SPONSOR BRIEFING DOCUMENT

ARYMO™ ER
(MORPHINE SULFATE) EXTENDED-RELEASE TABLETS

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

MEETING DATE: August 4, 2016

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Table of Contents

List of Tables

List of Figures

List of Abbreviations and Definition of Terms

ADF	abuse-deterrent formulation
API	active pharmaceutical ingredient
AQ	abuse quotient
CDC	Centers for Disease Control and Prevention
CI	confidence interval
ER	extended-release
FDA	United States Food and Drug Administration
HAP	human abuse potential
IN	intranasal
IR	immediate-release
IV	intravenous
LA	long-acting
LS	least squares
NDA	New Drug Application
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic(s)
PEO	polyethylene oxide
PK	pharmacokinetic(s)
q8h	every 8 hours
q12h	every 12 hours
PSR	particle size reduction
RLD	reference listed drug
SD	standard deviation
SE	standard error
TEAE	treatment emergent adverse event
VAS	visual analog scale

1 EXECUTIVE SUMMARY

Arymo™ ER is an abuse-deterrent, extended-release (ER), oral morphine formulation that, if approved, will be indicated 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. Arymo ER will be provided as 15 mg, 30 mg, and 60 mg tablets for oral administration. Egalet Corporation (Egalet) submitted a New Drug Application (NDA) to the Food and Drug Administration (FDA) on December 14, 2015 requesting approval of Arymo ER.

The abuse-deterrent properties of Arymo ER are based on Egalet's proprietary Guardian™ Technology. Guardian Technology is a polymer matrix tablet technology that utilizes a novel application of injection molding to manufacture pharmaceutical tablets. This technology results in tablets with controlled-release properties as well as physical and chemical barriers that resist both simple and rigorous methods of manipulation. Arymo ER tablets are extremely hard, resistant to particle size reduction (PSR), and inhibit attempts at chemical extraction of the active pharmaceutical ingredient (API). In addition, the technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe. These features are intended to address the risk of accidental misuse (e.g., chewing) in patients with chronic pain as well as intentional abuse via alternate routes of administration (i.e., manipulated oral, intranasal, intravenous).

The purpose of this joint Advisory Committee meeting is to provide a forum for the Committee members to discuss and provide guidance to the FDA on the approvability and abuse-deterrent labeling language for Arymo ER. This briefing document was prepared in order to provide the Advisory Committee members the data needed to assist in making these determinations and answering the questions posed by the FDA.

Background

Millions of Americans suffer from chronic pain, which is a complex clinical condition that can be difficult to treat. Non-opioid therapies can be effective treatments, although some patients do not find adequate pain relief from these therapies alone. A guideline published jointly by the America Pain Society and the American Academy of Pain Medicine support opioid treatment as a useful component of a pain management plan in non-cancer patients (Chou et al., 2009). However, it is well-recognized that the need for patient access to these medications must be balanced against the public health imperative to address the ongoing prescription opioid abuse epidemic.

Opioid abusers seek the rapid rise in opioid blood level that occurs with immediate-release (IR) formulations in order to achieve a quick onset of the positive psychoactive effects. Extended-release opioids are often manipulated to defeat the ER profile, effectively rendering them into an IR form and/or to access alternate routes of abuse (e.g., nasal, IV). Abusers want extended-release opioids that can be manipulated easily with a high yield of opioid.

Abuse-deterrent formulations (ADFs) of prescription opioid products are designed to be more difficult to misuse and manipulate for the purposes of abuse and/or make a product less desirable to abusers. These formulations have been developed as one strategy, among many (e.g., proper

prescribing, safe disposal, education), to address this public health crisis. It is important to keep in mind that because these products need to deliver effective analgesia for appropriate patients with chronic pain, they are designed to be abuse-deterrent and not 'abuse-proof'.

While there is a perception that the number of prescriptions for ER/LA opioids have been increasing with the introduction of new opioids, including ADFs, they have actually decreased from 22.3 million in 2011 to 20.7 million in 2015 (IMS, 2016). As of June 30, 2016, FDA has approved six abuse-deterrent opioids. Of these, reformulated abuse-deterrent OxyContin® (oxycodone hydrochloride) extended-release tablets have the greatest market penetration. Emerging post-marketing data suggest that this product, which also uses a physical-chemical barrier approach to abuse deterrence, has led to a meaningful reduction in the rates of misuse, abuse, and diversion since its reformulation (Dart et al., 2015; Coplan et al., 2016). These data support ADF technology as an effective component of the overall public health response to reduce opioid abuse.

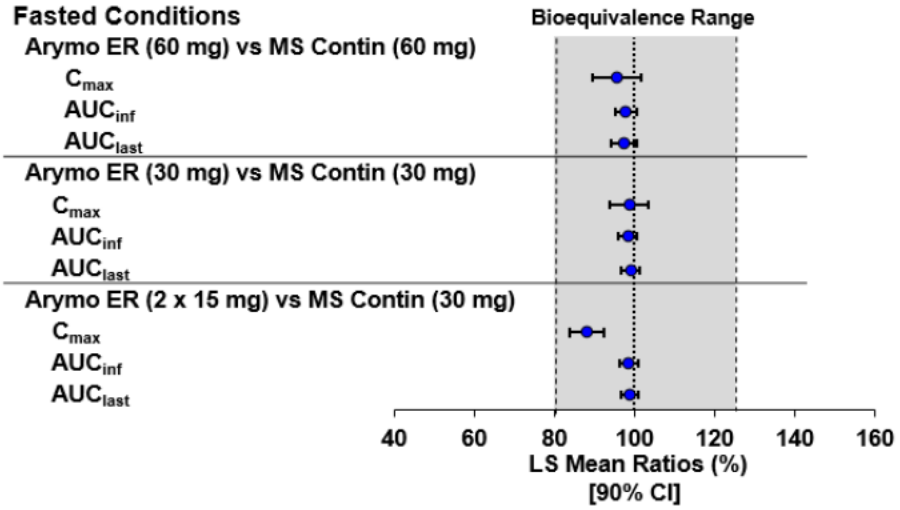
Morphine is the most commonly prescribed ER opioid analgesic with approximately 6.4 million prescriptions filled in outpatient retail pharmacies in 2015 (IMS, 2016). Epidemiologic data suggest that manipulated oral, nasal, and intravenous (IV) routes are all employed by abusers of morphine products, with IV abuse being the most common non-oral route. IV injection is also the most dangerous route of abuse, and presents a particular public health challenge due to the risk of overdose and death as well as other serious health consequences including blood-borne infectious diseases (e.g., HIV and hepatitis) and other medical complications.

In the first 4 months of 2016, 98.5% of prescriptions filled for ER morphine were for products with no abuse-deterrent properties (IMS, 2016). These products can be easily crushed into a fine powder, converted into an immediate-release (IR) form, and snorted or prepared for IV injection with minimal time and effort. The goal of ADFs is to offer an opportunity for non-abuse-deterrent formulations to eventually be replaced. Arymo ER was developed in order to help address this unmet public health need by providing a formulation of ER morphine with robust physical and chemical properties that are expected to deter abuse against the manipulated oral, nasal, and intravenous routes.

Development of Arymo ER for the Proposed Indication

Arymo ER was developed under the 505(b)(2) regulatory pathway, which provides for product approval based, in part, on the demonstration of bioequivalence to a reference listed drug (RLD). In two clinical pharmacokinetic (PK) studies, Arymo ER demonstrated bioequivalence to the RLD, MS Contin® (morphine sulfate extended-release tablets), across the proposed dosage range for Arymo (Figure 1). Bioequivalence to MS Contin provides the scientific bridge to safety and efficacy to support regulatory approval, and thus, a Phase 3 study was not required by the Agency.

Figure 1: Bioequivalence Parameters for Arymo ER Relative to MS Contin under Single-Dose Fasted Conditions – Studies EG-011 and EG-012



Clinical PK data show that there is no clinically relevant food effect with Arymo ER, so the product may be taken without regard to food. In addition, an *in vitro* alcohol dissolution study showed no increase of morphine release with increasing concentrations of alcohol; rather, the release of morphine slowed with higher concentrations of alcohol. This provides evidence that Arymo ER does not dose dump in the presence of alcohol. However, consistent with opioid products, Arymo ER should not be taken with alcohol.

Abuse-Deterrent Properties for the Manipulated Oral, Nasal, and IV Routes

Arymo ER was designed with physical and chemical properties to deter common and relevant routes of misuse and abuse of ER morphine products. These features are summarized in Table 1.

Table 1: Abuse-Deterrent Features of Arymo ER

Route of Abuse	Method of Abuse	Abuse-Deterrent Feature of Arymo ER	Clinical Relevance
Manipulated Oral	**Chewing or Crushing**	Hardness of the tablet	Arymo ER would be difficult to accidentally misuse or intentionally abuse by chewing; physical manipulation does not transform Arymo ER into an IR form, which could increase liking and euphoria
Nasal	**Snorting**	Resistance to particle size reduction	Physical manipulation is not effective at producing particles amenable for snorting
Intravenous	**Injection**	Hydrophilic nature of the tablet matrix	Isolating morphine from Arymo ER is difficult
		Gelling upon contact with liquid	Arymo ER is very difficult to draw into a syringe
Inhalation	**Smoking**	Poor combustion	Smoking or freebasing is not feasible

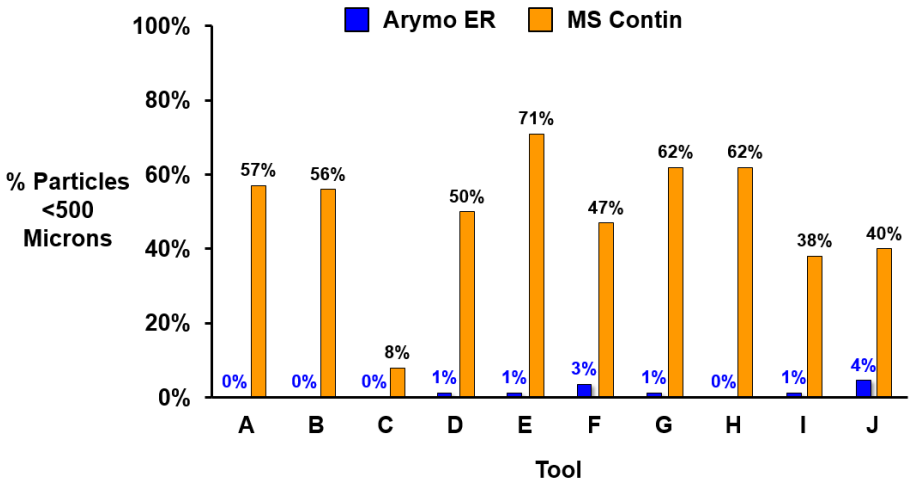
Egalet conducted a comprehensive battery of studies (Categories 1, 2, and 3) to evaluate the abuse-deterrent properties of Arymo ER compared to MS Contin, a non-ADF ER comparator, in accordance with the FDA Guidance "*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*" (FDA, 2015).

Category 1 Studies

Category 1 *in vitro* studies evaluate the resistance of products to physical manipulation and chemical extraction. These experiments assess the ability to transform a product into forms suitable for abuse via alternate routes (i.e., manipulated oral, nasal, IV, smoking) and measure the yield from these procedures. Key findings from Category 1 investigations include:

- Arymo ER demonstrated considerable resistance to particle size reduction (PSR) compared to MS Contin, which could be easily crushed into a fine powder
    - Single-step manipulations could not effectively reduce Arymo ER into particles of a size amenable to snorting (<500 microns) (Figure 2)
    - Arymo ER broke numerous tools used during attempts at PSR due to the extreme hardness of the tablets
    - Sequential, multi-tool methods were tested to identify the maximal PSR of Arymo ER, but still yielded limited output of particles amenable for snorting
    - Pre-treatment with heating and freezing did not impact the PSR of Arymo ER

Figure 2: Particle Size Reduction Results with 10 Tools



- The gelling properties of Arymo ER make it difficult to draw into a syringe and recover morphine
    - Under Temperature B and Agitation A, 0-9% of morphine was recovered from manipulated Arymo ER vs. 52-66% with crushed MS Contin after 5 minutes
    - Longer incubation times for Arymo ER through 24 hours did not improve morphine yield; 16-18% morphine could be recovered, but only with Needle Gauge D, which is not preferred for IV abuse

- Arymo ER was more resistant than MS Contin to extraction in large volumes of ingestible and non-ingestible, toxic solvents
- Heating/vaporization yields very little API, so smoking is not a viable route of abuse

Category 2/3 Studies

Category 2 PK studies evaluate whether a product maintains its ER profile after manipulation and administration through different routes of abuse. Category 3 pharmacodynamic (PD) studies evaluate Drug Liking and other secondary endpoints (e.g., Take Drug Again, Overall Drug Liking, Feeling High) in nondependent recreational opioid users. The abuse-deterrent development program for Arymo ER included two Category 3 human abuse potential (HAP) studies that evaluated the manipulated oral and nasal routes of abuse. These studies also included Category 2 PK assessments for each of these routes and evaluated the consistency between the PK and PD outcomes. Key findings from the Category 2/3 studies of Arymo ER include:

- The oral HAP study met its primary endpoint by demonstrating a statistically significant reduction in maximum Drug Liking (E_{max}) for manipulated Arymo ER compared to crushed MS Contin (p=0.0069)
- The intranasal HAP study also met its primary endpoints by demonstrating statistically significant reductions in Drug Liking E_{max} for two treatment arms of manipulated Arymo ER (i.e., without and with sieving to remove large particles that were difficult to snort) compared to crushed MS Contin ($p<0.0001$ for both)
- The primary endpoints in the manipulated oral and intranasal HAP studies were supported by positive findings on the majority of key secondary PD endpoints
- Manipulated Arymo ER was rated as being more difficult to snort than crushed MS Contin due to resistance to PSR (i.e., large particle sizes)
- Arymo ER was not converted into an IR profile after manipulation and oral or intranasal administration, unlike crushed MS Contin
- There was consistency between the PK and PD findings for Arymo ER across both HAP studies

Conclusion

Overall, the development program for Arymo ER provides the evidence for approvability based on the demonstration of bioequivalence to the RLD, MS Contin. Bioequivalence provides the scientific bridge for the safety and efficacy of Arymo ER 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. Arymo ER was also shown to have no clinically relevant interaction with food and does not dose-dump in the presence of alcohol.

Arymo ER is formulated with physical and chemical barriers designed to make abuse and misuse of the product more difficult and to make abuse less rewarding. The abuse-deterrent studies for Arymo ER demonstrate that the product has properties that can be expected to deter abuse by the manipulated oral, nasal, and IV routes. If approved, Arymo ER would provide a public health benefit over the currently available non-ADF ER morphine products by mitigating the risk for misuse and abuse while offering the same therapeutic effects for patients with chronic pain.

2 UNMET PUBLIC HEALTH NEED FOR ABUSE-DETERRENT EXTENDED-RELEASE MORPHINE PRODUCTS

Summary

- Approximately 25 million people in the US are afflicted with chronic pain. For select patients who do not respond to alternative treatments, long-term opioid therapy can provide substantial relief from chronic pain.
- There is an ongoing epidemic of prescription opioid abuse in the United States, which requires a comprehensive, multi-faceted public health response. This response requires both preventative and treatment-oriented strategies.
- The purpose of manipulation of an ER opioid is to convert it into an IR form and/or to access alternate routes of abuse (e.g., nasal, IV).
- One of the approaches to prevent abuse is the development of abuse-deterrent formulations (ADFs). Post-marketing data from reformulated OxyContin suggest that ADFs can meaningfully reduce the rates of misuse, abuse, and diversion.
- ER morphine is the most frequently prescribed ER opioid analgesic with approximately 6.4 million prescriptions filled in U.S. outpatient retail pharmacies in 2015.
- ER morphine is abused through all routes of administration (oral, nasal, and IV). The most common non-oral route of abuse of ER morphine products is IV injection, which is also the most dangerous route.
- 98.5% of the ER morphine prescriptions dispensed thus far in 2016 had no abuse-deterrent properties. These can be quickly and easily crushed, snorted, or prepared for IV injection.
- To address the unmet public health need, the goal of ADFs is to eventually replace opioid products that do not have abuse-deterrent properties with products formulated with barriers to abuse.

