CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208603
Priority or Standard	Standard
Submit Date(s)	December 14, 2015
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Division/Office	Division of Anesthesia, Analgesia and Addiction Products/ODE 2
Reviewer Name(s)	John Hariadi, MD, FAAFP
Review Completion Date	September 23, 2016
Established Name	Morphine Sulfate extended-release tablets
(Proposed) Trade Name	Arymo ER
Applicant	Egalet US, Inc.
Formulation(s)	15mg, 30mg, 60mg oral tablets
Dosing Regimen	Every 8 to 12 hours
Applicant Proposed Indication(s)/Population(s)	Management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adults

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Glossary

AC	Advisory committee
AE	Adverse event
AQ	Abuse quotient (C_{max}/t_{max})
ALERRT^{SM}	Assessing Labor, Effort and Resources Required for Tampering
AUC	Area under the concentration time curve
AUC_{∞}	Area under the concentration time curve from time zero extrapolated to infinity
$AUC_{0\text{-}24h}$	Area under the concentration time curve from time zero to 24 hours postdose
AUC_{ss}	AUC at steady-state through the dosing interval τ
BA	Bioavailability
BE	Bioequivalence
BLA	Biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
cAMP	Cyclic adenosine monophosphate
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Peak concentration in plasma
$C_{max,ss}$	C_{max} at steady state following multiple doses
CMC	Chemistry, manufacturing, and controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case report form
CRM	Controlled-release morphine
CRO	Contract research organization
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
CYP	Cytochrome P450
DEQ	Drug Effects Questionnaire
DMC	Data monitoring committee
ECG	Electrocardiogram
eCTD	Electronic common technical document
E_{max}	Maximum (peak) effect

EOP2	End-of-Phase 2
ER/LA	Extended-Release/Long-acting
ETASU	Elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good clinical practice
GRMP	Good review management practice
HAL	Human Abuse Liability
ICH	International Conference on Harmonization
IN	Intranasal
IND	Investigational New Drug
IR	Immediate release
IRMS	Immediate release morphine sulfate
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent to treat
IVIVC	*In vitro/in vivo* correlation
LH	Luteinizing hormone
LS	Least Squares
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MAOIs	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NME	New molecular entity
OA	Osteoarthritis
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
P-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetics
PMC	Post marketing commitment
PMR	Post marketing requirement
PP	Per protocol

PPI	Patient package insert
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred term
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical analysis plan
SGE	Special government employee
SOC	System organ class
SULT	Sulfotransferase
$T_{1/2}$	Elimination half-life
TDAA	Take Drug Again Assessment
TDF	Transdermal fentanyl
TEAE	Treatment emergent adverse event
t_{max}	Time to peak concentration
UGT	Uridine diphosphate glucuronosyl transferase
VAS	Visual Analog Scale

1 Executive Summary

1.1. Product Introduction

Arymo™ ER (morphine sulfate) is an abuse-deterrent, extended-release, oral morphine formulation 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 available as 15mg, 30mg and 60mg tablets for oral administration, with a proposed dosing regimen of every 8 or 12 hours. The active ingredient, morphine sulfate, in Arymo ER is the same as that of the listed drug, MS Contin®, but the drug product is differentiated by abuse-deterrent properties based on Egalet's proprietary Guardian™ Technology platform.
Morphine sulfate is an opioid agonist and a Schedule II controlled substance with an acknowledged abuse liability. The risk of misuse and abuse of morphine was the focus of the development program for Arymo ER, which the Applicant claims demonstrated physical and chemical features that make Arymo resistant to common methods of manipulation. Egalet's proprietary Guardian™ Technology is a polymer matrix tablet technology that utilizes plastic injection molding, resulting in tablets that are extremely hard, resistant to particle size reduction and inhibit/block attempts at chemical extraction of the active pharmaceutical ingredient. In addition, the technology results in a viscous hydrogel on contact with liquid, making syringeability very difficult. These features are important in addressing the risk of accidental misuse in patients with chronic pain, as well as intentional abuse using more rigorous methods of manipulation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has not conducted any clinical studies evaluating or comparing the analgesic effectiveness of Arymo ER in the target pain population. They are relying on FDA's previous finding of safety and efficacy for MS Contin (NDA 019516) under the provision of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The clinical program for Arymo ER consisted of five Phase 1 comparative bioavailability studies and two Phase 3 human abuse liability studies. The Phase 1 studies showed bioequivalence of Arymo ER to MS CONTIN in the proposed dosage strengths of 15mg, 30mg and 60mg. The Phase 3 studies indicate that Arymo ER has properties that are expected to reduce misuse or abuse via intravenous injection and nasal insufflation, although misuse or abuse by these routes may still be possible.

As a result, Arymo ER is expected on be effective for its intended use of managing pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Benefit-Risk Summary and Assessment

Arymo ER is an extended-release morphine sulfate tablet designed with abuse-deterrent properties. It is indicated for management of pain severe enough to require daily, around-the-clock, long term opioid treatment for which alternative options are inadequate.

Chronic pain is a significant public health issue, affecting approximately one-third of U.S. adults, with 5% receiving chronic opioid treatment. The total annual incremental cost of health care due to chronic pain ranges from $560 billion to $635 billion (in 2010 dollars) in the United States[1], which combines the medical costs of pain care and the economic costs related to disability days and lost wages and productivity. Morphine sulfate is the most frequently prescribed extended-release opioid in the U.S., with 6.4 million prescriptions in 2015 accounting for 31% of all extended-release/long acting (ER/LA) opioid prescriptions. Opioid prescribing for chronic pain has also resulted in worrying trends of misuse, abuse, and diversion for sale. In response to this rising concern, six extended-release opioids have been approved to date with abuse-deterrent labelling. However, only two (Embeda and Morphabond) have morphine sulfate as the active moiety. Embeda accounted for (b) (4)% of all morphine prescriptions while Morphabond was approved in October 2015 but has yet to be marketed.

Arymo ER is formulated in a polyethylene oxide polymer matrix, which has properties expected to reduce abuse or misuse via intravenous injection or nasal insufflation. In five Phase 1 clinical trials, Arymo ER has been shown to be bioequivalent to MS Contin at the to-be-marketed 15mg, 30mg and 60mg doses. Two Phase 3 Human Abuse Liability studies demonstrated that nasal insufflation of ground Arymo ER was associated with significantly lower scores for the abuse-deterrent metrics of Drug Liking, Drug High, Take Drug Again, and Overall Drug Liking compared to that produced by the insufflation of ground MS Contin. However, they failed to show a significant difference for the oral manipulated Arymo ER compared to MS Contin. Category 1 In-vitro manipulation/extraction studies showed that it was difficult to prepare suitable intravenous solutions using intact, cut, or ground Arymo ER tablets due to such factors as low recovery of fluid, increased fluid viscosity, and low recovery of morphine.

No major safety issues related specifically to Arymo ER were identified in this review. The safety issues associated with extended-release opioids are well-known, and Arymo ER did not perform any differently in that regard. If approved, Arymo ER will be part of the current class-

[1] Berland D, Rodgers P. Rational use of opioids for management of chronic non terminal pain. Am Fam Physician. 2012; 86(3): 252-258

wide ER/LA Opioid Risk Evaluation and Mitigation Strategy (REMS) to ensure appropriate management of safety concerns in the post-market setting.

Approval of Arymo ER for use in adult patients with chronic pain requiring around-the-clock opioid treatment is supported by the available evidence of safety and efficacy. It provides patients and healthcare providers with an additional morphine sulfate product that has abuse-deterrent properties, of which 99% of current morphine prescriptions do not have. With opioid misuse, abuse and diversion a growing public health concern, Arymo ER can potentially contribute by reducing such instances.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic pain is a significant public health issue, affecting approximately one-third of U.S. adults, with 5% receive chronic opioid treatment. The total annual incremental cost of health care due to chronic pain ranges from $560 billion to $635 billion (in 2010 dollars) in the United States, which combines the medical costs of pain care and the economic costs related to disability days and lost wages and productivity. • Chronic pain is also associated with several psychological issues such as depression, anxiety, and substance abuse, placing further burden on the healthcare system. • Opioid prescribing for chronic pain has also resulted in worrying trends of misuse, abuse, and diversion for sale.	Chronic pain is a serious condition and public health concern. Patients often experience symptoms that are severe and debilitating. Opioid abuse, misuse and diversion are also significant and growing health concerns that need to be addressed.
Current Treatment Options	• The current indication for extended-release opioids such as Arymo ER is to manage pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.	Although it is the most commonly prescribed extended-release opioid, the vast majority (>99%) of morphine sulfate prescribed does not have any abuse-deterrent properties.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are currently 6 approved extended-release opioids that have abuse-deterrent labelling. Only two (Embeda and Morphabond) have morphine sulfate as the active moiety. • Morphine Sulfate is the most frequently prescribed extended-release opioid in the U.S., with 6.4 million prescriptions in 2015 accounting for 31% of all extended-release opioid prescriptions. Embeda accounted for 27,775 prescriptions, (b) (4) % of total morphine sulfate prescriptions; Morphabond was approved in October 2015 but has yet to be marketed.	While other opioid moieties (such as oxycodone) with abuse-deterrent properties can be utilized in place of morphine sulfate for chronic pain management, having an additional morphine sulfate extended-release formulation with abuse-deterrent properties would enhance the current treatment armamentarium, while potentially decreasing abuse, misuse and diversion.
Benefit	• Arymo was shown to be bioequivalent to the reference –listed drug, MS Contin, at the 15mg, 30mg and 60mg doses through five Phase 1 clinical trials in 311 adult subjects. • Two Phase 3 Human Abuse liability studies were also conducted on 89 adult subjects. They demonstrated that nasal insufflation of ground Arymo was associated with significantly lower scores for the abuse-deterrent metrics of Drug Liking, Drug High, Take Drug Again, and Overall Drug Liking compared to that produced by the insufflation of ground MS Contin. However, they failed to show a significant difference for the oral manipulated Arymo compared to MS Contin. • Category 1 In-vitro manipulation/extraction studies showed that it was difficult to prepare suitable intravenous solutions using intact, cut, or ground Arymo tablets due to such factors as low recovery of fluid, increased fluid viscosity, and low recovery of morphine.	Arymo would be expected to provide comparable analgesic efficacy as MS Contin. In addition, Arymo has properties that are expected to reduce abuse or misuse via intravenous injection or nasal insufflation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for Arymo includes all patients from the five Phase 1 and two Phase 3 clinical trials, and the drug exposure data is considered adequate. • The safety profile demonstrated for Arymo was consistent with the known safety profile of currently approved extended-release opioids. • Somnolence, headache, dizziness, nausea, and vomiting were commonly reported across all trials. These symptoms are commonly associated with opioid use.	No major safety issues that are specifically related to Arymo have been identified. The safety issues associated with extended-release opioids are well-known, and Arymo did not perform any differently in that regard.
Risk Management	• The safety concerns associated with extended-release opioid use are well documented. Healthcare providers are familiar with the treatments and adverse effects of extended-release/long acting (ER/LA) opioids. Arymo will be part of a class-wide ER/LA REMS program. • Arymo does not trigger the requirements of PREA.	Labelling indicates that approval is only for adults. As part of the ER/LA REMS program, a medication guide will be required and there will be postmarketing study requirements.

2 Therapeutic Context

Analysis of Condition

The proposed indication for this application is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

In contrast to acute pain, which plays a distinct role in the body's defense to environmental stimuli and tissue response/recovery, chronic pain has no specific physiological role and does not aid tissue recovery. Although difficult to define, chronic pain is generally considered to be pain that persists beyond the typical course of acute disease or beyond the time for resolution of an acute injury; is associated with a chronic pathological process that causes continuous or intermittent pain for an extended period of time; or, is persistent and is not responsive to routine pain control. The prevalence of chronic pain has been reviewed by several groups and these studies suggest that prevalence in the adult population ranges from 2% to 40%. Chronic pain is also seen in children and the elderly, and, although prevalent in cancer patients, various non-cancer related pain syndromes have been identified, including arthritic pain, neuropathic pain, and spinal pain. Chronic pain is widely associated with significant economic and health impact, including significant health care costs and expenditures and impacts on workplace productivity and quality of life. Chronic pain is also associated with several psychological issues such as depression, anxiety, and substance abuse, placing further burden on the healthcare system[1,2]

2.2. Analysis of Current Treatment Options

The primary treatments for non-cancer and cancer-related pain are based on the underlying diagnosis, patient characteristics, and severity of pain[1]. For non-cancer patients with chronic pain, a holistic approach is typically recommended, such that other physical and psychological factors are addressed, in addition to prescription medication for pain relief. These measures include identification and treatment of specific pain generators; promoting healthy behaviors; adjuvant pain medication (e.g., antidepressants); and physical therapy. Opioids are typically used in patients for which other modes of treatment have been unsuccessful or the severity of the pain is high. The World Health Organization (WHO) has developed a stepwise approach to managing pain in cancer patients, which emphasizes the intensity of pain, rather than its

[2] Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al. Opioids in the Management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. Pain Physician. 2008 11:S5-62

mechanism or stage of disease, such that those patients exhibiting moderate or greater severity of pain are treated with a trial of opioid therapy[3]. In non-cancer patients, opioids are typically only considered after other measures of pain control have been optimized yet pain continues[1].

Opioid receptors are primarily coupled to pertussis toxin-sensitive G_i/G_0 proteins, which upon activation interact with multiple downstream effector systems to inhibit adenylyl cyclases (i.e., cAMP, cyclic adenosine monophosphate) and voltage-gated Ca^{2+} channels[4]. Opioid receptor activation by endogenous and exogenous ligands results in a variety of pharmacological outcomes, given that each opioid receptor modulates different pharmacological responses. These outcomes are primarily due to central nervous system effects and include analgesia, respiratory depression, euphoria, and sedation. Semi-synthetic opioid agonists, such as morphine, are often used in the treatment of chronic pain; however, their long-term use is limited by the development of tolerance, a phenomenon that has been linked to a variety of pharmacological mechanisms, including receptor down-regulation, receptor desensitization, and uncoupling from the downstream cAMP pathway (characterized by elevated cAMP levels resulting from cellular tolerance to G_i/G_0 stimulation).

Several extended-release oral dosage forms of morphine sulfate have received FDA approval, including MS Contin (extended-release tablet), Oramorph® SR (extended-release tablet), Kadian® (extended-release capsule), Avinza® (extended-release capsule), Embeda® (extended-release capsule also containing naltrexone hydrochloride), and Morphabond™ (extended-release tablet), along with numerous generic versions.

In a comprehensive review of the clinical efficacy data for oral morphine in relieving cancer pain, Wiffen et al[5]concluded that the effectiveness of oral morphine has stood the test of time, with oral morphine being the opioid of choice for moderate to severe cancer pain. There is qualitative evidence that oral morphine has similar efficacy to other available opioids and newer studies support the use of modified-release morphine to titrate to analgesic effect.

There are two current FDA approved morphine sulfate extended-release formulations on the market that are considered to have abuse-deterrent properties: Embeda® and Morphabond™. Embeda® contains an opioid antagonist (Naltrexone), while Morphabond™ relies on physical/chemical properties to make it more difficult to manipulate and extract its content. This appears to be a similar abuse-deterrent mechanism as proposed by the applicant's product, Arymo. The table below briefly summarizes their characteristics.

[3] Cherny N. New strategies in opioid therapy for cancer pain. J. Oncol Manage. 2000. 9:8-15
[4] Waldhoer W, Bartlett SE, Whistler JL. Opioid Receptors. Annu. Rev. Biochem. 2004; 73: 953-990
[5] Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cocharane Database of Systematic Reviews 2013, Issue 7. Art. No. : CD003868. DOI: 10.1002/14651858.CD003868.pub3.

Table 1: Summary of Treatment Alternatives for Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Abuse-Deterrent Formulations						
EMBEDA™	Management of moderate to severe pain when a continuous, around the-clock opioid analgesic is needed for an extended period of time	2009	Capsules (morphine sulfate/ naltrexone hydrochloride): 20 mg/ 0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/ 4 mg Administered once or twice daily	The analgesic efficacy of EMBEDA has been evaluated in one randomized, double-blind, placebo-controlled clinical trial in osteoarthritis patients with moderate to severe pain. This study, conducted over 12 weeks, started open-label treatment with EMBEDA and titrated to effect. Once their pain was controlled, they were randomized to either active treatment with EMBEDA or tapered off EMBEDA using double-dummy design and placed on placebo. The mean change in weekly average pain score from randomization baseline to end of study was statistically superior for those treated with EMBEDA compared to placebo	There were 1251 subjects exposed to at least one dose of EMBEDA in the clinical program. Adverse reactions observed in at least 2% of subjects treated with EMBEDA. The most common adverse reactions leading to study discontinuation were nausea, constipation, vomiting, fatigue, dizziness, pruritus, and somnolence.	Misuse or abuse of EMBEDA by crushing or chewing will result in the uncontrolled release of both morphine and naltrexone, posing the risk of overdose and death. In opioid-tolerant individuals, the absorption of naltrexone may increase the risk of precipitating withdrawal.
MORPHABOND™	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	2015	Extended-release tablets (Morphine Sulfate): 15mg, 30mg, 60mg, 100mg Administered once or twice daily	Efficacy studies were not performed. However, MORPHABOND was shown in clinical trials to be bioequivalent to FDA approved Morphine sulfate formulations.	In clinical trials, the most common adverse reactions with morphine sulfate extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.	MORPHABOND is formulated with inactive ingredients that make the tablet more difficult to adulterate while maintaining extended-release properties even if the tablet is subjected to physical manipulation, and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of MORPHABOND, a series of in vitro laboratory manipulation, extraction, and syringeability studies was conducted. An in vivo clinical abuse potential study was also conducted. Overall, the results indicate that MORPHABOND has properties that are expected to reduce abuse or misuse via injection or insufflation; however, abuse by these routes is still possible.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Arymo ER is not currently marketed in the U.S., but the active moiety, morphine sulfate, has a long marketing history. The extended-release formulation for morphine sulfate, marketed as MS Contin®, has been approved by FDA since May 29, 1987. The risks associated with the use of MS Contin appear similar to the risks of other extended-release opioids. These risks would include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and over-dosage (intended or accidental). The class of opioids, in general, carries label warnings regarding concomitant use with CNS depressants such as alcohol, other opioids, anesthetic agents, sedative hypnotics and skeletal muscle relaxants which can potentiate respiratory depressant effects and increase the risk of adverse outcome.

On April 19, 2011, the Food and Drug Administration (FDA) notified companies that have New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) for certain opioid analgesic drug products of the elements required for a single Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioids (collectively referred to as ER/LA) opioid analgesic products, whether branded or generic, that are:

- extended-release, oral-dosage forms containing: hydrocodone, hydromorphone, morphine, oxycodone, tapentadol, and oxymorphone;
- fentanyl and buprenorphine-containing transdermal delivery systems; and
- methadone tablets or liquid

The elements of the REMS include:

- Medication Guides
- Elements to Assure Safe Use
  - The NDA/ANDA holders must ensure that training is available to prescribers who prescribe the ER/LA opioid analgesics.
  - The NDA/ANDA holders must provide to prescribers information that the prescriber can use to educate patients about the risks of ER/LA opioid analgesics, and their safe use, storage and disposal.
  - The NDA/ANDA holders must inform prescribers of the existence of the ER/LA Opioid Analgesics REMS and the need to successfully complete the necessary training.
- Timetable for Submission of Assessments
  - Post-marketing study requirements

3.2. Summary of Pre-submission/Submission Regulatory Activity

The Applicant had several interactions with the Agency during drug development under IND 117317 which are summarized below:

- 03/02/2013 Pre-IND Written Response Only Type C Meeting
  - *"If you demonstrate that Egalet® Morphine PR is bioequivalent to the proposed listed drug, MS CONTIN, then additional efficacy studies will not be necessary. In addition, the pharmacokinetic profile for Egalet® Morphine PR must support the proposed dosing interval, or additional clinical studies may be required. A safety database of no fewer than 300 subjects is required"*

- 08/27/2014 End of Phase 2 Type B Meeting
  - *"We do not agree* (b) (4) [redacted] *"*
  - Oral human abuse potential study 067-EG-008 was allowed to proceed with recommended revisions, including the requirement that the study must be conducted using the to-be-marketed formulation.
  - The product is exempted from PREA since it does not represent a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

- 08/14/2015 Pre-NDA Type B Meeting
  - The Applicant stated that the safety profile of Egalet Morphine will be based on a minimum of 100 subjects. FDA reminded them that the 100 subjects are acceptable but must have been treated with the "to-be-marketed formulation" via the oral route.
  - Both an ISE and an ISS are required which should include comprehensive discussions of how the product (EG-001) will rely on the Agency's findings for the listed drugs as well as any cited literature references to support an overall finding of efficacy and safety.

