
	43	4Q2014	2	8,120,391.53	0.0246 (0.0030,0.0890)
	43	1Q2015	5	7,764,100.97	0.0644 (0.0209,0.1503)
	43	2Q2015	1	7,483,666.60	0.0134 (0.0003,0.0745)
	43	3Q2015	5	7,453,463.20	0.0671 (0.0218,0.1565)
	43	4Q2015	3	7,430,213.05	0.0404 (0.0083,0.1180)
	43	1Q2016	6	7,093,310.98	0.0846 (0.0310,0.1841)
	43	2Q2016	3	6,946,705.98	0.0432 (0.0089,0.1262)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 3.1.3.3.]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

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Figure 35: OPANA ER Intentional Abuse Exposure Mentions via Injection per 100,000 Population - Quarterly Rates from January 2010 through June 2016



* Data not available in 2009

Source: RADARS Poison Center Program Report Information Amendment 1 [Figure 3.1.2.1]

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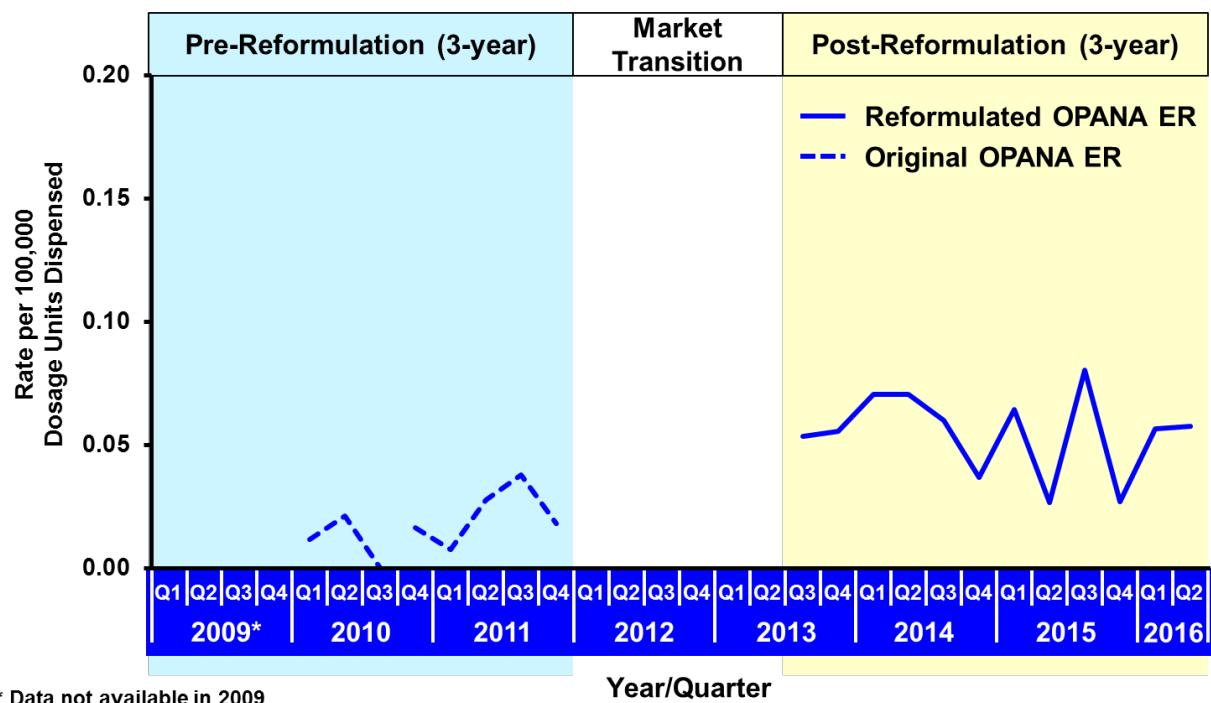
Table 22: OPANA ER Intentional Abuse Exposure Mentions via Injection per 100,000 Population - Quarterly Rates from January 2010 through June 2016

Period	Number of Centers Participating	Year-Quarter	Number of Mentions	Population Covered	Population Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	1Q2010	1	250,171,020.40	0.0004 (0.0000,0.0022)
	43	2Q2010	2	250,846,976.00	0.0008 (0.0001,0.0029)
	43	3Q2010	0	251,554,728.71	0.0000 (0.0000,0.0015)
Post-ORF/Pre-CRF	43	4Q2010	2	252,262,481.43	0.0008 (0.0001,0.0029)
	43	1Q2011	1	252,970,234.14	0.0004 (0.0000,0.0022)
	43	2Q2011	4	253,677,986.85	0.0016 (0.0004,0.0040)
	43	3Q2011	6	254,385,739.56	0.0024 (0.0009,0.0051)
	43	4Q2011	3	255,093,492.28	0.0012 (0.0002,0.0034)
Post-ORF/Post-CRF	43	3Q2013	5	260,047,761.26	0.0019 (0.0006,0.0045)
	43	4Q2013	5	260,755,513.98	0.0019 (0.0006,0.0045)
	43	1Q2014	6	261,463,266.69	0.0023 (0.0008,0.0050)
	43	2Q2014	6	262,171,019.40	0.0023 (0.0008,0.0050)
	43	3Q2014	5	262,878,772.11	0.0019 (0.0006,0.0044)
	43	4Q2014	3	263,586,524.83	0.0011 (0.0002,0.0033)
	43	1Q2015	5	264,294,277.54	0.0019 (0.0006,0.0044)
	43	2Q2015	2	265,002,030.25	0.0008 (0.0001,0.0027)
	43	3Q2015	6	265,709,782.96	0.0023 (0.0008,0.0049)
	43	4Q2015	2	266,417,535.68	0.0008 (0.0001,0.0027)
	43	1Q2016	4	267,125,288.39	0.0015 (0.0004,0.0038)
	43	2Q2016	4	267,833,041.10	0.0015 (0.0004,0.0038)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 3.1.2.1.]
CRF=Crush resistant formulation; ORF=Reformulated OxyContin

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Figure 36: OPANA ER Intentional Abuse Exposure Mentions via Injection per 100,000 Dosing Units - Quarterly Rates from January 2010 through June 2016



Source: RADARS Poison Center Program Report Information Amendment 1 [Figure 3.1.2.3]

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Table 23: OPANA ER Intentional Abuse Exposure Mentions via Injection per 100,000 Dosing Units - Quarterly Rates from January 2010 through June 2016

Period	Number of Centers Participating	Year-Quarter	Number of Mentions	Dosage Units Dispensed Covered	Dosage Units Dispensed Per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	1Q2010	1	8,471,197.86	0.0118 (0.0003,0.0658)
	43	2Q2010	2	9,422,800.27	0.0212 (0.0026,0.0767)
	43	3Q2010	0	10,277,231.57	0.0000 (0.0000,0.0359)
Post-ORF/Pre-CRF	43	4Q2010	2	12,280,431.16	0.0163 (0.0020,0.0588)
	43	1Q2011	1	13,228,628.80	0.0076 (0.0002,0.0421)
	43	2Q2011	4	14,505,052.19	0.0276 (0.0075,0.0706)
	43	3Q2011	6	15,827,574.66	0.0379 (0.0139,0.0825)
	43	4Q2011	3	16,560,848.65	0.0181 (0.0037,0.0529)
Post-ORF/Post-CRF	43	3Q2013	5	9,370,992.54	0.0534 (0.0173,0.1245)
	43	4Q2013	5	8,990,973.90	0.0556 (0.0181,0.1298)
	43	1Q2014	6	8,502,778.12	0.0706 (0.0259,0.1536)
	43	2Q2014	6	8,495,817.31	0.0706 (0.0259,0.1537)
	43	3Q2014	5	8,332,029.11	0.0600 (0.0195,0.1400)
	43	4Q2014	3	8,120,391.53	0.0369 (0.0076,0.1080)
	43	1Q2015	5	7,764,100.97	0.0644 (0.0209,0.1503)
	43	2Q2015	2	7,483,666.60	0.0267 (0.0032,0.0965)
	43	3Q2015	6	7,453,463.20	0.0805 (0.0295,0.1752)
	43	4Q2015	2	7,430,213.05	0.0269 (0.0033,0.0972)
	43	1Q2016	4	7,093,310.98	0.0564 (0.0154,0.1444)
	43	2Q2016	4	6,946,705.98	0.0576 (0.0157,0.1474)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 3.1.2.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

4.5.3.1.4. Intentional Abuse Case Exposure in Tennessee and All States Except Tennessee

The rate of OPANA ER intentional abuse exposure mentions per 100,000 population by quarter and time period is displayed in Table 24 for Tennessee and in Table 25 for all states except Tennessee. In each time period, the rate of abuse in Tennessee was higher than in all states except Tennessee. In Tennessee, the rate of intentional abuse exposures in the Post-ORF/Post-CRF period was similar to that immediately before the reformulation of OPANA ER (the Post-ORF/Pre-CRF period). In all states except Tennessee, the rate of intentional abuse exposures in the Post-ORF/Post-CRF period was lower compared to that immediately before the reformulation of OPANA ER (the Post-ORF/Pre-CRF period). This pattern in the RADARS poison center data is similar to that in the NAVIPPRO data, reaffirming the fact that Tennessee is an outlier.

Table 24: OPANA ER Intentional Abuse Exposure Mentions per 100,000 Population in Tennessee - Mean Rates from January 2009 through June 2016

Period	Number of Centers Participating	Number of Quarters Covered	Number of Mentions	Population Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	3	7	7	0.0159 (0.0064,0.0327)
Post-ORF/Pre-CRF	2	5	17	0.0530 (0.0309,0.0848)
Post-ORF/Post-CRF	2	12	40	0.0497 (0.0355,0.0677)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 4.1.1]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

Table 25: OPANA ER Intentional Abuse Exposure Mentions per 100,000 Population in All States Except Tennessee - Mean Rates from January 2009 through June 2016

Period	Number of Centers Participating	Number of Quarters Covered	Number of Mentions	Population Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	7	86	0.0050 (0.0040,0.0062)
Post-ORF/Pre-CRF	43	5	226	0.0183 (0.0160,0.0208)
Post-ORF/Post-CRF	43	12	150	0.0049 (0.0041,0.0057)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 4.2.1]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

The rate of OPANA ER intentional abuse exposure mentions per dosing units dispensed is higher in Tennessee ([Table 26](#)) and lower outside of Tennessee ([Table 27](#)) during the Post-ORF/Post-CRF period compared to the Post-ORF/Pre-CRF period. Again, this is the pattern that was seen in the NAVIPPRO data.