2.1 Background on Chronic Pain

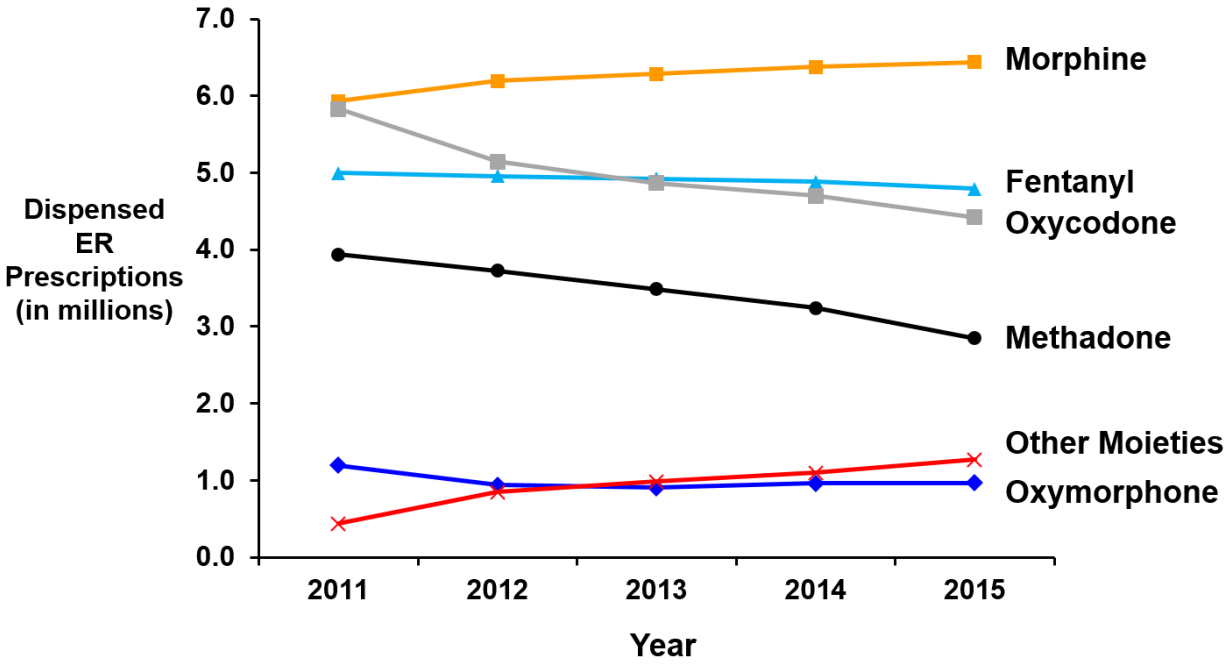
Over 25 million individuals in the U.S. suffer from chronic pain, defined as experiencing pain every day for the previous 3 months (Nahin, 2015). Chronic pain is associated with physical, mental, emotional, and societal burdens that substantially impact quality of life. The economic burden of chronic pain amounts to $560-630 billion each year for healthcare expenses and lost productivity (IOM, 2011).

Chronic pain is complex and can be difficult to treat. Non-opioid alternatives such as nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, or surgery, are appropriate and adequate therapies for many patients with chronic pain. For patients who do not respond to or are inadequately treated by non-opioid therapies, extended-release/long-acting (ER/LA) opioid analgesics represent an important option for pain relief (Chou et al., 2009).

2.2 Medical Use and Abuse of ER Opioid Products

Morphine is the most frequently prescribed ER opioid analgesic (Figure 3), with 6.4 million prescriptions dispensed in 2015 (IMS, 2016). This is partly because morphine has a long history of medical use, is effective orally, and health care professionals are familiar with prescribing it.

Figure 3: Estimated Number of Extended-Release and Long-Acting Opioid Analgesics Dispensed in the United States (IMS, 2016)



ER opioid products play an important role in the management of chronic pain. While there is a perception that the number of prescriptions for ER/LA opioids have been increasing with the introduction of new opioids, including ADFs, they have actually decreased from 22.3 million in 2011 to 20.7 million in 2015 (IMS, 2016). Despite this decline in prescribing, the public health risk from abuse and diversion remains significant. This risk applies both to patients in pain as well as anyone with access to their medicines. In fact, nearly 70% of the prescription opioids used for the purposes of abuse are obtained from a family member or a friend (SAMHSA, 2014).

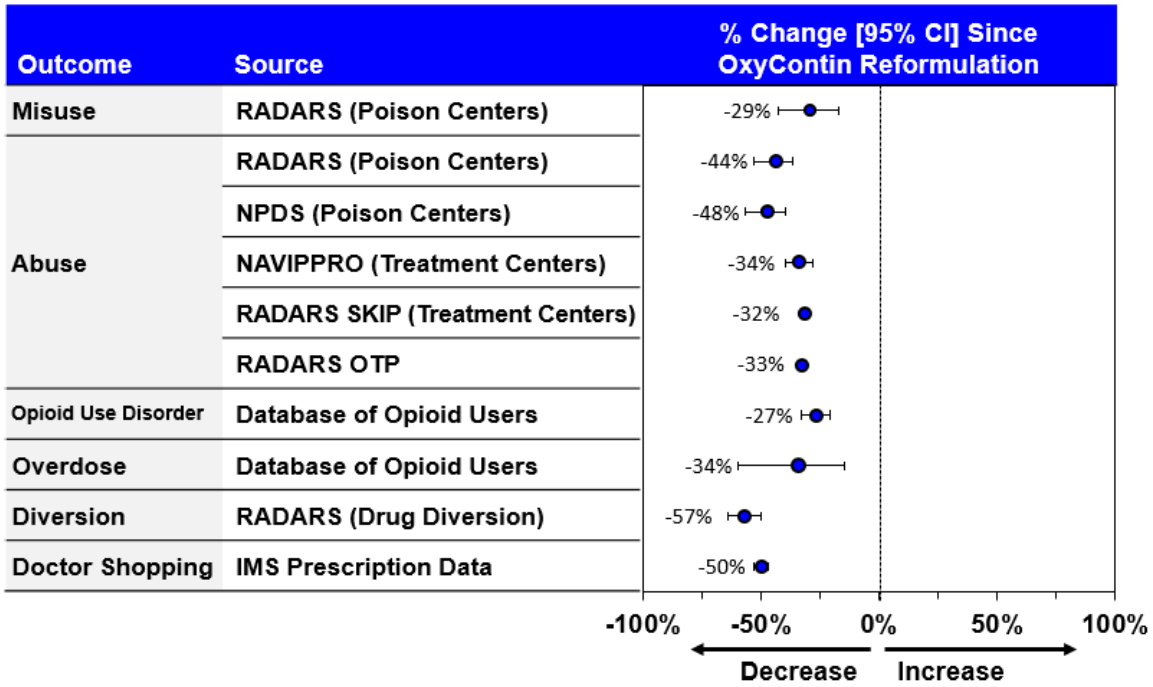
Prescription ER opioids are often manipulated in order to get the product into forms suitable for abuse via alternate routes (i.e., manipulated oral, nasal, IV, smoking) rather than taking the product intact orally. Usually this involves crushing or grinding an ER product in order to convert it into an IR form, ideally with high yield of the opioid. The combination of altering the release profile of an ER product to that of an IR product, and accessing alternate routes of abuse, increases the speed of entry of opioid into the brain, which can result in faster and greater euphoria, drug liking, and risk of abuse.

2.3 Role of Abuse-Deterrent Technology

One approach to combat opioid abuse is the development of opioid formulations with abuse-deterrent features. As of June 30, 2016, the FDA has approved six ER/LA opioid analgesic products with labeling language regarding their abuse-deterrent properties. These include products with physical chemical barriers (reformulated OxyContin®, Hysingla® ER, MorphaBond™, and Xtampza™ ER) as well as combination agonist/antagonist opioid products (Embeda® and Targiniq™ ER).

The ADF with the largest post-marketing database is reformulated OxyContin, an ER oxycodone product whose abuse deterrence is based on physical and chemical barriers. Emerging epidemiologic data support a decrease in the rate of OxyContin abuse since its reformulation (Dart et al., 2015; Coplan et al., 2016). Figure 4 illustrates the reduction in misuse, abuse, overdose, and diversion from 1 year before to 3 years after OxyContin reformulation, which has been noted across multiple epidemiologic databases and studies, even after taking the decrease in oxycodone prescriptions into consideration (Coplan et al., 2016). These data provide evidence as to the real-world effect that greater adoption of ADF technologies could have in reducing opioid abuse.

Figure 4: Percent Changes in the Rates of Various Adverse Outcomes from 1 Year Before to 3 Years After Reformulation of OxyContin into an Abuse-Deterrent Form, Controlling for Prescription Volume

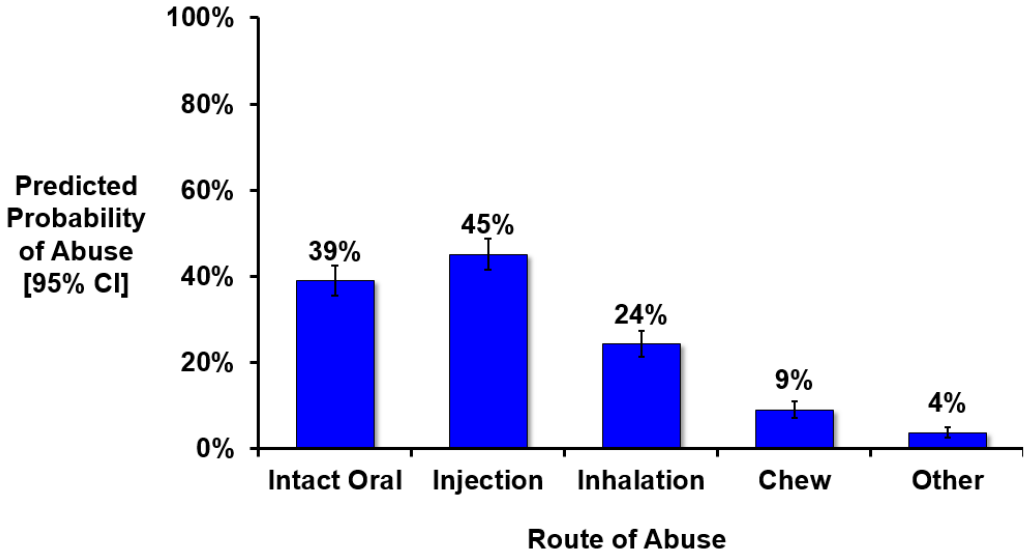


RADARS: Researched Abuse, Diversion, and Addiction-Related Surveillance; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients Program; NPDS: National Poison Data System; NAVIPPRO: National Addiction Vigilance and Intervention Prevention Program

2.4 Routes of Abuse of ER Morphine Products

Extended-release morphine products are abused by all of the most common routes of administration, namely oral (intact and manipulated), intranasal, and IV injection. Figure 5 shows a summary of the relative rates of abuse of ER morphine as determined by assessment of 59,792 patients aged 18 or older entering treatment for substance use disorders at 464 treatment facilities in 34 states (Butler et al., 2011). The patients could endorse multiple routes used over the past 30 days. Data from the RADARS® Poison Center Program evaluating rates of intentional abuse exposure among individuals 12 years or older calling a poison center found that the oral route of administration is most common (72%) followed by IV injection (24%), and snorting (4%) (RADARS, 2016). Taken together, these data show that IV injection is the most common non-oral route of abuse of ER morphine products.

Figure 5: Prevalence of Routes of Past 30-day Abuse for Extended-Release Morphine in ASI-MV (Addiction Severity Index-Multimedia Version) Network (Butler, 2011)

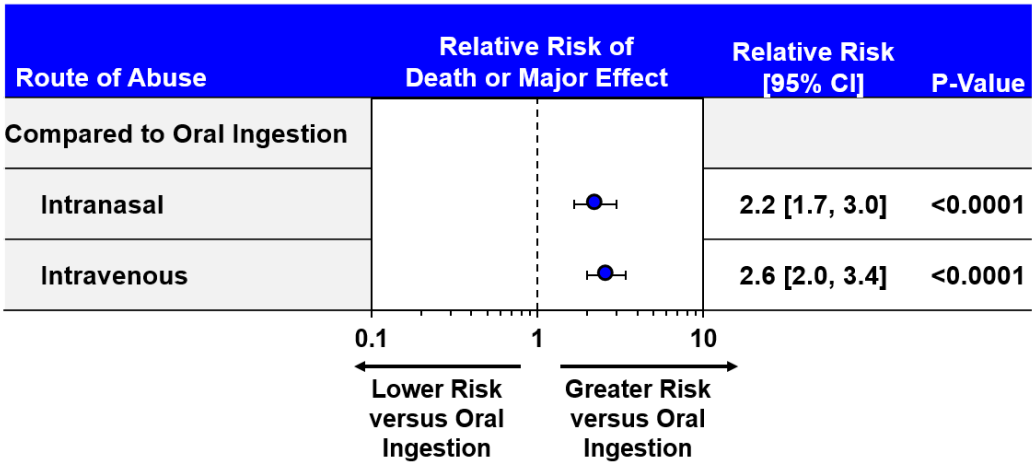


IV injection is not only the most prevalent non-oral route of abuse for ER morphine, it is also the most dangerous. IV abuse of prescription opioids is associated with serious health consequences including transmission of infectious diseases such as Hepatitis C (Bruneau et al., 2012; Lankenau et al., 2015; Valdiserri et al., 2014; Zibbell et al., 2014) and HIV (Conrad et al., 2015; Surratt et al., 2011; Ronan et al., 2016) in addition to risk of local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury (Chong et al., 2009; Ho et al., 2009; Nguyen et al., 2014). Intranasal abuse is also associated with a risk of hepatitis transmission through the use of shared drug implements and a risk of tissue necrosis with potential septal and palatal perforation and serious fungal infections (Houlton et al., 2012; McMahon et al., 2003; Ronan et al., 2016; Tortu et al., 2004).

According to data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System (2016), the risk of death or a major effect (i.e., life-threatening or resulting

in significant residual disability or disfigurement) is 2.2 times higher for intranasal and 2.6 times higher for intravenous abuse compared to oral abuse (Figure 6).

Figure 6: Relative Risk of Death or Major Effect for Intranasal and Intravenous Routes of Opioid Abuse Compared to Oral Route (RADARS, 2016)



2.5 Description and Utilization of Currently-Approved Abuse-Deterrent ER Morphine Products

Currently, two abuse-deterrent ER morphine products are approved in the U.S.:

- **Embeda** is a morphine sulfate and naltrexone hydrochloride combination tablet that uses an agonist/antagonist mechanism for abuse deterrence. Embeda is formulated to release sequestered opioid antagonist upon physical manipulation. This abuse-deterrent feature is expected to reduce the potential for abuse by oral ingestion, insufflation, and IV injection. Embeda was approved in 2009, removed from the market in 2011 for stability issues, and reintroduced to the market in late 2015. Product considerations include:
  - Dose-dumping in the presence of alcohol, which is included as a boxed warning in the product label, related to the risk of overdose and death
  - Potential for acute opioid withdrawal following ingestion of chewed or crushed product (Ruan et al., 2010)
  - Ability to syringe the product, exposing abusers to the health risks of IV injection
- **MorphaBond** is a morphine sulfate tablet with physical and chemical barriers that is not currently marketed. Data on the oral human abuse potential and extent of its resistance to small volume extraction could not be found in the public domain.

In 2015, there were 6.4 million prescriptions filled in outpatient retail pharmacies for ER morphine products. Of the 2.15 million prescriptions filled between January and April of 2016, 98.5% were for products without abuse-deterrent features (IMS, 2016). These non-abuse-deterrent products can be easily crushed, snorted, or prepared for IV injection. An unmet public health need remains for ER morphine products with properties to address all common routes of abuse without the risk of alcohol dose-dumping or opioid withdrawal for patients with chronic

pain. The intention of ADF products is not to increase the number of prescriptions for ER opioids, but rather to replace existing products without abuse-deterrent features. Arymo ER, an extended-release morphine product formulated with physical and chemical barriers to deter misuse and abuse, would provide a new treatment option and help address this unmet public health need.

3 OVERVIEW OF ARYMO ER FORMULATION AND DEVELOPMENT PROGRAM

Summary

- The abuse-deterrent properties of Arymo ER are a result of Egalet's proprietary 3™ Technology, a polymer matrix tablet technology coupled with an injection molding manufacturing process that results in tablets with controlled-release properties as well as physical and chemical barriers to resist both simple and rigorous methods of manipulation.
- Guardian Technology results in tablets that are extremely hard, resistant to particle size reduction, and inhibit attempts at chemical extraction of the API. Upon contact with liquid, Arymo tablets become a viscous hydrogel, making extraction of morphine and drawing into a syringe for the purposes of IV injection very difficult.
- Demonstration of bioequivalence of Arymo ER to the reference listed drug MS Contin is a scientific bridge to safety and efficacy and a basis for approval of Arymo ER.
- Arymo ER's abuse-deterrent properties were assessed in a comprehensive battery of studies (Categories 1, 2, and 3) consistent with FDA's final Guidance on abuse-deterrent opioid development (FDA, 2015).

3.1 Formulation Development

Egalet Corporation (Egalet) has developed Arymo ER (morphine sulfate) extended-release oral tablets (known during development as EG-001), an abuse-deterrent, morphine product indicated 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. The active pharmaceutical ingredient (API), morphine sulfate, is the same as that of the reference listed drug (RLD), MS Contin, but the drug product is differentiated by abuse-deterrent properties based on Egalet's proprietary Guardian Technology.