3.3. Foreign Regulatory Actions and Marketing History

This product has not been marketed in other countries.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was only requested for the clinical site where the pivotal bioequivalence studies were conducted. The site was PPD Phase I Clinic located in Austin, TX and the inspection was conducted by ORA Investigator Maira Brading from May 23 to June 3, 2016.

The clinical portions of the following studies were audited:

Study #: 067-EG-011

Study Title: "A randomized, open-label, 2-cohort, crossover design study to determine the bioequivalence Of Egalet Morphine PR 60 mg tablets versus MS Contin®60 mg tablets and to evaluate the effect of food on Egalet Morphine PR 60 mg tablets in healthy subjects with naltrexone blockade"

Study Period: 3/16/2015-5/13/2015

Study #: 067-EG-012

Study Title: "A randomized, open-label, 3-way crossover study to evaluate the bioequivalence of Egalet Morphine PR 30 mg to MS Contin 30 mg and Egalet Morphine PR 2 × 15 mg To MS Contin® 30 mg under fasting conditions in healthy subjects under naltrexone blockade"

Study Period: 11/12/2014-01/27/2015

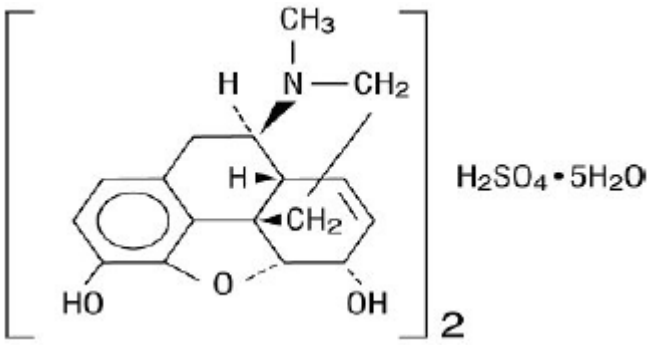
The audit involved a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, case report forms, examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff. Following the inspection, no objectionable conditions were found and no Form FDA-483 was issued. The OSI reviewer recommended that results from clinical portions of studies 067-EG-011 and 067-EG-012 should be accepted for further Agency review. OSI also further recommended that we accept the data without an onsite inspection of the analytical facility for the above trials, (b) (4) due to a recently completed OSI inspection of the site which was classified as No Action Indicated (NAI).

The two human abuse liability (HAL) studies (067-EG-008 and 067-EG-009), discussed later in the review, were both performed at PRA Health Services (formerly Lifetree Clinical Research) in Salt Lake City, Utah. The principal investigator in both studies was Lynn Webster, MD. While PRA Health Services was not formally inspected for the Arymo™ ER application, Dr. Webster's site was inspected from July 13-21, 2015 as part of a different application (NDA 206544). That inspection also involved looking at HAL studies that were conducted at the site. No significant deficiencies were observed and a Form 483 was not issued. Study conduct appeared adequate, including IRB oversight and sponsor monitoring of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the HAL study

appeared reliable as reported in the NDA.

4.2. Product Quality

Morphine sulfate is an odorless, white, crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol: water partition coefficient of morphine is 1.42 at physiologic pH and the pKb is 7.9 for the tertiary nitrogen (mostly ionized at pH 7.4). Its structural formula is:



Arymo ER tablets intended for oral administration are formulated for extended-release of morphine sulfate at dosage strengths of 15 mg, 30 mg, and 60 mg morphine sulfate. The quantitative compositions of Arymo ER tablets for all dosage strengths are provided in Table 2 below.

Table 2. Composition of To-be-marketed Arymo ER (EG-001) tablets

Component	Dosage Strengths of EG-001 Tablets			Function
	15 mg	30 mg	60 mg	
	Mg per Tablet (%)	Mg per Tablet (%)	Mg per Tablet (%)	
Morphine Sulfate	15.00 (1.98)	30.00 (3.94)	60.00 (7.83)	Drug Substance
Polyethylene Oxide 400,000 (b) (4)	(b) (4)			Release controlling; Abuse-Deterrent properties
Butylated Hydroxytoluene (b) (4)				(b) (4)
Total Weight	759.21 (100.0)	761.69 (100.00)	766.53 (100.00)	----

Source: FDA Controlled Substance Staff Review of Arymo ER, page 6.

Polyethylene oxide (PEO) is a commonly used release controlling excipient in abuse-deterrent products and comprises (b) (4)% of the Arymo ER matrix tablet composition, (b) (4) The drug release from the Arymo ER tablet is controlled by erosion of the polyethylene oxide tablet matrix (b) (4), thereby extending the drug release. Arymo ER tablets are produced using a hot-melt extrusion process resulting in a hard tablet. (b) (4)

Please see Dr. Ciby Abraham's review for further details.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please see Dr. Elizabeth Bolan's review for details.

4.5. Clinical Pharmacology

Please see Dr. Srikanth Nallani's review for details.

4.5.1. Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the μ receptor, although it can interact with the κ and δ-opioid receptors at higher doses in the CNS and periphery.[6,7] In addition to analgesia, the widely diverse effects of morphine sulfate include dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems. Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia[8].

Binding of morphine to opioid receptors activates G proteins, which serve various functions in a number of different cell types. The activation of G proteins eventually leads to decreasing excitability along the cell membranes of neurons in the pain pathways[7].G protein activation leads to inhibition of adenylate cyclase, which results in a reduction of cyclic adenosine monophosphate (cAMP), modulation of nociceptive neurotransmitters, and suppression of sodium and calcium channels.[7,9,10] Overstimulation can also cause receptor desensitization, resulting in drug tolerance and dose escalation to achieve desired therapeutic effect.[11]

The two main metabolites of morphine are morphine-3-glucoronide (M3G) and morphine-6-glucoronide (M6G). M3G is biologically inactive; however, M6G shows analgesic activity.[12] Several studies have demonstrated that M6G contributes to the analgesic effects of morphine, especially following chronic exposure[10].

The principal therapeutic actions of morphine are based on its effects on the CNS, including analgesia and sedation. Secondary PD effects of morphine include, but are not limited to, respiratory depression, cough reflex depression, increased smooth muscle tone (resulting in delayed gastrointestinal transit), peripheral vasodilation and histamine release (resulting in

[6]Andersen G, Christrup L, Sjøgren P. Relationships among morphine metabolism, pain and side effects during long-term treatment: an update. J Pain Symptom Manage. 2003 Jan; 25(1):74-91.
[7] DuPen A, Shen D, Ersek M. Mechanism of opioid induced tolerance and hyperalgesia. Pain Management Nursing. 2007:8(3):113-121
[8] Purdue Pharma L.P. MS CONTIN®(morphine sulfate extended-release tablets). Prescribing Information. Revised: June 2014. Purdue Pharma L.P. Stamford, CT
[9] Dinda A, Gitman M, Singhal PC. Immunomodulatory effect of morphine: therapeutic implications. Expert Opin Drug Saf. 2005 Jul; 4(4):669-75
[10] Kilpatrick GJ, Smith TW. Morphine-6-glucoronide: actions and mechanisms. Med Res Rev.2005 Sep;25(5): 521-44
[11] Joshi GP. Morphine-6-glucuronide, an active morphine metabolite for the potential treatment of post-operative pain. Curr Opin Investig Drugs. 2008 Jul; 9(7):786-99
[12] Klimas R, Mikus G. Morphine-6-glucoronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucoronide, and morphine-3-glucoronide. Br J Anaesth.2014 Dec; 113(6):935-44.

hypotension), inhibited secretion of some hormones (adrenocorticotropic hormone, cortisol, testosterone, and luteinizing hormone) and increased secretion of others (prolactin, growth hormone, insulin, glucagon), and modest immunosuppressive effects[8].

4.5.2 Pharmacodynamics

The clinical pharmacology of Arymo has not been investigated in clinical trials. The pharmacological activity of morphine sulfate is well known and Egalet is relying on the FDA's previous findings of safety and efficacy for MS Contin (NDA 019516) to support the pharmacodynamic and pharmacological properties of morphine sulfate.
Pharmacokinetic/pharmacodynamic relationships for morphine are influenced by a wide variety of factors and are generally not useful to guide the clinical use of morphine. As such, dosages of morphine should be chosen and must be titrated on the basis of clinical response of a patient and the balance between therapeutic and adverse effects[8]. Faura et al[13] reported that there was no simple relationship between plasma morphine concentrations and analgesic effect in cancer patients, though there was some evidence of a relationship between plasma concentrations of morphine plus M6G and analgesic effect.
The potential drug interactions of morphine are well known and include pharmacodynamic interactions with CNS depressants, opioid analgesics, muscle relaxants, monoamine oxidase inhibitors (MAOIs), cimetidine, diuretics, anticholinergics, and pharmacokinetic interactions with P-gp inhibitors[8].

4.5.3 Pharmacokinetics

Absorption

The oral bioavailability of morphine is approximately 20 to 40%. When Arymo is given on a fixed dosing regimen, steady-state is achieved in about a day[8].

Food Effect

Food has been shown to possibly have an effect on the pharmacokinetics of morphine following oral administration of immediate-release and modified-release preparations[14].However, bioequivalence is generally maintained between the fed and fasting states for most preparations[14]. Kaiko et al[15]reported no significant differences in PK parameters following a single dose of MS Contin (30 mg) administered to fasted or fed subjects. As described later in

[13] Faura CC, Moore RA, Horga JF, Hand CW, McQuay HJ. Morphine and Morphine-6-glucoronide plasma concentrations and effect in cancer pain. J Pain Symptom Manage. 1996 Feb; 11(2): 95-102
[14] Gourlay GK. Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine. Clin Pharmacokinet. 1998 Sep; 35(3):173-90
[15] Kaiko RF, Lazarus H, Cronin C, Grandy R, Thomas G, Goldenheim P. Controlled-release morphine bioavailability (MS Contin tablets) in the presence and absence of food. Hosp J. 1990;6(4):17-30

the bioequivalence studies, Arymo was shown to not have a food effect as well.

Distribution

Once absorbed, morphine is widely distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain[8]. Morphine also crosses placental membranes and has been found in breast milk. The volume of distribution (Vd) for morphine is approximately 3 to 4 liters per kilogram and morphine is 30 to 35% reversibly bound to plasma proteins.

Metabolism

Morphine is metabolized by demethylation, glucuronidation, and sulfation, with glucuronidation being the predominant metabolic pathway[8]. In humans, the two main metabolites of morphine are M3G and M6G following oral or parenteral administration. Approximately 10% of morphine is metabolized to M6G and 50% to M3G, and 5% of the drug is demethylated into normorphine. Other minor metabolites include morphine-3,6-diglucuronide, morphine-3-etheral sulfate, and normorphine-6-glucuronide .

Glucuronidation occurs almost immediately after morphine enters the systemic circulation in both hepatic and extra hepatic sites with a limited amount of intrahepatic recycling that also occurs. Glucuronidation of morphine is primarily carried out by uridine diphosphate glucuronosyl transferase (UGT)2B7, and to a lesser extent by UGT1A8 and UGT2A1. Demethylation via cytochrome P450 (CYP)3A4 and CYP2C8 produces normorphine , but this is considered a minor route of metabolism (approximately 5%).Morphine is also metabolized in small amounts to codeine and hydromorphone . The major sulfotransferase (SULT) responsible for sulfation of morphine is SULT1A3. In contrast to other opioids such as tramadol, oxycodone, and codeine, CYP3A4 and CYP2D6 do not play a significant role in the metabolism of morphine.

Although there is genetic variability (polymorphisms) of the UGT enzymes 2B7 and 1A3, this has not clearly been shown to alter levels of M3G/M6G production or to change the efficacy of the analgesic response to morphine. M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G, which has a very low affinity for the primary μ-opioid receptor, has no significant analgesic activity[8].

Excretion

Morphine is primarily renally excreted as M3G; however, approximately 10% of the dose is excreted unchanged in the urine, a small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling[8]. The $t_{½}$ of morphine following intravenous administration is 2 to 4 hours. A longer terminal $t_{½}$ of about 15 hours has been reported in some studies involving longer periods of plasma sampling[8].

4.6 Devices and Companion Diagnostic Issues

Not Applicable

4.7 Consumer Study Reviews

Not Applicable

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

Egalet conducted five Phase 1 clinical trials investigating the bioavailability and bioequivalence of Arymo compared to MS Contin in healthy adult subjects (067-EG-001, 067-EG-002, 067-EG-006, 067-EG-011, and 067-EG-012). Egalet also conducted two other studies evaluating the 100 mg formulation (067-EG-004 and 067-EG-005). The tabular listing of all studies is described below. In addition, Egalet sponsored two clinical abuse potential studies in non-dependent recreational opioid users in order to support abuse-deterrent claims for the product (067-EG-008, 067-EG-009).

Table 3. Listing of Clinical Studies for Arymo/EG-001 (morphine sulfate) extended-release tablets

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Pilot Studies (PK/BA/BE)							
067-EG-001	Single center, randomized, single-dose, open-label, 6 way crossover, IVIVC, comparative BA to evaluate the safety, tolerability and PK profiles of 3 formulations of EG-001 versus Kadian®, Avinza® and MS Contin® morphine reference products under fasted conditions and using naltrexone blockade	EG-001 extended-release tablet 60mg (three compositions: 1,2,3) versus: Kadian®60mg ER Capsule Avinza®60mg ER Capsule MS Contin®60mg CR Tablet Single Dose Oral	Determine IVIVC of 3 formulations of EG-001 60mg tablets Compare rate and extent of absorption of 3 formulations of EG-001 60mg tablets vs. 3 commercially available reference drug products Safety and tolerability of EG-001 60mg tablets when using naltrexone blockade	6 single doses, each separated by a minimum of a 7 day washout period	12 subjects randomized and dosed (9 females, 3 males)	Healthy adult males and females	1 Center Quebec, QC Canada
067-EG-002	Randomized, open-label, 5-way crossover comparative BA study of 4 formulations of EG-001 vs MS Contin® under fasted conditions using naltrexone blockade	EG-001 extended-release tablet 60mg (four compositions: 1,2,3,4) versus MS Contin®60mg CR tablet Single Dose Oral	Determine IVIC of 4 formulations of EG-001 60mg tablets Compare rate and extent of absorption of 4 formulations of EG-001 60mg tablets versus MS Contin® reference drug Safety and tolerability of EG-001 60mg tablets when using naltrexone blockade	5 single doses, each separated by a minimum 7 day washout period	30 subjects randomized and dosed (15 females, 15 males)	Healthy adult males and females	1 Center Quebec, QC Canada
067-EG-004	Randomized, open-label, 2 way crossover to determine BE of EG-001 100mg tablets versus MS Contin® under fed conditions with naltrexone blockade	EG-001 extended-release tablet 100 mg versus MS Contin®100 mg CR tablet Single Dose Oral	Assess BE of EG-001 100 mg tablet versus MS Contin®100 mg reference drug under fed Conditions Safety and tolerability of EG-001 100 mg tablets under fed conditions when using naltrexone blockade	2 single doses, each separated by a minimum 5-day washout period	59 subjects enrolled (36 females and 23 males)	Healthy adult males and females	1 Center Austin, TX USA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Pilot Studies(PK/BE)							
067-EG-005*	Randomized, open-label, 2-way crossover to determine BE of EG-001 100 mg tablets versus MS Contin® under fasted conditions with naltrexone blockade *Note: 100mg was not submitted as a dosage strength for this NDA	EG-001 extended-release tablet 100 mg versus MS Contin®100 mg CR tablet Single Dose Oral	Assess BE of EG-001 100 mg tablet versus MS Contin®100 mg reference drug under fasted Conditions Safety and tolerability of EG-001 100 mg tablets when using naltrexone blockade	2 single doses, each separated by a minimum 5-day washout period	63 subjects enrolled (41 females and 22 males)	Healthy adult males and females	1 Center Austin, TX USA
067-EG-006	Randomized, open-label, 2-way crossover to determine BE of EG-001 15 mg tablets versus MS Contin® under fasted conditions	EG-001 extended-release tablet 15 mg versus MS Contin®15 mg CR tablet Single Dose Oral	Assess BE of EG-001 15 mg tablet versus MS Contin®15 mg reference drug under fasted conditions Safety and tolerability of EG-001 15mg tablets	2 single doses, each separated by a minimum 5-day washout period	65 subjects enrolled (45 females and 20 males)	Healthy adult males and females	1 Center Austin, TX USA
BE Studies							
067-EG-011	Randomized, open-label, 2 cohort, crossover study to determine BE of EG-001 60 mg tablets versus MS Contin®60 mg reference product and to evaluate the effect of food on EG-001 60 mg tablets under naltrexone blockade	EG-001 extended-release tablet 60 mg versus MS Contin®60 mg CR tablet Single Dose Oral	Assess BE of EG-001 60 mg versus MS Contin® reference product under fasted conditions Characterize the effect of food on EG-001 60 mg tablets Safety and tolerability of EG-001 60 mg tablets in healthy subjects under fasted and fed conditions and naltrexone blockade	2 or 3 single doses, each separated by a minimum 7-day washout period	65 subjects enrolled (27 female and 38 male)	Healthy adult males and females	1 Center Austin, TX USA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
067-EG-012	Randomized, open-label, 3-way crossover to evaluate BE of EG-001 30 mg versus MS Contin®30 mg and EG-001 15 mg x 2 versus MS Contin®30 mg under fasted conditions and naltrexone blockade	EG-001 extended-release tablet 2 x 15 mg and EG-001 extended-release tablet 30 mg versus MS Contin®30 mg CR tablet Single Dose Oral	Assess BE of EG-001 30 mg versus MS Contin®30 mg reference product under fasted conditions and naltrexone blockade Assess BE of EG-001 2 x 15 mg versus MS Contin®30 mg reference product under fasted conditions and naltrexone blockade Safety and tolerability of EG-001 15 mg and 30 mg tablets under fasted conditions and naltrexone blockade	3 single doses, each separated by a minimum 7-day washout period	66 subjects enrolled (35 females and 31 males)	Healthy adult males and females	1 Center Austin, TX USA
Clinical Abuse Potential Studies							
067-EG-008	Randomized, double blind, triple-dummy, active and placebo controlled,4-way crossover with an exploratory 5th arm comparing the abuse potential of oral intact and oral manipulated EG-001 versus oral manipulated MS Contin®	Qualification Phase: Single oral dose of manipulated 30 mg IR morphine in solution and matching placebo Treatment Phase: EG-001 60 mg intact and manipulated (taken with juice because hard to get into solution) versus MS Contin®60 mg manipulated and mixed into 150 mL diet cranberry juice Matching placebo Exploratory Treatment: Manipulated EG-001 60 mg mixed into 150 mL diet cranberry juice	Compare the relative abuse potential of oral intact and oral manipulated EG-001 versus oral manipulated MS Contin® Determine the relationship between PK and PD parameters of oral manipulated EG-001and manipulated MS Contin® Safety/tolerability, and PK of intact and manipulated EG-001 following oral administration Exploratory: evaluate the relative abuse potential of oral EG-001 when manipulated and administered mixed in juice	Qualification Phase: 2 single doses separated by 24 hours Treatment Phase: 4 treatment sequences separated by a 5-day washout period Exploratory Treatment: 1 single dose after a 5-day washout period	Qualification Phase: 78 enrolled and went on to the drug discrimination test Treatment Phase: 39 enrolled (10 female and 29 male) 38 subjects completed the study. 12 participated in exploratory arm	Healthy adult males and females who are non-dependent recreational opioid users	1 Center Salt Lake City, UT USA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
067-EG-009	Randomized, double blind, double-dummy, active and placebo-controlled, 5-way crossover study comparing the abuse potential of manipulated and manipulated/sieved EG-001 versus manipulated MS Contin® following intranasal administration	Qualification Phase: Single dose of manipulated 30 mg IR morphine administered intranasally and matching placebo Treatment Phase: Manipulated for intranasal use EG-001 60 mg (high volume/large particle size) Manipulated then sieved for intranasal use EG-001 60-mg (low volume/small particle size) Manipulated for intranasal use MS Contin® 60 mg (low volume) Intact for oral administration EG-001 60 mg Matching placebo	When administered intranasally: Compare the relative abuse potential of manipulated and manipulated/sieved EG-001 versus manipulated MS Contin® Determine the relationship between PK and PD parameters of manipulated and manipulated/sieved EG-001 and manipulated MS Contin® Assess the PK of manipulated and manipulated/sieved EG-001 Safety/tolerability of manipulated and manipulated/sieved EG-001	Qualification Phase: 2 single doses separated by 24 hours Treatment Phase: 5 treatment sequences separated by a 5-day washout period	Qualification Phase: 80 enrolled and went on to the drug discrimination test Treatment Phase: 50 treated (11 female and 39 male) 46 subjects completed the study	Healthy adult males and females who are non-dependent recreational opioid users	1 Center Salt Lake City, UT USA