Table 26: OPANA ER Intentional Abuse Exposure Mentions per 100,000 Dosage Units Dispensed in Tennessee - Mean Rates from January 2009 through June 2016

Period	Number of Centers Participating	Number of Quarters Covered	Number of Mentions	Dosage Units Dispensed Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	3	7	7	0.1221 (0.0491,0.2516)
Post-ORF/Pre-CRF	2	5	17	0.1887 (0.1099,0.3021)
Post-ORF/Post-CRF	2	12	40	0.3458 (0.2470,0.4708)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 4.1.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

Table 27: OPANA ER Intentional Abuse Exposure Mentions per 100,000 Dosage Units Dispensed in All States Except Tennessee - Mean Rates from January 2009 through June 2016

Period	Number of Centers Participating	Number of Quarters Covered	Number of Mentions	Dosage Units Dispensed Rate per 100,000 (95% CI)
Pre-ORF/Pre-CRF	43	7	86	0.1646 (0.1316,0.2032)
Post-ORF/Pre-CRF	43	5	226	0.3565 (0.3115,0.4061)
Post-ORF/Post-CRF	43	12	150	0.1777 (0.1504,0.2085)

Source: RADARS Poison Center Program Report Information Amendment 1 [Table 4.2.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

4.5.3.2. Intentional Abuse Case Mentions That Resulted in Major Medical Outcomes or Death

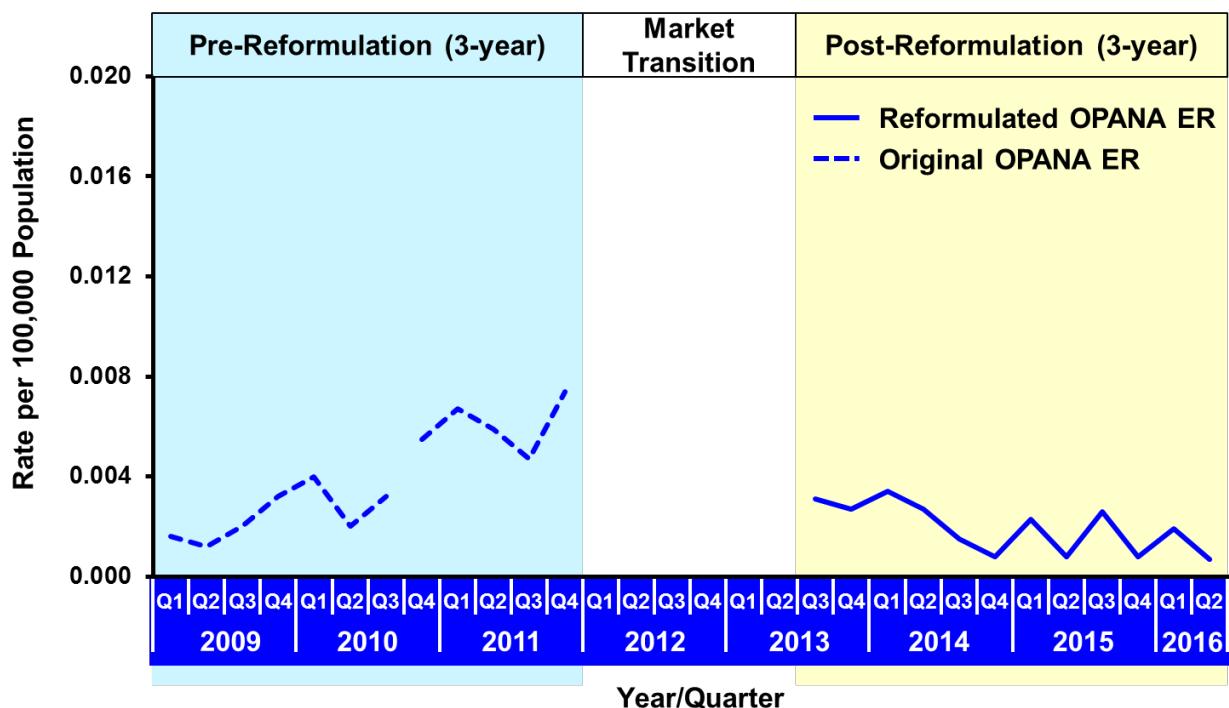
The results analyses of OPANA ER intentional abuse exposure cases that resulted in either a major medical outcome or death are shown for the rates per 100,000 population in [Table 28](#) and per 100,000 unit dispensed in [Table 29](#). [Figure 37](#) displays the major medical outcome and death rate per 100,000 population by quarter and time period. [Figure 38](#) shows the rate per 100,000 dosing units.

Findings indicate that following the introduction of reformulated OPANA ER, the rate of major medical outcome and death was lower per 100,000 population (0.0019 versus 0.0061 per 100,000 population) and per 100,000 units dispensed (0.0636 versus 0.1063 per 100,000 dosing units).

Data for the comparator ER Morphine and SE IR oxymorphone are presented in Appendix 5 ([Table 5-3](#) per 100,000 population and in [Table 5-4](#) per 100,000 dosing units dispensed).

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Figure 37: Major Medical Outcomes and Death Rates per 100,000 Population Dispensed of OPANA ER, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.3.1.1]

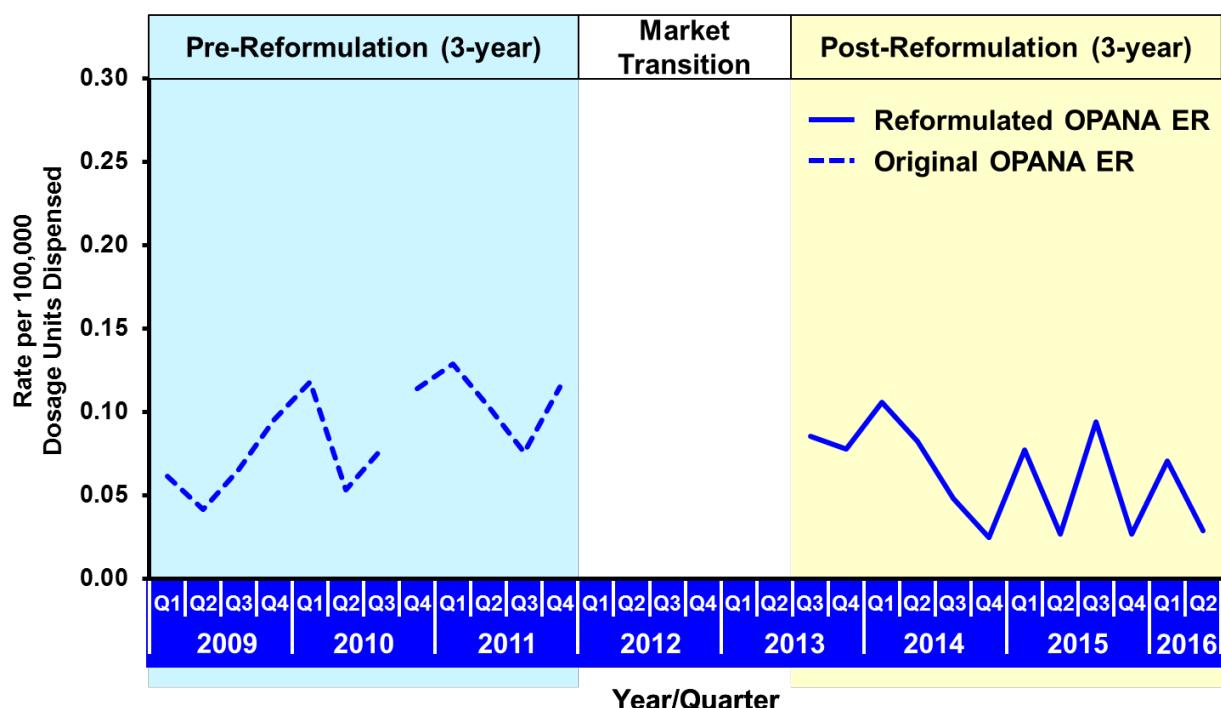
Table 28: Major Medical Outcomes and Death Rates of OPANA ER per 100,000 Population, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
Pre-ORF/Pre-CRF	0.0025 (0.0018, 0.0034)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-21.7% (-48.1%, 18.0%)
Post-ORF/Pre-CRF	0.0061 (0.0048, 0.0077)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	146.7% (66.7%, 265.2%)
Post-ORF/Post-CRF	0.0019 (0.0015, 0.0025)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-68.3% (-77.7%, -54.8%)

Source: RADARS Poison Center Program Report [Table 4.3.1.1]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

Figure 38: Major Medical Outcomes and Death Rates per 100,000 Units Dispensed of OPANA ER, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.3.1.3]

Table 29: Major Medical Outcomes and Death Rates of OPANA ER per 100,000 Units Dispensed, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
Pre-ORF/Pre-CRF	0.0742 (0.0559,0.0983)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-14.3% (-40.7%, 23.9%)
Post-ORF/Pre-CRF	0.1063 (0.0861,0.1313)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	43.4% (0.8%, 104.0%)
Post-ORF/Post-CRF	0.0636 (0.0501,0.0805)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-40.2% (-56.5%,-17.9%)

Source: RADARS Poison Center Program Report [Table 4.3.1.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