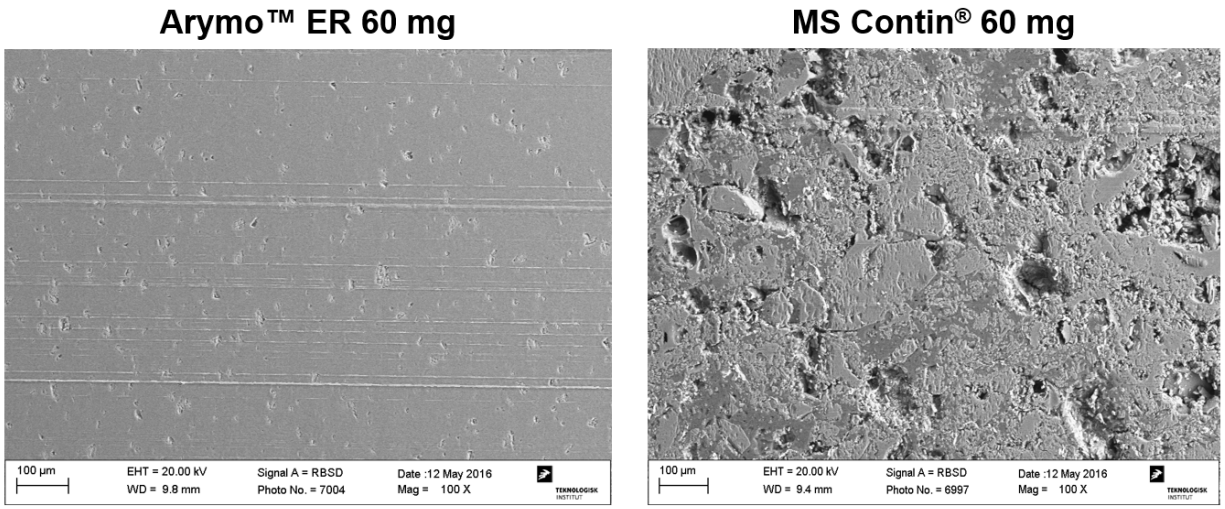
Arymo ER will be provided as 15 mg, 30 mg, and 60 mg tablets for oral administration every 8-12 hours. All Arymo ER dosage strengths are provided in tablets sized 7.5 mm by 19 mm, approximately the size of an Extra Strength Tylenol® tablet.

The abuse-deterrent properties of Arymo ER are based on Egalet's proprietary Guardian Technology. Guardian Technology is a polymer matrix tablet technology that utilizes a novel application of injection molding to manufacture pharmaceutical tablets. This technology results in tablets with controlled-release properties as well as physical and chemical barriers that resist both simple and rigorous methods of manipulation. Arymo ER tablets are extremely hard, resistant to particle size reduction (PSR), and inhibit attempts at chemical extraction of the active pharmaceutical ingredient (API). In addition, the technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe. These features are important to address the risk of accidental misuse (e.g., chewing) in patients with chronic pain as

well as intentional abuse via alternate routes of administration (i.e., manipulated oral, intranasal, intravenous).

Arymo ER is manufactured by blending morphine and polyethylene oxide (PEO), putting the blend into an injection molding machine, and molding under heat and high pressure. This creates a tablet with a dense matrix and low porosity, resulting in significant tablet hardness. Laboratory testing has demonstrated that the minimum tablet hardness of Arymo ER is 400 newtons, the upper limit of a conventional hardness tester. At this force, the tablet did not break. In contrast, the tablet hardness of MS Contin was 63 newtons. For reference, the force generated during routine mastication (chewing) is 70-150 newtons (Oxford Handbook of Applied Dental Sciences, 2002). Figure 7 illustrates the differences in porosity and denseness between Arymo ER tablets and MS Contin, which account for the differences in hardness of the tablets.

Figure 7: Scanning Electron Micrographs of Cross-sections of Arymo ER and MS Contin Tablets (100x magnification)



The extended-release properties of Arymo ER are based on surface erosion of the PEO matrix with morphine imbedded in the matrix. Imbedding morphine in the PEO matrix in this unique way (injection molding process using heat and high pressure) allows Arymo ER to maintain some of its extended-release properties after manipulation (e.g., particle size reduction) because morphine is blended together with the releasing agent. In contrast, the controlled-release properties of other tablets using PEO as the releasing agent are based on diffusion, and the tablets are formulated with smaller amounts of PEO with different molecular weights.

3.2 Overview of Development Program

Arymo ER was developed under the 505(b)(2) regulatory pathway and MS Contin was chosen as the RLD. The NDA for Arymo ER includes data comparing the PK profiles of Arymo ER to MS Contin as well as data from the *in vitro* and clinical abuse-deterrent program. The NDA was submitted in December 2015 and has a PDUFA goal date of October 14, 2016.

FDA provided input to Egalet through regular meetings and advice letters on specific aspects of the development program and abuse-deterrent study designs. In addition, Egalet consulted with experts in the development of abuse-deterrent opioids to ensure that appropriate methods were used to evaluate Arymo ER.

3.2.1 Clinical PK Studies and Effect of Food

Egalet conducted two clinical PK studies to compare the PK profiles of Arymo ER to MS Contin to establish bioequivalence and to evaluate the effect of food (Table 2). PK model simulations were conducted to determine the bioavailability of Arymo ER to MS Contin under multiple dose, steady-state conditions.

Table 2: Overview of Clinical PK Studies to Assess Bioequivalence and Effect of Food

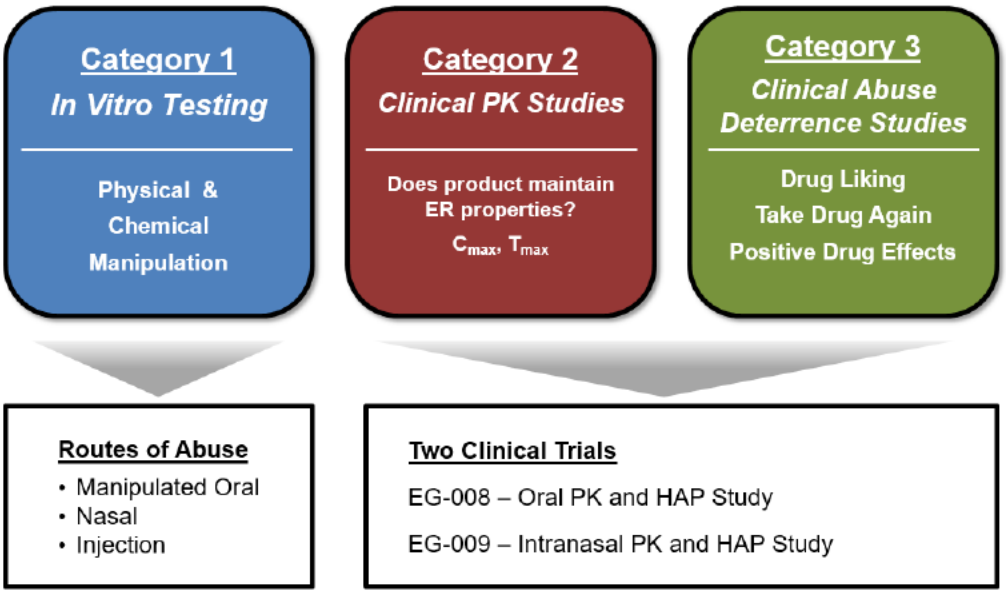
Study	Subjects	Conditions	Treatment Arms	Key Objectives
EG-011	65	• Single dose, crossover • Naltrexone-blocked • Fed and fasted	• Arymo ER (60 mg) • MS Contin (60 mg)	• Determine if Arymo ER is bioequivalent to MS Contin • Assess the effect of food on the PK profile of Arymo ER • Safety and tolerability
EG-012	66	• Single dose, crossover • Naltrexone-blocked • Fasted	• Arymo ER (2 x 15 mg) • Arymo ER (30 mg) • MS Contin (30 mg)	• Determine if Arymo ER is bioequivalent to MS Contin • Safety and tolerability

3.2.2 Abuse-Deterrent Studies

Arymo ER abuse-deterrent studies were designed based on FDA's draft guidance on the evaluation and labeling of abuse-deterrent opioids (FDA, 2013) and FDA's feedback during product development. The studies are consistent with the final FDA Guidance, which identifies three categories of pre-marketing studies that contribute to the totality of the evidence needed to support abuse-deterrent label claims (Figure 8) (FDA, 2015).

There were no abuse-deterrent ER morphine products commercially available during the development of Arymo ER. The comparator used in the abuse-deterrent studies for Arymo ER was MS Contin, a non-abuse-deterrent ER morphine product.

Figure 8: Overview of Category 1-3 Evaluations



3.2.2.1 Category 1 Studies – In Vitro Manipulation and Extraction Studies

Category 1 *in vitro* laboratory studies were performed to evaluate the time and effort required to transform Arymo ER into an abusable form in comparison to MS Contin. These studies were designed to challenge Arymo ER's physical and chemical properties under methods known to be used, or might plausibly be attempted, to defeat abuse-deterrent properties in the real-world. As shown in Table 3, these studies included general manipulations (e.g., single- and multi-tool particle size reduction) that would apply to several routes of abuse as well as route-specific evaluations for IV injection and smoking.

Table 3: Summary of Category 1 Studies and Relevant Routes of Abuse

	Route of Abuse			
Manipulation Process	**Manipulated Oral**	**IV Injection**	**Nasal**	**Smoking**
Single-tool PSR	✓	✓	✓	✓
Multi-tool PSR	✓	✓	✓	✓
Multi-tool PSR after Pre-treatment	✓	✓	✓	✓
Small Volume Extraction		✓		
Syringeability		✓		
Large Volume Extraction	✓			
Simulated Smoking Studies				✓

3.2.2.2 Category 2/3 Studies – Pharmacokinetics/Human Abuse Potential Studies

Egalet conducted two combined Category 2 and Category 3 clinical studies that evaluated both the PK and human abuse potential (HAP) or PD outcomes of manipulated Arymo ER compared to crushed MS Contin in non-dependent recreational opioid users. These studies assessed effects of the drug via the manipulated oral and nasal routes of abuse (Table 4).

Table 4: Overview of Category 2 and Category 3 Studies

Study	Subjects	Treatment Arms	Key Objectives
EG-008 (Oral)	39	• Manipulated Arymo ER with juice • Crushed MS Contin in juice • Intact oral Arymo ER with juice • Placebo	• Evaluate the abuse potential of intact and manipulated Arymo ER via the oral route of abuse compared to crushed MS Contin • Assess the PK of manipulated Arymo ER compared to crushed MS Contin • Assess safety of manipulated and intact Arymo ER following oral administration
EG-009 (Intranasal)	50	• IN Manipulated Arymo ER • IN Manipulated/sieved Arymo ER • IN Crushed MS Contin • Intact oral Arymo ER • Placebo	• Evaluate the abuse potential of manipulated Arymo ER via the nasal route of abuse compared to crushed MS Contin • Assess the PK of manipulated Arymo ER compared to crushed MS Contin • Assess safety of manipulated Arymo ER following intranasal administration

4 BIOEQUIVALENCE AND EFFECT OF FOOD

Summary

- Arymo ER was demonstrated to be bioequivalent, across its dosage range, to the reference listed drug, MS Contin.
- Steady-state simulation studies determined that Arymo ER is bioequivalent to MS Contin when administered as intended every 8-12 hours for the treatment of chronic pain.
- There was no clinically significant effect of food on the bioavailability of morphine after administration of Arymo ER in the fed versus fasted states.

4.1 Assessment of Bioequivalence to MS Contin in Single-Dose Studies

Two clinical PK studies were conducted to evaluate the relative bioavailability of Arymo ER to the RLD, MS Contin, for each proposed dosage strength. These studies were randomized, open-label, 2- or 3-period crossover studies in healthy volunteers under fasted conditions and naltrexone blockade. Subjects in each study received a single dose of each of the following treatments, separated by a 5- to 7-day wash-out period:

- EG-011: 60 mg Arymo ER, 60 mg MS Contin
- EG-012: 30 mg Arymo ER, 2 x 15 mg Arymo ER, 30 mg MS Contin

Of note, in Study EG-011, a subset of subjects also received a dose of Arymo ER 60 mg under fed conditions.

4.1.1 Study EG-011 – 60 mg Arymo ER vs. 60 mg MS Contin

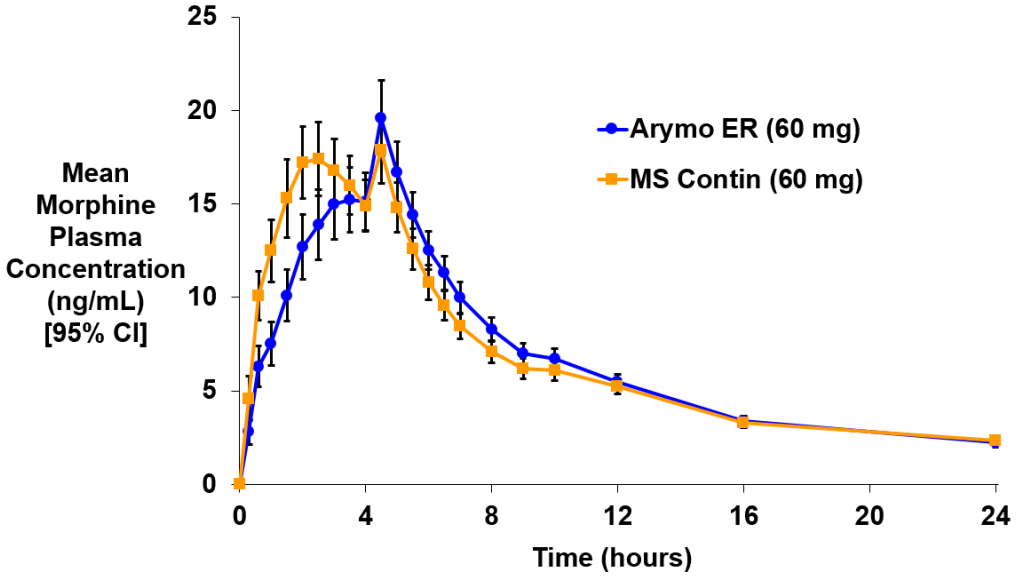
Of the 65 subjects enrolled, 61 subjects provided evaluable PK data. Table 5 provides a summary of the key PK parameters for the subjects who completed each treatment arm. Figure 9 illustrates the morphine plasma PK profiles of both products through 24-hours post-dose.

Table 5: Summary of Plasma Morphine PK Parameters in Study EG-011

PK Parameter (unit)	Arymo ER (60 mg) [Fasted Conditions] (n=60)	MS Contin (60 mg) [Fasted Conditions] (n=60)
C_{max} (ng/mL), mean (CV%)	21.6 (35.6)	22.7 (36.5)
AUC_{last} (ng•h/mL), mean (CV%)	189.1 (27.3)	192.8 (26.3)
AUC_{inf} (ng•h/mL), mean (CV%)	196.6 (27.3)	200.5 (26.8)
T_{max} (h), median (min, max)	4.5 (1.0, 6.0)	2.5 (0.67, 4.5)
$t_{1/2}$ (h), mean (CV%)	9.6 (26.3)	9.9 (28.5)

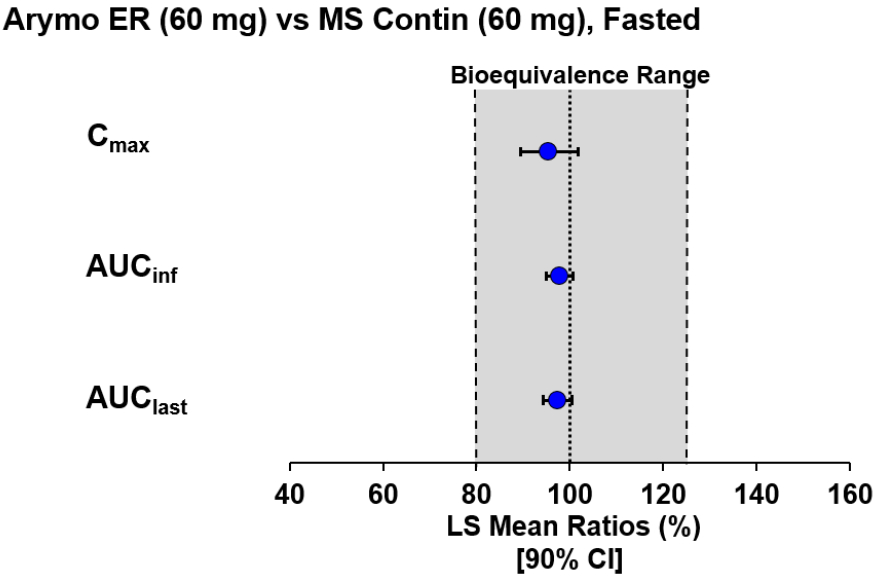
CV% = percent coefficient of variation; h = hour

Figure 9: Morphine Plasma Concentrations for Arymo ER (60 mg) and MS Contin (60 mg) under Single-Dose Fasted Conditions – Study EG-011



Arymo ER was bioequivalent to MS Contin at the 60 mg strength. According to FDA Guidance, bioequivalence is demonstrated when the 90% confidence intervals (CIs) for the least squares (LS) means for the ratio of C_{max} and AUC for the test product compared to the reference product are contained within the 80% to 125% bioequivalence range (FDA, 2014). This finding is shown graphically in Figure 10, which illustrates that the LS mean ratios and 90% CIs for the relevant PK parameters are within the bioequivalence range (denoted by gray shading).

Figure 10: Bioequivalence Assessment for Arymo ER (60 mg) Relative to MS Contin (60 mg) under Single-Dose Fasted Conditions – Study EG-011



The only notable difference between the two products under single-dose conditions was a median T_{max} for Arymo ER, which was 2 hours longer than MS Contin. However, the range of the median T_{max} values overlap, which were 1-6 hours for Arymo ER and 0.67 to 4.5 hours for MS Contin. In addition, T_{max} for a drug that is dosed to steady state is not considered clinically relevant as opposed to an immediate release product requiring a rapid onset of effect. The steady-state PK simulations of Arymo ER are discussed in Section 4.2.