5.2 Review Strategy

The Applicant did not conduct any efficacy studies. As a result, the review is focused on safety, with the database consisting of the comparative bioavailability studies conducted in healthy, naltrexone-blocked adults and the human abuse liability studies in healthy adults who were opioid-experienced, recreational drug users. These studies will be described in greater detail in Sections 7 and 8 but essentially consisted of the following:

- Five Phase 1 clinical trials investigating the bioavailability and bioequivalence of EG-001 (Arymo) compared to MS Contin in healthy adult subjects (067-EG-001, 067-EG-002, 067-EG-006, 067-EG-011, and 067-EG-012).
- Two Phase 1 Studies evaluating the 100mg formulation (067-EG-004 and 067-EG-005), which ended up not being submitted as one of the to-be-marketed dosage strengths.
- Two Clinical Abuse Potential Studies in non-dependent recreational opioid users to support abuse-deterrent claims for the product (067-EG-008, 067-EG-009).

6 Review of Relevant Individual Trials Used to Support Efficacy

Efficacy Studies

No efficacy studies were conducted

6.1.1 Study Design

Overview and Objective

Not Applicable

Trial Design

Not Applicable.

Study Endpoints

Not applicable

Statistical Analysis Plan

Not Applicable.

Protocol Amendments

Not Applicable.

Data Quality and Integrity: Sponsor's Assurance

Not Applicable.

6.1.2 Study Results

Compliance with Good Clinical Practices

As mentioned previously in section 4.1 of this review, on-site inspections conducted by the Office of Study Integrity and Surveillance (OSIS) did not reveal any deficiencies and study conduct appeared in accordance with good clinical practices.

Financial Disclosure

The applicant's submission included the completed FDA form 3454: Certification of Financial Interests and Arrangements of Clinical Investigators, in compliance with 21 CFR part 54. This certified that the applicant has not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined by 21 CFR 54.2(a). In addition, each clinical investigator had no financial interests to disclose and that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). See Section 13.2 below.

Patient Disposition

Not Applicable

Protocol Violations/Deviations

Not Applicable

Table of Demographic Characteristics

Not Applicable

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Not Applicable

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not Applicable

Efficacy Results – Primary Endpoint

Not Applicable

Data Quality and Integrity – Reviewers' Assessment

Not Applicable

Efficacy Results – Secondary and other relevant endpoints

Not Applicable

Dose/Dose Response

Not Applicable

Durability of Response

Not Applicable

Persistence of Effect

Not Applicable

Additional Analyses Conducted on the Individual Trial

Not Applicable

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy Across Trials

7.1.1 Primary Endpoints

Not Applicable

7.1.2 Secondary and Other Endpoints

Not Applicable

7.1.3 Subpopulations

Not Applicable

7.1.4 Dose and Dose-Response

Not Applicable

7.1.5 Onset, Duration, and Durability of Efficacy Effects

Not Applicable

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Post-market Setting

As a class, opioid medications have a high potential for abuse in the post-market setting, and are often subject to misuse, abuse, addiction and criminal diversion. This is especially the case with extended-release formulation of opioids, such as Arymo ER, with the relatively high opioid content compared with immediate-release formulations, thus adding to the risk of adverse outcomes from abuse and misuse.

The applicant proposed Arymo ER as an abuse-deterrent formulation of extended-release morphine sulfate, and submitted Category 1 in-vitro manipulation/extraction studies as well as the two human abuse liability clinical studies previously mentioned (EG-008, EG-009) to support the abuse-deterrent claims. The studies were reviewed in detail by the Controlled Substance Staff at FDA, and covered in depth in Dr. James Tolliver's memorandum to the Division Director dated August 15, 2016. I will summarize the results and conclusions of the Category 1 studies, as well as briefly describe the clinical studies in the following sections:

<u>Category 1 In-Vitro Manipulation and Extraction Studies</u>

- Category 1 studies demonstrate that Arymo ER (EG-001) tablets are difficult to physically manipulate using available household tools. These tablets can be cut into numerous pieces (i.e., 2, 4, 8, 16, and 32 pieces). Of the household tools evaluated, the spice grinder was determined to be most efficient in reducing the particle size of EG-001 tablets, although approximately 75% by weight of the particles were greater than 1000 microns in size. The difficulty in reducing the particle size provides additional evidence of a potential deterrent effect of EG-001 tablets to intranasal abuse. In contrast to what

is found with EG-001, MS Contin tablets, the positive control, can be reduced to a fine powder using a mortar and pestle.

- Category 1 large volume (200 mL) extraction studies demonstrate that with cutting of EG-001 Tablets into pieces using a knife or grinding of EG-001 tablets using a spice grinder, the controlled release properties for morphine from tablets is compromised, as indicated by elevated rates of morphine extraction using tap water and other solvents. Extractions with hot water and other heated solvents also can compromise the controlled release of morphine, resulting in rapid extraction of morphine from EG-001 tablets. These studies suggest a potential susceptibility of EG-001 tablets to manipulation with oral abuse.
- Category 1 dissolution studies conducted on EG-001 tablets cut (Chef's knife) into 2, 4, 8, 16, and 32 pieces, demonstrate that with each increase in number of EG-001 tablet pieces, there is a concomitant increase in the rate of release of morphine into the dissolution media, reflecting greater compromise in the controlled release of morphine. These studies suggest a potential susceptibility of EG-001 tablets to manipulation with oral abuse (see figure 1 below)

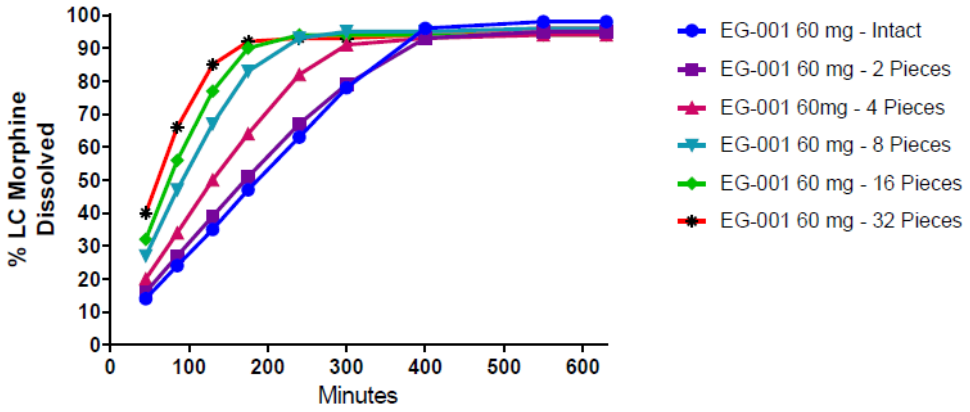


Figure 1. Dissolution Study in 0.1N HCl Demonstrating the Percent Label Claim of Morphine Recovered as a Function of Time from EG-001 60 mg Tablets Intact as well as Cut into 2, 4, 8, 16, and 32 Pieces. (N =3 or 2). (Source: Sponsor Submission eCTD 19, July 20, 2016)

- The results of Category 1 injectability/syringeability studies support an abuse-deterrent claim for EG-001 with regard to abuse by intravenous injection. With use of 2, 5, or 10 mL of tap water, it is difficult to prepare suitable intravenous solutions using intact, cut, or ground EG-001 60 mg tablets due to such factors as low recovery of fluid, increased fluid viscosity, and low recovery of morphine. By contrast, placement of a single ground tablet of the positive control, 60 mg MS Contin, in 2 mL or 5 mL of tap water for 10 minutes resulted in solutions of sufficient volume with little viscosity and containing concentrations of morphine likely to produce subjective reinforcing effects.
- Under the conditions utilized by the applicant in a simulated smoking study, EG-001 60 mg tablet when ground and heated, resulted in less than 3.1% Label Claim (LC) of

morphine recovered in vapor suggesting that under the conditions utilized, EG-001 tablets cannot be smoked. At the same time, the Applicant did not evaluate the positive control, MS Contin, for possible abuse by smoking. In the absence of assessing the comparator, no abuse-deterrent claim can be given to EG-001 tablets regarding abuse by smoking

Category 2/3 Human Abuse Liability (HAL) Study 067-EG-008

Title: A randomized, double-blind, triple-dummy, active and placebo-controlled, four-way crossover study with an exploratory fifth arm comparing the abuse potential of manipulated and intact EG-001 morphine tablets versus manipulated MS Contin following oral administration in nondependent recreational opioid users

Primary Objective: To compare the relative abuse potential of oral intact and oral manipulated formulations of EG-001 morphine vs oral manipulated MS Contin.

Secondary Objectives:

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of oral manipulated EG-001.
- To assess the safety and pharmacokinetics of intact and manipulated formulations of EG-001 following oral administration

Exploratory Objective: To evaluate the relative abuse potential of oral EG-001 morphine when manipulated and administered mixed in juice

Design: Single-center (PRA Health Sciences in Salt Lake City, UT), randomized, double-blind, triple-dummy, 4-way crossover study comprising a Screening Visit, a Qualification Phase, a Treatment Phase (with 4 treatment periods, each of which included a 3 day/2 night in-clinic visit), and a Follow-up Visit.

38 adult subjects completed the study. They consist of non-dependent recreational opioid users who had used opioids for non-medical purposes on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Visit. Subjects were required to pass the naloxone challenge test to show they were non-dependent to opioids.

In order to advance to the Treatment Phase, subjects were required to discriminate between oral 30 mg immediate release morphine and placebo during the Drug Discrimination Phase using the bipolar 0-100 point Drug Liking VAS based on the following criteria:

- Peak effect (E_{max}) score of ≥ 65 points for Drug Liking in response to morphine
- ≥15-point E_{max} difference between morphine and placebo treatments during the first 2 hours following drug administration

- Placebo response ≥40 and ≤60 points for Drug Liking during the first 2 hours following drug administration.

During the Treatment Phase, subjects were randomized in a 1:1:1:1 ratio, where each subject received all study treatments separated by a minimum 5-day washout period as indicated below:

- EG 001, 60 mg oral intact
- EG 001, 60 mg oral manipulated added directly to tongue
- MS Contin, 60 mg oral manipulated added directly to tongue
- Placebo

Manipulation of EG-001 tablets was accomplished using a 7 inch Chef's knife, cutting board, and weight boat, with one EG-001 tablet cut into 32 pieces. The MS Contin tablet manipulation involved crushing with a mortar and pestle. Each treatment was dispensed onto the tongue followed by several rinses with liquid not to exceed 240 mL.

12 subjects who completed the study were also invited to participate in an additional exploratory treatment arm during which they received a fifth treatment of EG-001, 60 mg oral manipulated and administered mixed in juice. However, it was unclear how these subjects were selected.

Blood samples were taken pre-dose; at 30 and 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Various pharmacokinetic parameters for plasma morphine were conducted including, but not limited to the maximum observed plasma concentration (C_{max}) and the time to achieve C_{max} (T_{max}).
The applicant also conducted a variety of pharmacodynamic measures, to include the primary endpoint of Drug Liking VAS, as well as the secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS. During Treatment Periods Drug Liking VAS and High VAS were collected at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. High VAS was also administered pre-dose. Take Drug Again VAS and Overall Drug Liking VAS were administered at 12 and 24 hours post-dosing.

Results:
Both the C_{max} and T_{max} following oral treatments during the Treatment Phase are shown in Table 4 below**:**

Table 4. Pharmacokinetic Results from Oral Treatment arms (PK Population N=39)

Morphine Plasma Pharmacokinetic Parameter	Statistic	Manipulated MS Contin 60mg (N=39)	Manipulated EG-001 60 mg (N=38)	Intact EG-001 60 mg (N=38)
Cmax (ng/mL	Mean (SD)	42.34 (14.31)	28.74 (9.09)	17.81 (6.60)
	Median	42.20	29.20	16.70
	Range	14.2, 79.0	12.5, 47.8	8.5, 32.3
	% CV	33.8	31.6	37.0
Tmax (hours)	Median	0.880	2.120	4.120
	Range	0.63, 4.13	0.88, 4.15	1.63, 6.13

Source: Applicant's submission (Table 11.4.2.2-1, Clinical Study report for 067-EG-008)

Relative bioavailability analyses for plasma morphine conducted by the applicant showed that treatment with manipulated EG-001 60 mg produced a lower C_{max} (28.74 ng/mL) of plasma morphine compared to treatment with manipulated MS Contin 60mg (C_{max} = 42.34 mg), but a higher plasma level of morphine than intact EG-001 60 mg (17.81ng/mL). The calculated times to C_{max} (T_{max}) were 0.88, 2.12, and 4.12 hours for manipulated MS Contin, manipulated EG-001, and intact EG-001, respectively.

The summary for pharmacodynamic results are shown below in Table 5:

Table 5. Summary of Descriptive Statistics for the Oral Treatment Arms in 067-EG-008

Measure	Statistics	Maximum Effect (Emax)			
		EG001 60 mg		Manipulated MS Contin 60 mg (n=38)	Placebo (n=38)
		Manipulated (n=38)	Intact (n=38)		
Bipolar Drug Liking VAS	Mean (SE)	68.3 (2.0)	63.2 (1.64)	73.3 (1.59)	53.3 (1.27)
	Median	67.0	62.0	74.0	50.0
	Q1,Q2	61, 75	56, 68	68, 79	50, 52
Unipolar High VAS	Mean (SE)	38.8 (4.15)	26.8 (3.97)	51.9 (3.83)	5.3 (1.87)
	Median	38.0	18.5	49.0	0
	Q1, Q2	18, 58	7, 47	34, 72	0, 1
Bipolar Take Drug Again VAS	Mean (SE)	62.9 (3.18)	54.8 (3.37)	70.1 (2.84)	51.0 (1.65)
	Median	61.5	56.0	68.0	50.0
	Q1, Q2	51, 71	50, 65	56, 80	50, 50
Bipolar Overall Drug Liking VAS	Mean (SE)	65.1 (3.02)	55.7 (3.21)	69.8 (2.50)	52.2 (1.31)
	Median	63.5	57.0	67.5	50.0
	Q1, Q2	51, 75	50, 66	57, 81	50, 50

Source: CDER CSS Review by Dr. James Tolliver (Table 7, page 20)

Oral manipulated MS Contin 60 mg (control) produced a mean E_{max} of Drug Liking of 73.3 mm

which was significantly greater (p=0.0385) than that produced by oral manipulated EG-001 60 mg (68.3 mm). The median times to achieve E_{max} (TE_{max}) were 1.02 and 1.99 hours for manipulated MS Contin and manipulated EG-001, respectively, although the mean Drug Liking time course profile suggests that much of the rise in Drug Liking occurred within 1.5 hours following ingestion of manipulated EG-001. The clinical relevance of the 5 mm difference in Drug Liking VAS between oral manipulated MS Contin and oral manipulated EG-001 with respect to a possible oral abuse-deterrent effect is not known.

Other important outcome measures from study 067-EG-008 provided inconsistent results or did not provide supportive evidence for a potential deterrent effect of EG-001 to oral abuse. With respect to the important metric, Take Drug Again, the E_{max} produced by oral manipulated MS Contin 60 mg (70.1 mm) was not significantly different (p=0.0967)from that produced by oral manipulated EG-001 60 mg (62.9 mm). This does not support a possible deterrent effect of EG-001 to oral abuse.

Oral manipulated MS Contin 60 mg produced a mean E_{max} of High (51.9 mm) that was significantly higher (p=0.0175) than that produced by oral manipulated EG-001 60 mg (38.8 mm). The median times to E_{max} of High were 1.5 and 3.0 hours for manipulated MS Contin 60 mg and manipulated EG-001 60 mg, respectively. Mean High time effect profile demonstrates a plateau of High which is mostly reached within 1.5 to 2 hours, following ingestion with manipulated EG-001.

Oral administration of manipulated EG-001 60 mg produced a mean E_{max} of Overall Drug Liking (65.1 mm) that was not significantly different (p=0.226) from that produced by oral manipulated MS Contin 60 mg (69.8 mm). This also does not support a deterrent effect of EG-001 to oral abuse.

Category 2/3 Human Abuse Liability (HAL) Study 067-EG-009

Title: A randomized, double-blind, double-dummy, active and placebo-controlled crossover study comparing the abuse potential of manipulated and manipulated/sieved EG-001 morphine tablets versus manipulated MS Contin following intranasal administration in nondependent recreational opioid users

Primary Objective: To compare the relative abuse potential of manipulated and manipulated/sieved EG-001 morphine vs manipulated MS Contin when administered intranasally.

Secondary Objectives:

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of manipulated and manipulated/sieved EG-001 and manipulated MS Contin following intranasal administration.
- To assess the pharmacokinetics of manipulated and manipulated/sieved EG-001 following intranasal administration.

- To assess the safety of manipulated and manipulated/sieved EG-001 following intranasal administration.

Design: Single-center (PRA Health Sciences in Salt Lake City, UT), randomized, double-blind, double-dummy crossover study comprising a Screening Visit, a Qualification Phase (Naloxone Challenge and Drug Discrimination test), a Treatment Phase and a Follow-up Visit.

46 adult subjects completed the study. They consist of non-dependent recreational opioid users who had used opioids for non-medical purposes on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Visit. Subjects also had to have experience with intranasal opioid administration, defined as intranasal (IN) use on at least 3 occasions within the last year prior to Screening.
In order to advance to the Treatment Phase, subjects were required to discriminate between manipulated intranasal 30 mg immediate release morphine and placebo during the Drug Discrimination Phase using the bipolar 0-100 point Drug Liking VAS based on the following criteria:

- Peak effect (E_{max}) score of ≥ 65 points for Drug Liking in response to morphine
- ≥15-point E_{max} difference between morphine and placebo treatments during the first 2 hours following drug administration
- Placebo response ≥40 and ≤60 points for Drug Liking during the first 2 hours following drug administration.