4.5.3.3. Overdose Case Mentions

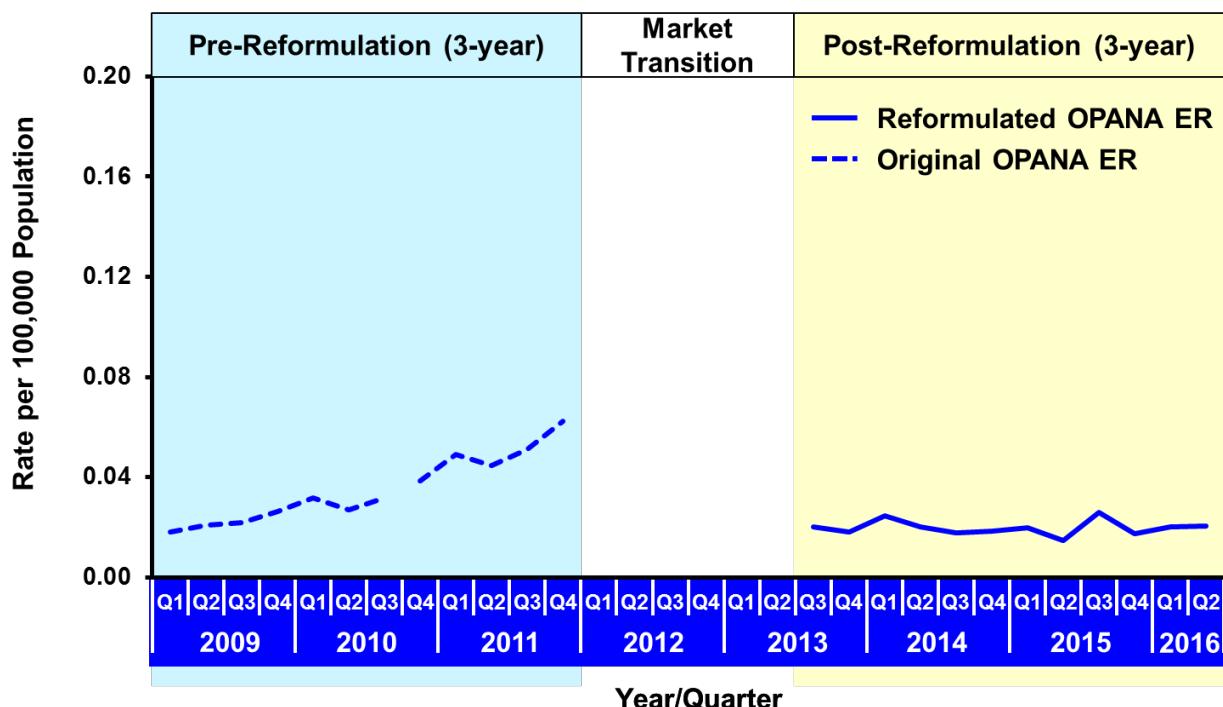
The results of analyses of OPANA ER intentional abuse exposure cases that resulted in overdose are shown for the rates per 100,000 population in [Table 30](#) and per 100,000 unit dispensed in [Table 31](#). [Figure 39](#) displays the overdose rate per 100,000 population by quarter and time period, [Figure 40](#) shows the rate per 100,000 dosage units dispensed.

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Findings indicate that following the introduction of reformulated OPANA ER, the rate was lower per 100,000 population (0.0198 versus 0.0491 per 100,000 population) and per 100,000 units dispensed (0.6543 versus 0.8605 per 100,000 dosing units).

Data for the comparators ER Morphine and SE IR oxymorphone are presented in Appendix 5 (Table 5-5 per 100,000 population and in Table 5-6 per 100,000 dosing units dispensed).

Figure 39: Overdose Rates of OPANA ER per 100,000 Population, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.4.1.1]

Note: Predicted rates based on the comparison of means model by time period are displayed as solid black lines. The 95% CIs based on the comparison of means model are represented by dashed black lines.

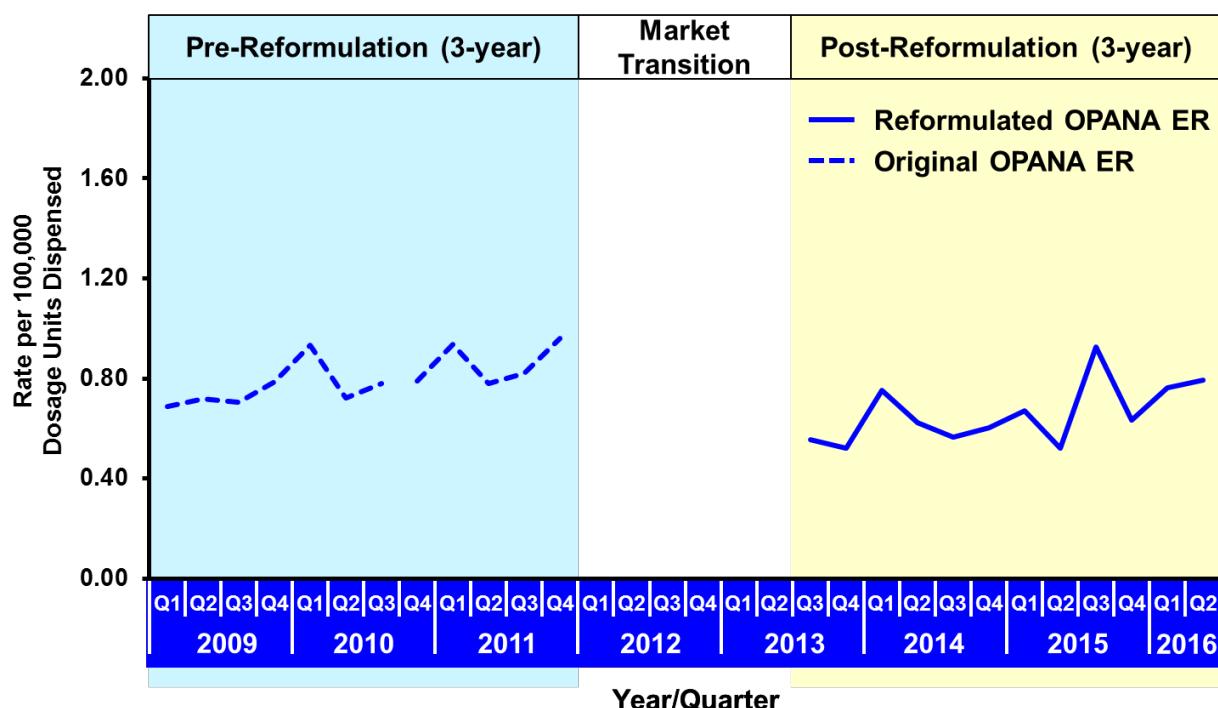
Table 30: Overdose Rates of OPANA ER per 100,000 Population, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage Change (95% CI)
Pre-ORF/Pre-CRF	0.0254 (0.0221,0.0292)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-22.0% (-34.8%,-6.6%)
Post-ORF/Pre-CRF	0.0491 (0.0437,0.0552)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	93.3% (61.4%, 131.5%)
Post-ORF/Post-CRF	0.0198 (0.0177,0.0223)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-59.6% (-65.7%,-52.4%)

Source: RADARS Poison Center Program Report [Table 4.4.1.1]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

Figure 40: Overdose Rates of OPANA ER per 100,000 Dosage Units, January 2009 to June 2016 – Comparison of Means Model



Source: RADARS Poison Center Program Report [Figure 4.4.1.3]

Table 31: Overdose Rates of OPANA ER per 100,000 Units Dispensed, January 2009 to June 2016 – Comparison of Means Model

Period	Estimate (95% CI)	Comparison	Percentage Change (95% CI)
Pre-ORF/Pre-CRF	0.7657 (0.6855, 0.8552)	Post-ORF/Post-CRF over Pre-ORF/Pre-CRF	-14.5% (-26.0%, -1.3%)
Post-ORF/Pre-CRF	0.8605 (0.7838, 0.9447)	Post-ORF/Pre-CRF over Pre-ORF/Pre-CRF	12.4% (-2.8%, 29.9%)
Post-ORF/Post-CRF	0.6543 (0.5962, 0.7180)	Post-ORF/Post-CRF over Post-ORF/Pre-CRF	-24.0% (-33.3%, -13.3%)

Source: RADARS Poison Center Program Report [Table 4.4.1.3]

CRF=Crush resistant formulation; ORF=Reformulated OxyContin

4.5.4. Conclusion

Results of the formal postmarketing epidemiology study using OPANA ER intentional abuse exposure mentions to poison centers participating in the RADARS System Poison Center program demonstrated that per population, intentional abuse exposures, major medical outcome and death rates and overdose rates for OPANA ER increased in association with the introduction of OxyContin ADF in August 2010 (the Post-ORF/Pre-CRF period compared to the Pre-ORF/Pre-CRF period). Increases were also observed in both oral and non-oral ROA intentional abuse exposures.

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After the introduction of the reformulated OPANA ER, rates of abuse, overdose, and major medical outcomes and deaths were lower. This was observed for both population and drug utilization denominated rates. Rates via oral and non-oral ROA were lower as well compared to the post-ORF/pre-CRF period.

Broken out by state, intentional abuse exposure mentions declined in all states except Tennessee and remained stable in Tennessee compared to the peak of abuse in Q4 2011. The rate of abuse in Tennessee is about 10 times higher than in any other state.

Overall, these findings indicate that the reformulation of OxyContin coincided with increases in abuse, overdose, and major medical outcome and death exposures for OPANA ER. The reformulation of OPANA ER coincided with a reduction in rates of OPANA ER abuse, overdose, and major medical outcomes and deaths and abuse via oral and non-oral ROA.