4.1.2 Study EG-012 – 30 mg Arymo ER and 2 x 15 mg Arymo ER vs. 30 mg MS Contin

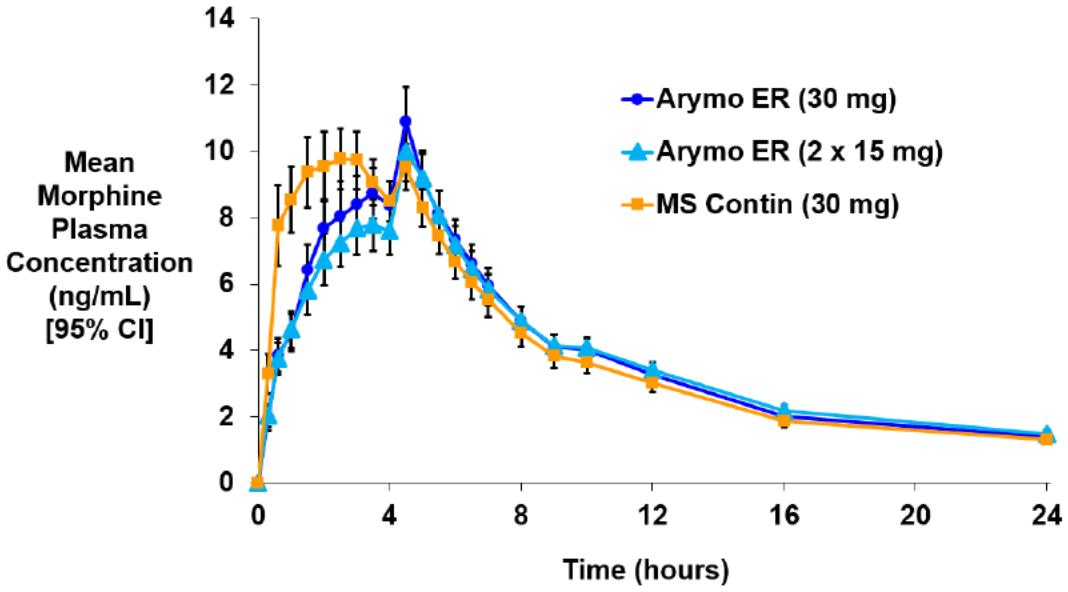
Of the 66 subjects enrolled, 63 provided evaluable PK data. Table 6 summarizes the key PK parameters for the completers within each treatment arm, and Figure 11 illustrates the mean morphine plasma concentration profiles over the first 24 hours after dosing.

Table 6: Summary of Plasma Morphine PK Parameters in Study EG-012

PK Parameter (unit)	Arymo ER (30 mg) [Fasted] (N=60)	Arymo ER (2 x 15 mg) [Fasted] (N=61)	MS Contin (30 mg) [Fasted] (N=59)
C_{max} (ng/mL), mean (CV%)	12.0 (33.5)	10.8 (33.1)	12.1 (33.3)
AUC_{last} (ng•h/mL), mean (CV%)	111.9 (25.6)	112.3 (27.1)	113.9 (29.0)
AUC_{inf} (ng•h/mL), mean (CV%)	115.7 (26.1)	117.3 (27.1)	119.2 (29.1)
T_{max} (h), median (min, max)	4.5 (0.67, 6.0)	4.5 (1.5, 8.0)	2.0 (0.67, 5.5)
$t_{1/2}$ (h), mean (CV%)	10.0 (23.6)	10.5 (23.9)	10.9 (21.2)

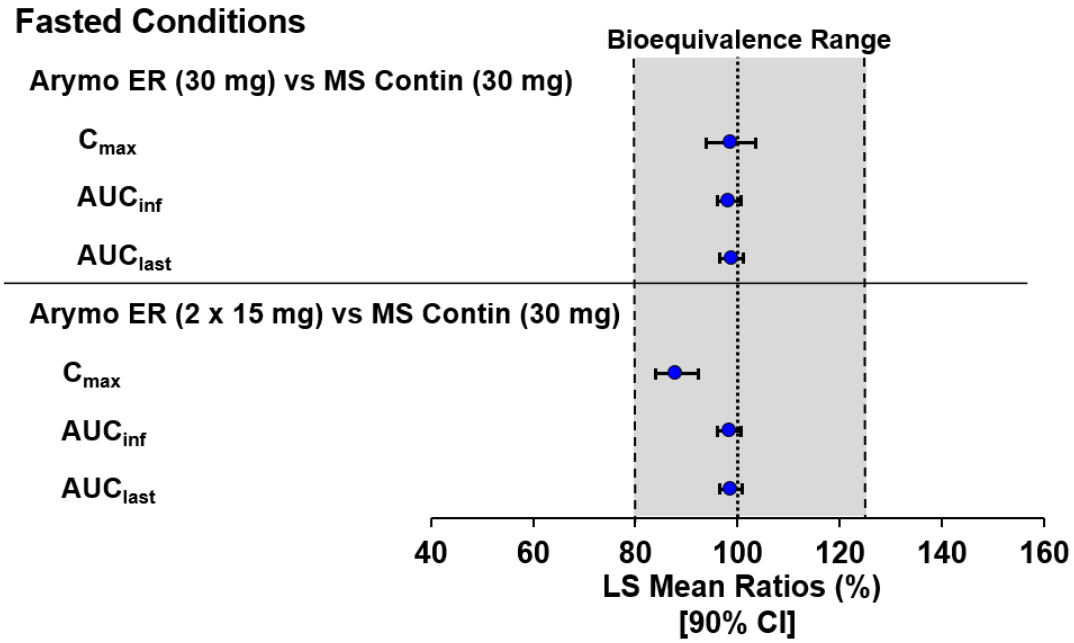
CV% = percent coefficient of variation; h = hour

Figure 11: Morphine Plasma Concentrations for Arymo ER (30 mg and 2 x 15 mg) and MS Contin (30 mg) under Single-Dose Fasted Conditions – Study EG-012



Study EG-012 demonstrated that Arymo ER was bioequivalent to 30 mg MS Contin when taken as either one 30 mg tablet or two 15 mg tablets, as illustrated in Figure 12.

Figure 12: Bioequivalence Assessment for Arymo ER (30 mg and 2 x 15 mg) Relative to MS Contin (30 mg) under Single-Dose Fasted Conditions – Study EG-012



4.2 Assessment of Bioequivalence to MS Contin in Models of Steady State Pharmacokinetics

Multiple-dose bioequivalence was demonstrated in steady-state simulations using data from the single-dose pivotal bioavailability study EG-011 at the highest to-be-marketed dose (60 mg) of Arymo ER. Given that morphine has a well-established metabolic profile, modeling and simulation is considered a scientifically sound method of estimating steady-state exposure and maximum concentrations (AUC and C_{max}). One hundred replicates, each containing 50 subjects, were run to compare Arymo ER to MS Contin under two multiple-dose regimens, 60 mg once every 12 hours (q12h) and once every 8 hours (q8h).

Arymo ER was bioequivalent to MS Contin in all simulated replicates under single-dose and both multiple-dose regimens (Table 7). All 100 replicates met the criteria for bioequivalence (i.e., pass rate) for both the q12h and q8h simulated regimens.

Table 7: Bioequivalence Assessment for Arymo ER (60 mg) Relative to MS Contin (60 mg) under Simulated Steady-State Conditions

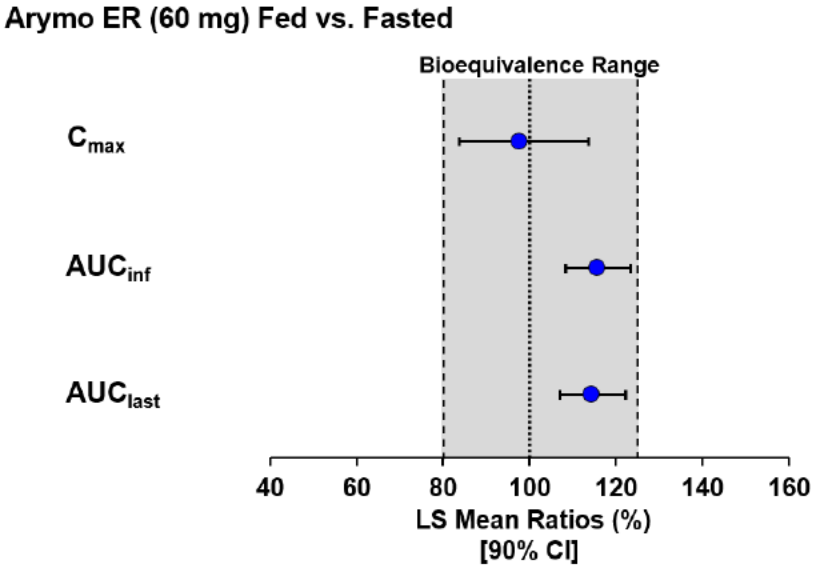
PK Parameter	Geometric LS Mean Ratio (%) (Arymo ER : MS Contin) (90% CI)	Pass Rate
Single Dose		
C_{max}	99.9 (94.2, 106.0)	100%
AUC	97.8 (94.3, 101.4)	100%
Multiple Dose, q12h		
$C_{max,ss}$	95.7 (90.8, 100.9)	100%
AUC_{ss}	97.7 (94.4, 101.1)	100%
Multiple Dose, q8h		
$C_{max,ss}$	93.5 (89.0, 98.3)	100%
AUC_{ss}	97.5 (94.3, 100.9)	100%

Note: Bioequivalence range is 80% to 125%.

4.3 Effect of Food on Absorption and Bioavailability

The effect of food on the bioavailability of Arymo ER was assessed in a subset of subjects in Study EG-011. In addition to completing the fasted conditions with Arymo ER and MS Contin, these subjects also received a single dose of 60 mg Arymo ER after a standardized high-fat, high-calorie meal. Fourteen subjects provided evaluable PK data. Morphine parameters were bioequivalent in the fed and fasted states, suggesting that there is no clinically significant effect of food on the bioavailability of Arymo ER (Figure 13).

Figure 13: Bioequivalence Parameters for Arymo ER (60 mg) in the Fed Relative to the Fasted State under Single-Dose Conditions – Study EG-011



5 CATEGORY 1 LABORATORY MANIPULATION AND EXTRACTION STUDIES

Summary

Findings Relevant to Manipulated Oral, Nasal, and IV Routes of Abuse

- Particle size reduction (PSR) is a common manipulation of ER opioid formulations in order to convert the product into an IR form (e.g., manipulated oral) and/or to get the product into an abusable form for alternate routes of abuse (e.g., nasal, IV).
- Arymo ER was highly resistant to PSR, and yielded primarily large, coarse particles even after maximal, multi-tool manipulations. The hardness of Arymo ER tablets often broke the tools during attempts at PSR.
- The maximal PSR method identified for Arymo ER involved a sequential application of multiple tools, which still resulted in limited output of small particles. In contrast, MS Contin could be easily crushed into a fine powder using a single tool.

Findings Relevant to IV Route of Abuse

- Small volume extraction resulted in minimal recovery of morphine from Arymo ER.
- The gelling properties of Arymo ER made it very difficult to draw into a syringe, even after extended incubation periods of up to 24 hours.

Findings Relevant to Manipulated Oral Route of Abuse

- Large volume extraction studies showed that Arymo ER was more resistant to extraction than MS Contin in a variety of ingestible and non-ingestible solvents.

Findings Relevant to Smoking Route of Abuse

- Isolation of free-base morphine for further processing was not possible. Simulated smoking studies demonstrated that smoking is not a viable route of abuse for Arymo ER.

Findings Relevant to Interactions with Alcohol

- Alcohol had no effect on the dissolution profile of Arymo ER, with no evidence of dose-dumping in the presence of alcohol.

5.1 Overview of Category 1 Evaluation

Category 1 studies were conducted at an independent laboratory to assess the difficulty with which Arymo ER could be altered to compromise the intended drug release (Table 8). These studies include general physical and chemical manipulations, which are important to consider for several routes of abuse, as well as route-specific studies for IV injection and smoking. MS Contin, a non-abuse-deterrent ER morphine product, served as the comparator.

Table 8: Category 1 Abuse-Deterrent Studies

	Experiment	Routes of Abuse	Objective
Physical	Particle Size Reduction (PSR) studies	Manipulated Oral Snorting IV injection Smoking	Investigate ability of mechanical and electric household tools to reduce particle size
Chemical	Large volume extraction studies	Manipulated Oral	Assess amount of drug extraction in various ingestible and non-ingestible solvents under different conditions
Route-Specific	Small volume extraction studies	IV injection	Evaluate extraction of drug into injectable amounts of liquid
	Syringeability	IV injection	Assess ability to syringe and expel solution
	Simulated smoking abuse study	Smoking	Quantify drug vaporized on application of heat

5.2 Particle Size Reduction Studies with Single-Tool Manipulations

Particle size reduction (PSR) increases the surface area of a drug tablet and is a practice commonly pursued to increase the release rate of an API and turn an ER product into an IR form and/or to prepare the product for an alternate route of abuse (e.g., nasal, IV). The feasibility of PSR using 25 different tools was evaluated in order to identify tools for further testing. The final selection of 10 mechanical and electrical tools was based on:

- PSR optimization of either Arymo ER or MS Contin
- Tools representative of different mechanisms for PSR – either by crushing, cutting, grating, or grinding the tablets
- Tools known to be used by abusers

The 10 tools were applied systematically to Arymo ER and MS Contin in single-tool manipulations. Each single-tool manipulation followed a standard procedure (i.e., time of manipulation, equipment) and was initially carried out on 100 mg Arymo ER and 100 mg MS Contin tablets. The amount of time required to manipulate MS Contin to a fine powder was determined for each tool. Then, Arymo ER was manipulated for up to 5 times the amount of time used on MS Contin (unless attempts to reduce PSR for Arymo ER broke the tool).

The 5 times amount of time employed during the screening phase for the 10 tools was to help identify the tools most effective for PSR for Arymo ER. Two tools were identified as being most effective for PSR and were further studied in sequential multi-tool manipulation procedures. From this, the maximal PSR method was identified and tested for different amounts of time, which demonstrated that no further PSR could be achieved.

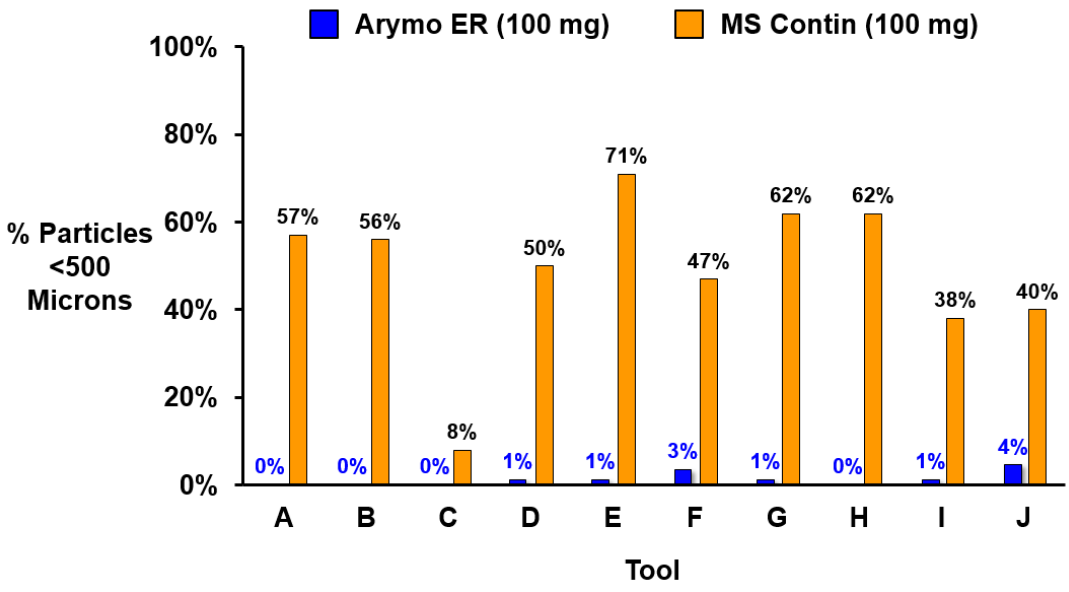
The particle size distribution of Arymo ER and MS Contin was analyzed following manipulation. Of note, this Category 1 experiment was conducted prior to the decision to seek

regulatory approval for 60 mg as the maximum dose of Arymo ER. Therefore, evaluations with the same 10 tools were repeated with Arymo ER at the 60 mg strength, which produced consistent results to Arymo ER 100 mg.

The peer-reviewed literature suggests that particle sizes greater than 280 to 300 microns are difficult to deliver intranasally and are not well absorbed through the nasal mucosa (Vosburg et al., 2012). The FDA Draft Guidance for industry on evaluation of the abuse-deterrent properties of generic oral opioid products states that product manipulation yielding less than 10% of particles under 500 microns are considered "unsuitable for insufflation" (FDA, 2016).

As shown in Figure 14, none of the tools were able to produce significant particle size reduction (less than 500 microns) of Arymo ER tablets. The most effective single-tool PSR procedure for Arymo ER produced 4% of output with particle sizes less than 500 microns. Therefore, none of the single-tool procedures produced an output that was considered suitable for insufflation per FDA Draft Guidance (FDA, 2016). In contrast, 6 of the 10 tools produced considerable PSR with MS Contin (at least 50% of particles less than 500 microns). Nine of the 10 tools produced yields that were considered suitable for insufflation.