The Treatment Phase consisted of five treatment periods administered under fasted conditions with treatments separated by at least 5 days. All subjects received the manipulated intranasal EG-001 treatment (high volume) in Treatment Period 1 in order to minimize any potential sequence effect. For the remaining 4 periods, consisting of low volume treatments, all subjects received each of the treatments (1 per treatment day). The volume of the investigational products during the 4 latter treatment periods was standardized and the low-volume intranasal treatment (active drug or placebo) used in Treatments C (manipulated MS Contin), D (oral EG-001) and E (placebo) was matched to the volume of Treatment B (manipulated/sieved EG-001) to ensure appropriate blinding of the study treatments. Descriptions of the treatments are provided in Table 6 below:

Table 6. Treatments Administered during the Treatment Phase for Study EG-067-009

Treatment Designation	Treatment	Description of Treatment (As Obtained from Pharmacy Manual)
A	EG-001 60 mg IN High Volume	EG-001 60 mg manipulated IN high volume (including particle sizes greater than 1000 microns) + Placebo for EG001 60 mg Intact Oral.
B	EG-001 60 mg IN Low Volume	EG-001 60 mg manipulated/sieved IN low volume (only particles sized less than 1000 microns) + Placebo for EG001 60 mg Intact Oral
C	MS Contin 60 mg IN Low Volume	MS Contin 60 mg manipulated IN low volume + Placebo for EG-001 60 mg Intact Oral
D	EG-001 60 mg Intact Oral	EG-001 60 mg Intact Oral + Placebo EG001 manipulated IN low volume
E	Placebo IN	Placebo for MS Contin 60 mg manipulated IN low volume + Placebo for EG001 60 mg intact oral

Source: CDER CSS Review by Dr. James Tolliver (Table 8, page 24)

Manipulation of both EG-001 60 mg tablets and placebo consisted of initially cutting each tablet into 4 pieces, following by grinding the pieces with a Spice Grinder (Waring Model #WSG30K) for 15 second intervals for a total grinding time of 2.5 minutes. The high volume treatment included all powder obtained including particle sizes above 1000 microns. For producing the low volume EG-001 Intransal treatments, the resulting powder following grinding was passed through a 1000 micron mini sieve to remove all particles greater than 1000 microns.
Manipulation of MS Contin for intranasal administration involved crushing 60 mg tablets with a glass pestle**.**
Subjects were instructed to complete study drug administration within 5 minutes; an additional 10 minutes was allowed if needed. If administration was not fully completed within 15 minutes, dosing was stopped and the amount (weight) not administered was recorded. Subjects who were unable to complete an intranasal administration were allowed to continue in the study. The amount of time needed for intranasal administration was recorded. For each treatment, the oral administration preceded the intranasal administration. Subjects were required to sit upright for 4 hours after each dose. Subjects were not allowed to blow their noses for 2 hours following dosing, and any episodes of sneezing within 1 hour were documented.

Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dose. Various pharmacokinetic parameters for plasma morphine were conducted including, but not limited to the maximum observed plasma concentration (C_{max}) and the time to achieve C_{max} (T_{max}).
The applicant also conducted a variety of pharmacodynamic measures, to include the primary endpoint of Drug Liking VAS, as well as the secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS. During Treatment Periods Drug Liking VAS and High VAS were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. High VAS was also assessed pre-dose. Take Drug Again VAS and Overall Drug Liking VAS were administered at 12 and 24 hours post-dosing.
A bipolar Ease of Snorting VAS, administered within 5 minutes following intranasal

administration, was used for a subject rated assessment of the difficulty associated with snorting the various treatments. Subject rated nasal tolerability was determined using a Nasal Effects Assessment which was administered at 5, 15, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

Results:
Both C_{max} and T_{max} for plasma morphine following treatments during the Treatment Phase are shown in Table 7 below:

Table 7. Plasma Pharmacokinetics of Morphine following treatments

Plasma PK Parameter for Morphine	Statistic	Intranasal MS Contin 60 mg (n = 37)	Intranasal EG001 60 mg High Volume (n = 45)	Intranasal EG001 60 mg Low Volume (n = 46)	Intact Oral EG001 60 mg (n = 39)
Cmax (ng/mL)	Mean (SD)	36.33 (12.90)	19.02 (9.56)	4.47 (2.25)	17.20 (4.26)
	Median	34.60	19.80	4.08	18.10
	Range	6.5 – 62.3	4.2 – 40.1	1.0 – 11.3	9.3 – 24.8
Tmax (h)	Median	1.13	2.17	2.66	3.65
	Range	0.42 – 2.67	1.13 – 6.13	0.85 – 6.10	1.13 – 6.17

Source: CDER CSS Review by Dr. James Tolliver (Table 9, page 25)

Intranasal MS Contin was associated with a higher mean morphine maximum plasma level (C_{max}) of 36.3 ng/mL compared to either intranasal high volume EG-001 (19.02 ng/mL) or intranasal low volume EG-001 60 mg (4.77 ng/mL). Median time to achieve C_{max} for plasma morphine was shorter for intranasal MS Contin (1.13 hours) compared to high or low volumes of EG-001 (2.17 and 2.66 hours, respectively)
The summary for pharmacodynamics measures in this study are shown below in Table 8:

Table 8. Descriptive Statistics for Pharmacodynamic Measures in Study 067-EG-009

Measures	Statistics	Treatments – Maximum Effect (Emax)				
		Intranasal EG001 60 mg High Volume (n=46)	Intranasal EG001 60 mg Low Volume (n=46)	Oral EG001 60 mg Intact (n=46)	Intranasal MS Contin 60 mg (n=46)	Placebo (n=46)
Bipolar Drug Liking VAS	Mean (SD)	65.5 (14.3)	59.6 (12.5)	68.5 (13.6)	77.7 (11.7)	54.7 (10.6)
	Median	62.0	52.5	68.0	77.5	51.0
	Q1,Q2	52, 76	51, 65	59, 77	70, 85	50, 58
Unipolar High VAS	Mean (SD)	27.7 (28.2)	16.0 (23.2)	36.7 (28.1)	61.2 (23.6)	10.7 (20.2)
	Median	20	5	34	65.5	0
	Q1, Q2	2, 50	0, 20	11, 52	42,79	0, 9
Bipolar Take Drug Again VAS	Mean (SD)	43.1 (29.6)	52.6 (17.2)	58.9 (24.9)	69.9 (27.4)	52.5 (12.7)
	Median	50.0	50.0	56.0	73.0	50.0
	Q1, Q2	19, 66	50, 58	45.75	57, 90	50, 51
Bipolar Overall Drug Liking VAS	Mean (SD)	53.9 (21.7)	54.4 (13.6)	59.4 (24.2)	72.7 (18.1)	52.1 (11.2)
	Median	51.0	50.5	59.0	71.0	50.0
	Q1, Q2	50, 67	50, 55	50, 77	61, 87	50, 51

Source: CDER CSS Review by Dr. James Tolliver (Table 10, page 26)

Intranasal EG-001 high volume and intranasal EG-001 60 mg low volume produced mean E_{max} scores of Drug Liking of 65.5 mm and 59.6 mm, respectively, that were significantly lower ($p<0.0001$) than the mean E_{max} of Drug Liking produced by intranasal MS Contin 60 mg (77.7 mm). The median times to achieve E_{max} of Drug Liking were 1.01, 1.75, and 1.01 hours for intranasal MS Contin and intranasal high volume and low volume EG-001, respectively.
The mean E_{max} of intranasal MS Contin 60 mg (61.2 mm) was significantly higher ($p<0.0001$) than that produced by either high volume (27.7 mm) or low volume (16.0 mm) intranasal EG-001 60 mg. The median times to achieve E_{max} of High were 2.00, 2.01, and 0.75 hours for the intranasal administration of MS Contin 60 mg, high volume EG001, and low volume EG-001 60 mg, respectively.
Treatment with intranasal MS Contin 60 mg resulted in a mean Take Drug Again E_{max} of 69.9 mm, which was significantly higher ($p<0.0001$) than that observed following intranasal EG-001 60 mg high or low volume (43.1 mm and 52.6 mm, respectively).
With respect to Overall Drug Liking, the mean E_{max} produced by intranasal MS Contin 60 mg was significantly higher ($p<0.0001$) than that produced by intranasal low volume and high volume EG-001 60 mg (54.4 mm and 53.9 mm, respectively).
For the Ease of Snorting VAS, only the intranasal EG-001 60 mg high volume treatment had a low mean score within the “difficult” range of the scale (mean of 17.0 mm out of 100 mm). Mean scores for all other treatments were in the “easy” range of the scale and within 5 points of each other (range of mean scores 73.8 mm to 78.0 mm).
For intranasal treatments including MS Contin, EG-001 low volume, and placebo, the mean maximum scores were less than 1 for all six nasal symptoms, indicating at most mild nasal adverse effects resulting from these treatments. Following intranasal EG-001 high volume, mean maximum subjective nasal scores for “need to blow nose”, “nasal congestion”, “intranasal irritation”, and “nasal congestion” were 2.1, 2.1, 1.5, and 1.3, respectively,

indicating some mild-to-moderate nasal effects.

Overall Conclusions
Data for all the Category 1 and HAL studies indicates support for deterrent claims of Arymo ER /EG-001 to abuse by nasal insufflation and intravenous injection, but not to oral administration. The results of the Category 2/3 intranasal study 067-EG-009 demonstrate a potential deterrent effect of EG-001 to nasal insufflation. Difficulty in reducing the particle size of EG-001 Tablets as evidenced by Category 1 physical manipulation studies provide additional support for a deterrent effect to insufflation. Results of Category 1 syringeability/injectability studies indicate a potential deterrent effect of EG-001 to intravenous abuse. Based on the results of Category 2/3 oral study 067-EG-008, EG-001 tablets do not appear to have a deterrent effect to oral abuse.

7.2.2 Other Relevant Benefits

Not Applicable

7.3 Integrated Assessment of Effectiveness

The Applicant has not conducted any clinical studies evaluating or comparing the analgesic effectiveness of Arymo/Egalet Morphine in the target pain population. They are relying on FDA's previous finding of safety and efficacy for MS CONTIN (morphine sulfate ER) tablets (NDA 019516) under the provision of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

There will be no differences between the labelling of Arymo compared to MS CONTIN with respect to effectiveness in 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 Division agreed that no efficacy studies would be required provided that the BE of Arymo to the proposed RLD, MS CONTIN, was demonstrated in the comparative BA studies.

The Applicant has evaluated the comparative BA of Arymo versus MS CONTIN following single administrations of 15mg, 30mg, 60mg, and 100mg in healthy volunteers under naltrexone blockade. The following briefly summarizes the results:

(b) (4)

(b) (4)

2) 60mg dose is bioequivalent, no food effect noted.

067-EG-011 was a Phase 1 randomized, open-label 2 cohort, crossover study to determine the bioequivalence of Egalet Morphine PR 60mg Tablet versus MS CONTIN 60mg tablets and to evaluate the effect of food on Egalet Morphine PR 60mg tablets in healthy subjects with naltrexone blockade. 65 adult subjects (ages 18 to 55) were enrolled. The study consisted of a screening period (Days –28 through –2), 2 treatment periods (2-period cohort) or 3 treatment periods (3-period cohort) with confinement (Days –1 through 3 of each period), and an end-of-study/early termination visit (within 4 to 14 days of the last dose of study drug). There was a washout interval of at least 7 days between doses of any 2 consecutive treatment periods.

Before dosing on Day 1 of Period 1, all subjects (both cohorts) were randomly assigned to receive study drug according to 1 of 2 treatment sequences (AB or BA). In the 3-period cohort, subjects completing Periods 1 and 2 continued into Period 3 and received Treatment C as shown below in Table 9:

Table 9. Treatment cohorts for Study 067-EG-011

	2-Period Cohort		3-Period Cohort		
Period	1	2	1	2	3
Sequence 1	A	B	A	B	C
Sequence 2	B	A	B	A	C

Treatment A: Egalet® morphine prolonged-release, 60-mg tablet, fasting conditions.
Treatment B: MS CONTIN, 60-mg tablet, fasting conditions.
Treatment C: Egalet® morphine prolonged-release, 60-mg tablet, fed conditions.

Source: Applicant's Submission (Study 067-EG-011 Synopsis, page 2)

On Day 1 of Periods 1 and 2, each subject received 1 of 2 study drug treatments as follows:
• Treatment A: Egalet® morphine PR, 60-mg tablet, fasting conditions
• Treatment B: MS CONTIN, 60-mg tablet, fasting conditions
In the 3-period cohort, subjects received the following study treatment on Day 1 of Period 3:

• Treatment C: Egalet® morphine PR, 60-mg tablet, fed conditions
Subjects also received naltrexone 50 mg orally approximately 3 and 15 hours before each study drug administration and approximately 9 and 21 hours after each study drug administration.
For Periods 1 and 2, subjects in both cohorts fasted overnight for at least 10 hours before each dose of study drug.
For Period 3, subjects in the 3-period cohort received study drug 30 minutes after starting a standard Food and Drug Administration high-fat breakfast (consumed within 30 minutes).

When Treatment A (test; Egalet® morphine PR 60 mg) was compared with Treatment B (reference; MS CONTIN 60 mg), the point estimate and 90% CIs of the geometric LS mean ratio for C_{max} (95.35 [89.40, 101.69]) of morphine were all contained within the 80.00% to 125.00% BE interval. Therefore, Egalet® morphine PR 60 mg was demonstrated to be bioequivalent to MS CONTIN 60 mg in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.
When Treatment C (test; Egalet® morphine PR 60 mg) under fed conditions and naltrexone blockade was compared with Treatment A (test; Egalet® morphine PR 60 mg) under fasting conditions and naltrexone blockade, the point estimate and 90% CIs of the geometric LS mean ratio for C_{max} (97.67 [83.83, 113.79]) of morphine were all contained within the 80.00% to 125.00% BE interval. Therefore, there was no evidence of a food effect for Egalet® morphine PR 60 mg when dosed with, as compared to without, food in healthy subjects following single-dose oral administration under naltrexone blockade.

3) Bioequivalence of 30mg, 15mg doses

067-EG-012 was a Phase 1 randomized, open-label, 3-way crossover study to evaluate the bioequivalence of Egalet® morphine PR 30 mg to MS CONTIN® 30 mg and Egalet® morphine PR 2 × 15 mg to MS CONTIN® 30 mg under fasting conditions in healthy subjects under naltrexone blockade. 66 adult subjects (ages 18 to 55) were enrolled. The study consisted of a screening period (Days –28 through –2), 3 treatment periods with confinement (Days –1 through 3 of each period), and an end-of-study/early termination visit (within 4 to 14 days of the last dose of study drug). There was a washout interval of at least 7 days between doses of any 2 consecutive treatment periods.
Before dosing on Day 1 of Period 1, subjects were randomly assigned to receive study drug according to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, and CBA).
On Day 1 of each period, each subject received 1 of 3 study drug treatments as follows:

- Treatment A: Egalet® morphine PR 30 mg, fasting conditions
- Treatment B: MS CONTIN 30 mg, fasting conditions
- Treatment C: Egalet® morphine PR 2 × 15 mg, fasting conditions

Subjects also received naltrexone 50 mg orally approximately 3 and 15 hours before each study drug administration and approximately 9 and 21 hours after each study drug administration.
All subjects fasted overnight for at least 10 hours before each dose of study drug.

When the test Treatment A (Egalet® morphine PR 30 mg) was compared with the reference treatment (MS CONTIN 30 mg), the point estimate and 90% CIs of the geometric LS mean ratio for C_{max} [98.61 (93.91, 103.55)] of morphine were all contained within the 80.00% to 125.00% bioequivalence interval. Therefore, Egalet® morphine PR 30 mg was demonstrated to be bioequivalent to MS CONTIN 30 mg in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.
When the test Treatment C (Egalet® morphine PR 2 × 15 mg) was compared with the reference treatment (MS CONTIN 30 mg), the point estimate and 90% CIs of the geometric LS mean ratio for C_{max} [88.04 (83.87, 92.43)] of morphine were all contained within the 80.00% to 125.00% bioequivalence interval. Therefore, Egalet® morphine PR 2 × 15 mg was demonstrated to be bioequivalent to MS CONTIN 30 mg in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.
When Treatment A (Egalet® morphine PR 30 mg) was compared with Treatment C (Egalet® morphine PR 2 × 15 mg), the point estimate and 90% CIs of the geometric LS mean ratio for C_{max} [112.00 (106.70, 117.57)] of morphine were all contained within the 80.00% to 125.00% bioequivalence interval. Therefore, Egalet® morphine PR 30 mg was demonstrated to be bioequivalent to Egalet® morphine PR 2 × 15 mg in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.
The extra step of demonstrating bioequivalence of the 2x15mg Egalet morphine to the 30mg doses of Egalet morphine and MS CONTIN was necessary because the initial study conducted by the applicant: 067-EG-006, a randomized, open-label, 2-way crossover study to determine the bioequivalence of the Egalet® Morphine PR 15-mg tablet versus MS CONTIN® under fasting conditions in healthy subjects, failed to demonstrate bioequivalence for the 15mg dose. The lower limit of the 90% CI of the geometric LS mean ratio for C_{max} of morphine was slightly below the 80% to 125% bioequivalence interval (78.99), indicating an approximately 16% lower morphine C_{max} for the Egalet® morphine PR 15-mg tablet compared with the MS CONTIN 15-mg tablet.
Although the C_{max} is lower for the 15mg dose, I am not concerned due to the fact that this represents the lowest dose for Egalet Morphine, which would typically be used as an initiation/titration dose. In addition, a lower C_{max} would not pose a safety concern.

As illustrated previously in Section 7.2.1 of this review, Arymo ER was submitted as an abuse-deterrent formulation of morphine sulfate, with properties that would render it more difficult to adulterate for misuse/abuse while maintaining its extended-release characteristics. I concur with the review of the abuse potential studies by FDA's Controlled Substance Staff, which made the following recommendations:

- Consideration should be given to allow abuse-deterrent claims for Arymo with respect to abuse by intravenous injection. The Category 1 injectability/syringeability studies demonstrated that it was difficult to produce suitable intravenous solutions using Arymo. At the same time, these studies demonstrated that the positive control, MS CONTIN, could be readily used to produce intravenous solutions.

- Consideration should also be given to allow abuse-deterrent claims for Arymo with respect to abuse by snorting (insufflation). Category 1 physical manipulation studies demonstrated that with use of available household tools, it was difficult to crush/ grind Arymo tablets, whereas MS CONTIN tablets could be easily ground into a fine powder. The Clinical Abuse Liability study 067-EG-009 demonstrated that the insufflation of ground Arymo was associated with statistically significant, lower maximum scores for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS compared to that produced by the insufflation of the positive control, ground MS CONTIN.
- With respect to oral abuse, consideration should be given to not allow abuse-deterrent claims. In clinical abuse liability study 067-EG-008, although the E_{max} of Drug Liking is significantly lower following oral manipulated 60 mg Arymo compared to following oral manipulated 60 mg MS CONTIN (positive control), this difference is small and of questionable clinical relevance. Subjects expressed a similar willingness to take again, if given the opportunity, either oral manipulated 60 mg Arymo or oral manipulated 60 mg MS CONTIN; as revealed by Take Drug Again VAS. With use of the Overall Drug Liking VAS, subjects displayed a similar drug liking experience when given either of the oral manipulated treatments.
- Although the in vitro data suggests that Arymo tablets may not likely be smoked, the Applicant did not conduct similar simulated smoking studies on the positive control, MS CONTIN, to determine the likelihood it might be abused by smoking. Therefore, Arymo should not be granted an abuse-deterrent claim with regards to smoking.