4.6. RADARS Drug Diversion (Law Enforcement) Program

Measures of diversion can be used as an indicator of abuse in the community by assessing the number of diversion reports by law enforcement associated with a drug that is distributed via the illegal market. Diversion refers to prescription drugs found outside of controlled distribution channels. The number of diversion cases of a drug in the illegal market may reflect the desirability of the drug among individuals who abuse opioids. Declines in diversion would offer supportive data for abuse deterrence as outlined in FDA Guidance for Industry “Abuse-Deterrent Opioids — Evaluation and Labeling” (section IV, part C of the guidance).^(1,2)

4.6.1. Design

This was a secondary postmarketing epidemiology study using OPANA ER drug diversion mentions from the RADARS System Drug Diversion Program to examine differences in drug diversion mentions before and after introduction of reformulated OPANA ER in February 2012. The objectives of this study were to:

1. Determine if rates of OPANA ER drug diversion mentions declined following the introduction of reformulated OPANA ER in 1Q 2012.
2. Determine if changes in rates of OPANA ER drug diversion mentions following the introduction of the reformulated OPANA ER in 1Q 2012 were different from changes observed for the comparator groups: single-entity IR oxymorphone and ER morphine.

Reformulated OPANA ER was launched in February 2012. Drug Diversion Program data are collected quarterly. These analyses are restricted to agencies that provided data every quarter between 1Q 2011 and 2Q 2016. For the purposes of these analyses, data were divided into the following 3 time periods:

- Pre-CRF period: This period includes data collected prior to the introduction of reformulated OPANA ER. Data collection on OPANA ER in the Drug Diversion Program began in January 2011. Therefore, this period covers data collected between January 2011 and December 2011.
- Transition period: This period includes only data for reformulated OPANA ER after the transition from the original formulation. Therefore, this period covers data collected between January 2012 and June 2013.

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- Post-CRF period: This period includes only data after the transition from original formulation OPANA ER to reformulated OPANA ER. This period includes all quarters from July 2013 and through June 2016.

Note: RADARS Drug Diversion Program Report uses CRF (crush-resistant formulation) to refer to reformulated OPANA ER, and this section of results will report data using that convention.

4.6.2. Strengths and Limitations

The strengths of the RADARS System Drug Diversion Program are that it samples from each state within the United States. Data for numerators and denominators are obtained with geographic specificity. The RADARS System data are available within 3 months of data capture, allowing for rapid recognition of trends.

Numerator data are product specific allowing for the isolation of the effect of OPANA ER from other opioids and other oxymorphone products. As drugs or prescriptions are seized in these drug diversion investigations, product identification is excellent. Changes in rates over time have been shown to be sensitive indicators of product formulation changes.

Limitations of the research methods include the following: Drug diversion investigators are not randomly drawn from the pool of all possible or responding drug diversion officers. Furthermore, response rates may be inconsistent from one quarter to the next. Therefore, response rates may be relatively small. These limitations may affect model selection, however, it is not thought that they would bias results in any direction with respect to introduction of reformulated OPANA ER.

4.6.3. Results

4.6.3.1. Change in Diversion Rates (Pre-reformulation/Post-reformulation)

The rate of drug diversion reports per 100,000 population was lower in the post-period (0.0232 per 100,000 population) compared to the pre-period (0.0939 per 100,000 population) (Table 32).

These results were consistent with those of the analysis of diversion based on estimated dosage units dispensed. The rate of drug diversion reports was lower (0.5958 per 100,000 dosage units) in the post-period compared to the pre-period (1.0295 per 100,000 dosage units) ([Table 33](#)).

Table 32: Drug Diversion Reports per 100,000 Population, Percent Change, January 2011 to June 2016 – Comparison of Means Model

Drug Group	Period	Estimate (95% CI)	Percentage Change (95% CI)
OPANA ER	Pre-CRF	0.0939 (0.0754,0.1168)	Reference
	Post-CRF	0.0232 (0.0180,0.0297)	-75.3% (-82.3%,-65.6%)

Source: RADARS Drug Diversion Program Report [Table 4.1.1.1]

CRF=Crush-resistant formulation

Table 33: Drug Diversion Reports per 100,000 Dosage Units Dispensed, Percent Change, January 2011 to June 2016 – Comparison of Means Model

Drug Group	Period	Estimate (95% CI)	Percentage Change (95% CI)
OPANA ER	Pre-CRF	1.0295 (0.8438,1.2560)	Reference
	Post-CRF	0.5958 (0.4746,0.7479)	-42.1% (-57.2%,-21.7%)

Source: RADARS Drug Diversion Program Report [Table 4.1.1.3]

CRF=Crush-resistant formulation

4.6.4. Conclusion

Overall, findings from the RADARS System Drug Diversion Program suggest a reduction in diversion reports following reformulation of OPANA ER when adjusting for population and dosage units dispensed.

The attenuation of OPANA ER mean rate declines, when adjusting for dosage units dispensed relative to population rates, suggests that changes in rates of OPANA ER diversion reports are associated with declines in prescriptions filled for the drug (as detailed in section 4.4.1.8). The changes in drug utilization could be a direct result of the introduction of the reformulation. OPANA ER may be less desirable to individuals who abuse opioids and, subsequently, fewer prescriptions for the drug are filled for patients who abuse or divert their medication. The decline in prescriptions may also be due to the introduction of generic ER oxymorphone products.

4.7. Category 4 Conclusion

The three Category 4 postmarketing epidemiology studies were conducted to determine whether the marketing of reformulated OPANA ER resulted in a meaningful change in abuse, misuse, and related adverse clinical outcomes, including overdose and death in “real-world” settings.

Observational data have limitations including the inability to identify, isolate, and control for all of the changes occurring over time, particularly in an area as challenging as opioid abuse. With those limitations in mind, the studies demonstrated that after the introduction of reformulated OPANA ER, measures of abuse generally declined across multiple streams of data. The decline in abuse measures was particularly notable in comparison to the peak period of abuse of original OPANA ER in 2011 and by the route of intranasal administration. With the exception of Tennessee, other routes of abuse such as intravenous administration did not increase. Tennessee is a region where abuse has been notable for a number of opioid products before the introduction of reformulated OPANA ER and a meaningful proportion of that abuse has been by intravenous route. Rates of intravenous abuse of OPANA ER increased in Tennessee after the introduction of the reformulated product but to levels similar to or less than those of other opioids. The experience in Tennessee represents an outlier and review of the data does not show that such a pattern has influenced other states of the country over the 3 years of the observation period following reformulation.

5. BENEFIT/RISK ASSESSMENT

5.1. Benefits of Reformulated OPANA ER

Reformulated OPANA ER demonstrates a favorable benefit-risk profile for people with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

OPANA ER demonstrated efficacy in moderate to severe chronic pain in non-malignant and malignant indications and in patients with suboptimal response to their prior opioid therapy. Both opioid-inexperienced subjects and opioid-experienced subjects with moderate to severe chronic low back pain were able to initiate treatment with a low dose of OPANA ER, gradually titrating to a maintenance dose that provided appropriate pain relief, and continuing treatment on their maintenance dose while maintaining the same pain relief for at least 12 weeks compared to placebo.

The AE profile in the placebo-controlled clinical trials is consistent with the class of opioid analgesics. Nausea, constipation, dizziness, somnolence, and vomiting are the most common AEs that occurred at a higher frequency on OPANA ER than on placebo.

Effective chronic pain management necessitates the availability of a variety of opioids due to a highly variable patient response in pharmacological efficacy and tolerability to members of the same class of analgesics. Therefore, opioid rotation is a critical element in therapy to overcome these limitations which are based on multiple factors such as age, gender, comorbidities, concomitant medications, renal and hepatic function, as well as genetic variations in receptor subtypes.

As an opioid metabolized via the UGT pathway OPANA ER represents an important treatment choice for patients who previously did not tolerate an opioid metabolized by CYP450 due to drug-drug interactions or problematic metabolism (on a genetic basis).^(59,60) Although the importance of drug-drug interactions of opioids has received little attention, it is estimated that in a managed care setting about 30% of all patients taking opioids metabolized by CYP450 were also exposed to other CYP450 substrates, including potentially interacting drugs.⁽¹⁴⁾ It is estimated that about 75% of chronic pain patients are treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) that are substrates for CYP450. The average chronic pain patient takes about 10 concomitant medications, some of which have the potential to interact with CYP450. Potential consequences can include excess opioid effects or loss of analgesic efficacy. Therefore, opioids utilizing the UGT metabolic pathway such as oxymorphone are indispensable choices in the treatment of chronic pain in a patient population with comorbidities requiring multiple concomitant medications.

Oxymorphone is further characterized by the extremely low level of active metabolites, which have a potential to complicate treatment.

The diversion and abuse of prescription opioid analgesic products poses serious public health and safety risks. FDA, other US government agencies/legislators, academia, and industry have identified the need for development of abuse-deterrent opioid formulations that can hinder the ability to extract extremely high concentrations of medication and deter abuse and diversion.

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Original OPANA ER was approved in 2006 for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Postmarketing surveillance data revealed that the primary route of abuse of OPANA ER was intranasal abuse. Subsequently, reformulated OPANA ER was developed to resist crushing, with the intention of reducing both overall abuse and abuse via intranasal insufflation while not creating a new route of abuse. Reformulated OPANA ER was approved in 2011 without ADF labeling.

The findings of the Category 1 studies demonstrated that crush-resistant reformulated OPANA ER, while not abuse proof, does provide a barrier to misuse and abuse. Its physicochemical properties are similar to OxyContin ADF and require a higher degree of effort, time, tools, and experience to crush or manipulate, when compared to non-crush-resistant generic oxymorphone ER formulations. Results of the Category 2 studies showed that reformulated OPANA ER has an approximately 13-fold lower abuse quotient compared to oxymorphone powder and that the abuse-deterring properties of reformulated OPANA ER limit the rate and extent of rise of drug concentration following intranasal administration of the manipulated product.

The Category 3 study showed a statistically significant reduction in peak “Drug Liking at this moment” following intranasal administration of reformulated manipulated OPANA ER compared with oxymorphone HCl powder. Based on these observations, the results of this human abuse potential study suggest that reformulated OPANA ER may have lower abuse potential via the intranasal ROA. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that reformulated OPANA ER has physicochemical properties that are expected to reduce abuse via the intranasal route when manipulated.