Figure 14: Particle Size Reduction Results with 10 Tools



No tools were broken during manipulation of MS Contin, which offered no resistance to cutting, crushing, grating, or grinding and was easily reduced to fine powder suitable for insufflation, typically in a matter of seconds. Due to the extreme hardness of Arymo ER tablets, multiple tools were damaged or destroyed during the PSR experiments. Examples of a few tools broken during the PSR studies are illustrated in Figure 15.

Figure 15: Sample Images of Tools Broken during Physical Manipulation Attempts with Arymo ER

Tool B was identified as the most effective PSR method for MS Contin given its ease of use and high yield of small particles. Tool F and Tool J were determined to be the most effective PSR tools for Arymo ER, and in addition, these tools sustained less damage than the other tools that were evaluated. These tools were carried forward in the multi-tool manipulation evaluations of Arymo ER (see Section 5.3).

5.3 Multi-Tool Particle Size Reduction Studies

Based on interactions with the Agency during the End of Phase 2 meeting in August 2014 and their request to further challenge the physical abuse-deterrent features of Arymo ER, serial multi-tool manipulation procedures were designed to investigate whether further PSR could be achieved beyond that which was obtained by the most successful single-tool physical

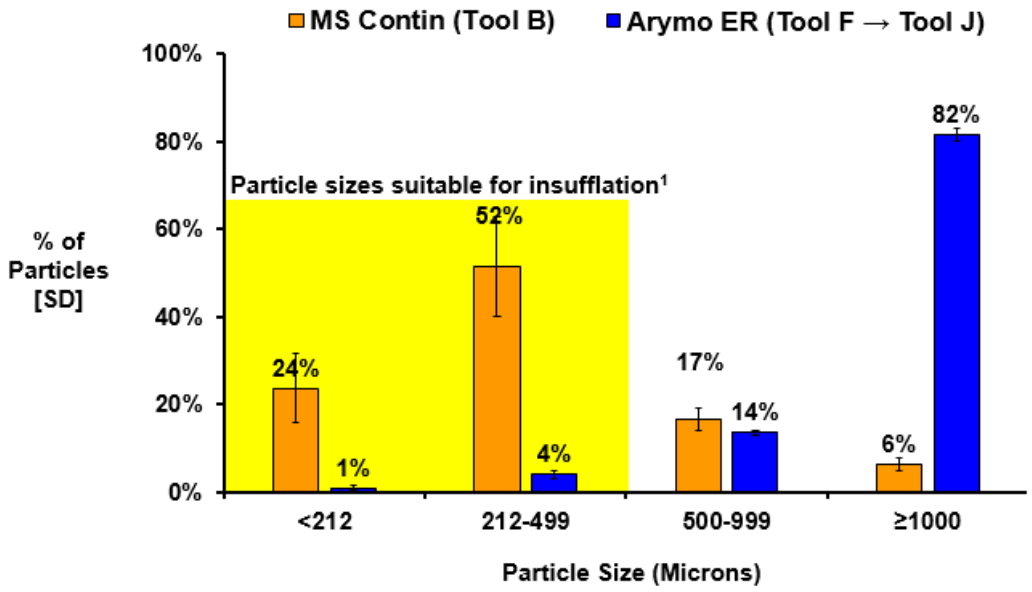
manipulations. The following combinations of tools were evaluated and were representative of the different types of physical manipulations:

- Tool F → Tool B
- Tool F → Tool J
- Tool F → Tool J → Tool B

No additional PSR was achieved with Tool F → Tool B procedure relative to Tool F alone. Minimal additional PSR was achieved with the Tool F → Tool J procedure (5% of particles <500 microns) relative to either of the single-tool procedures (3-4% of particles <500 microns). The addition of a third tool (Tool F → Tool J → Tool B) actually made PSR less effective than the two-step (Tool F → Tool J) procedure.

Based on the results of these additional experiments, manipulation with Tool F → Tool J was identified as the maximal PSR technique for Arymo ER. The particle size distribution achieved through the maximal PSR method for Arymo ER is shown in Figure 16 along with the successful PSR method for MS Contin (manipulated with Tool B). With maximal manipulation, approximately 5% of particles of manipulated Arymo ER were smaller than 500 microns compared to 76% of MS Contin particles.

Figure 16: Particle Size Reduction Results Following Maximal Manipulation of Arymo ER and MS Contin



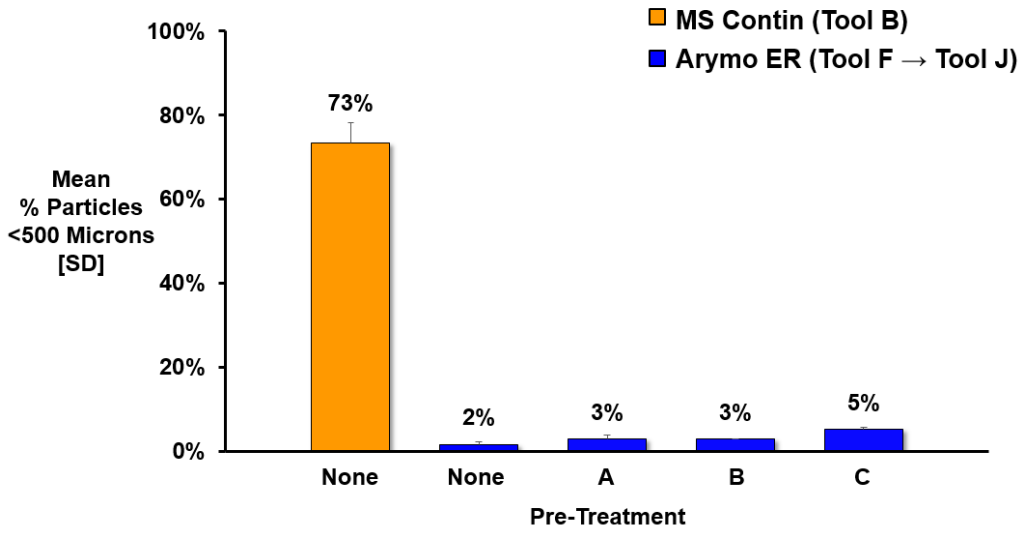
5.4 Multi-Tool Particle Size Reduction after Pre-Treatment

Particle size reduction of Arymo ER was assessed after pre-treatment with temperature (e.g., heating or freezing) followed by maximal multi-tool manipulation. Subjecting abuse-deterrent opioid formulations to heat or freezing is a potential strategy to weaken the drug's resistance to manipulation, thereby improving the results obtained through PSR attempts. Three pre-treatment conditions of Arymo ER were evaluated with the maximal multi-tool method (Tool F → Tool J).

The resulting particle size distribution was compared to crushed MS Contin and manipulated Arymo ER without pre-treatment.

Pre-treatment of Arymo ER had little effect on PSR, increasing the percentage of particles <500 microns from 2% without pre-treatment to between 3% and 5% with pre-treatment (Figure 17). These results demonstrate that various pre-treatment conditions had no appreciable effect on PSR of Arymo ER.

Figure 17: Particle Size Reduction Results with Pre-Treated Arymo ER

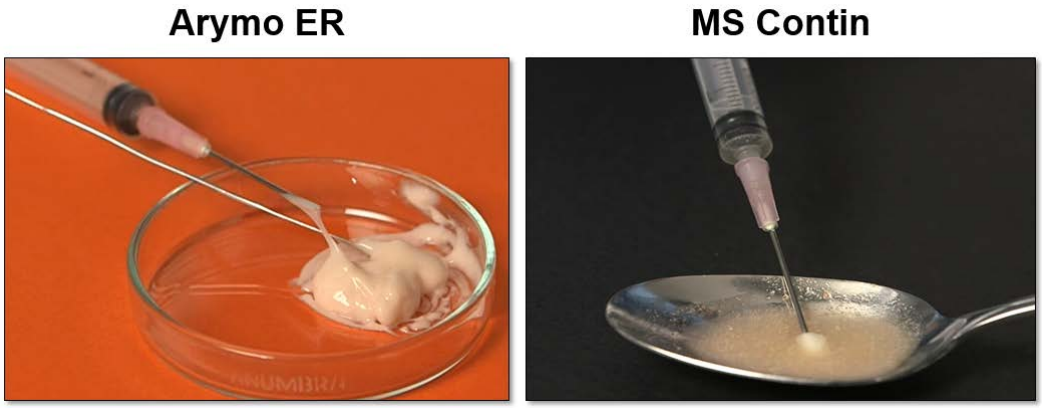


5.5 Small Volume Extraction and IV Injection Studies

The IV route of abuse is the most common non-oral route of abuse for ER morphine products. Extraction studies with a variety of potentially injectable solvents were conducted at small, injectable volumes to determine the relative feasibility of preparing a solution for injection. Physically manipulated tablets using the maximal respective PSR method for Arymo ER and MS Contin were dissolved in small volumes of an injectable solvent (i.e., IV Solvent 1) at three volumes (i.e., 2, 5, and 10 mL) under various extraction conditions for time, temperature, and agitation.

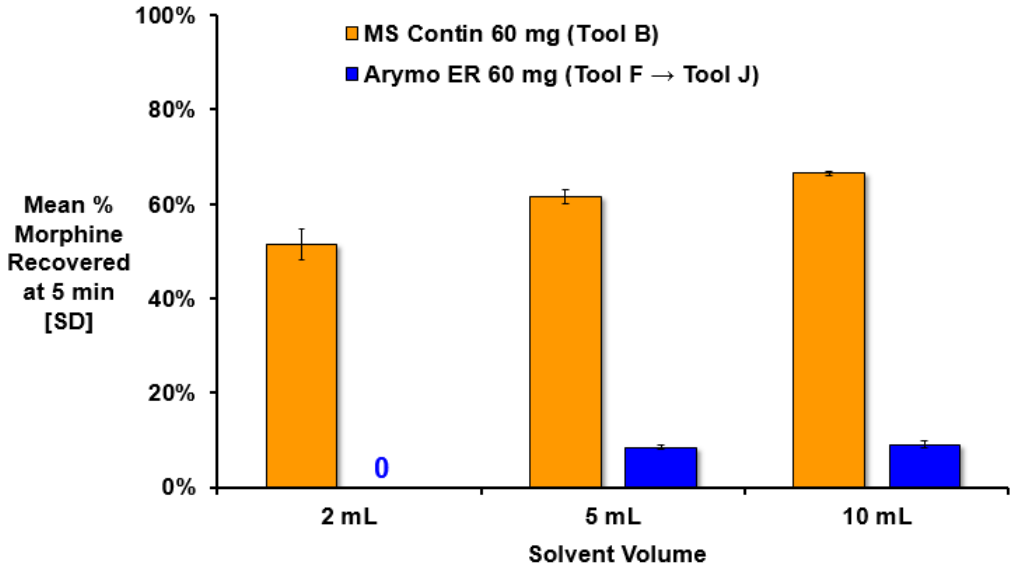
MS Contin could be consistently prepared for injection under all conditions tested. The ER properties and gelling features of Arymo ER resisted morphine extraction despite application of the maximal, multi-tool PSR procedure. Because of its high viscosity when hydrated in small aqueous volumes, Arymo ER was difficult, if not impossible, to prepare into an injectable solution and draw into a syringe. Figure 18 illustrates the gelling effect of Arymo ER when subjected to a small volume of IV Solvent 1.

Figure 18: Example Illustrating Arymo ER and MS Contin in 3 mL of IV Solvent 1 at Temperature A with Stirring



Results for Arymo ER and MS Contin are shown in Figure 19, which illustrates the final yield (i.e., amount of morphine recovered from syringed and expelled material) after 5 minutes of incubation under Temperature B with Agitation A. Similar results were observed at Temperature A and Agitation B at other time points.

Figure 19: Morphine Recovery from Syringed and Expelled Solutions with Temperature B and Agitation A in IV Solvent 1 at 5 Minutes



Another syringeability study was performed to evaluate whether the gelling effect of Arymo ER could be overcome with longer incubation times (4 and 24 hours) using two IV solvents and three conditions of Arymo ER (intact tablet, manipulated with Tool F, and maximal manipulation method with Tool F → Tool J). Results showed the following:

- Nine of the 12 conditions recovered <10% morphine with any needle gauge.
- Three of the 12 conditions recovered between 16-18% morphine, but required Needle Gauge D to do so; this represents an extreme scenario that abusers do not prefer to use.

5.6 Large Volume Extraction Studies

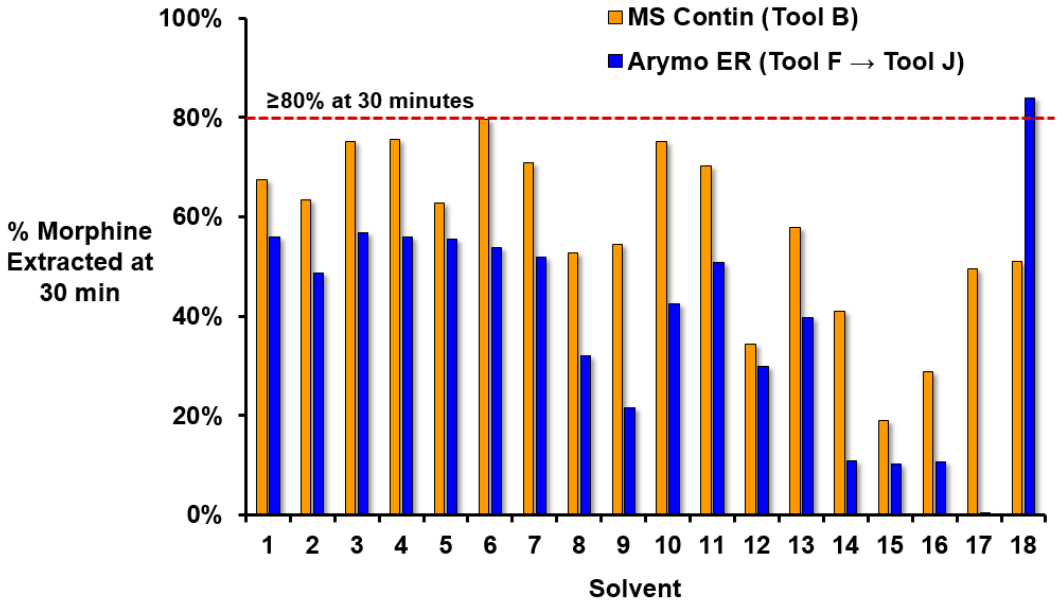
Large volume extraction studies of Arymo ER and MS Contin were conducted to assess the relative ability of a large volume of a solvent to result in preparation of solutions containing dissolved morphine, which would be administered by the oral route. Eighteen ingestible and non-ingestible solvents were tested on Arymo ER and MS Contin at the 100 mg dose strength to determine how easily the ER properties could be defeated. Solvents 1, 2, and 4-12 are ingestible. Solvents 3 and 13-18 are non-ingestible and would be toxic to consume. The maximal PSR manipulations, which demanded more time and effort for Arymo ER than MS Contin, were employed. Studies were later repeated with 2 model solvents (reflective of different pH and polarity) on the intended commercial dosage strengths of Arymo ER (15 mg, 30 mg, and 60 mg).

The FDA Draft Guidance for industry on evaluation of the abuse-deterrent properties of generic oral opioid products has highlighted ≥80% extraction at 30 minutes as a threshold to indicate defeat or failure of abuse deterrence at multiple temperature and agitation conditions (FDA, 2016). This threshold is considered to assist in the interpretation of the results of these studies.

5.6.1 Large Volume Extraction of Arymo ER and MS Contin at 100 mg Dose

Compared to manipulated MS Contin, Arymo ER was less readily extracted with 17 of the 18 different solvents tested at Temperature A and Agitation B (Figure 20). Solvent 18 achieved a peak morphine extraction of >80% of the label claim at 30 minutes with Arymo ER, exceeding the threshold outlined in the FDA Draft Guidance (FDA, 2016). This result was time-sensitive because the percentage of morphine extracted decreased at all subsequent time points. Moreover, Solvent 18 is toxic and non-ingestible.

Figure 20: Morphine Extraction in Large Volumes of Ingestible and Non-Ingestible Solvents at Temperature A and Agitation B with Maximal Manipulation at 30 Minutes

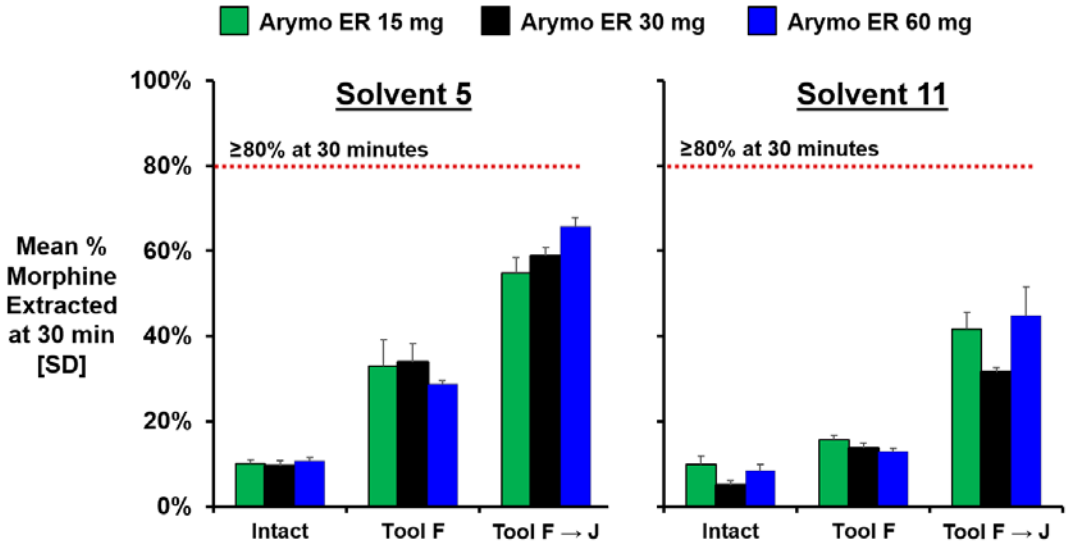


The effect of Temperature B with Agitation B was evaluated for the aqueous-based solvents. None achieved ≥80% extraction at 30 minutes for either Arymo ER or MS Contin.