8 Review of Safety

Safety Review Approach

The Applicant is relying on FDA's previous finding of safety for the RLD MS CONTIN (morphine sulfate ER) tablets (NDA 019516, Purdue Pharma, LP) under the provision of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. As a result, the Applicant did not conduct any clinical studies evaluating or comparing the safety of Arymo/Egalet Morphine in the target pain population. Instead, the Applicant conducted seven BA and PK studies that compared the use of Arymo to MS CONTIN in healthy volunteers between the ages of 18 and 55 years. Two human abuse potential studies were also conducted in healthy volunteers who were experienced opioid users that were not dependent upon the drug.

In six of the seven PK studies in healthy volunteers (067-EG-001, 097-EG-002, 067-EG-004, 067-EG-005, 067-EG-011, and 067-EG-012), all subjects were naltrexone-blocked. Naltrexone was used to mitigate the pharmacological effects of morphine in the studies in healthy subjects; consequently, the safety data from these studies are not an accurate reflection of the

pharmacological safety profile as would be observed in patients for the approved indication.

In the two human abuse potential studies (067-EG-008 and 067-EG-009), the subject population (healthy, non-dependent recreational opioid users) was not naltrexone-blocked but adverse events (AEs) reported are potentially confounded by the drug manipulation methods utilized (crushing) and unintended route of administration (intranasal), which limits direct comparison.

The Applicant also did not provide detailed safety data in this NDA submission on the two PK studies conducted with the 100mg dose (067-EG-004 and 067-EG-005), since that is not a dose planned for marketing.

For these reasons, I will discuss the sections of the safety analysis by individual studies.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

A total of 442 healthy adult subjects from nine studies were exposed to Arymo/Egalet Morphine: 297 subjects received one single-dose and 145 subjects received between two and three doses. Overall, 400 subjects were exposed to the to-be-marketed formulation. This database is adequate to assess any formulation-related safety concerns, as agreed upon between the applicant and review division during the pre-NDA meeting (minimum of 100 subjects exposed to the to-be-marketed formulation).

8.2.2 Relevant characteristics of the safety population:

The three pilot Phase 1 PK studies of Arymo were conducted in healthy adult volunteers. These three studies were considered pilot by the applicant because they did not provide the BE data to support this NDA. Subjects enrolled in these studies had similar baseline characteristics (see Table 10 below). There were fewer males than females in these studies with males representing 22.2%, 44.0%, and 30.8% of the population for 067-EG-001, 067-EG-002, and 067-EG-006, respectively. Subjects were mostly White (≥72%), with Hispanic and Non-Hispanic ethnicity well represented, except in 067-EG-001 where there was only one Hispanic or Latino subject. The mean age in these studies was similar across studies (33-36 years), with the exception of 067-EG-001 where the mean age was 40.6 years. The populations were also comparable for baseline weight, height, and body mass index (BMI).

Table 10: Summary of Subject Demographic and Baseline Characteristics for Pilot Studies Conducted with Arymo

Demographic and Other Characteristics	067-EG-001 (PK population)	067-EG-002 (PK population)	067-EG-006 (all randomized subjects)
n	9	25	65
Age (years)			
Mean	40.6	35.5	33.0
SD	10.5	9.6	10.57
Minimum, Maximum	21, 53	23, 54	18, 55
Sex, n (%)			
Male	2 (22.2)	11 (44.0)	20 (30.8)
Female	7 (77.8)	14 (56.0)	45 (69.2)
Race, n (%)			
White	9 (100)	22 (88.0)	47 (72.3)
Black	0	3 (12.0)	17 (26.2)
Multi-racial	0	0	1 (1.5)
American Indian or Alaska Native	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	1 (11.1)	5 (20.0)	26 (40.0)
Not Hispanic or Latino	8 (88.9)	20 (80.0)	39 (60.0)
Weight at Baseline (kg)			
Mean	69.86	68.39	73.4
SD	4.77	10.38	13.85
Minimum, Maximum	62.5, 79.5	48.0, 91.1	50.5, 113.5
Height at Baseline (cm)			
Mean	166.44	166.90	165.1
SD	7.96	9.74	10.13
Minimum, Maximum	152.5, 176.0	148.0, 180.5	150.1, 198.0

Demographic and Other Characteristics	067-EG-001 (PK population)	067-EG-002 (PK population)	067-EG-006 (all randomized subjects)
BMI (kg/m^2)			
Mean	25.329	24.512	26.8
SD	2.524	2.777	3.22
Minimum, Maximum	22.10, 29.15	19.84, 28.91	19.4, 31.8

BMI = body mass index; PK = pharmacokinetics; SD = standard deviation
Source: 067-EG-001 Table 11.2.1.1; 067-EG-002 Table 11.2.1.1; 067-EG-006 Table 11-1

Source: Applicant's Submission (ISS, pages 10-11)

For the pooled bioequivalence studies in healthy adults, the mean age and age range of subjects was similar across studies: 30.8 years (range: 18-54 years) for 067-EG-011, 33.3 years (range: 20-54 years) for 067-EG-012, and 32.1 years (range: 18-54 years) for the studies combined (Table 11). Males and females were generally equally represented with 47.0%-58.5% male and 41.5%-53.0% female. Most of the subjects in the studies were White (>66%). Hispanic or Latino and not Hispanic or Latino ethnicity were generally equally represented. Height, weight, and BMI were similar across studies.

Table 11: Summary of Subject Demographic and Baseline Characteristics for Bioequivalence Studies Conducted with Arymo

Number of Subjects (%)	067-EG-011 Overall Combined Arms (N=65)	067-EG-012 Overall Combined Arms (N=66)	067-EG-011+ 067-EG-012 Combined (N=131)
Age (years)			
Mean (SD)	30.8 (9.26)	33.3 (8.75)	32.1 (9.06)
Minimum, Maximum	18, 54	20, 54	18, 54
Sex, No. (%)			
Female	27 (41.5)	35 (53.0)	62 (47.3)
Male	38 (58.5)	31 (47.0)	69 (52.7)
Race, No. (%)			
White	43 (66.2)	48 (72.7)	91 (69.5)
Black or African American	19 (29.2)	16 (24.2)	35 (26.7)
Multiracial	2 (3.1)	2 (3.0)	4 (3.1)
American Indian or Alaska Native	1 (1.5)	0	1 (0.8)
Ethnicity, No. (%)			
Hispanic or Latino	27 (41.5)	31 (47.0)	58 (44.3)
Not Hispanic or Latino	38 (58.5)	35 (53.0)	73 (55.7)

Number of Subjects (%)	067-EG-011 Overall Combined Arms (N=65)	067-EG-012 Overall Combined Arms (N=66)	067-EG-011+ 067-EG-012 Combined (N=131)
Height (cm)			
Mean (SD)	170.9 (11.18)	166.5 (10.42)	168.7 (10.99)
Minimum, Maximum	148.5, 199.4	148.5, 191.0	148.5, 199.4
Weight (kg)			
Mean (SD)	78.5 (14.53)	72.6 (11.87)	75.5 (13.53)
Minimum, Maximum	51.7, 118.9	52.1, 107.9	51.7, 118.9
BMI (kg/m^2)			
Mean (SD)	26.73 (3.190)	26.15 (3.039)	26.44 (3.116)
Minimum, Maximum	20.0, 32.0	20.1, 31.9	20.0, 32.0

BMI = body mass index; SD = standard deviation

Source: Applicant's Submission (ISS, pages 11-12)

For the pooled clinical abuse potential studies, the mean age of subjects was similar across studies: 24.3 years for 067-EG-008, 27.9 years for 067-EG-009, and 26.3 years for the studies combined (Table 12). The age range was narrower for 067-EG-008 (18-35 years) than for 067-EG-009 (19-55 years). The majority of subjects were male (74.4%-78.0%), White (>92%), and not Hispanic or Latino (>87%). Height, weight, and BMI were similar across studies.

Table 12: Summary of Subject Demographic and Baseline Characteristics for Clinical Abuse Potential Studies Conducted with Arymo

Number of Subjects (%)	067-EG-008 Overall Combined Arms (N=39)	067-EG-009 Overall Combined Arms (N=50)	067-EG-008+ 067-EG-009 Combined (N=89)
Age (years)			
Mean (SD)	24.3 (4.13)	27.9 (8.01)	26.3 (6.81)
Minimum, Maximum	18, 35	19, 55	18, 55
Sex, No. (%)			
Female	10 (25.6)	11 (22.0)	21 (23.6)
Male	29 (74.4)	39 (78.0)	68 (76.4)
Race, No. (%)			
White	36 (92.3)	47 (94.0)	83 (93.3)
Black or African American	1 (2.6)	3 (6.0)	4 (4.5)
Native Hawaiian or Other Pacific Islander	1 (2.6)	0	1 (1.1)
Other	1 (2.6)	0	1 (1.1)

Number of Subjects (%)	067-EG-008 Overall Combined Arms (N=39)	067-EG-009 Overall Combined Arms (N=50)	067-EG-008+ 067-EG-009 Combined (N=89)
Ethnicity, No. (%)			
Hispanic or Latino	5 (12.8)	5 (10.0)	10 (11.2)
Not Hispanic or Latino	34 (87.2)	45 (90.0)	79 (88.8)
Height (in)			
Mean (SD)	68.1 (3.54)	68.7 (3.16)	68.4 (3.32)
Minimum, Maximum	61.0, 75.8	61.5, 76.5	61.0, 76.5
Weight (lb)			
Mean (SD)	160.2 (26.90)	162.4 (25.28)	161.4 (25.88)
Minimum, Maximum	110.3, 220.0	120.0, 213.0	110.3, 220.0
BMI (kg/m^2)			
Mean (SD)	24.28 (3.827)	24.17 (3.012)	24.22 (3.373)
Minimum, Maximum	19.4, 31.9	18.7, 31.2	18.7, 31.9

BMI = body mass index; SD = standard deviation

Source: Applicant's Submission (ISS, pages 12-13)

8.2.3 Adequacy of the safety database:

As mentioned above, the total safety database of Arymo/Egalet Morphine consisting 400 subjects appears adequate, although the length of exposure/duration of treatment is lower than the intended population of this drug, which is indicated for pain severe enough to require daily, around-the-clock, long term opioid treatment. The studies utilized generally healthy volunteers, which again is not reflective of the target pain population for which the drug is intended. Since Arymo is bioequivalent to MS Contin, which has a long history of safety when used in a similar target population, we can reasonably conclude that Arymo will exhibit similar safety characteristics.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

The submission appeared to be of good quality. It was well-organized and generally easy to navigate through the information provided. No information requests (IR) were made to the Applicant from the clinical team during this review although there were some IRs sent by the Chemistry, Manufacturing and Controls (CMC) review team. In general, the applicant responded to the IRs in a timely fashion.

8.3.2 Categorization of Adverse Events

The Applicant utilized the same definitions for adverse events in the clinical protocols of the bioequivalence trials as well as the human abuse liability studies. The definitions are described below:

An Adverse Event/Experience (AE) is any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In accordance with the above definition, AEs may include:
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
• A new condition detected or diagnosed after Investigational Medicinal Product administration even though it may have been present prior to the start of the study.
• Signs, symptoms, or clinical sequelae of a suspected overdose of either Investigational Product or a concurrent medication ("overdose" per se, should not be reported as an AE).
• Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g. invasive protocol-defined procedures, modification of a subject's previous drug treatment regimen).

An AE does not include:
• Medical or surgical procedures (e.g. colonoscopy, biopsy). The medical condition that leads to the procedure is an AE.
• Social or convenience hospital admissions where an untoward medical occurrence did not occur.
• Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.

A Serious Adverse Event (SAE) is any adverse drug experience occurring at any dose that:
• Results in death;
• Is life-threatening (at risk of death at the time of the event, does not refer to an event which hypothetically might have caused death if it was more severe);
• Requires inpatient hospitalization or prolongation of existing hospitalization [NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization for elective treatment of a pre-existing condition that did not worsen from Screening is not considered to be a SAE];
• Results in disability/incapacity [NOTE: The term disability means a substantial disruption of a

person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (ie, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a disruption] or;
• Is a congenital anomaly/ birth defect.
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any adverse reaction suspected to be related to the investigational medicinal product (IMP), and which is both unexpected (adverse reactions not listed in the labelling for the drug) and meets the criteria for being serious.

An AE or SAE was considered as a treatment-emergent adverse event (TEAE) if it occurred after first dosing in the Drug Discrimination Test and the Treatment phase through the follow-up visit.
These definitions for AEs and SAEs as described by the applicant above are sufficiently accurate and consistent with our understanding of the definitions.

Adverse events were classified as either treatment-related or not, serious or not, with severity of the events assessed as mild, moderate, or severe. Withdrawals due to adverse events were also recorded. In pilot studies 067-EG-001 and 067-EG-002, AEs were classified as not related, unlikely, possibly, probably, or definitely related to study; or unassessable/unclassifiable. In 067-EG-006, the pivotal bioequivalence studies 067-EG-011 and 067-EG-012, and the clinical abuse potential studies 067-EG-008 and 067-EG-009, AEs were classified as unrelated, possibly, probably, or definitely related to study drug. Only Treament emergent AEs will be discussed in detail in this review

A brief summary of the TEAEs reported in the three pilot Phase 1 clinical studies of Arymo is provided below in Table 13.

Table 13: Brief Summary of Treatment-Emergent Adverse Events in Pilot Studies with Arymo

	Number of Subjects Reporting (%)												
	067-EG-001 N=12						067-EG-002 N=30					067-EG-006 N=65	
	EG-001 (Composition #1) 60 mg N=12	EG-001 (Composition #2) 60 mg N=11	EG-001 (Composition #3) 60 mg N=11	Kadian 60 mg N=11	Avinza 60 mg N=11	MS Contin 60 mg N=7	EG-001 (Composition #1) 60 mg N=27	EG-001 (Composition #2) 60 mg N = 26	EG-001 (Composition #3) 60 mg N=26	EG-001 (Composition #4) 60 mg N=26	MS Contin 60 mg N=29	EG-001 15 mg N=64	MS Contin 15 mg N=64
Number of subjects with TEAEs, N (%)	4 (33.3)	4 (36.4)	3 (27.3)	7 (63.6)	5 (45.5)	2 (28.6)	11 (40.7)	14 (53.8)	8 (30.8)	10 (37.0)	14 (48.3)	14 (21.9%)	7 (10.9%)
Number of TEAEs, n	4	7	4	18	10	8	23	37	9	16	37	21	12
Number of treatment-related TEAEs, n	1	6	3	12	10	8	20	33	8	16	33	9	5
Number of severe TEAEs, n	1	0	0	0	1	0	0	0	0	0	0	0	0
Number of serious TEAEs, n	1	0	0	0	0	0	0	0	0	0	0	0	0
Withdrawals due to TEAEs, n	1	0	0	0	0	0	0	0	0	0	0	0	1
Deaths, n	0	0	0	0	0	0	0	0	0	0	0	0	0

TEAE = treatment-emergent adverse event
Source: 067-EG-001 Table 12.2.1.1; 067-EG-002 Table 12.2.1.1; 067-EG-006 Table 14.3.1.1 and Table 14.3.1.3

Source: Applicant's Submission (ISS, page 15)

A summary of the TEAEs reported in the bioequivalence studies of Arymo is provided below in Table 14.

Table 14: Brief Summary of Treatment-Emergent Adverse Events in Bioequivalence Studies with Arymo

	Number of Subjects Reporting (%) Number of Events							
	067-EG-011 (N=65)				067-EG-012 (N=66)			
	EG-001 60 mg Fasting (N=64)	MS Contin 60 mg Fasting (N=62)	EG-001 60 mg Fed (N=22)	Overall (N=65)	EG-001 30 mg Fasting (N=62)	MS Contin 30 mg Fasting (N=59)	EG-001 2x15 mg Fasting (N=62)	Overall (N=66)
Subjects with ≥1 TEAE	12 (18.8%) 28	10 (16.1%) 15	4 (18.2%) 5	21 (32.3%) 48	7 (11.3%) 11	7 (11.9%) 11	11 (17.7%) 22	20 (30.3%) 44
Any Study Drug-Related TEAE	8 (12.5%) 16	4 (6.5%) 5	1 (4.5%) 2	10 (15.4%) 23	1 (1.6%) 1	3 (5.1%) 4	2 (3.2%) 4	6 (9.1%) 9
Subjects with ≥ 1 TEAE, by severity								
Mild	6 (9.4%) 16	9 (14.5%) 14	3 (13.6%) 3	14 (21.5%) 33	5 (8.1%) 9	7 (11.9%) 11	9 (14.5%) 18	16 (24.2%) 38
Moderate	6 (9.4%) 12	1 (1.6%) 1	1 (4.5%) 2	7 (10.8%) 15	2 (3.2%) 2	0	2 (3.2%) 4	4 (6.1%) 6
Severe	0	0	0	0	0	0	0	0
Withdrawals due to TEAEs	4 (6.3%) 4	1 (1.6%) 1	0	5 (7.7%) 5	2 (3.2%) 2	0	2 (3.2%) 2	4 (6.1%) 4
SAEs	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0

SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: 067-EG-011 Table 14.3.1.1 and Table 14.3.1.3; 067-EG-012 Table 14.3.1.1 and Table 14.3.1.3

Source: Applicant's Submission (ISS, page 16)

A summary of the TEAEs reported in the clinical abuse potential studies of EG-001 is provided in

Table 15 below.

Table 15: Brief Summary of Treatment-Emergent Adverse Events in Clinical Abuse Potential Studies with Arymo

	Number of Subjects Reporting (%)									
	067-EG-008 (N=39)					067-EG-009 (N=50)				
	Manipulated MS Contin (N=39)	Manipulated EG-001 (N=38)	Intact EG-001 (N=38)	Placebo (N=38)	Exploratory Treatment (N=12)	Manipulated Intranasal MS Contin (N=47) n (%)	Manipulated Intranasal EG-001 (N=50) n (%)	Manipulated /Sieved Intranasal EG-001 (N=47) n (%)	Intact Oral EG-001 (N=49) n (%)	Placebo (N=48) n (%)
Subjects with ≥ 1 TEAE	19 (48.72)	18 (47.37)	12 (31.58)	2 (5.26)	7 (58.33)	28 (59.57)	15 (30.00)	15 (31.91)	20 (40.82)	5 (10.42)
Subjects with ≥ 1 TEAE, by severity										
Mild	19 (48.72)	16 (42.11)	12 (31.58)	2 (5.26)	7 (58.33)	26 (55.32)	15 (30.00)	15 (31.91)	19 (38.78)	5 (10.42)
Moderate	1 (2.56)	2 (5.26)	1 (2.63)	0 (0.00)	0 (0.00)	4 (8.51)	0 (0.0)	0 (0.0)	7 (14.29)	0 (0.0)
Severe	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals due to TEAEs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: 067-EG-008 Table 12.2.1-2; 067-EG-009 Table 12.2.1-2

Source: Applicant's Submission (ISS, page 17)

8.3.3 Routine Clinical Tests

In each of the Phase 1 clinical studies with Arymo, clinical laboratory tests (chemistry, hematology and urinalysis) were performed at screening and study exit. In the clinical abuse potential studies, clinical laboratory tests were performed at check-in and follow-up (or early termination). Since the subjects were for the most part healthy adult volunteers, the routine clinical testing performed during the development program of Arymo appears adequate.