Results of three Category 4 observational studies demonstrated:

- For NAVIPPRO data from addiction treatment centers:
 - Abuse of original OPANA ER was increasing during the pre-period and continued to increase after the introduction of a reformulated version of OxyContin in August 2010.
 - During the post-period, following the introduction of reformulated OPANA ER, the prevalence of abuse by alternate ROA was higher although intranasal abuse was lower. The effect on abuse by alternate ROA was driven by an apparent higher prevalence of intravenous abuse.
 - However, the results for abuse by alternate ROA are explained by a high degree of data heterogeneity with Tennessee being an outlier:
 - Within Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period, but intravenous abuse was higher.
 - Outside of Tennessee, the prevalences of abuse by alternate ROA and intranasal abuse were lower during the post-period and intravenous abuse remained stable at levels reached in 2011.

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- Not only did Tennessee provide the majority of abuse reports during the post-period, but intravenous abuse was higher in this state for many opioid products both during the pre-period and the post-period and the higher level of intravenous abuse for OPANA ER was similar to or less than the levels for other opioids in both time periods.
- During the post-period, abuse by alternate ROA and intranasal abuse of generic oxymorphone ER was higher than for OPANA ER and intravenous abuse was similar.
- For RADARS poison center data:
 - Abuse of original OPANA ER was increasing during the pre-period and increased even more after the introduction of a reformulated version of OxyContin in August 2010.
 - During the post-period, following the introduction of reformulated OPANA ER, overall abuse, abuse by oral and non-oral routes, major medical outcomes and death, and overdoses were lower compared to the pre-period.
- For RADARS drug diversion data:
 - Rate of drug diversion of OPANA ER was lower in the post-period compared to the pre-period.

Thus, the introduction of reformulated OPANA ER was associated with a favorable change in the abuse profile in most of the United States. In Tennessee, where intravenous abuse is prevalent, such abuse of OPANA ER rose, but to levels similar to or less than those of other intravenously abused opioid products in that state. Still, observational studies can only show associations, not causal relationships. With the available epidemiology sources for assessing opioid abuse, there are important methodological limitations related to regional heterogeneity, changes in sampling over time, and overall changes in background abuse ecology.

5.2. Risks of OPANA ER

5.2.1. Class-Wide Risks of Opioids

Prescription opioids are essential, effective treatments for moderate-to-severe chronic pain patients. In parallel with the extended use of opioids, an unintentional consequence of greater prescription opioid utilization emerged. The increase in abuse, abuse-related AEs, overdose, and death are serious risks associated with all opioid analgesics. The FDA has recognized the risks associated with the use of opioid formulations, in particular ER/LA formulations given the large amount of active ingredient contained within a dose and the prolonged time to elimination. Under the authority of the Food and Drug Administration Amendments Act of 2007, and as a result of stakeholder, industry, public, and advisory committee meetings, the FDA announced a class-wide REMS for ER opioid analgesics in April 2011, which became operational in July 2012). The intent of the class wide REMS is to ensure that the therapeutic benefits of ER/LA opioid formulations continue to outweigh the risks, particularly addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

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A specific serious risk of all ER opioids that utilize PEO as an inactive ingredient is TMA when that substance is injected intravenously instead of being swallowed orally. Reports of TMA were first received in August 2012 for OPANA ER from Tennessee and other states but more recently there has been less reporting of this complication. Appropriate changes to product labeling have been made. Reports of TMA have now been published for reformulated OxyContin, which also contains PEO.

5.2.2. Risks of OPANA ER

While the Category 4 study data show a reduction in the overall abuse of reformulated OPANA ER in the community setting after its peak in 2011, such abuse is still possible. The product's abuse-deterrent properties, which were designed to deter snorting, do not deter all routes of abuse. Given the complex patterns of abuse presented for reformulated OPANA ER and for non-abuse-deterrent generic formulations, it is particularly important that monitoring continue to evaluate any possible changes to the routes of abuse observed that may happen in the future.

5.3. Overall Conclusion

OPANA ER is an efficacious and safe treatment option for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. In addition, oxymorphone is characterized by specific, pharmacokinetic and pharmacodynamics characteristics that make oxymorphone an important option for chronic pain treatment.

In conclusion, the totality of the evidence demonstrates a favorable benefit-risk profile for OPANA ER in the intended population which is not altered by the Category 4 data in the unintended population. Endo is prepared to work with the FDA, Inflexxion, RADARS, and other interested partners in improving Category 4 data collection and analysis.

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**APPENDIX 1. IN VITRO COMPARISON OF REFORMULATED
OPANA ER VS OXYCONTIN ADF**

Table 1-1 Comparison of Reformulated OPANA ER vs OxyContin ADF

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Table 1-1: Comparison of Reformulated OPANA ER vs OxyContin ADF

Experiment	Experimental Details	Results		Comments
		Reformulated OPANA ER	OxyContin ADF	
Physical Manipulation				
Tool C	Breaking force (N)	>1000 N	>1000 N	Similar – deformed not broken
Tool G	Force (N) required to crack a tablet. Note tool G can only apply max 550 N	5 mg = 550 20 mg = 550 40 mg = 550	10 mg = 550 40 mg = 272 80 mg = 302	Less force to crack OxyContin ADF, OPANA ER did not crack
Tool H	Force (N) required to compress a tablet. Note tool G can only apply max 550 N	5 mg = 339 20 mg = 319 40 mg = 332	10 mg = 219 40 mg = 220 80 mg = 289	More force required to compress reformulated OPANA ER
Tool J or tool I	Cut a tablet	Yes	Yes	Difficult to perform
Tool W	Cut a tablet	Yes	Yes	Similar results
Tool A or tool E	Crush a tablet	No	Not Tested	Similar results expected, if tested
Tool B	Crush a tablet	No	No	Similar – both are flattened
Tool L	Flatten and bend	Yes	Yes	Similar results
Tool L	Flatten and bend until broken	No	Yes	Reformulated OPANA ER does not break
Tool V or tool N	Grind a tablet	Yes	Yes	Similar results
Tool M	Grind a tablet	No	Not tested	Reformulated OPANA ER cannot be ground by tool M
Dissolution of Manipulated Tablets @ 30 minutes				
Intact tablets	Tested as control; performed dissolution testing	19% LC	17% LC	Dissolution of manipulated tablet increases compared to intact tablet. Similar results for both products for each type of manipulation.
Tablet manipulated by tool B	Flattened a tablet; Transferred material to dissolution bath and performed dissolution testing	26% LC	24% LC	
Tablet manipulated by tool I, or tool J, or tool W	Cut a tablet into 5 pieces; Transferred material to dissolution bath and performed dissolution testing	29% LC	36% LC	
Tablet manipulated by tool I, or tool J, or tool W	Cut a tablet into 16 pieces; Transferred material to dissolution bath and performed dissolution testing	50% LC	57% LC	
Tablet manipulated by tool N	Ground a tablet; Transferred material to dissolution bath and performed dissolution testing	75% LC	73% LC	

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Table 1-1: Comparison of Reformulated OPANA ER vs OxyContin ADF (Continued)

Experiment	Experimental Details	Results		Comments
		Reformulated OPANA ER	OxyContin ADF	
Tablet manipulated by tool V Particle Size Analysis	Determine particle size distribution by sieve analysis	Median range 0.355 – 0.5 mm	Median range 0.355 – 0.5 mm	Similar Results
Tablet manipulated by tool N Particle Size Analysis	Determine particle size distribution by sieve analysis	Median range >1.4 mm	Median range 0.5 – 0.71 mm	OxyContin ADF has smaller median particle size range
Extraction into Solvents Using Tablets Manipulated by Tool B				
Extraction into 30 mL solvent 'a'	Analyze aliquot at specified time	15 min. = 13% LC 1 hour = 22% LC 6 hours = 57% LC	15 min. = 15% LC 1 hour = 26% LC 6 hours = 61% LC	Similar results
Extraction into 30 mL solvent 'b'		15 min. = 18% LC 1 hour = 21% LC 6 hours = 35% LC	15 min. = 31% LC 1 hour = 41% LC 6 hours = 57% LC	OxyContin ADF more soluble
Extraction into 30 mL solvent 'g'		15 min. = 1.3% LC 1 hour = 2.0% LC 6 hours = 4.3% LC	15 min. = 5.1% LC 1 hour = 7.6% LC 6 hours = 15.5% LC	Low solubility for both
Extraction into 30 mL solvent 'l'		15 min. = 0.3% LC 1 hour = 0.4% LC 6 hours = 0.6% LC	15 min. = 2.1% LC 1 hour = 2.6% LC 6 hours = 3.9% LC	Low solubility for both
Extraction into 30 mL solvent 'e'		15 min. = 15% LC 1 hour = 19% LC 6 hours = 38% LC	15 min. = 17% LC 1 hour = 21% LC 6 hours = 44% LC	Similar results
Preparation for Injection				
0.355–0.5 mm particles extracted with 3 mL boiling solvent 'a' (tool N3 and tool N1)	Heat T2 for 5 minutes with tool A2, then cool; Use N1 syringe to draw sample through a filter; if <0.1 mL withdrawn, use tool N3	Not syringeable	Not syringeable	Similar results; small particles hydrogel; neither product syringeable in a tool N1 or tool N3 syringe
Tablet manipulated by tool B; extracted with 5 mL boiling solvent 'a' (tool N1)	Heat T2 for 5 minutes; Use N1 syringe to draw sample through a filter	~4 mL withdrawn with a N1 syringe; 26%-40% LC	~ 5 mL withdrawn with a N1 syringe; 42%-46% LC	Similar results; limited hydrogelling, matrix releases API
Tablet manipulated by tool W into 5 pieces, extracted with 2 mL hot solvent 'a' (tool N3)	Heat T2 until half volume reached; Use N3 syringe to draw a sample; repeat 4 more times (total of 5 extractions); total extraction time about 25 minutes	39% LC (5 extractions)	36% LC (5 extractions)	Similar Results

APPENDIX 2. IN VITRO COMPARISON OF REFORMULATED OPANA ER VS GENERIC OXYMORPHONE ER

Table 2-1 Reformulated OPANA ER vs Generic Oxymorphone HCl ER Tablets from Impax and/or Actavis