5.6.2 Large Volume Extraction of Arymo ER at Intended Commercial Dosage Strengths

Additional evaluations of Arymo ER at the intended commercial dosage strengths (15 mg, 30 mg, and 60 mg) were conducted with two model solvents (Solvents 5 and 11), reflective of different pH and polarity. Extraction was evaluated using intact tablets as well as tablets manipulated using Tool F and the maximal manipulation method, Tool F → Tool J. Neither solvent was able to produce ≥80% extraction at 30 minutes at either Temperature A (Figure 21) or Temperature B (results not shown). The rate of extraction was dependent on the PSR achieved in the physical manipulation. Dosage strength did not appear to have an impact on the relative rate of extraction.

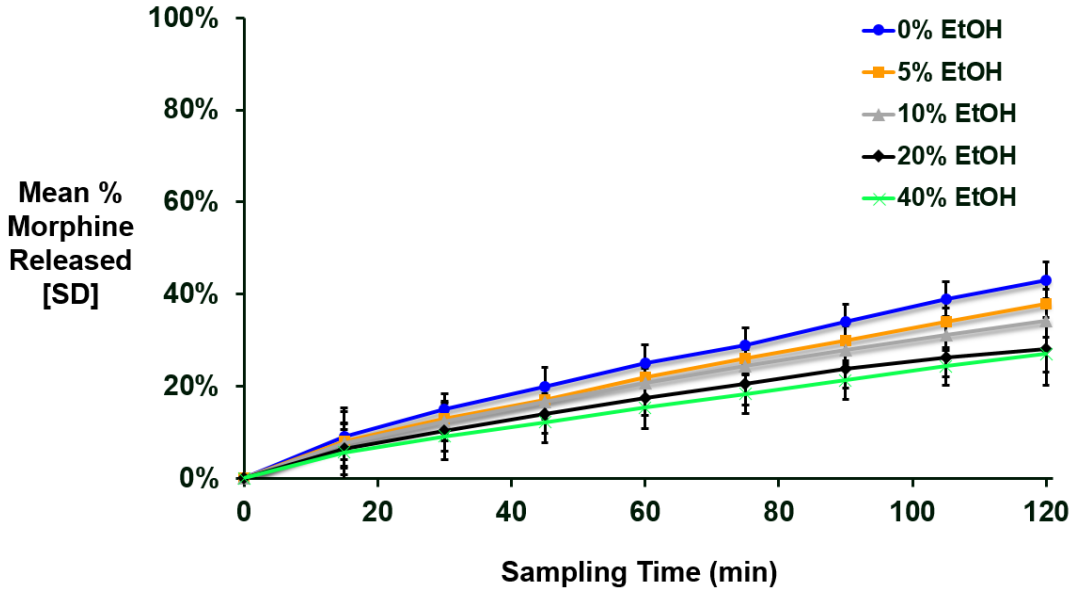
Figure 21: *In Vitro* Morphine Release in Solvents 5 and 11 at Temperature A and Agitation B at 30 Minutes



5.7 *In Vitro* Dissolution Studies with Alcohol

In vitro dissolution studies assessed the potential for alcohol-induced dose dumping with Arymo ER. The dissolution profile of morphine from 60 mg Arymo ER tablets was measured in 0.1 N HCl (which simulates conditions in the stomach) with various concentrations of alcohol. Alcohol at concentrations of 5% to 40% did not increase dissolution rates of Arymo ER. In fact, drug release was slower with increasing concentrations of alcohol (Figure 22), suggesting that Arymo ER will not dose dump following co-ingestion with alcohol. However, like all opioid products, Arymo ER should not be taken with alcohol.

Figure 22: *In Vitro* Morphine Release in the Presence of Alcohol



5.8 Isolation of Free-base Morphine Study

Free-base morphine may be isolated for smoking or for more complex conversion to other abusable opioid forms. A procedure to derive free-base morphine was developed for reference standard morphine material and optimized for use on Arymo ER. When executed on Arymo ER in 3 separate attempts, a viscous cloudy solution was obtained rather than a precipitate – a phenomenon attributed to the gelling effects of the excipient. No free base could be attained.

5.9 Simulated Smoking Study

In an *in vitro* smoking study, optimized heating conditions were used to assess the amount of morphine that could be recovered through vaporization of manipulated Arymo ER. Only trace amounts (≤3%) of vaporized morphine were released from Arymo ER. Therefore, smoking does not appear to be a viable route of abuse for Arymo ER.

6 CATEGORY 2 PHARMACOKINETIC AND CATEGORY 3 CLINICAL HUMAN ABUSE POTENTIAL STUDIES

Summary

Study EG-008 –Oral Abuse Potential Study of Arymo ER vs. MS Contin

- Maximum Drug Liking was significantly lower for manipulated Arymo ER compared to crushed MS Contin after oral administration.
- Take Drug Again and Overall Drug Liking were numerically lower for manipulated Arymo ER than crushed MS Contin but did not reach statistical significance.
- Maximum scores on Feeling High and Good Effects were significantly lower for manipulated Arymo ER than crushed MS Contin.
- Pharmacodynamic (PD) findings were consistent with the pharmacokinetic (PK) results. PK analyses demonstrated that Arymo ER is not converted to an IR profile after being manipulated for oral abuse, with manipulated Arymo ER exhibiting a lower morphine C_{max} and later T_{max} compared to crushed MS Contin. Abuse Quotient for Arymo ER was lower than MS Contin.

Study EG-009 – Intranasal (IN) Abuse Potential Study of Arymo ER vs. MS Contin

- Two Arymo ER treatment arms were evaluated for IN abuse potential:
  - Manipulated Arymo ER using maximal, multi-tool PSR method
  - Manipulated Arymo ER using maximal, multi-tool PSR method followed by sieving to isolate particles amenable to snorting
- Maximum Drug Liking for manipulated and manipulated/sieved Arymo ER was significantly lower than crushed MS Contin after snorting.
- Scores for Take Drug Again and Overall Drug Liking were significantly lower for manipulated and manipulated/sieved Arymo ER compared to MS Contin, and were similar to or lower than placebo.
- Manipulated Arymo ER was reported by recreational IN abusers to be significantly more difficult to snort than crushed MS Contin.
- PD results were consistent with the PK findings. Manipulated Arymo ER exhibited a lower morphine C_{max} and delayed T_{max} when compared to crushed MS Contin, which exhibited a PK profile consistent with an IR product. Abuse Quotient was also lower with manipulated and manipulated/sieved Arymo ER compared to MS Contin.
- Sieving Arymo ER after manipulation results in the loss of a considerable amount of the API due to the formulation's resistance to particle size reduction.

Two studies were conducted to evaluate the clinical human abuse potential of Arymo ER compared to MS Contin in nondependent recreational opioid users. Study EG-008 assessed the oral route of administration and Study EG-009 evaluated abuse potential via the intranasal (IN) route. These studies incorporated assessments for both PK (Category 2) and PD (Category 3) endpoints of interest. Based on Category 1 studies, it was determined that a clinical IV HAP study was not feasible because of the low yield of morphine from Arymo ER in small volume extraction studies, difficulty drawing manipulated Arymo ER into a syringe, and potential safety risks to study subjects because of the gelling properties of the product.

6.1 Study EG-008 – Oral PK and HAP Study of Arymo ER

6.1.1 Study Design

Study EG-008 was a single-center, randomized, double-blind, triple-dummy, 4-period crossover study assessing the abuse potential of manipulated Arymo ER versus crushed MS Contin when administered orally in nondependent recreational opioid users. Eligible subjects needed to use opioids for nonmedical purposes at least 10 times in the last year and at least once in the last 12 weeks prior to Screening. The highest dose of Arymo ER (60 mg) was evaluated in this study. An overview of the study design is shown in Figure 23.

Subjects satisfying the inclusion and exclusion criteria during the Screening Visit were eligible for the Qualification Phase, where subjects were required to pass a Naloxone Challenge Test to rule out physical dependence on opioids and a Drug Discrimination Test to ensure that they could differentiate between 30 mg of IR morphine and placebo when taken orally.

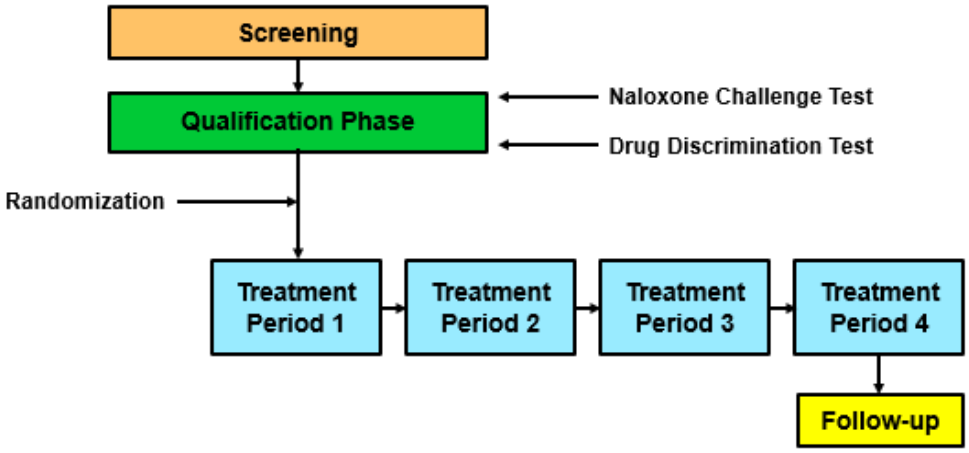
All subjects received each of four treatments with corresponding dummy treatments in randomized order during the four treatment periods. All study drugs were manipulated by the site pharmacy prior to being given to the subjects for administration (i.e., subjects did not manipulate the product on their own). Each treatment period involved a 3-day/2-night in-clinic visit and there was a 5-day washout period between dosing.

The treatment periods of the study included:

- **Arymo ER, Manipulated Oral** (60 mg) – prepared using single-tool manipulation with Tool F
- **MS Contin, Manipulated Oral** (60 mg) – prepared using single-tool manipulation with Tool B
- **Arymo ER, Intact Oral** (60 mg)
- **Placebo**

Tool F was used as the manipulation method for Arymo ER because the yield of small particles from Tool F was similar to the maximal PSR method for Arymo ER (Tool F → Tool J) and it was a relevant method to test the oral route of abuse. The output could be consistently delivered by the oral route and it was also a practical method for the clinical pharmacist to prepare manipulated Arymo ER for oral ingestion.

Figure 23: Overview of Study Design for Oral HAP Study EG-008



6.1.2 Pharmacodynamic (Category 3) Study Endpoints

The primary PD endpoint of the study was maximum Drug Liking (E_{max}) through 24 hours, measured on a 0-100 point bipolar visual analog scale (VAS). A score of 0 indicates "strong disliking", a score of 50 indicates "neither like nor dislike" and 100 indicates "strong liking".

The key secondary PD endpoints of interest included:

- Take Drug Again assessment on a 0-100 point bipolar VAS (measured at 12 and 24 hours post-dose)
- Overall Drug Liking on a 0-100 point bipolar VAS (measured at 12 and 24 hours post-dose)
- Drug Effects Questionnaire: Any Drug Effects, Feeling High, Good Effects, Bad Effects, Sick, Nausea, Sleepy, and Dizzy on a 0-100 point unipolar VAS (measured at multiple time points through 24 hours)

Safety was evaluated through collection of adverse events, vital signs, and laboratory assessments.

6.1.3 Pharmacokinetic (Category 2) Study Endpoints

For Category 2, the PK parameters that were measured included C_{max}, T_{max}, and AUC. The Abuse Quotient ($AQ = C_{max}/T_{max}$) was also calculated for each subject to assess the rate of rise in drug concentration. Per FDA Guidance (FDA, 2015), the rate of rise "is thought to contribute to differential abuse among drugs, formulations, and routes of administration."

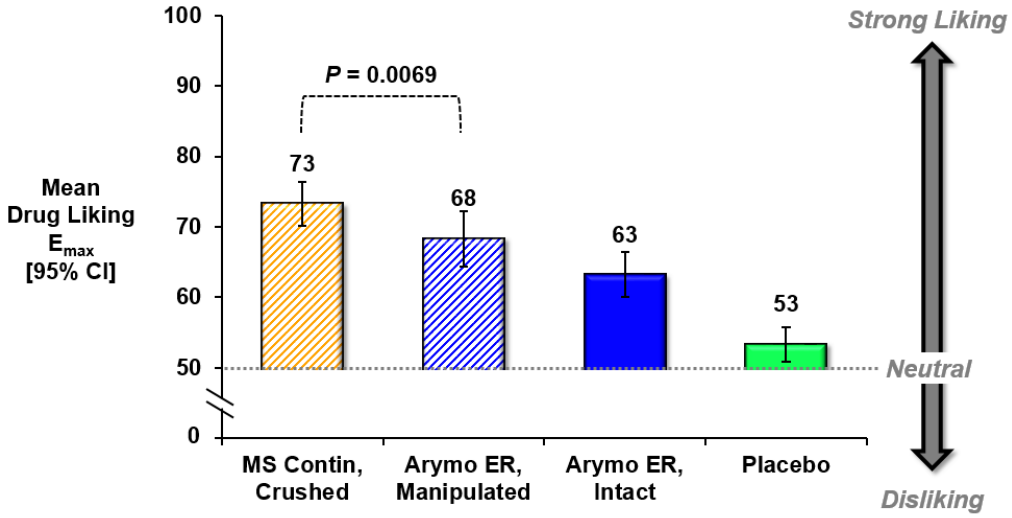
6.1.4 Study Population

Of the 39 subjects that started the treatment phase of the study, 38 subjects completed the study. The majority of subjects were white (92%), male (74%), and non-Hispanic (86%). Subjects ranged in age from 18 to 35 years (mean, 24).

6.1.5 Pharmacodynamic (Category 3) Results

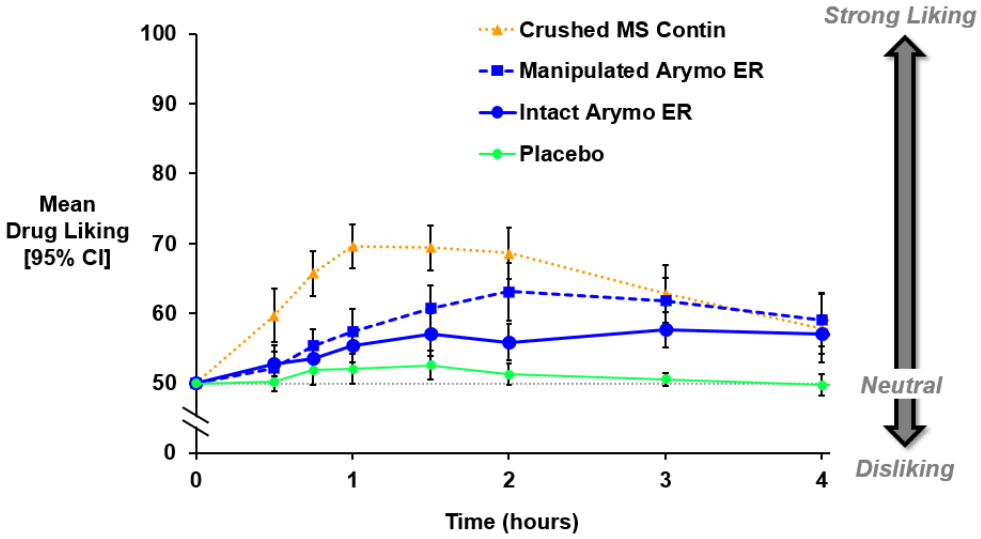
On the primary endpoint, the maximum Drug Liking (E_{max}) for manipulated Arymo ER was statistically significantly lower than crushed MS Contin (p=0.0069) (Figure 24). The difference between manipulated and intact Arymo ER was not significantly different.

Figure 24: Maximum Drug Liking (E_{max}) in Oral HAP Study EG-008



The Drug Liking profile over time provides additional context for the primary endpoint results (Figure 25). Drug Liking for crushed MS Contin rose quickly after administration similar to the profile that would be expected from an IR product. The Drug Liking scores for manipulated Arymo ER rose more gradually to a lower peak than MS Contin. The onset of E_{max} was one hour earlier with crushed MS Contin (median TE_{max}, 1.0 hour) than with manipulated Arymo ER (median TE_{max}, 2.0 hours).

Figure 25: Mean Drug Liking Profile over the First 4 Hours after Dosing in Oral HAP Study EG-008



Manipulated Arymo ER was associated with lower scores on key secondary PD measures compared to crushed MS Contin (Table 9). Of these, the differences in Take Drug Again and Overall Drug Liking scores, while directionally supportive, did not reach statistical significance (p=0.054 and 0.128, respectively). The differences in Feeling High and Good Effects were lower for manipulated Arymo ER than crushed MS Contin and were statistically significant.