8.4 Safety Results

Deaths

No deaths occurred during the entire clinical development program for Arymo

8.4.2 Serious Adverse Events

Only one SAE was reported in the clinical development program of Arymo, which occurred in the initial pilot study (067-EG-001).
A 52-year old female (Subject #11) experienced an SAE of Abortion approximately 16 days following morphine administration in Period 1 (EG-001 60 mg Composition 1). The urine pregnancy test performed at screening and the serum pregnancy test performed prior to study drug administration in Period 1 were negative. However, the serum pregnancy tests performed prior to dosing in Period 2 yielded an equivocal result (Beta human chorionic gonadotropin [β-

HCG] of 18.7 IU/L). A repeat serum pregnancy test was performed three days later and the result was positive (β-HCG of 29.3IU/L). The subject was withdrawn by the Medical Sub-Investigator prior to drug administration in Period 2. Approximately 6 days later the subject had an episode of spotting and was seen by a gynecologist. On the next day, her regular menses started.
According to the gynecologist, the event was considered to be a spontaneous abortion after which the β-HCG result returned to negative. This SAE was assessed as severe and judged to be not related to study medication.

Reviewer's Comments: This subject only received one 60mg dose of the early formulation of Arymo and was subsequently withdrawn from the study due to an equivocal and later positive serum pregnancy test. Morphine products such as MS Contin are classified as pregnancy category C, with no adequate and well-controlled studies in pregnant women[8]. In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy[8]. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy. The applicant states that this SAE may not be related to Arymo, but attribution cannot truly be assigned with any certainty.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

In the clinical development program for Arymo, there were a total of 11 droputs/ discontinuations due to adverse events: 2 in the pilot studies (067-EG-001 and EG-006); 9 in the bioequivalence studies (067-EG-011, EG-012) and none in the human abuse liability studies.

In Study EG-001, there were two withdrawals: 52 year old white female that received one dose of the 60mg Arymo formulation 1, and later found to have a spontaneous abortion. She was withdrawn from the study after the first treatment phase. Please refer to the Serious AE section for a complete description of her case.
The second withdrawal was a 39-year old white female who experienced a significant AE of abdominal pain approximately 2.5 hours following morphine administration with Avinza. The event was treated with acetaminophen. The subject also experienced an event of vomiting approximately 37 minutes after the start of her abdominal pain. The subject was withdrawn from the study and was transferred to the hospital emergency unit with a staff member for further investigation (approximately 12 hours after dosing). The subject received acetaminophen (500 mg tablets and 650 mg suppository). The subject returned to the clinic the next day (approximately 16 hours after her transfer to the hospital). The TEAE was assessed as "moderate" in intensity and was judged to be possibly related to the study medication. The event resolved within one day.
In Study EG-006, there was one discontinuation: Subject 0016015, a 24 year old white female

who had moderate, intermittent emesis after being treated with MS Contin 15mg while under fasting conditions. Her screening physical examination, labs, vital signs and ECG were all within normal limits. She was not taking any medications other than multi-vitamins. The emesis started approximately 5 hours after the treatment dose and lasted for 4 hours, with complete resolution. Based on the protocol criteria that she had experienced an 'intolerable AE', subject was withdrawn from the study.

In Study EG-011, there were 5 discontinuations due to AEs, 1 withdrew due to personal choice.

1) Subject 0011137 was a 24 year old African American female who had nausea, abdominal cramping, lightheadedness and moderate constant vomiting after being dosed with Arymo 60mg while under fasting conditions. Her screening physical examination, labs, vital signs and ECG were all within normal limits. She was not taking any medications other than the birth control device, Mirena. She did receive 3 doses of ondansetron ODT 4mg which alleviated the nausea. All her symptoms eventually resolved the following day. Based on the protocol criteria that she had experienced an 'intolerable AE', subject was withdrawn from the study.
2) Subject 0011145 was a 41 year old bi-racial (White/African American) female who had nausea, abdominal cramping, lightheadedness, loose stools and moderate intermittent vomiting after being dosed with Arymo 60mg while under fasting conditions. Her screening physical examination, labs, vital signs and ECG were all within normal limits. She was not taking any medications. She received 1 dose of ondansetron ODT 4mg which alleviated the nausea. All her symptoms eventually resolved 2 hours later. Based on the protocol criteria that she had experienced an 'intolerable AE', subject was withdrawn from the study.
3) Subject 0011165 was a 26 year old African American female who had nausea, abdominal cramping, headache, lightheadedness, decreased frequency of bowel movements and moderate intermittent vomiting after being dosed with Arymo 60mg while under fasting conditions. She initially complained of mild nausea after receiving the naltrexone, roughly 4 hours prior to receiving the study medication. Her screening physical examination, labs, vital signs and ECG were all within normal limits. She was not taking any other medication. Her nausea intensified after receiving the study medication, which led to vomiting roughly five hours after Arymo was administered. She received 3 doses of ondansetron ODT 4mg which eventually alleviated the nausea 48 hours later. Based on the protocol criteria that she had experienced an 'intolerable AE', subject was withdrawn from the study.
4) Subject 0011226 was a 25 year old white male who had mild headache and fever (up to 38.2 C) after being dosed with MS Contin 60mg while under fasting conditions. His prior medical history was significant only for an appendectomy, and his screening physical examination, labs, vital signs and ECG were all within normal limits. He was not taking any medications. The fever was detected 6 days after the morphine dose, on routine vital signs check prior to the start of dosing in period 2. The fever resolved 13 hours

later. Although the causality of the fever was not clear, the investigator felt it was prudent to discontinue the subject from the study.

5) Subject 0011234 was a 22 year old African American female who had nausea, and moderate constant vomiting 3 hours after being dosed with Arymo 60mg while under fasting conditions. Her screening physical examination, labs, vital signs and ECG were all within normal limits. She was not taking any medications other than oral contraceptives. She had received 60mg MS Contin 8 days prior in the period 1 treatment phase and only experienced some mild pruritus which lasted 2.5 hours. Her nausea eventually resolved 2 hours later without documented use of anti-emetics. Based on the protocol criteria that she had experienced an 'intolerable AE', subject was withdrawn from the study. *Reviewer Comments: Subject had nausea and vomiting only with Arymo, but not with MS Contin, which gave her some mild pruritus. Both are known adverse events associated with morphine products.*

In Study EG-012, there were 4 subject withdrawals due to adverse events. Detailed review of the case report forms reveal that all were due to vomiting after taking Arymo 30mg under fasting conditions. All resolved without requiring treatment with anti-emetics. They are summarized in the table below:

Table 16: Adverse Events Leading to Early Discontinuation in Study 067-EG-012

Subject/ Sequence [1]	System Organ Class [2]/ Preferred Term [2]/ Adverse Event	Start Date Time/ Stop Date Time	Treatment at AE Onset [1]	AE ID	Frequency/ Severity/ Relationship	Action/ Outcome/ Serious	Treatment Required
123/ACB	Gastrointestinal disorders/ Vomiting/ EMESIS	05DEC2014 09:44/ 05DEC2014 09:45	A	207465	CONSTANT/ MODERATE/ UNRELATED	DRUG WITHDRAWN/ RECOVERED/ RESOLVED/ No	NONE
125/CAB	Gastrointestinal disorders/ Vomiting/ EMESIS	05DEC2014 12:10/ 05DEC2014 12:11	C	207475	CONSTANT/ MODERATE/ PROBABLE	DRUG WITHDRAWN/ RECOVERED/ RESOLVED/ No	NONE
127/ACB	Gastrointestinal disorders/ Vomiting/ EMESIS	05DEC2014 09:52/ 05DEC2014 09:53	A	207464	CONSTANT/ MODERATE/ UNRELATED	DRUG WITHDRAWN/ RECOVERED/ RESOLVED/ No	NONE

146/CBA	Gastrointestinal disorders/ Vomiting/ EMESIS	09JAN2015 18:50/ 09JAN2015 18:51	C	208023	CONSTANT/ MODERATE/ UNRELATED	DRUG WITHDRAWN/ RECOVERED/ RESOLVED/ No	NONE

[1] Treatment A: Egalet morphine PR 30-mg tablet, fasting conditions;
Treatment B: MS CONTIN 30-mg tablet, fasting conditions;
Treatment C: Egalet morphine PR 2 × 15-mg tablets, fasting conditions.
[2] From MedDRA (version 17.1).
\\wilbtib\wilbtib04\EgaletEG067EG012\ProductionSafetyTLs\TLF\L16020702.SAS Executed: 24MAR2015 10:34

Source: Applicants Submission (Protocol 067-EG-012 Listing 16.2.7.2, pages 15-16)

Reviewer Comments: Gastrointestinal adverse events such as nausea/vomiting are commonly associated with morphine products so it is not surprising to see that as the reason for subject withdrawals.

8.4.4 Significant Adverse Events

Other than the Serious AE discussed previously, only one significant AE was reported in the clinical development program of Arymo, the 39-year old female who experienced abdominal pain approximately 2.5 hours following morphine administration with Avinza during study 067-EG-001. The event was treated with acetaminophen and resolved the next day, but she was withdrawn from the study. Her case was already detailed above in section 8.8.4

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

Based on System Organ Class (SOC), nervous system and gastrointestinal disorders were the most frequently reported TEAEs across all phases of the clinical development program. Most TEAEs were common opioid related side effects. This will be discussed in the following sections.

1) Pilot Studies: The most commonly reported TEAEs in the pilot studies with Arymo (reported by ≥4 subjects in at least one treatment arm) included somnolence, headache, dizziness, nausea, and vomiting. A summary of the TEAEs reported by two or more

subjects within each of the pilot studies is provided in Table 17 below:

Table 17: Treatment Emergent Adverse Events Reported by Two or More Subjects in each of the Arymo/EG-001 Pilot Studies

All TEAEs	Number of Subjects Reporting (%)												
	067-EG-001 N=12						067-EG-002 N=30					067-EG-006 N=65	
System Organ Class Preferred Term	EG-001 (Com-position #1) 60 mg N=12	EG-001 (Com-position #2) 60 mg N=11	EG-001 (Com-position #3) 60 mg N=11	Kadian 60 mg N=11	Avinza 60 mg N=11	MS Contin 60 mg N=7	EG-001 (Com-position #1) 60 mg N=27	EG-001 (Com-position #2) 60 mg N = 26	EG-001 (Com-position #3) 60 mg N=26	EG-001 (Com-position #4) 60 mg N=26	MS Contin 60 mg N=29	EG-001 15 mg N=64	MS Contin 15 mg N=64
Nervous system disorders	2 (16.7)	4 (36.4)	2 (18.2)	4 (36.4)	1 (9.1)	1 (14.3)	8 (29.6)	9 (34.6)	6 (23.1)	5 (18.5)	11 (37.9)	8 (12.5)	4 (6.3)
Somnolence	2 (16.7)	2 (18.2)	2 (18.2)	3 (27.3)	0	0	4 (14.8)	6 (23.1)	5 (19.2)	4 (14.8)	8 (27.6)	0	0
Headache	0	2 (18.2)	0	0	1 (9.1)	0	4 (14.8)	5 (19.2)	1 (3.8)	1 (3.7)	2 (6.9)	5 (7.8)	2 (3.1)
Dizziness	0	0	0	1 (9.1)	0	1 (14.3)	2 (7.4)	2 (7.7)	0	0	5 (17.2)	3 (4.7)	2 (3.1)
Gastro-intestinal disorders	1 (8.3)	2 (18.2)	0	4 (36.4)	5 (45.5)	2 (28.6)	6 (22.2)	3 (11.5)	0	3 (11.1)	8 (27.6)	4 (6.3)	4 (6.3)
Nausea	1 (8.3)	2 (18.2)	0	2 (18.2)	2 (18.2)	2 (28.6)	6 (22.2)	3 (11.5)	0	3 (11.1)	6 (20.7)	3 (4.7) 3	2 (3.1) 3
Vomiting	0	1 (9.1)	0	2 (18.2)	4 (36.4)	2 (28.6)	1 (3.7)	1 (3.8)	0	0	5 (17.2)	0	1 (1.6%)
Abdominal discomfort	0	0	0	0	0	0	0	0	0	1 (3.7)	3 (10.3)	0	0
Dyspepsia	0	0	0	1 (9.1)	0	0	0	2 (7.7)	0	0	2 (6.9)	0	0
Abdominal pain	0	0	0	1 (9.1)	1 (9.1)0	0	1 (3.7)	0	0	0	2 (6.9)	1 (1.6%)	0
Diarrhoea	0	0	0	2 (18.2)	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	2 (18.2)	0	0	1 (3.7)	4 (15.4)	1 (3.8)	1 (3.7)	1 (3.4)	1 (1.6%)	1 (1.6%)
Asthenia	0	0	0	0	0	0	1 (3.7)	0	1 (3.8)	1 (3.7)	1 (3.4)	0	0
Chest discomfort	0	0	0	0	0	0	0	3 (11.5)	0	0	0	0	0

All TEAEs	Number of Subjects Reporting (%)												
	067-EG-001 N=12						067-EG-002 N=30					067-EG-006 N=65	
System Organ Class Preferred Term	EG-001 (Composition #1) 60 mg N=12	EG-001 (Composition #2) 60 mg N=11	EG-001 (Composition #3) 60 mg N=11	Kadian 60 mg N=11	Avinza 60 mg N=11	MS Contin 60 mg N=7	EG-001 (Composition #1) 60 mg N=27	EG-001 (Composition #2) 60 mg N = 26	EG-001 (Composition #3) 60 mg N=26	EG-001 (Composition #4) 60 mg N=26	MS Contin 60 mg N=29	EG-001 15 mg N=64	MS Contin 15 mg N=64
Metabolism and nutrition disorders	0	0	0	1 (9.1%)	0	0	1 (3.7)	1 (3.8)	1 (3.8)	1 (3.7)	0	0	0
Decreased appetite	0	0	0	1 (9.1%)	0	0	1 (3.7)	1 (3.8)	1 (3.8)	1 (3.7)	0	0	0
Cardiac disorders	0	0	0	0	0	0	0	1 (3.8)	0	2 (7.4)	0	0	0
Palpitations	0	0	0	0	0	0	0	0	0	2 (7.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	2 (7.7)	0	1 (3.7)	0	3 (4.7)	1 (1.6)
Dry throat	0	0	0	0	0	0	0	1 (3.8)	0	1 (3.7)	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	0	0	0	0	0	3 (4.7)	0
Cough	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	1 (1.6)
Psychiatric disorders	0	0	0	0	0	0	0	2 (7.7)	0	0	0	1 (1.6)	0
Anxiety	0	0	0	0	0	0	0	2 (7.7)	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	0	0	1 (3.8)	0	0	1 (1.6)	1 (1.6)
Dermatitis contact	0	0	0	0	0	0	0	0	0	0	0	1 (1.6)	1 (1.6)

All TEAEs	Number of Subjects Reporting (%)												
	067-EG-001 N=12						067-EG-002 N=30					067-EG-006 N=65	
System Organ Class Preferred Term	EG-001 (Composition #1) 60 mg N=12	EG-001 (Composition #2) 60 mg N=11	EG-001 (Composition #3) 60 mg N=11	Kadian 60 mg N=11	Avinza 60 mg N=11	MS Contin 60 mg N=7	EG-001 (Composition #1) 60 mg N=27	EG-001 (Composition #2) 60 mg N = 26	EG-001 (Composition #3) 60 mg N=26	EG-001 (Composition #4) 60 mg N=26	MS Contin 60 mg N=29	EG-001 15 mg N=64	MS Contin 15 mg N=64
Vascular disorders	0	0	0	1 (9.1)	1 (9.1)	2 (28.6)	0	0	0	0	0	0	0
Hot flush	0	0	0	1 (9.1)	1 (9.1)	2 (28.6)	0	0	0	0	0	0	0

Source: 067-EG-001 Table 12.2.2.1 and Table 14.3.1.1.1; 067-EG-002 Table 12.2.2.1 and Table 14.3.1.1.1; 067-EG-006 Table 12-1 and Table 14.3.1.2

Source: Applicant's Submission (ISS, pages 19-21)

2) Bioequivalence Studies: From the pivotal bioequivalence studies in healthy adults, the pooled safety data show that the percentage of subjects with at least one TEAE was similar across studies (approximately 30%) (Table 18). Of TEAEs reported by two or more subjects overall within an SOC, TEAEs in the gastrointestinal disorders and nervous system disorders SOCs were the most common (Table 18). Other SOCs with TEAEs reported by two or more subjects included eye disorders; general disorders and administration site conditions; musculoskeletal and connective tissue disorders; respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue

disorders. Preferred Terms (PTs) occurring in the gastrointestinal disorders SOC in two or more subjects included nausea, vomiting, abdominal pain, diarrhea, and infrequent bowel movements. PTs occurring in the nervous system disorders SOC in two or more subjects included headache, dizziness, and somnolence. These are all common opioid-related side effects.

Table 18: Treatment Emergent Adverse Events Reported by Two or More Subjects Overall within a System Organ Class in Arymo/EG-001 Bioequivalent Studies

System Organ Class Preferred Term	067-EG-011 Overall Combined Arms (N=65) n (%) E	067-EG-012 Overall Combined Arms (N=66) n (%) E	067-EG-011+ 067-EG-012 Combined (N=131) n (%) E
Total Subjects with at Least one TEAE	21 (32.3) 48	20 (30.3) 44	41 (31.3) 92
Eye disorders	0 (0.0) 0	2 (3.0) 2	2 (1.5) 2
Photophobia	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Vision blurred	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Gastrointestinal disorders	12 (18.5) 32	11 (16.7) 15	23 (17.6) 47
Nausea	9 (13.8) 14	5 (7.6) 5	14 (10.7) 19
Vomiting	7 (10.8) 8	4 (6.1) 4	11 (8.4) 12
Abdominal pain	4 (6.2) 5	0 (0.0) 0	4 (3.1) 5
Diarrhoea	2 (3.1) 3	0 (0.0) 0	2 (1.5) 3
Infrequent bowel movements	1 (1.5) 1	1 (1.5) 1	2 (1.5) 2
Abdominal discomfort	1 (1.5) 1	0 (0.0) 0	1 (0.8) 1
Abdominal distension	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Flatulence	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Gastrooesophageal reflux disease	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Lip dry	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Regurgitation	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1

System Organ Class Preferred Term	067-EG-011 Overall Combined Arms (N=65) n (%) E	067-EG-012 Overall Combined Arms (N=66) n (%) E	067-EG-011+ 067-EG-012 Combined (N=131) n (%) E
General disorders and administration site conditions	1 (1.5) 1	2 (3.0) 3	3 (2.3) 4
Feeling abnormal	0 (0.0) 0	2 (3.0) 2	2 (1.5) 2
Fatigue	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Pyrexia	1 (1.5) 1	0 (0.0) 0	1 (0.8) 1
Musculoskeletal and connective tissue disorders	0 (0.0) 0	3 (4.5) 4	3 (2.3) 4
Arthralgia	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Back pain	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Muscle spasms	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Muscle tightness	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Nervous system disorders	9 (13.8) 10	11 (16.7) 13	20 (15.3) 23
Headache	5 (7.7) 5	7 (10.6) 7	12 (9.2) 12
Dizziness	2 (3.1) 2	4 (6.1) 4	6 (4.6) 6
Somnolence	2 (3.1) 3	1 (1.5) 1	3 (2.3) 4
Disturbance in attention	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Respiratory, thoracic and mediastinal disorders	2 (3.1) 2	3 (4.5) 4	5 (3.8) 6
Oropharyngeal pain	0 (0.0) 0	3 (4.5) 3	3 (2.3) 3
Cough	2 (3.1) 2	0 (0.0) 0	2 (1.5) 2
Rhinorrhoea	0 (0.0) 0	1 (1.5) 1	1 (0.8) 1
Skin and subcutaneous tissue disorders	1 (1.5) 2	2 (3.0) 2	3 (2.3) 4
Dermatitis contact	1 (1.5) 1	2 (3.0) 2	3 (2.3) 3
Macule	1 (1.5) 1	0 (0.0) 0	1 (0.8) 1

E = number of events; n = number of subjects with at least one event

Source: Applicant's Submission (ISS, pages 22-23)

3) Clinical Abuse Potential Studies: The pooled safety data show that the total number of subjects with at least one TEAE was similar across studies and whether Arymo was taken orally intact or manipulated and dosed orally or intranasally (Table 19). Of TEAEs reported by two or more subjects overall within an SOC, TEAEs in the gastrointestinal disorders and nervous system disorders SOCs were most common, as well as in the respiratory, thoracic and mediastinal disorders SOC for the intranasal study (067-EG-009) (Table 19). PTs occurring in the gastrointestinal disorders SOC in two or more subjects included nausea, vomiting, and upper abdominal pain. These TEAEs occurred at a similar incidence for manipulated and intact Arymo. PTs occurring in the nervous system disorders SOC in two or more subjects included dizziness, somnolence, and headache. These TEAEs also occurred at a similar incidence for manipulated and intact Arymo. The PTs in the respiratory, thoracic and mediastinal disorders SOCs occurring in two or more subjects in 067-EG-009 included nasal congestion and dysphonia. These TEAEs occurred more frequently in the manipulated Arymo group.