Table 2-2 Median Particle Size Range Results with Pretreatment

Table 2-3 Extraction Results for Reformulated OPANA ER, 40-mg Tablets – 5 mL

Table 2-4 Extraction Results for OPANA ER, 40-mg Tablets – 10 mL

Table 2-5 Extraction Results for Generic Oxymorphone HCl ER Company B, 40-mg Tablets – 5 mL

Table 2-6 Extraction Results for Generic Oxymorphone HCl ER Company B, 40-mg Tablets – 10 mL

Table 2-7 Extraction Results for Generic Oxymorphone HCl ER Company A, 40-mg Tablets – 5 mL

Table 2-8 Extraction Results for Generic Oxymorphone HCl ER Company A, 40-mg Tablets – 10 mL

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Table 2-1: Reformulated OPANA ER vs Generic Oxymorphone HCl ER Tablets from Impax and/or Actavis

Experiment	Experimental Details	OPANA ER	Generic Oxymorphone HCl ER		Comments
			Generic B	Generic A	
Physical Manipulation					
Tool J	Tablets cut / crushed/ ground by the specified tool.	Yes	Yes	Yes	Reformulated OPANA ER can be cut with difficulty Generic tablets can be easily manipulated and therefore there was no need to test some of the tools
Tool I		Yes	No need to	No need to	
Tool W		Yes	No need to	No need to	
Tool A		No	Yes	Yes	
Tool E		No	No need to	No need to	
Tool B		No	Yes	Yes	
Tool N		Yes	Yes	No need to	
Dissolution @ 30 Minutes					
Intact	No manipulation	19%	17%	30%	Release rate for manipulated generic tablets are higher than reformulated OPANA ER tablets; tool A crushed generic tablet behaves like an immediate-release formulation
Manipulated by tool A	Dissolution was performed	Cannot be crushed	102%	96%	
Manipulated by tool B	Dissolution was performed	26%	83%	88%	
Particle Size					
Manipulated by tool A	Measure particle size by sieve analysis	No particles formed	Median range 0.25-0.355 mm	Median range 0.125-0.18 mm	Generic is easily crushable to fine powder
Manipulated by tool N	Reformulated OPANA ER – tool N Generic tablet – half time of reformulated OPANA ER The particle size distribution was determined by sieve analysis	Median range >1.4 mm	Median range 0.18-0.25 mm	No need to do	Generic has much smaller median particle size range

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Table 2-1: Reformulated OPANA ER vs Generic Oxymorphone HCl ER Tablets (Continued)

Experiment	Experimental Details	OPANA ER	Generic Oxymorphone HCl ER		Comments
			Generic B	Generic A	
Preparation for Injection					
Tablet manipulated by tool B; extracted with solvent 'a'	Heat T2 for 5 minutes; Use N3 syringe to draw sample through a filter	Reformulated OPANA ER tablet was flattened Difficult to syringe 26% – 40% LC	Generic tablet was crushed to powder / particles Easy to syringe 66% – 74% LC	Generic tablet was crushed to powder / particles Easy to syringe 61% - 80% LC No filter used	Generic is easily syringeable; more API extracted from Generic

GRT=Grünenthal GmbH (Aachen, Germany)

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Table 2-2: Median Particle Size Range Results with Pretreatment

Pretreatment	Pretreatment	Sample Type	Median Particle Size Range (mm)
Reformulated OPANA ER (40 mg)	P3	Intact/Heated/Grated	0.71 - 1.0
		Grated/Heated	0.71 - 1.0
	P4	Intact/Heated/Grated	0.71 - 1.0
		Grated/Heated	1.0 - 1.4
	P6	Intact/Heated/Grated	0.71 - 1.0
		Grated/Heated	0.71 - 1.0
Generic Oxymorphone ER – company A (40 mg)	P3	Intact/Heated/ Ground	0.09-0.125
		Ground /Heated	≤ 0.09
		Control (no heat)	≤ 0.09
	P5	Intact/Heated/ Ground	≤ 0.09
		Ground /Heated	≤ 0.09
		Control	≤ 0.09
Generic Oxymorphone HCl ER – company B (40 mg)	P3	Intact/Heated/ Ground	≤ 0.09
		Ground /Heated	≤ 0.09
		Control (no heat)	≤ 0.09
	P5	Intact/Heated/ Ground	≤ 0.09
		Ground /Heated	≤ 0.09
		Control	Not tested

ER=Extended-release; HCl=Hydrochloride

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Table 2-3: Extraction Results for Reformulated OPANA ER, 40-mg Tablets – 5 mL

Pretreatment	Sample Type	Solvent 'a'			Solvent 'e'		
		Filterable/ Needle Size ^a	Extraction Solution (mL)	% Extracted ^b	Filterable / Needle Size ^a	Extraction Solution (mL)	% Extracted ^b
P3	Intact/Heated/Grated	No / N3	2.2, 3.3, 2.5	36.6, 59.3, 43.2 ^c 46.7	No / N4	3.1, 3.1	59.0, 56.0 57.5
	Grated/Heated	No / N3	3.1, 2.8	59.0, 52.2 55.6	No / N4	3.0, 2.8	54.9, 52.8 53.9
P4	Intact/Heated/Grated	No / N3	2.3, 2.0	38.0, 34.1 36.1	No / N4	3.4, 3.0	69.1, 60.8 65.0
	Grated/Heated	No / N3	4.1, 3.0, 4.3	69.8, 51.6, 78.4 ^c 66.6	No / N3	3.1, 3.0	59.6, 59.6 59.6
P6	Intact/Heated/Grated	No / N4	3.5, 3.5	60.1, 58.8 59.5	No / N4	2.7, 3.0	51.8, 60.6 56.2
	Grated/Heated	No / N4	3.1, 3.3	51.0, 54.8 52.9	No / N4	2.8, 3.1	55.3, 57.8 56.6
P7	Intact/Heated/Grated	No / N3	1.8, 2.6	28.1, 37.5 32.8	Not tested		
	Grated/Heated	No / N3	3.0, 3.1	51.6, 56.1 53.9	Not tested		
P8	Intact/Heated/Grated	No / N4	3.4, 3.4	63.4, 61.9 62.7	No / N4	2.7, 2.8	51.6, 54.4 53.0
	Grated/Heated	No / N3	2.1, 2.8, 2.1	36.4, 50.4, 38.0 ^c 41.6	No / N4	1.5, 2.2., 2.3	29.5, 48.6, 44.2 ^c 40.8

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

^b Individual results reported, average result in bold.

^c Additional sample preparation and extraction performed due to variability of the duplicate results.

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Table 2-4: Extraction Results for OPANA ER, 40-mg Tablets – 10 mL

Pretreatment	Sample Type	Solvent 'a'			Solvent 'e'		
		Filterable/ Needle Size ^a	% Assay of Filtrate ^b	% Extracted ^b	Filterable / Needle Size ^a	% Assay of Filtrate ^b	% Extracted ^b
P3	Intact/Heated/Grated	No / N3	NA	72.3, 78.7 75.5	No / N3	NA	40.4, 45.0, 49.1 ^c , 56.9 ^c 47.9
	Grated/Heated	No / N3	NA	78.2, 74.6 76.4	No / N3	NA	53.6, 67.9, 59.7 ^c , 54.7 ^c 59.0
P4	Intact/Heated/Grated	Yes / N3	48.2, 50.7 49.5	68.3, 68.4 68.4	No / N3	NA	79.9, 88.5 84.2
	Grated/Heated	Yes / N3	25.0, 28.6 26.8	74.3, 76.3 75.3	Yes / N3	21.0, 23.8 22.4	70.6, 79.1 74.9
P6	Intact/Heated/Grated	No / N4	NA	72.1, 78.0 75.1	No / N4	NA	73.8, 80.9 77.4
	Grated/Heated	No / N4	NA	82.6, 75.8 79.2	No / N4	NA	88.2, 89.4 88.8
P7	Intact/Heated/Grated	No / N3	NA	67.6, 60.7 64.2	Not tested		
	Grated/Heated	No / N3	NA	70.7, 67.6 69.2	Not tested		
P8	Intact/Heated/Grated	No / N3	NA	74.7, 77.4 76.1	No /	(b) (4)	NA
					No /		NA
	Grated/Heated	No / N3	NA	73.5, 74.4 74.0	No /		NA
					No /		NA

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

^b Individual results reported, average result in bold.

^c Additional sample preparation and extraction performed due to variability of the duplicate results.

NA=Not applicable

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Table 2-5: Extraction Results for Generic Oxymorphone HCl ER Company B, 40-mg Tablets – 5 mL

Pretreatment	Sample Type	Solvent ‘a’				Solvent ‘e’		
		Filterable/ Needle Size ^a	Extraction Solution (mL)	%Assay of Filtrate ^b	% Extracted ^b	Filterable / Needle Size ^a	Extraction Solution (mL)	% Extracted ^b
P3	Intact/Heated/Ground	Yes / N1	1.9, 2.5	Not tested	33.6, 46.0 39.8	No / N3	3.4, 3.3	67.2, 67.8 67.5
	Ground /Heated	Yes / N1	2.2, 1.1	Not tested	38.5, 19.3 28.9	No / N3	3.2, 3.4	70.2, 73.0 71.6
	Control (no heat)	Not tested				No / N3	3.4, 2.9	64.4, 60.0 62.2
P5	Intact/Heated/ Ground	Yes / N1	2.8, 2.8	49.0, 48.2 48.6	49.0, 48.2 48.6	Not tested		
	Ground /Heated	Yes / N1	2.8, 3.5	49.8, 66.5 58.2	49.8, 66.5 58.2	Not tested		
	Control (no heat)	Yes / N1	2.8, 2.5	49.0, 42.4 45.7	49.0, 42.4 45.7	Not tested		
P6	Intact/Heated/ Ground	Yes / N1	2.0. 2.8	34.7, 50.6 42.7	34.7, 50.6 42.7	No / N3	3.6, 3.6	68.3, 76.4 72.4
	Ground /Heated	Yes / N1	2.6, 2.7	45.0, 48.2 46.6	45.0, 48.2 46.6	No / N3	3.2, 3.1	57.4, 64.7 61.1
	Control (no heat)	Yes / N1	2.8, 2.3	53.3, 43.6 48.5	53.3, 43.6 48.5	No / N3	3.5, 3.5	70.2, 70.7 70.5

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

^b Individual results reported, average result in bold.