Table 9: Results of Secondary PD Measures in Oral HAP Study EG-008

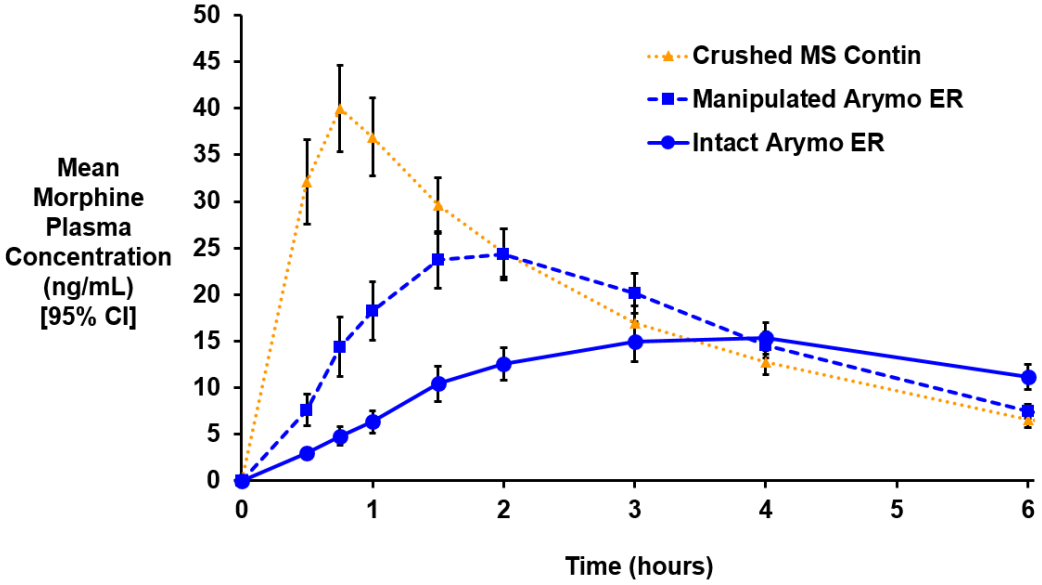
Treatment	Take Drug Again		Overall Drug Liking		Feeling High		Good Effects	
	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value
Crushed MS Contin	70	-	70	-	52	-	51	-
Manipulated Arymo ER	63	0.054	65	0.128	39	0.0035	35	0.0025
Intact Arymo ER	55	0.0005	56	0.0004	27	<0.0001	26	<0.0001
Placebo	51	<0.0001	52	<0.0001	5	<0.0001	6	<0.0001

An important consideration in the interpretation of these results is that the subjects in this study were dosed in a blinded fashion and did not experience the rigorous physical manipulation required to get Arymo ER into an abusable form themselves. Therefore, the scores reflect recreational opioid users' relative subjective experiences about the products when all real-world considerations of effort for tampering are removed. Abusers in the real world would need to expend time and effort to achieve particle size reduction with Arymo ER, which could be a deterrent to abuse in and of itself.

6.1.6 Pharmacokinetic (Category 2) Results

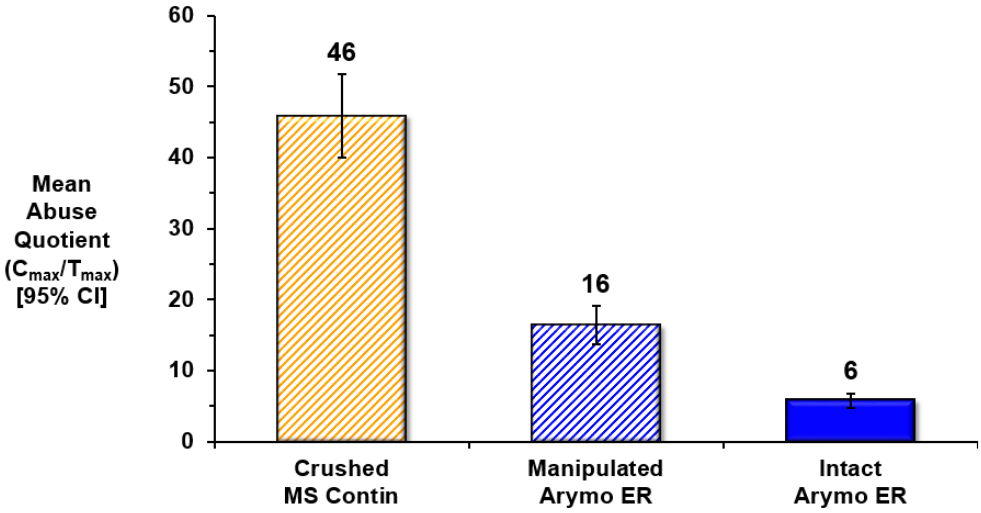
Figure 26 displays the mean morphine plasma concentrations over the first 6 hours after dosing. Consistent with the Drug Liking curves, crushed MS Contin displays a profile consistent with an IR product with a high C_{max} and early T_{max} (median, 0.9 hours). In contrast, manipulated Arymo ER maintained some of its extended-release properties with a lower C_{max} and longer T_{max} (median, 2.1 hours).

Figure 26: Mean Morphine Plasma Concentrations in Oral HAP Study EG-008



The differences in the rate of rise in drug concentrations with crushed MS Contin and manipulated Arymo ER are reflected in the Abuse Quotients (Figure 27). The mean AQ of manipulated Arymo ER (16) was more similar to intact oral dosing of Arymo ER (6) than crushed MS Contin (46).

Figure 27: Abuse Quotient for Morphine in Oral HAP Study EG-008



6.1.7 Safety

The rates of treatment emergent adverse events (TEAEs) across study arms are shown in Table 10. These TEAEs are consistent with common opioid-related adverse events.

Table 10: Treatment Emergent Adverse Events with ≥5% Rate in Oral HAP Study EG-008

Adverse Event	Arymo ER, Manipulated (N = 38)	Arymo ER, Intact (N = 38)	Crushed MS Contin (N = 39)	Placebo (N = 38)
Any TEAE	47.4%	31.6%	48.7%	5.3%
Nausea	7.9%	13.2%	17.9%	2.6%
Vomiting	18.4%	7.9%	15.4%	0.0%
Dizziness	5.3%	0.0%	7.7%	0.0%
Headache	10.5%	5.3%	7.7%	0.0%
Somnolence	5.3%	2.6%	12.8%	0.0%
Pruritus generalized	13.2%	2.6%	17.9%	0.0%
Hot flush	0.0%	0.0%	5.1%	0.0%

6.2 Study EG-009 – Intranasal Abuse Potential Study of Arymo ER

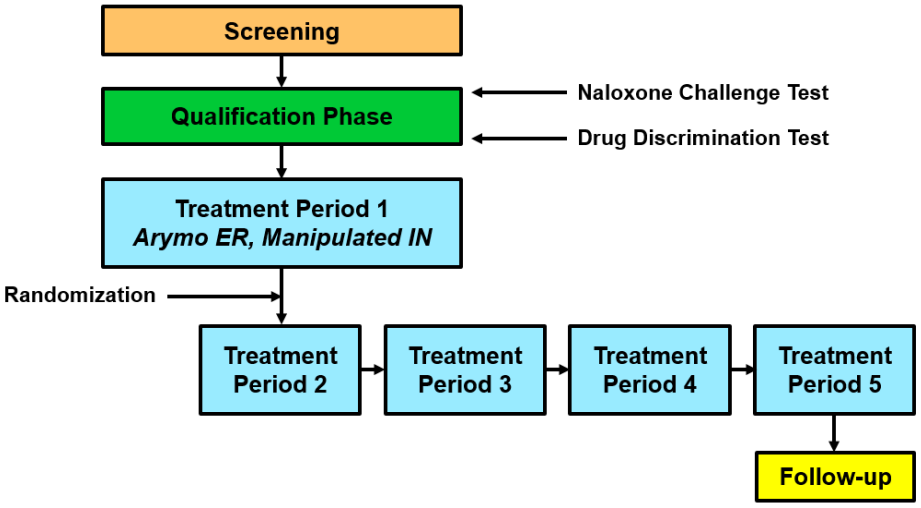
6.2.1 Study Design

EG-009 was a single-center, randomized, double-blind, double-dummy, 5-period crossover study assessing the abuse potential of manipulated and manipulated/sieved Arymo ER versus crushed MS Contin when administered intranasally in nondependent recreational opioid users. Eligible subjects had to have used opioids recreationally at least 10 times in the last year and at least once in the 12 weeks prior to Screening. Subjects also needed to be experienced with nasal insufflation, having snorted opioids at least 3 times in the prior year. The highest dose of Arymo ER (60 mg) was evaluated in this study compared to MS Contin 60 mg. An overview of the study design is shown in Figure 28.

Subjects satisfying the inclusion and exclusion criteria during the Screening Visit were eligible for the Qualification Phase, where subjects were required to pass a Naloxone Challenge Test to rule out physical dependence on opioids and a Drug Discrimination Test to ensure that they could differentiate between 30 mg of IR morphine and placebo after insufflation.

During the Treatment Phase, all subjects received manipulated Arymo ER intranasally during the first treatment period and then received the remaining four treatments in a randomized fashion during the second through fifth treatment periods. All study drugs were manipulated by the site pharmacy prior to being given to the subjects for administration. Each treatment period involved a 3-day/2-night in-clinic visit and there was a 5-day washout period between dosing.

Figure 28: Overview of Study Design for Intranasal HAP Study EG-009



The design, determined in consultation with the FDA at the End-of-Phase 2 meeting, addressed the challenge of blinding manipulated Arymo ER due to the limited amount of small particles that could be achieved with the maximal PSR procedure. Due to these challenges, all subjects received this treatment in the first period. Subjects were then randomized to the four remaining treatment periods, where the particle sizes for insufflation were similar and the intranasal treatments were all matched for volume. Initially, a filter size expected to produce particles amenable for snorting was planned; however, because the yield was negligible, a larger filter was utilized for the study.

The treatment periods of the study included:

- **Arymo ER, Manipulated IN** (60 mg) – prepared using the maximal, multi-tool manipulation procedure using Tool F → Tool J
- **Arymo ER, Manipulated/Sieved IN** (60 mg) – prepared using the same maximal, multi-tool manipulation procedure, followed by sieving
- **MS Contin, Crushed IN** (60 mg) – prepared using the optimal, single-tool manipulation with Tool B to generate a fine powder
- **Arymo ER, Intact Oral** (60 mg)
- **Placebo** – powder for IN insufflation and intact tablet for oral administration

6.2.2 Pharmacodynamic (Category 3) Study Endpoints

The primary PD endpoint of the study was maximum Drug Liking (E_{max}) through 24 hours, measured on a 0-100 point bipolar visual analog scale (VAS). A score of 0 indicates “strong disliking”, a score of 50 indicates “neither like nor dislike” and 100 indicates “strong liking”.

The key secondary PD endpoints of interest included:

- Take Drug Again assessment on a 0-100 point bipolar VAS (measured at 12 and 24 hours post-dose)
- Overall Drug Liking on a 0-100 point bipolar VAS (measured at 12 and 24 hours post-dose)
- Drug Effects Questionnaire: Any Drug Effects, Feeling High, Good Effects, Bad Effects, Sick, Nausea, Sleepy, and Dizzy on a 0-100 point unipolar VAS (measured at multiple time points through 24 hours)
- Ease of Snorting on a 0-100 point unipolar VAS (measured within 5 minutes)
- Nasal Effects assessment (measured through 24 hours)

Safety was evaluated through collection of adverse events, vital signs, and laboratory assessments.

6.2.3 Pharmacokinetic (Category 2) Study Endpoints

For Category 2, PK parameters including C_{max}, T_{max}, AUC, and AQ for morphine were evaluated.

6.2.4 Study Population

Of the 50 subjects that started the treatment phase of the study, 46 subjects completed the study. In the per-protocol population, the majority of subjects were white (90%), male (78%), and non-Hispanic (91%). Subjects ranged in age from 18 to 55 years (mean, 28).

6.2.5 Pharmacodynamic (Category 3) Results

On the primary endpoint of maximum Drug Liking (E_{max}), both IN Arymo ER treatments (manipulated and manipulated/sieved) showed statistically significantly lower maximum Drug Liking scores compared to crushed and snorted MS Contin ($P<0.0001$ for both) (Figure 29).

Figure 29: Maximum Drug Liking (E_{max}) in Intranasal HAP Study EG-009

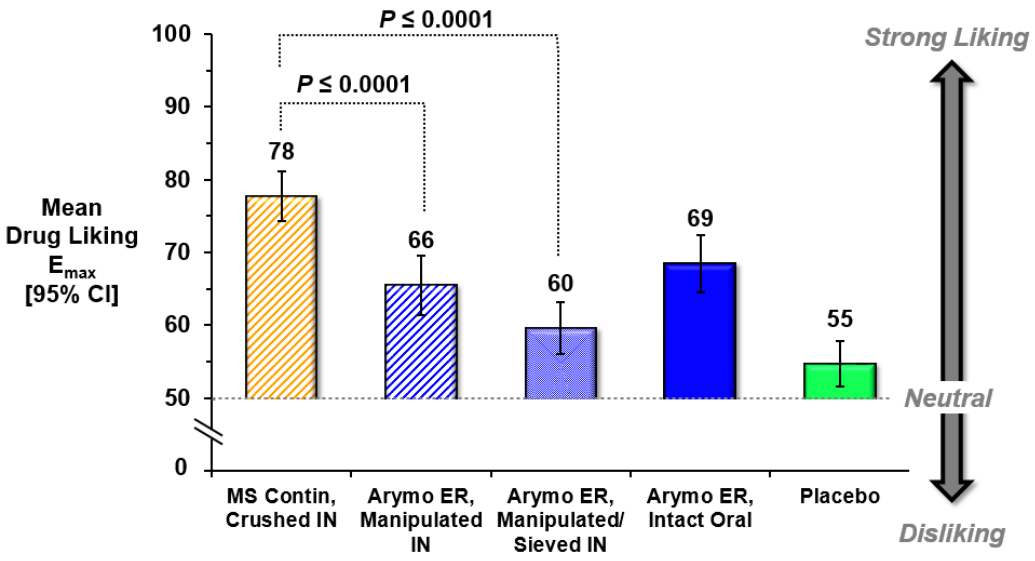
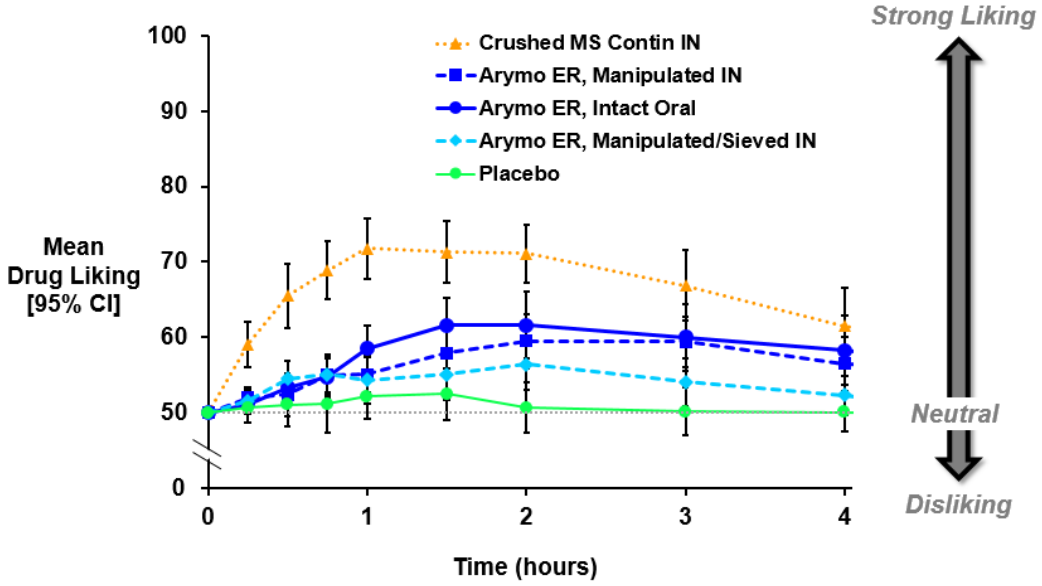


Figure 30 illustrates the time course of mean Drug Liking over the first 4 hours after dosing. Crushed and snorted MS Contin had a Drug Liking profile that rapidly increased in the first hour after administration, consistent with an IR product. The Drug Liking profiles of all Arymo ER treatment arms were statistically significantly lower through the first 2 hours after dosing. The median time to E_{max} (TE_{max}) was notably shorter for crushed and snorted MS Contin (1.0 hour) than manipulated and snorted Arymo ER (1.75 hours) and intact oral Arymo ER (2.0 hours).