Table 19: Treatment-Emergent Adverse Events Reported by Two or More Subjects Overall within a System Organ Class in Arymo/EG-001 Clinical Abuse Potential Studies

System Organ Class Preferred Term	067-EG-008 Manipulated EG-001[1] (N=38) n (%) E	067-EG-009 Manipulated EG-001[2] (N=50) n (%) E	067-EG-008 + 067-EG-009 Manipulated EG-001 Combined (N=88) n (%) E	067-EG-008 + 067-EG-009 Oral Intact EG-001 Combined (N=87) n (%) E
Subjects with at Least One TEAE	21 (55.3) 35	24 (48.0) 43	45 (51.1) 78	32 (36.8) 55
Gastrointestinal disorders	16 (42.1) 18	10 (20.0) 12	26 (29.5) 30	20 (23.0) 25
Nausea	6 (15.8) 6	6 (12.0) 7	12 (13.6) 13	13 (14.9) 13
Vomiting	10 (26.3) 11	1 (2.0) 1	11 (12.5) 12	10 (11.5) 10
Abdominal pain upper	1 (2.6) 1	2 (4.0) 2	3 (3.4) 3	2 (2.3) 2
Constipation	0	1 (2.0) 1	1 (1.1) 1	0
Gingival pain	0	1 (2.0) 1	1 (1.1) 1	0
Nervous system disorders	8 (21.1) 10	7 (14.0) 9	15 (17.0) 19	12 (13.8) 15
Dizziness	2 (5.3) 2	1 (2.0) 1	3 (3.4) 3	3 (3.4) 3
Somnolence	2 (5.3) 3	1 (2.0) 1	3 (3.4) 4	2 (2.3) 2
Headache	5 (13.2) 5	5 (10.0) 7	10 (11.4) 12	9 (10.3) 10
Respiratory, thoracic and mediastinal disorders	1 (2.6) 1	10 (20.0) 11	11 (12.5) 12	3 (3.4) 3
Epistaxis	0	1 (2.0) 1	1 (1.1) 1	1 (1.1) 1
Nasal discomfort	0	1 (2.0) 1	1 (1.1) 1	0
Nasal congestion	0	6 (12.0) 6	6 (6.8) 6	2 (2.3) 2
Dysphonia	0	2 (4.0) 2	2 (2.3) 2	0
Hiccups	1 (2.6) 1	1 (2.0) 1	2 (2.3) 2	0
Skin and subcutaneous tissue disorders	5 (13.2) 6	5 (10.0) 5	10 (11.4) 11	5 (5.7) 5
Rash	0	1 (2.0) 1	1 (1.1) 1	0
Pruritus generalised	5 (13.2) 6	4 (8.0) 4	9 (10.2) 10	3 (3.4) 3
Pruritus	0	0	0	2 (2.3) 2

System Organ Class Preferred Term	067-EG-008 Manipulated EG-001[1] (N=38) n (%) E	067-EG-009 Manipulated EG-001[2] (N=50) n (%) E	067-EG-008 + 067-EG-009 Manipulated EG-001 Combined (N=88) n (%) E	067-EG-008 + 067-EG-009 Oral Intact EG-001 Combined (N=87) n (%) E
General disorders and administration site conditions	0	2 (4.0) 2	2 (2.3) 2	3 (3.4) 3
Feeling hot	0	1 (2.0) 1	1 (1.1) 1	1 (1.1) 1
Malaise	0	1 (2.0) 1	1 (1.1) 1	0
Chest pain	0	0	0	1 (1.1) 1
Pain	0	0	0	1 (1.1) 1
Eye disorders	0	1 (2.0) 2	1 (1.1) 2	1 (1.1) 1
Eye pain	0	1 (2.0) 1	1 (1.1) 1	0
Vision blurred	0	1 (2.0) 1	1 (1.1) 1	0
Photophobia	0	0	0	1 (1.1) 1
Musculoskeletal and connective tissue disorders	0	1 (2.0) 1	1 (1.1) 1	2 (2.3) 2
Arthralgia	0	1 (2.0) 1	1 (1.1) 1	1 (1.1) 1
Pain in extremity	0	0	0	1 (1.1) 1

E = number of events; n = number of subjects with at least one event
[1] Treatment B (EG-001 60 mg oral manipulated) and Exploratory Arm (EG-001 manipulated in the same way as Treatment B but then mixed in juice) combined
[2] Treatment A (EG-001 60 mg manipulated intranasal, high volume) and Treatment B (EG-001 60 mg manipulated/sieved intranasal, low volume) combined

Source: Applicant's Submission (ISS, pages 24-25)

As illustrated above, the TEAEs observed are similar to other morphine extended-release products, and thus labelling of the adverse reactions section should closely mirror that of MS Contin.

8.4.6 Laboratory Findings

In each of the phase 1 clinical studies with Arymo/EG-001, clinical laboratory tests (chemistry, hematology and urinalysis) were performed at screening and study exit. In the clinical abuse potential studies, clinical laboratory tests were performed at check-in and follow-up (or early termination). The laboratory findings will be discussed below:

1) Pilot Studies:

None of the individual clinically significant abnormalities in pilot study *067-EG-001* were considered TEAEs.

In study *067-EG-002*, out-of-reference range laboratory values judged to be clinically significant and possibly treatment-related were reported for three subjects.

- Subject 05 receiving EG-001 60 mg (Treatment B) during the last sequence had decreased blood phosphorus (from baseline of 0.92mmol/L to 0.51 mmol/L) 6 days after morphine administration. Normal test range is 0.87-1.45mmol/L.
- Subject 13 receiving EG-001 60 mg (Treatment A) during the last sequence was determined to have protein (1g/L) in urine 6 days after morphine administration.

His baseline screening urine had no protein.

- Subject 22 had increased eosinophil count (from 0.73 to 0.93 $x10^9$/L) 4 days after morphine administration during the last sequence (Treatment B).

In all cases, these TEAEs were classified as mild, possibly related to study treatment and did not resolve by the end of the study. Subjects were directed to follow up with their family physicians.

In study *067-EG-006*, one subject had a gamma glutamyl transferase (GGT) value of 164 IU/L (reference range: 5 to 85 IU/L) at end of study that was considered clinically significant by the investigator but was not documented as a TEAE. This elevated GGT value occurred 17 days after the last dose of study drug, which was outside the window of the end of study visit (4 to 14 days from the last dose of study drug). The subject's GGT values were within the reference range at screening and Day –1 of Period 1 (76 and 83 IU/L, respectively) but were elevated starting on Day –1 of Period 2 (ranged between 137 and 164 IU/L). This subject also had elevated alanine aminotransferase (61 IU/L; reference range: 4 to 45 IU/L) and aspartate aminotransferase (44 IU/L; reference range: 10 to 40 IU/L) on Day –1 of Period 2; however, these values were considered not clinically significant by the investigator. I tend to agree that these do not appear significant.

2) Bioequivalent Studies and Clinical Abuse Potential Studies:

No unexpected or significant hematologic abnormalities were noted in the pooled analyses for the studies with Arymo/ EG-001. There was no evidence of an effect of EG-001 on erythrocytes, hematocrit, hemoglobin, leukocytes, or platelets based on change from baseline to end of study/early termination in the pooled data from the pivotal bioequivalence studies (Table 20) or the clinical abuse potential studies (Table 21). In addition, no individual hematologic abnormality was considered clinically significant by the investigators in the bioequivalence studies or the clinical abuse potential studies. After reviewing the results, I agree that the hematological abnormalities seen do not appear clinically significant.

Table 20: Hematology: Summary Statistics and Change from Baseline to End of Study/Early Termination in Bioequivalence Studies with Arymo

		Actual Values 067-EG-011 + 067-EG-012 Combined (N=131)					Change from Baseline 067-EG-011 + 067-EG-012 Combined (N=131)				
Parameter	Time Point	n	Mean	SD	Median	Min/Max	n	Mean	SD	Median	Min/Max
Erythrocytes (10/L)	Baseline	131	4.720	0.5188	4.740	3.69, 6.03					
	EOS/ET	131	4.521	0.5140	4.550	3.49, 5.72	131	-0.1992	0.24703	-0.2000	-0.85, 0.63
Hematocrit (fraction of 1)	Baseline	131	0.4158	0.04039	0.4170	0.336, 0.506					
	EOS/ET	131	0.3989	0.04163	0.4040	0.309, 0.493	131	-0.0168	0.02151	-0.0170	-0.065, 0.054
Hemoglobin (g/L)	Baseline	131	137.3	14.34	139.0	110, 170					
	EOS/ET	131	132.1	14.68	133.0	102, 165	131	-5.20	6.829	-5.00	-22, 19
Leukocytes (10/L)	Baseline	131	6.56	1.411	6.40	3.6, 11.5					
	EOS/ET	131	6.31	1.572	6.10	3.6, 12.7	131	-0.247	1.2757	-0.400	-3.5, 4.8
Platelets (10/L)	Baseline	131	256.3	57.82	247.0	138, 457					
	EOS/ET	131	249.2	59.28	238.0	139, 417	131	-7.04	31.442	-5.00	-101, 86

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, page 71)

Table 21: Hematology: Summary Statistics and Change from Baseline to End of Study/Early Termination in Clinical Abuse Studies

		Actual Values 067-EG-008 + 067-EG-009 Combined (N=89)					Change from Baseline 067-EG-008 + 067-EG-009 Combined (N=89)				
Parameter	Time Point	n	Mean	SD	Median	Min/Max	n	Mean	SD	Median	Min/Max
Erythrocytes (10/L)	Baseline	89	5.104	0.3951	5.150	3.98, 5.91					
	EOS/ET	82	4.889	0.4732	4.945	3.67, 6.08	82	-0.2188	0.26961	-0.2200	-0.82, 0.40
Hematocrit (%)	Baseline	89	45.64	3.352	45.90	36.2, 52.9					
	EOS/ET	82	43.61	4.007	44.10	33.9, 53.1	82	-1.977	2.3496	-1.700	-7.9, 4.0
Hemoglobin (g/L)	Baseline	89	15.5	1.39	15.7	12, 18					
	EOS/ET	82	14.8	1.55	14.9	11, 18	82	-0.73	0.801	-0.70	-2, 1
Leukocytes (10/L)	Baseline	89	6.39	1.654	6.10	3.2, 11.1					
	EOS/ET	82	5.82	1.433	5.70	2.2, 9.1	82	-0.511	1.6095	-0.550	-5.5, 4.2
Platelets (10/L)	Baseline	89	258.9	58.54	251.0	155, 520					
	EOS/ET	82	264.9	70.88	252.5	151, 659	82	7.45	40.059	4.50	-163, 139

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, page 72)

No unexpected or significant serum chemistry abnormalities were noted. There was no evidence of an effect of EG-001 on serum chemistry parameters based on change from baseline to end of study/early termination in the pooled data from the bioequivalence studies (Table 22) or the clinical abuse potential studies (Table 23). No individual serum chemistry abnormality was considered clinically significant or reported as a TEAE by the investigators in the bioequivalence studies or the clinical abuse potential studies.

Table 22: Serum Chemistry: Summary Statistics and Change from Baseline to End of Study/Early Termination in Bioequivalence Studies

		Actual Values 067-EG-011 + 067-EG-012 Combined (N=131)					Change from Baseline 067-EG-011 + 067-EG-012 Combined (N=131)				
Parameter	**Time Point**	**n**	**Mean**	**SD**	**Median**	**Min/Max**	**n**	**Mean**	**SD**	**Median**	**Min/Max**
Alanine Aminotransferase (IU/L)	Baseline	131	18.1	9.52	16.0	7, 54					
	EOS/ET	131	14.7	6.55	13.0	6, 37	131	-3.45	6.209	-2.00	-28, 13
Albumin (g/L)	Baseline	131	45.5	2.70	45.0	39, 55					
	EOS/ET	131	44.7	2.62	44.0	37, 54	131	-0.80	2.374	-1.00	-9, 5
Alkaline Phosphatase (IU/L)	Baseline	131	61.4	15.16	59.0	32, 107					
	EOS/ET	131	60.8	14.91	58.0	32, 106	131	-0.60	7.184	-1.00	-26, 19
Aspartate Aminotransferase (IU/L)	Baseline	131	18.2	5.12	17.0	10, 34					
	EOS/ET	131	16.2	3.84	16.0	10, 32	131	-1.95	3.959	-1.00	-19, 6
Bilirubin (umol/L)	Baseline	131	8.89	3.919	7.90	3.1, 21.4					
	EOS/ET	131	8.37	3.897	7.40	3.4, 20.4	131	-0.524	2.8997	-0.500	-10.6, 6.9
Blood Urea Nitrogen (mmol/L)	Baseline	131	4.641	1.3427	4.430	1.79, 9.25					
	EOS/ET	131	4.391	1.2476	4.280	2.03, 9.57	131	-0.2506	1.10376	-0.1800	-3.25, 2.36
Calcium (mmol/L)	Baseline	131	2.390	0.0802	2.380	2.15, 2.65					
	EOS/ET	131	2.377	0.0830	2.380	2.13, 2.58	131	-0.0131	0.08681	0.0000	-0.32, 0.25
Carbon Dioxide (mmol/L)	Baseline	131	29.7	2.06	30.0	23, 34					
	EOS/ET	131	30.1	2.11	30.0	24, 35	131	0.42	1.877	0.00	-4, 7
Chloride (mmol/L)	Baseline	131	102.4	2.00	102.0	97, 107					
	EOS/ET	131	102.9	1.99	103.0	96, 107	131	0.48	2.092	0.00	-5, 6
Creatinine (umol/L)	Baseline	131	76.40	16.321	76.90	46.9, 114.9					
	EOS/ET	131	75.88	15.362	76.00	44.2, 122.0	131	-0.526	6.3415	0.000	-16.8, 22.1
Gamma Glutamyl Transferase (IU/L)	Baseline	131	18.7	11.76	16.0	5, 79					
	EOS/ET	131	15.7	8.14	14.0	5, 52	131	-2.93	5.363	-2.00	-41, 12
Glucose (mmol/L)	Baseline	131	5.174	0.3547	5.160	4.38, 6.11					
	EOS/ET	131	5.036	0.5921	5.000	4.11, 10.38	131	-0.1376	0.57854	-0.1700	-1.17, 4.72
Potassium (mmol/L)	Baseline	131	4.07	0.285	4.00	3.3, 4.9					
	EOS/ET	131	4.18	0.357	4.10	3.5, 5.4	131	0.108	0.3489	0.100	-0.8, 1.3
Lactate Dehydrogenase (IU/L)	Baseline	131	137.0	21.80	135.0	96, 221					
	EOS/ET	131	130.1	17.42	129.0	98, 184	131	-6.95	15.003	-7.00	-78, 29
Protein (g/L)	Baseline	131	72.4	3.92	73.0	62, 83					
	EOS/ET	131	71.2	3.88	71.0	61, 82	131	-1.19	3.388	-1.00	-14, 7
Sodium (mmol/L)	Baseline	131	137.3	1.71	137.0	133, 142					
	EOS/ET	131	137.9	1.76	138.0	134, 143	131	0.62	1.915	1.00	-4, 6
Urate (umol/L)	Baseline	131	286.8	70.22	286.0	149, 476					
	EOS/ET	131	291.8	67.97	286.0	167, 464	131	4.99	41.622	6.00	-137, 137

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, pages 74-75)

Table 23: Serum Chemistry: Summary Statistics and Change from Baseline to End of Study/Early Termination in Clinical Abuse Potential Studies

		Actual Values 067-EG-008 + 067-EG-009 Combined (N=89)					Change from Baseline 067-EG-008 + 067-EG-009 Combined (N=89)				
Parameter	Time Point	n	Mean	SD	Median	Min/Max	n	Mean	SD	Median	Min/Max
Alanine Aminotransferase (IU/L)	Baseline	89	21.1	11.96	17.0	7, 81					
	EOS/ET	82	19.9	11.91	17.0	9, 83	82	-0.78	12.711	-1.00	-67, 51
Albumin (g/L)	Baseline	89	48.3	3.53	48.0	39, 55					
	EOS/ET	82	47.6	2.74	47.0	40, 54	82	-0.85	2.855	-1.00	-7, 6
Alkaline Phosphatase (IU/L)	Baseline	89	67.4	18.00	67.0	27, 110					
	EOS/ET	82	66.0	16.36	66.0	29, 109	82	-1.76	6.825	-2.00	-19, 16
Aspartate Aminotransferase (IU/L)	Baseline	89	20.2	7.97	19.0	9, 74					
	EOS/ET	82	18.4	5.84	17.0	10, 41	82	-1.79	8.683	-1.00	-57, 24
Bilirubin (umol/L)	Baseline	87	8.96	5.369	8.55	3.4, 29.1					
	EOS/ET	71	7.88	3.894	6.84	3.4, 22.2	71	-1.156	4.7650	0.000	-13.7, 10.3
Blood Urea Nitrogen (mmol/L)	Baseline	89	4.047	1.0267	3.927	2.14, 6.78					
	EOS/ET	82	4.245	1.0950	3.927	2.50, 6.78	82	0.1698	1.10388	0.3570	-2.50, 2.50
Calcium (mmol/L)	Baseline	89	2.444	0.0974	2.450	2.23, 2.65					
	EOS/ET	82	2.410	0.0817	2.413	2.25, 2.68	82	-0.0326	0.09327	-0.0375	-0.23, 0.23
Carbon Dioxide (mmol/L)	Baseline	89	24.8	2.36	25.0	19, 30					
	EOS/ET	82	24.7	2.19	25.0	19, 30	82	0.02	2.699	0.00	-6, 7
Chloride (mmol/L)	Baseline	89	102.2	2.37	102.0	95, 108					
	EOS/ET	82	102.5	2.28	103.0	97, 109	82	0.38	3.050	1.00	-8, 7
Creatinine (umol/L)	Baseline	89	78.92	12.753	79.56	56.6, 113.2					
	EOS/ET	82	80.26	13.162	79.12	53.0, 132.6	82	1.628	9.2574	1.326	-21.2, 31.8
Gamma Glutamyl Transferase (IU/L)	Baseline	89	23.1	15.75	18.0	6, 107					
	EOS/ET	82	20.5	14.04	16.0	6, 94	82	-2.29	9.456	-1.00	-57, 21
Glucose (mmol/L)	Baseline	85	4.888	0.4106	4.829	4.00, 6.27					
	EOS/ET	78	4.764	0.7568	4.802	2.05, 8.99	78	-0.1153	0.74575	-0.0555	-2.22, 4.05
Potassium (mmol/L)	Baseline	89	1.12	0.084	1.13	0.9, 1.3					
	EOS/ET	82	1.12	0.076	1.13	0.9, 1.3	82	0.006	0.0963	0.026	-0.3, 0.2
Lactate Dehydrogenase (IU/L)	Baseline	89	150.2	25.97	150.0	92, 214					
	EOS/ET	82	152.3	29.23	148.5	88, 265	82	1.80	24.164	2.00	-89, 71
Protein (g/L)	Baseline	85	71.4	5.02	72.0	55, 80					
	EOS/ET	78	71.1	4.01	71.5	62, 81	78	-0.45	4.451	-1.00	-10, 10
Sodium (mmol/L)	Baseline	89	141.3	2.26	141.0	132, 146					
	EOS/ET	82	141.9	2.09	142.0	137, 146	82	0.83	2.862	1.00	-7, 8
Urate (umol/L)	Baseline	89	330.1	64.77	333.1	178, 512					
	EOS/ET	82	333.9	74.44	324.2	184, 559	82	6.60	58.993	5.95	-178, 131

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, pages 76-77)

No unexpected or significant abnormalities in urinalysis were noted. There was no evidence of an effect of Arymo/EG-001 on specific gravity or pH from baseline to end of study/early termination in the pooled data from the bioequivalence studies (Table 24) or the clinical abuse potential studies (Table 25). No individual clinical laboratory abnormality was considered

clinically significant or reported as a TEAE by the investigators in studies *067-EG-011*, *067-EG-008*, or *067-EG-009*.
In *067-EG-012*, one female subject had an abnormal urine erythrocyte value of 3 to 5/HPF (reference range: 0 to 2/HPF) at the end of study that was considered clinically significant by the investigator but was not documented as a TEAE. This elevated urine erythrocyte value occurred 7 days after Arymo 30 mg was dosed (on Day 1 of Period 1 under fasting conditions and naltrexone blockade). The subject's urine erythrocyte values were within the reference range at screening and Day -1 of Period 1 and she had abnormal urine erythrocyte values of 3 to 5/HPF on Day -1 of Period 2 and repeat on Day -1 of Period 2 that were considered not clinically significant by the investigator. This subject also had abnormal occult blood values at screening (trace; reference range: negative); Day -1 of Period 1 (trace), Day -1 of Period 2 (1+), repeat on Day -1 of Period 2 (trace); and end of study (trace); however, these values were considered not clinically significant by the investigator, and I agree with that assessment.