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Table 2-6: Extraction Results for Generic Oxymorphone HCl ER Company B, 40-mg Tablets – 10 mL

Pretreatment	Sample Type	Solvent 'a'			Solvent 'e'	
		Filterable/ Needle Size ^a	% Assay of Filtrate ^b	% Extracted ^b	Filterable / Needle Size ^a	% Extracted ^b
P3	Intact/Heated/ Ground	Yes / N1	63.1, 58.1 60.6	63.1, 58.1 60.6	No / N3	80.4, 79.3 79.9
	Ground /Heated	Yes / N1	68.2, 66.9 67.6	68.2, 66.9 67.6	No / N3	80.4, 86.2 83.3
	Control (no heat)	Not tested			No / N3	78.3, 79.3 78.8
P5	Intact/Heated/ Ground	Yes / N1	59.8, 62.4 61.1	59.8, 62.4 61.1	Not tested	
	Ground /Heated	Yes / N1	59.5, 59.4 59.5	59.5, 59.4 59.5	Not tested	
	Control (no heat)	Not tested			Not tested	
P6	Intact/Heated/ Ground	Yes / N1	67.4, 69.5 68.5	67.4, 69.5 68.5	No / N3	81.5, 82.6 82.1
	Ground /Heated	Yes / N1	55.6, 54.5 55.1	55.6, 54.5 55.1	No / N3	82.5, 81.2 81.9
	Control (no heat)	Yes / N1	73.7, 75.5 74.6	73.7, 75.5 74.6	No / N3	82.2, 85.0 83.6

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

^b Individual results reported, average result in bold.

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Table 2-7: Extraction Results for Generic Oxymorphone HCl ER Company A, 40-mg Tablets – 5 mL

Pretreatment	Sample Type	Solvent ‘a’				Solvent ‘e’	
		Filterable/ Needle Size ^a	Extraction Solution (mL)	% Assay of Filtrate ^b	% Extracted ^b	Filterable / Needle Size ^a	% Extracted ^b
P3	Intact/Heated/ Ground	Yes / N1	2.8, 2.1	46.6, 37.4 42.0	46.6, 37.4 42.0	Not tested	
	Ground /Heated	Yes / N1	2.4, 2.5	41.1, 41.6 41.4	41.1, 41.6 41.4	Not tested	
	Control (no heat)	Yes / N1	2.7, 2.6	43.6, 42.9 43.3	43.6, 42.9 43.3	Not tested	
P5	Intact/Heated/ Ground	Yes / N1	2.3, 2.5	33.6, 35.3 34.5	33.6, 35.3 34.5	Not tested	
	Ground /Heated	Yes / N1	2.7, 2.6	40.7, 40.1 40.4	40.7, 40.1 40.4	Not tested	
	Control (no heat)	Yes / N1	2.8, 2.8	41.5, 44.2 42.9	41.5, 44.2 42.9	Not tested	

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

^b Individual results reported, average result in bold.

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Table 2-8: Extraction Results for Generic Oxymorphone HCl ER Company A, 40-mg Tablets – 10 mL

Pretreatment	Sample Type	Solvent 'a'			Solvent 'e'	
		Filterable/ Needle Size ^a	% Assay of Filtrate ^b	% Extracted ^b	Filterable / Needle Size ^a	% Extracted ^b
P3	Intact/Heated/ Ground	Yes / N1	69.7, 65.4 67.6	69.7, 65.4 67.6	Not tested	
	Ground /Heated	Yes / N1	73.2, 69.6 71.4	73.2, 69.6 71.4	Not tested	
	Control (no heat)	Yes / N1	60.2, 71.3 65.8	60.2, 71.3 65.8	Not tested	

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

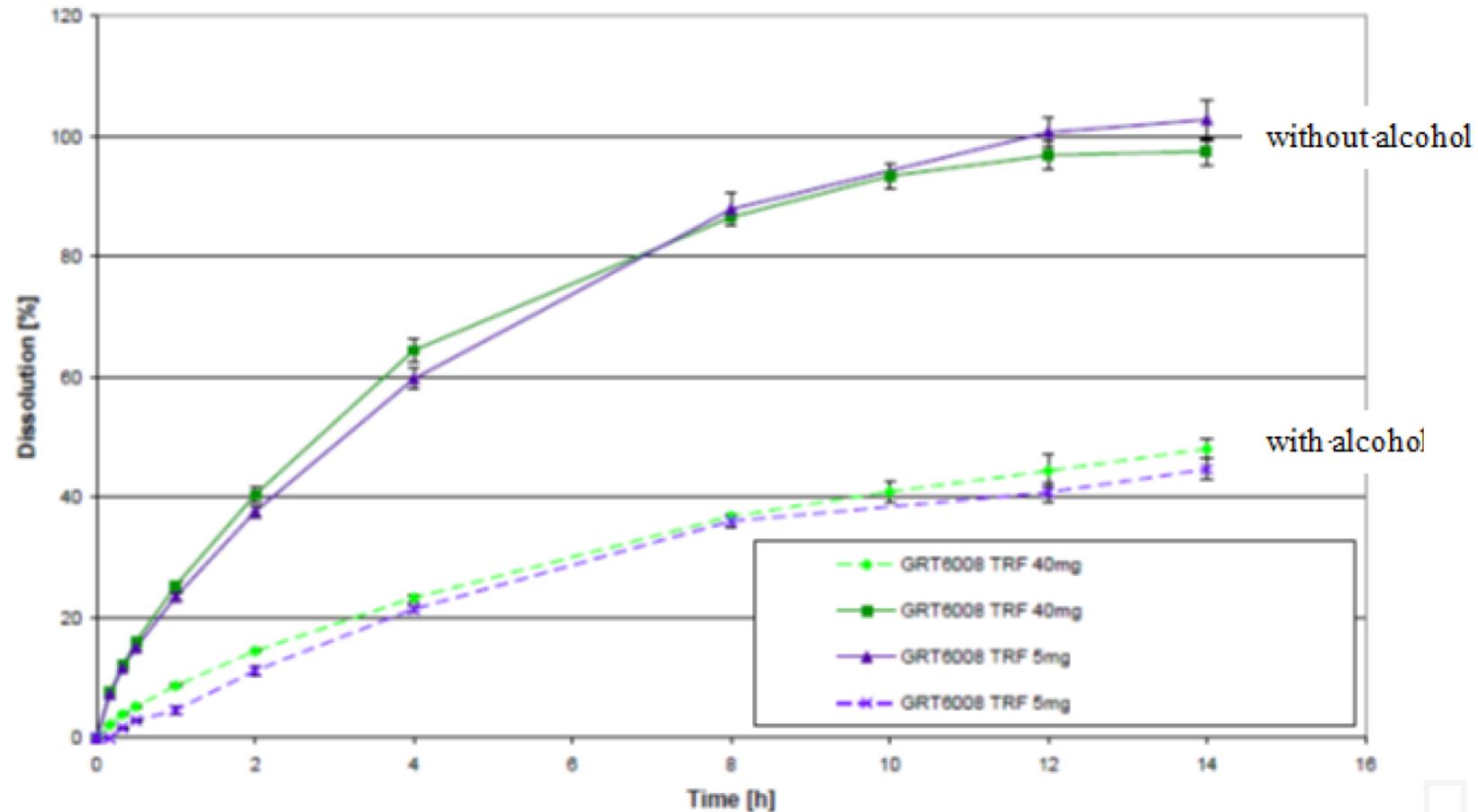
^b Individual results reported, average result in bold.

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APPENDIX 3. CATEGORY 1 STUDIES – EFFECT OF ALCOHOL

Figure 3-1 Dissolution of Reformulated OPANA ER with and without Alcohol

Figure 3-1: Dissolution of Reformulated OPANA ER with and without Alcohol



GRT6008 TRF = Reformulated OPANA ER

Dissolution profiles of 5-mg and 40-mg strengths of intact reformulated OPANA ER tablets (GRT6008 TRF tablets) in solvent 'e'/solvent 'j' in comparison to that in an ethanol-free medium (solvent 'j'); error bars depict standard deviation (b(4)).

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APPENDIX 4. PRESPECIFIED ANALYSES IN CATEGORY 4 STUDIES

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NAVIPPRO: "Post-Marketing Epidemiology Study to Assess Abuse of OPANA® ER Among Adults Assessed for Substance Abuse Treatment" (Primary Study)				
Route of Administration	Measure	Comparator	Time Period	Denominator
Alternate routes (not swallowed whole)	Prevalence rate of 30-day abuse	Original OPANA ER	Pre-period versus post period	Per 100 ASI-MV Per 10,000 tablets
By individual route of administration (Oral, Intranasal, Injection)	Prevalence rate of 30-day abuse	Original OPANA ER	Pre-period versus post period	Per 100 ASI-MV Per 10,000 tablets
Alternate routes (not swallowed whole)	Prevalence rate of 30-day abuse	Generic Oxymorphone ER	Post-period	Per 100 ASI-MV Per 10,000 tablets
By individual route of administration (Oral, Intranasal, Injection)	Prevalence rate of 30-day abuse	Generic Oxymorphone ER	Post-period	Per 100 ASI-MV Per 10,000 tablets
All States except Tennessee				
Alternate routes (not swallowed whole)	Prevalence rate of 30-day abuse	Original OPANA ER	Sensitivity Pre-period versus Post period	Per 100 ASI-MV
By individual route of administration (Oral, Intranasal, Injection)	Prevalence rate of 30-day abuse	Original OPANA ER	Sensitivity Pre-period versus Post period	Per 100 ASI-MV
Tennessee only				
Alternate routes (not swallowed whole)	Prevalence rate of 30-day abuse	Original OPANA ER	Sensitivity Pre-period versus Post period	Per 100 ASI-MV
By individual route of administration (Oral, Intranasal, Injection)	Prevalence rate of 30-day abuse	Original OPANA ER	Sensitivity Pre-period versus Post period	Per 100 ASI-MV