Figure 30: Mean Drug Liking (95% CI) Profile over the First 4 Hours after Dosing in Intranasal HAP Study EG-009



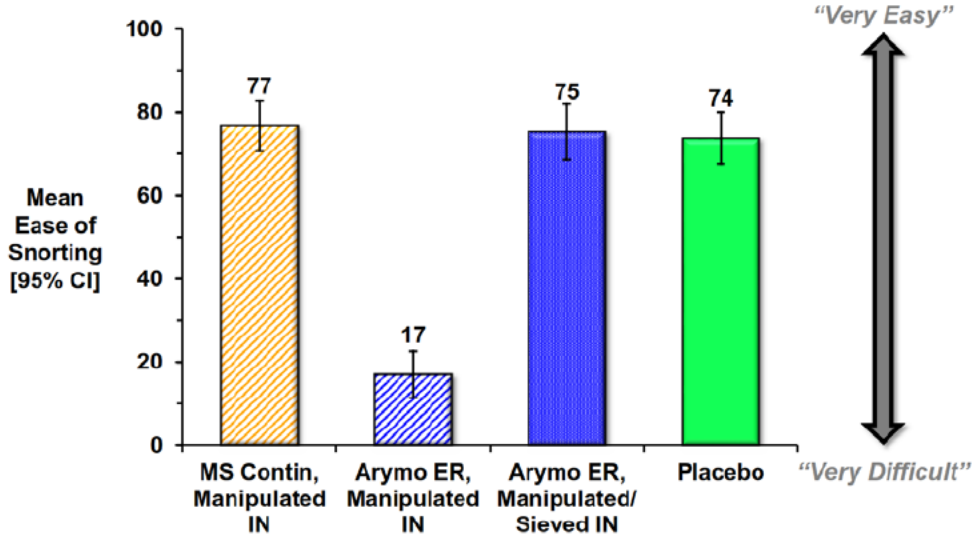
The primary endpoint was supported by positive findings on key secondary PD measures (Table 11). Scores of willingness to Take Drug Again and Overall Drug Liking for both snorted Arymo ER treatment arms were significantly lower than MS Contin, with scores similar to or lower than intact oral Arymo ER and placebo. Subjects also reported lower scores on Feeling High and Good Effects.

Table 11: Key Secondary PD Measures in Intranasal HAP Study EG-009

Treatment	Take Drug Again		Overall Drug Liking		Feeling High		Good Effects	
	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value	Mean E_{max}	*P*-value
MS Contin, Crushed IN	70	-	73	-	61	-	57	-
Arymo ER, Manipulated IN	43	<0.0001	54	<0.0001	28	<0.0001	29	<0.0001
Arymo ER, Manipulated/Sieved IN	53	<0.0001	54	<0.0001	16	<0.0001	18	<0.0001
Arymo ER, Intact Oral	59	<0.0001	59	<0.0001	37	<0.0001	37	<0.0001
Placebo	53	<0.0001	52	<0.0001	11	<0.0001	11	<0.0001

Due to the large particle sizes, manipulated Arymo ER was rated as harder to snort than manipulated/sieved Arymo ER and crushed MS Contin (Figure 31). Manipulated Arymo ER was also associated with significantly greater nasal effects in 5 out of the 6 categories (intranasal irritation, burning, runny nose/nasal discharge, facial pain/pressure, nasal congestion, and need to blow nose). While Ease of Snorting for manipulated/sieved Arymo ER was similar to placebo and MS Contin, its scores for Drug Liking and Take Drug Again were low and similar to placebo.

Figure 31: Ease of Snorting VAS Scores in Intranasal HAP Study EG-009

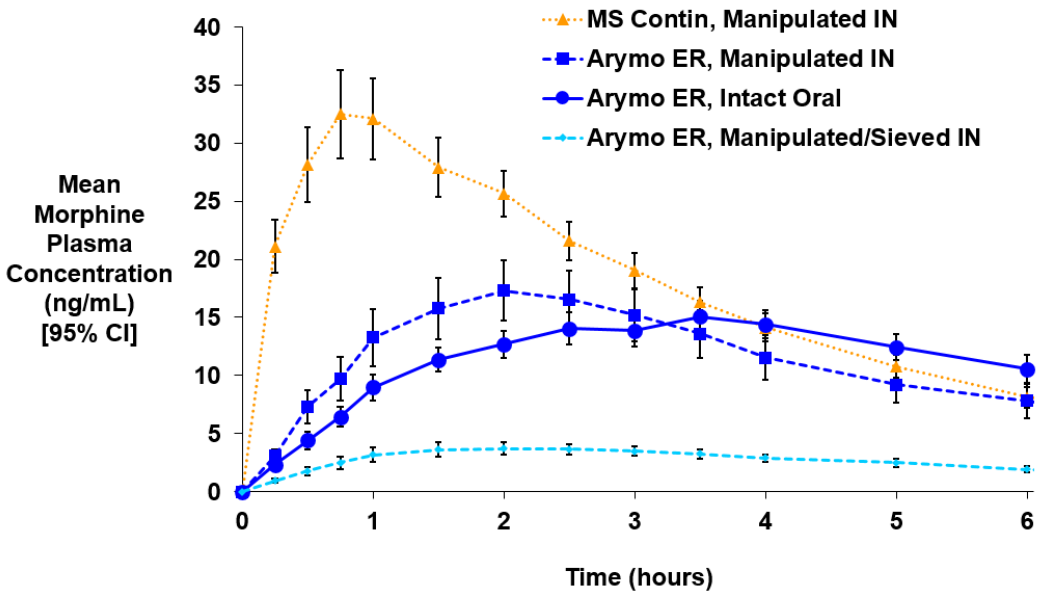


As was the case in the oral HAP study, subjects themselves did not experience the rigorous physical manipulation required to get Arymo ER into an abusable form, which is especially relevant because of the small particle sizes needed for snorting. The considerable effort required would be expected to be an additional deterrent to abuse by the intranasal route in the real world.

6.2.6 Pharmacokinetic (Category 2) Results

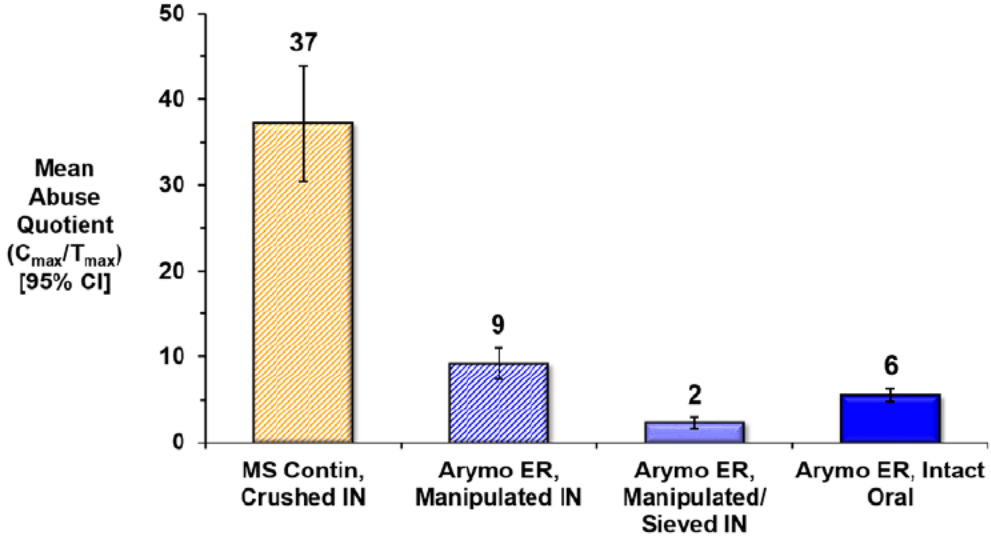
Figure 32 illustrates the mean PK profiles of each of the active treatments over the first 6 hours after dosing. The PK profile of crushed and snorted MS Contin resembles an IR formulation with a high C_{max} and an early T_{max}. After maximal, multi-tool manipulation, snorted Arymo ER had a slightly earlier T_{max} compared to intact oral dosing, but maintained much of its extended-release profile with a similar C_{max}. The low morphine plasma concentration in the snorted manipulated/sieved Arymo ER arm reflects that most of the API was removed after sieving out large particles.

Figure 32: Mean Morphine Plasma Concentrations in Intranasal HAP Study EG-009



When the PK parameters were calculated into Abuse Quotients, crushed and snorted MS Contin had the largest mean AQ of 37 (Figure 33). The mean AQ of manipulated Arymo ER (9) was similar to that of intact oral dosing (6). The lowest mean AQ was manipulated/sieved Arymo ER (2) likely due to the low morphine yield after sieving.

Figure 33: Abuse Quotient for Morphine in Intranasal HAP Study EG-009



6.2.7 Safety

The rates of TEAEs across study arms are provided in Table 12. These TEAEs (except for nasal congestion) are consistent with common opioid-related adverse events.

Table 12: Treatment Emergent Adverse Events with ≥5% Rate in Intranasal HAP Study EG-009

Adverse Event	MS Contin, Manipulated (N = 47)	Arymo ER, Manipulated (N = 50)	Arymo ER, Manipulated/ Sieved (N = 47)	Arymo ER, Intact Oral (N = 49)	Placebo (N = 48)
Any TEAE	59.6%	30.0%	31.9%	46.9%	10.4%
Nausea	21.3%	10.0%	4.3%	16.3%	0.0%
Headache	8.5%	10.0%	4.3%	14.3%	2.1%
Nasal congestion	4.3%	8.0%	4.3%	2.0%	2.1%
Pruritus generalized	12.8%	8.0%	0.0%	4.1%	0.0%
Vomiting	21.3%	2.0%	0.0%	14.3%	0.0%
Dizziness	6.4%	0.0%	2.1%	6.1%	0.0%
Pruritus	10.6%	0.0%	0.0%	4.1%	0.0%

7 CLINICAL RELEVANCE

7.1 Bioequivalence to MS Contin and Effects of Food and Alcohol

Arymo ER is bioequivalent to MS Contin, which provides the scientific bridge for the safety and efficacy of Arymo ER 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.

A fed/fasted analysis in a clinical PK study demonstrated no clinically significant effect of food, so patients may take Arymo ER without regard to meals. Furthermore, there is no evidence of alcohol dose-dumping with Arymo ER, unlike some other opioid analgesics (e.g., Embeda). However, as with all opioids, Arymo ER should not be taken with alcohol.

7.2 Class-wide Risks of Opioids and the Role of Abuse-Deterrent Formulations

While prescription opioid analgesics are an effective option for patients with chronic pain when taken as intended, they are associated with a significant risk for misuse and abuse. Extended-release morphine products are the most commonly prescribed ER opioids and are abused through all routes of administration (oral, nasal, and IV). The preponderance of ER morphine products prescribed today do not possess abuse-deterrent features. Furthermore, the only abuse-deterrent ER morphine product that is currently marketed in the United States, Embeda, is injectable, so abusers are still susceptible to the risks of injection-related medical consequences.

It stands to reason that the replacement of easily abusable formulations of ER morphine in the market with ADFs could play an important role in helping to curb misuse and abuse. While the effectiveness of ADF technologies had previously been a hypothesis, emerging epidemiologic data on reformulated, abuse-deterrent OxyContin provides evidence that an ADF technology with physical and chemical barriers is associated with meaningful reductions in the adverse outcomes of misuse, abuse, and diversion.

Acknowledging that abuse-deterrent technology alone cannot solve the opioid abuse epidemic is critical. While ADFs may deter abuse, they cannot be completely ‘abuse-proof’ because the formulations must be bioavailable to treat patients in chronic pain. An appropriate response to the opioid abuse crisis must employ strategies involving both prevention and treatment, some of which are highlighted in Table 13. Many of these approaches are also included in the FDA’s Opioid Action Plan (FDA, 2016).

Table 13: Key Strategies for Treatment and Prevention of Opioid Abuse

Treatment	Prevention

• Treatment of opioid use disorder
• Naloxone for acute treatment of overdose
	• Improved prescribing practices
	• Prescription Drug Monitoring Programs (PDMPs)
	• Patient and physician education
	• Universal precautions
	  o Patient risk assessment
	  o Urine drug screening
	  o Safe storage and disposal
	• Abuse-deterrent formulations

While treatment for abuse is important and necessary, the public health imperative should include methods to prevent abuse from occurring in the first place. ADFs are designed to deter individuals from initiating and progressing in abuse patterns that may ultimately necessitate treatment. Similar to other clinical conditions, such as cardiovascular disease and stroke, it is well recognized that preventative strategies can have an important impact on public health beyond what is possible with acute interventions alone.

7.3 Abuse-Deterrent Properties of Arymo ER

The extensive battery of abuse-deterrent studies, which included both Category 1 *in vitro* experiments and Category 2/3 clinical PK and HAP studies, demonstrate that Arymo ER requires more effort to get into an abusable form than a non-ADF ER morphine comparator. The key features of the abuse-deterrent profile of Arymo ER include:

- Resistance to PSR creates barriers to alternate routes of abuse (manipulated oral, nasal, and IV)
- Gelling properties result in Arymo ER being very difficult to extract in small volumes or draw into a syringe, which is expected to deter intravenous abuse
- Physiochemical properties of the tablet slow the rate of extraction in large volumes, making oral abuse via this method less desirable
- Maximum Drug Liking for manipulated Arymo ER was statistically significantly lower compared to crushed MS Contin when taken by the oral or nasal routes
- The majority of the key secondary endpoints were consistent with and supportive of the primary endpoint of Maximum Drug Liking
- Extended-release properties of Arymo ER are largely maintained after manipulation when taken by the oral or nasal routes
- PK findings across both clinical HAP studies are consistent with and supportive of the PD outcomes

7.4 Clinical Importance of Abuse-Deterrent Data for Arymo ER

As noted by the FDA in their final Guidance, "the science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving (FDA, 2015)". To date, only one study has attempted to determine the clinically important difference (CID) for HAP studies that would predict meaningful changes in drug-taking behavior (Eaton et al., 2012). At the time of the conduct of this study, the unipolar VAS Drug High scale from the Drug Effects Questionnaire was the endpoint with the most data from abuse liability studies, and therefore was chosen to estimate a CID. The study determined that differences in ratings of maximum Drug High (E_{max}) of approximately 8 to 10 mm on the unipolar Drug High scale were clinically significant using both anchor- and distribution-based statistical methods.

The differences between MS Contin and Arymo ER in Drug High E_{max} were approximately 13 points in the manipulated oral HAP study and between 33 and 45 for the intranasal HAP study (Table 14). The treatment differences between Arymo ER and MS Contin exceeded the CID threshold for both routes of abuse, predicting a clinically important reduction in real-world drug-taking behavior of Arymo ER compared to MS Contin for the manipulated oral and nasal routes.

Table 14: Summary of Mean VAS Drug High for Arymo ER via Manipulated Oral and Intranasal Routes

Study (Arymo ER Condition)	Mean VAS Drug High E_{max}			Clinically important? (>8-10 mm[1])
	MS Contin	Arymo ER	Treatment Difference	
Manipulated Oral HAP Study	51.9	38.8	13.1	***Yes***
Intranasal HAP (Manipulated Arymo ER)	61.2	27.7	33.5	***Yes***
Intranasal HAP (Manipulated/Sieved Arymo ER)	61.2	16.0	45.2	***Yes***

[1] Based on CID from Eaton et al., 2012

As it was determined that an IV HAP study could not be safely performed with Arymo ER because of the significant gelling properties, the clinical relevance of the laboratory *in vitro* findings can be evaluated in the context of other abuse-deterrent formulations with physio-chemical properties intended to prevent IV abuse. For example, reformulated OxyContin has a statement in its label that "when subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle (Purdue Pharma, L.P., 2015)".

Two studies have evaluated the impact of the reformulation of OxyContin with abuse-deterrent properties on the prevalence of IV abuse. A sentinel surveillance study found that among people being assessed for substance abuse treatment who had abused OxyContin within the last 30 days, the prevalence of the IV route declined from 35.7% prior to reformulation to 15.9% after

reformulation (Butler et al., 2013). Another study of 189 abusers of OxyContin in rural Kentucky found that the reformulation of OxyContin was associated with a decline in the prevalence of IV abuse from 30% to 0.5% once the abuse-deterrent formulation had replaced the original formulation (Havens et al., 2014).

Given that the *in vitro* Category 1 studies of Arymo ER have demonstrated that it also possesses gelling properties when being prepared for IV abuse that resist extraction and passage through a needle, it is reasonable to expect that Arymo ER can produce a similar real-world deterrent against IV abuse.

7.5 Post-Marketing Commitments

Egalet is currently a participant (Observer status) in the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Companies (RPC). If Arymo ER is approved, Egalet will convert to an active member and participate in the full range of activities of the RPC. In addition, Egalet will fulfill the post-marketing study requirements of the Opioid Post-marketing Consortium (OPC) regarding the safe use of ER/LA opioids.

If approved, Egalet would also design a Category 4 post-approval epidemiologic study in consultation with the FDA in order to investigate the real-world effect of Arymo ER on opioid abuse. Finally, Egalet is prepared to monitor the post-marketing safety experience of Arymo ER and comply with current regulatory reporting obligations with our existing pharmacovigilance and medical information call center resources.

7.6 Conclusion

The bioequivalence of Arymo ER to MS Contin provides the scientific bridge to safety and efficacy to support regulatory approval for its proposed indication for the treatment of patients with chronic pain for whom alternative treatment options are inadequate.

The totality of the evidence supports that Arymo ER has an abuse-deterrent profile that can be expected to deter abuse by the manipulated oral, nasal, and IV routes. If approved, Arymo ER would help to address a significant unmet public health need and help to reduce opioid abuse by offering a new abuse-deterrent, ER morphine treatment option that provides improvements over most ER morphine products that are currently prescribed that do not have abuse-deterrent properties and can be easily crushed and abused.

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