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RADARS: "Analysis of Reformulated OPANA® ER using the RADARS® Poison Center Program" (Primary Study)				
Route of Administration	Measure	Comparator	Time Period	Denominator
Intentional abuse	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF) Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Intentional abuse By route of administration (Oral and Non-oral)	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Intentional abuse By Inhalation	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Intentional abuse By Injection	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units

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Route of Administration	Measure	Comparator	Time Period	Denominator
Major Medical Outcomes & Death	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF) Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Overdose	Rate of intentional exposures, therapeutic errors and unintentional general exposures	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF) Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Tennessee only				
Intentional abuse	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
Major Medical Outcomes and Deaths	Rate of intentional abuse exposure	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units

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Route of Administration	Measure	Comparator	Time Period	Denominator
Overdose	Rate of intentional exposures, therapeutic errors and unintentional general exposures	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF): Post-ORF/post- reformulated OPANA ER (Post-CRF)	Per 100,000 Population Per 100,000 Dosing Units
RADARS: “Proposed Analysis of Reformulated OPANA® ER using the RADARS® Drug Diversion Program”(Secondary Study)				
Route of Administration	Measure	Comparator	Time Period	Denominator
Drug Diversion	Rate of drug buys, seizures, drug thefts, etc. by law enforcement authorities	Original OPANA ER	Pre-reformulated OxyContin (Pre-ORF)/Pre-reformulated OPANA ER Post-ORF/pre- reformulated OPANA ER (Pre-CRF)	Per 100,000 Population Per 100,000 Dosing Units

APPENDIX 5. COMPARATOR DATA – RADARS SYSTEM POISON CENTER PROGRAM

- Table 5-1** Intentional Abuse Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016
- Table 5-2** Intentional Abuse Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016
- Table 5-3** Major Medical Outcome and Death Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016
- Table 5-4** Major Medical Outcome and Death Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016
- Table 5-5** Overdose Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016
- Table 5-6** Overdose Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016

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Table 5-1: Intentional Abuse Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage Change (95% CI)
ER Morphine	Pre ORF/Pre CRF	0.0141 (0.0121,0.0165)	Post ORF/Post CRF over Pre ORF/Pre CRF	-50.9% (-60.8%,-38.5%)
	Post ORF/Pre CRF	0.0127 (0.0105,0.0154)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-10.2% (-29.8%, 14.8%)
	Post ORF/Post CRF	0.0069 (0.0059,0.0082)	Post ORF/Post CRF over Post ORF/Pre CRF	-45.3% (-57.5%,-29.6%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0006 (0.0003,0.0011)	Post ORF/Post CRF over Pre ORF/Pre CRF	-44.8% (-77.0%, 32.5%)
	Post ORF/Pre CRF	0.0013 (0.0008,0.0021)	Post ORF/Pre CRF over Pre ORF/Pre CRF	120.4% (0.1%, 385.7%)
	Post ORF/Post CRF	0.0003 (0.0002,0.0006)	Post ORF/Post CRF over Post ORF/Pre CRF	-75.0% (-88.6%,-44.9%)

Table 5-2: Intentional Abuse Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
ER Morphine	Pre ORF/Pre CRF	0.0442 (0.0380,0.0516)	Post ORF/Post CRF over Pre ORF/Pre CRF	-61.3% (-69.1%,-51.7%)
	Post ORF/Pre CRF	0.0353 (0.0292,0.0426)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-20.3% (-37.6%, 1.7%)
	Post ORF/Post CRF	0.0171 (0.0145,0.0201)	Post ORF/Post CRF over Post ORF/Pre CRF	-51.5% (-62.2%,-37.7%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0464 (0.0242,0.0890)	Post ORF/Post CRF over Pre ORF/Pre CRF	-64.0% (-85.7%,-9.5%)
	Post ORF/Pre CRF	0.0738 (0.0441,0.1235)	Post ORF/Pre CRF over Pre ORF/Pre CRF	59.1% (-30.7%, 265.2%)
	Post ORF/Post CRF	0.0167 (0.0087,0.0320)	Post ORF/Post CRF over Post ORF/Pre CRF	-77.4% (-90.1%,-48.1%)

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Table 5-3: Major Medical Outcome and Death Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
ER Morphine	Pre ORF/Pre CRF	0.0106 (0.0092,0.0122)	Post ORF/Post CRF over Pre ORF/Pre CRF	-22.8% (-36.0%,-6.7%)
	Post ORF/Pre CRF	0.0106 (0.0089,0.0125)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-0.2% (-20.1%, 24.7%)
	Post ORF/Post CRF	0.0082 (0.0072,0.0092)	Post ORF/Post CRF over Post ORF/Pre CRF	-22.6% (-37.2%,-4.6%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0001 (0.0000,0.0004)	Post ORF/Post CRF over Pre ORF/Pre CRF	65.5% (-80.8%, 1326%)
	Post ORF/Pre CRF	0.0004 (0.0002,0.0009)	Post ORF/Pre CRF over Pre ORF/Pre CRF	588.9% (-10.7%, 5215%)
	Post ORF/Post CRF	0.0001 (0.0000,0.0003)	Post ORF/Post CRF over Post ORF/Pre CRF	-76.0% (-93.8%,-6.2%)

Table 5-4: Major Medical Outcome and Death Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
ER Morphine	Pre ORF/Pre CRF	0.0331 (0.0287,0.0382)	Post ORF/Post CRF over Pre ORF/Pre CRF	-39.2% (-49.6%,-26.8%)
	Post ORF/Pre CRF	0.0293 (0.0248,0.0347)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-11.4% (-28.9%, 10.3%)
	Post ORF/Post CRF	0.0201 (0.0179,0.0227)	Post ORF/Post CRF over Post ORF/Pre CRF	-31.4% (-44.2%,-15.7%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0046 (0.0007,0.0310)	Post ORF/Post CRF over Pre ORF/Pre CRF	8.0% (-88.0%, 869.5%)
	Post ORF/Pre CRF	0.0231 (0.0099,0.0540)	Post ORF/Pre CRF over Pre ORF/Pre CRF	397.1% (-38.0%, 3889%)
	Post ORF/Post CRF	0.0050 (0.0017,0.0150)	Post ORF/Post CRF over Post ORF/Pre CRF	-78.3% (-94.6%,-13.0%)

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Table 5-5: Overdose Exposure Mentions per 100,000 Population - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
Opana ER	Pre ORF/Pre CRF	0.0254 (0.0221,0.0292)	Post ORF/Post CRF over Pre ORF/Pre CRF	-22.0% (-34.8%,-6.6%)
	Post ORF/Pre CRF	0.0491 (0.0437,0.0552)	Post ORF/Pre CRF over Pre ORF/Pre CRF	93.3% (61.4%, 131.5%)
	Post ORF/Post CRF	0.0198 (0.0177,0.0223)	Post ORF/Post CRF over Post ORF/Pre CRF	-59.6% (-65.7%,-52.4%)
ER Morphine	Pre ORF/Pre CRF	0.1347 (0.1254,0.1447)	Post ORF/Post CRF over Pre ORF/Pre CRF	-23.9% (-30.7%,-16.4%)
	Post ORF/Pre CRF	0.1354 (0.1245,0.1472)	Post ORF/Pre CRF over Pre ORF/Pre CRF	0.5% (-10.0%, 12.2%)
	Post ORF/Post CRF	0.1025 (0.0965,0.1090)	Post ORF/Post CRF over Post ORF/Pre CRF	-24.2% (-31.7%,-16.0%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0024 (0.0017,0.0034)	Post ORF/Post CRF over Pre ORF/Pre CRF	-31.7% (-58.0%, 11.0%)
	Post ORF/Pre CRF	0.0035 (0.0025,0.0050)	Post ORF/Pre CRF over Pre ORF/Pre CRF	47.6% (-10.7%, 144.0%)
	Post ORF/Post CRF	0.0016 (0.0012,0.0023)	Post ORF/Post CRF over Post ORF/Pre CRF	-53.7% (-71.3%,-25.5%)

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Table 5-6: Overdose Exposure Mentions per 100,000 Dosage Units Dispensed - Comparison of Means from January 2009 through June 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)
Opana ER	Pre ORF/Pre CRF	0.7657 (0.6855,0.8552)	Post ORF/Post CRF over Pre ORF/Pre CRF	-14.5% (-26.0%,-1.3%)
	Post ORF/Pre CRF	0.8605 (0.7838,0.9447)	Post ORF/Pre CRF over Pre ORF/Pre CRF	12.4% (-2.8%, 29.9%)
	Post ORF/Post CRF	0.6543 (0.5962,0.7180)	Post ORF/Post CRF over Post ORF/Pre CRF	-24.0% (-33.3%,-13.3%)
ER Morphine	Pre ORF/Pre CRF	0.4216 (0.3940,0.4512)	Post ORF/Post CRF over Pre ORF/Pre CRF	-40.1% (-45.2%,-34.5%)
	Post ORF/Pre CRF	0.3760 (0.3473,0.4071)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-10.8% (-19.7%,-1.0%)
	Post ORF/Post CRF	0.2526 (0.2384,0.2676)	Post ORF/Post CRF over Post ORF/Pre CRF	-32.8% (-39.1%,-25.9%)
SE IR Oxymorphone	Pre ORF/Pre CRF	0.1948 (0.1345,0.2821)	Post ORF/Post CRF over Pre ORF/Pre CRF	-55.4% (-72.9%,-26.7%)
	Post ORF/Pre CRF	0.2075 (0.1451,0.2968)	Post ORF/Pre CRF over Pre ORF/Pre CRF	6.5% (-36.3%, 78.3%)
	Post ORF/Post CRF	0.0868 (0.0622,0.1211)	Post ORF/Post CRF over Post ORF/Pre CRF	-58.2% (-74.3%,-31.8%)