Table 24: Urinalysis: Summary Statistics and Change from Baseline to End of Study/Early Termination in Bioequivalence Studies

		Actual Values 067-EG-011 + 067-EG-012 Combined (N=131)					Change from Baseline 067-EG-011 + 067-EG-012 Combined (N=131)				
Parameter	**Time Point**	**n**	**Mean**	**SD**	**Median**	**Min/Max**	**n**	**Mean**	**SD**	**Median**	**Min/Max**
Specific Gravity	Baseline	131	1.0149	0.00919	1.0140	1.002, 1.036					
	EOS/ET	131	1.0164	0.00828	1.0170	1.002, 1.036	131	0.00147	0.009013	0.00000	-0.021, 0.027
pH	Baseline	131	6.05	0.505	6.00	5.0, 8.0					
	EOS/ET	131	5.97	0.548	6.00	5.0, 7.5	131	-0.088	0.5866	0.000	-2.0, 1.5

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, page 78)

Table 25: Urinalysis: Summary Statistics and Change from Baseline to End of Study/Early Termination in Clinical Abuse Potential Studies

		Actual Values 067-EG-008 + 067-EG-009 Combined (N=89)					Change from Baseline 067-EG-008 + 067-EG-009 Combined (N=89)				
Parameter	**Time Point**	**n**	**Mean**	**SD**	**Median**	**Min/Max**	**n**	**Mean**	**SD**	**Median**	**Min/Max**
Specific Gravity	Baseline	79	1.0170	0.00710	1.0180	1.005, 1.030					
	EOS/ET	67	1.0189	0.00657	1.0190	1.005, 1.030	67	0.00230	0.008749	0.00300	-0.018, 0.021
pH	Baseline	89	6.62	0.623	6.50	5.5, 8.0					
	EOS/ET	82	6.44	0.621	6.50	5.5, 8.5	82	-0.220	0.7861	0.000	-2.5, 1.5

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, page 78)

8.4.7 Vital Signs

In each of the Phase 1 clinical studies with Arymo/EG-001, safety evaluation included: physical examinations, vital signs measurements, clinical laboratory evaluations, cardiac telemetry and

pulse oximetry, and documentation of reported or observed adverse effects. The same safety variables were monitored in the clinical abuse potential studies of EG-001, with the addition of continuous oxygen saturation monitoring in both studies and a nasal cavity inspection in study *067-EG-009*.

During the Pilot Studies of EG-001, the following were noted:

- In study *067-EG-001*, only two abnormal vital sign values were considered TEAEs (blood pressure decreased experienced by one subject after receiving EG-001 60 mg [Period 3] and blood pressure increased experienced by one subject after receiving MS Contin 60 mg [Period 6]). These events were considered mild in intensity and resolved within a few hours.
- In study *067-EG-002*, one subject had sinus tachycardia approximately 2 hours after receiving EG-001 60 mg (Treatment B). This TEAE was assessed as moderate and possibly related to treatment and resolved within 30 minutes.
- In study *067-EG-006*, no individual vital sign abnormality was reported as a TEAE. No individual 12-lead ECG cardiac telemetry or pulse oximetry abnormality was considered clinically significant or reported as a TEAE by the investigator.

There were no clinically significant physical examination findings in the bioequivalence studies or the clinical abuse potential studies.

Vital signs measured in the bioequivalence studies and the clinical abuse potential studies included diastolic and systolic blood pressure (mm Hg), pulse rate (beats/min), respiratory rate (breaths per minute), and oxygen saturation (%). Changes from baseline to end of study/early termination were summarized for the pooled analyses. There was no evidence of an effect of EG-001 on vital signs in either the bioequivalence studies or the clinical abuse potential studies. No individual vital sign finding was reported as a TEAE by the investigators in the bioequivalence studies.

In the clinical abuse potential studies, mean vital signs were within the normal range at baseline and at final assessment. Most minimum or maximum values were also within normal range for vital signs parameters evaluated. One participant (subject 044) in *067-EG-009* had a TEAE related to vital signs after treatment with manipulated intranasal MS Contin (mild oxygen saturation decreased, which was considered possibly related to study drug). The subject received 2 liters of oxygen to treat the TEAE, which was resolved after approximately 24 hours, and the subject completed the study. No other TEAEs related to vital signs were recorded.

Reviewer's Comments: Subjects who experienced decreased blood pressure, tachycardia and oxygen desaturation are likely related to study drugs, since these are known AEs seen in opioids.

8.4.8 Electrocardiograms (ECGs)

Electrocardiogram (ECG) parameters that were measured in the bioequivalence studies and the clinical abuse potential studies included heart rate (beats/min), PR, RR, QT, and QTcF (Fridericia's Correction Formula) durations (msec), summary (mean) QRS duration (msec), and

summary (mean) QRS axis (deg). Changes from baseline to end of study/early termination were summarized by the applicant for the pooled analyses. There was no evidence of reported effects of Arymo/ EG-001 on ECG parameters in the bioequivalence studies. In the clinical abuse potential studies, there was a decrease in mean RR duration of 76.40 ± 177 msec, and an increase in mean QTcF of 7.04 ± 16 msec from baseline to end of study/early termination (Table 26). Although individual ECG abnormalities were recorded, none were considered clinically significant by the applicant in either the bioequivalence studies or the clinical abuse potential studies.

Table 26: ECG: Summary statistics and change from baseline to end of study/early termination in clinical abuse potential studies with Arymo/EG-001

		Actual Values 067-EG-008 + 067-EG-009 Combined (N=89)					Change from Baseline 067-EG-008 + 067-EG-009 Combined (N=89)				
Parameter	Time Point	n	Mean	SD	Median	Min/Max	n	Mean	SD	Median	Min/Max
Heart Rate (BEATS/MIN)	Baseline	89	63.5	9.35	62.0	44, 86					
	EOS/ET	84	69.4	11.21	70.0	46, 100	84	5.90	13.008	5.00	-28, 37
PR Duration (msec)	Baseline	89	156.5	46.69	151.0	95, 552					
	EOS/ET	84	151.2	20.29	150.0	94, 198	84	-5.63	41.697	-1.00	-358, 52
RR Duration (msec)	Baseline	89	957.5	139.03	958.0	691, 1340					
	EOS/ET	84	880.1	144.84	850.0	596, 1293	84	-76.40	177.312	-82.50	-477, 363
QT Duration (msec)	Baseline	89	389.4	24.82	389.0	344, 460					
	EOS/ET	84	385.0	28.48	385.0	326, 453	84	-3.87	27.224	-5.00	-62, 69
QTcF - Fridericia's Correction Formula (msec)	Baseline	89	395.3	17.37	396.0	359, 449					
	EOS/ET	84	401.9	18.21	403.0	362, 438	84	7.04	15.587	8.00	-35, 45
Summary (Mean) QRS Duration (msec)	Baseline	89	95.4	8.88	94.0	79, 126					
	EOS/ET	84	93.0	8.24	92.0	74, 121	84	-2.01	7.307	0.00	-34, 12

EOS/ET = End of Study/Early Termination

Source: Applicant's Submission (ISS, page 85)

8.4.9 QT

The IRT was not consulted for QT studies, since the active moiety, morphine sulfate, is a well-known entity.

8.4.10 Immunogenicity

Not applicable

8.5 Analysis of Submission-Specific Safety Issues

As mentioned previously in Section 4.2, Polyethylene oxide (PEO) is a commonly used release controlling excipient in abuse-deterrent products and comprises (b) (4) % of the Arymo ER matrix tablet composition, (b) (4) . Due to the amount of PEO utilized in

the Arymo ER tablet, there may be potential concerns that when exposed to water or gastric fluid, the tablet could swell significantly in size to present a swallowing/choking hazard. After an information request, the applicant submitted a tablet swelling study using water and simulated gastric fluid (under fasting conditions) as the media. The study was reviewed extensively by the Office of Pharmaceutical Quality at FDA's Center for Drug Evaluation and Research. Please refer to Dr. Ciby Abraham's review for details of the study, which I will briefly summarize below:

Study Procedure: Initial dimensions of Arymo ER tablets (15 mg or 60 mg dose strength) were recorded using a caliper and placed on a fixed glass base using a small piece of adhesive tape in a 2000 mL transparent vessel. 1600 mL of a selected liquid media (water or simulated gastric fluid) was added to the vessel, covering the Arymo ER tablet completely. Pictures were taken at relevant time points after exposing the tablet to the defined liquid media, until maximum swelling and subsequent decline was observed. Tablet dimensions were measured (length, height, width and calculated volume) for the pictures taken over time. Data for all three dimensions (i.e., length, height, and width) were used to calculate average values, for each tablet strength, liquid media and time point. The averaged length (l), height (h), and width (w) of the tablet for each strength/liquid media at each defined time point was used to calculate an approximate tablet volume (V)/time point using the calculation: VT = l × h × w.

Swelling, defined as the relative volume change (in percent) of the tablet for each strength and liquid media for each time point (T = x) relative to the average volume calculated at T = 0. Swelling was calculated according to the following formula:

$$Swelling = \frac{Volume\ at\ T = x}{Volume\ at\ T = 0} \cdot 100\%$$

Maximum Swelling (S_{MAX}) observed and Time to S_{MAX} was recorded, for each of the tablet strengths. Three replicates of each dosage strength were tested in each media, and experiments were conducted over an 8 hour time period.

Study Results: Reporting of the swelling was focused on two time point periods, i.e. T = 30 seconds to 3 min and T_{MAX}, time to maximum swelling of the tablet.
At T = 30 seconds, all tablets swelled to approximately 105%, independent of the liquid media. During the first three minutes, the outer coat of the tablet started to dissolve and diffuse away from the tablet. Swelling during the first three minutes was linear and reached 114-117%. T_{MAX} was reached between T = 3.75-4.75 hours and the range of S_{MAX} observed was between 249-274%, and no correlation was observed for S_{MAX} between either tablet strength or liquid media. The largest length of a tablet observed was between 22.9-24.4 mm, the largest width observed was between 11.8-12.8 mm, and the largest height was between 8.1-9.3 mm.

Reviewer Evaluation of swelling study: Dr. Abraham concluded that the study results were

acceptable, and based on those results, Arymo ER tablets do not swell rapidly in the first three minutes, allowing enough time for the patient to swallow the tablet without difficulty. The limited initial swelling is consistent with the erosion based release of the Arymo ER tablets, which is different from diffusion-controlled release tablets.

Review of the safety data from the clinical trials did not reveal any TEAEs that were associated with choking, sticking or obstruction. In addition, there were six TEAEs (3 in pilot study EG-006, and 3 in BE study EG-012) that were classified as 'Oropharyngeal Pain'. All 6 TEAEs were described as 'sore throat', with 4 TEAEs in subjects treated with Arymo ER tablets and 2 TEAEs subjects treated with MS Contin. All were listed as mild, with resolution within 24 hours without treatment.
Considering together the safety analysis in the clinical trials, coupled with the in vitro tablet swelling study described above, I concur that Arymo ER would not likely present a choking/swallowing hazard for patients.

8.6 Safety Analyses by Demographic Subgroups

Due to the small sample sizes and well-known active moiety (Morphine sulfate), the applicant did not conduct safety analyses by demographic subgroups.

8.7 Specific Safety Studies/Clinical Trials

There were two clinical abuse liability studies (067-EG-008 and EG-009) performed in healthy adult subjects who were opioid-experienced, recreational drug users. These have been incorporated into the overall safety review and will not be discussed separately here.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

Please refer to the Pharmacology/Toxicology review by Dr. Elizabeth Bolan

8.8.2 Human Reproduction and Pregnancy

There have been no adequate and well-controlled studies of Arymo or other extended-release morphine sulfate products in pregnant women. Arymo should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.8.3 Pediatrics and Assessment of Effects on Growth

No pediatric exposure was reported in the submission. Arymo was not studied in subjects younger than 18 years of age. The application for Arymo does not trigger the requirements of

PREA.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no overdose, withdrawal and rebound studies conducted for this submission.

8.9 Safety in the Post-market Setting

8.9.1 Safety Concerns Identified Through Post-market Experience

This product is not currently marketed, so no post-market information is available.

8.9.2 Expectations on Safety in the Post-market Setting

Arymo is an extended-release morphine sulfate product, and would be expected to have a similar safety profile as other extended-release morphine products currently in the market, such as MSCONTIN. Labelling of Arymo should closely mirror that of MSCONTIN, to include potential safety concerns in specific subpopulations such as geriatric patients over age 65. Arymo will be subject to the Extended-Release/Long Acting (ERLA) REMS program that all currently marketed ER/LA opioids are part of.

8.10 Additional Safety Issues From Other Disciplines

Not applicable.

8.11 Integrated Assessment of Safety

The Applicant has not conducted any clinical studies evaluating or comparing the safety of Arymo in the target pain population. Instead, the Applicant conducted seven BA and PK studies that compared the use of Arymo to MS CONTIN in healthy volunteers between the ages of 18 and 55 years. The applicant also conducted two clinical abuse potential studies in which the PD parameter of drug liking and PK following intranasal and oral administration were determined. The participants were healthy volunteers between ages 18 and 55 who were experienced opioid users that were not dependent upon the drug.

A total of 442 healthy adult subjects from nine studies were exposed to Arymo/Egalet Morphine: 297 subjects received one single-dose and 145 subjects received between two and three doses. Overall, 400 subjects were exposed to the to-be-marketed formulation. This database is adequate to assess any formulation-related safety concerns, as agreed upon between the applicant and review division during the pre-NDA meeting (minimum of 100 subjects exposed to the to-be-marketed formulation).

There were no deaths, and one reported SAE in the entire clinical development program. That

subject experienced a spontaneous abortion approximately 16 days following administration of a preliminary formulation of Arymo during one of the pilot clinical trials (067-EG-001). Relationship to study drug is unknown.
The common AEs were consistent with expected opioid AEs related to the GI and nervous systems, such as nausea, vomiting, somnolence, and headache.

Overall, I agree with the Applicant's review of the safety findings that the AEs seen in the safety population, albeit not in target pain population, are generally consistent with those of the known safety profile of extended-release morphine sulfate.

9 Advisory Committee Meeting and Other External Consultations

A Joint Advisory Committee meeting of the Anesthetic/Analgesic Drug Products and Drug Safety/Risk Management advisory committees was held on August 4, 2016 at the FDA headquarters in Silver Spring, MD. The Committee was asked to discuss whether there are sufficient data to support a finding that Arymo ER has properties that could be expected to deter abuse through oral, nasal and intravenous routes; as well as whether Arymo should be approved for the proposed indication: management of pain severe enough to require daily, around-the-clock, long term opioid treatment for which alternative treatment options are inadequate.
The majority of the discussion focused on the abuse-deterrent properties of Arymo, since the active moiety, morphine sulfate, already has a long marketing history. The bulk of the committee's deliberations focused on the oral claim, with some panelists suggesting the small but statistically significant reduction in Drug Liking score for manipulated Arymo compared to a crushed preparation of MS Contin was of uncertain significance.
Nevertheless, advisors found the oral deterrence claim justified, at the very least, by the hardness of the Arymo tablet, which prevents chewing and makes manipulation through particle size reduction difficult. In addition, the product lacks a dose-dumping effect in the presence of alcohol, reducing the likelihood of abuse by that means.
The advisory committee voted overwhelmingly to approve Arymo for the proposed indication by an 18 to 1 margin. They also voted to approve Arymo as an abuse-deterrent formulation by the oral, nasal and intravenous routes. The granting of an oral abuse-deterrent claim was based primarily on the belief based on tablet hardness that Arymo would provide resistance to abuse by chewing. There was no clear opinion expressed regarding whether or not the results of oral study 067-EG-008 supported an oral abuse-deterrent claim. The Controlled Substance Staff at the FDA's Center for Drug Evaluation and Research evaluated the studies and felt that study *067-EG-008* does not provide evidence of an oral abuse-deterrent effect.
This study did not involve manipulation of Arymo by chewing, but instead by cutting into pieces using a chopping block and Chef's knife. In addition, at this time there is no specific evidence that Arymo tablets cannot be chewed.

10 Labeling Recommendations

10.1 Prescribing Information

After reviewing the applicant's proposed label for Arymo ER, the following changes to the clinically relevant aspects of the prescribing information are recommended:

Box Warnings
Due to recent opioid class-wide labelling changes, the following are to be included in the boxed warning section of Arymo regarding the serious risks of profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioid analgesics and benzodiazepines or other central nervous system depressants, including alcohol:

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of MS CONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Section 5. Warnings and Precautions
The following subsection should replace **5.4** (b) (4)

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ARYMO ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.
If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly

with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.
Advise both patients and caregivers about the risks of respiratory depression and sedation when ARYMO ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7) and Patient Counseling Information (17)]*.

Section 7 Drug Interactions
The following subsection should replace Central Nervous System (CNS) Depressants in the Drug Interactions table.

Benzodiazepines and other Central Nervous System (CNS) Depressants

Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Section 9 Drug Abuse and Dependence

The Controlled Substance Staff at FDA's Center for Drug Evaluation and Research were consulted to assist with the review and analysis of the abuse-deterrent properties of Arymo ER. Please see my summarized conclusions previously mentioned in sections 7.2.1 and 7.3 as well as Dr. Tolliver's review for full details. I concur with Dr. Tolliver's assessment, and have included his recommendations in the following labelling changes to the applicant's proposed subsection 9.2.

9.2 Abuse

- (b) (4) was removed.
- (b) (4) was removed.
- (b) (4) was removed.

Reviewer's Comments: (b) (4) In vitro Category 1 extractability/ syringeability studies indicate that Arymo tablets are difficult to manipulate for intravenous injection. At the same time, these studies demonstrate that the positive control, MS Contin, can easily be used to prepare suitable intravenous solutions. Based on these findings, a claim of deterrent effect to intravenous abuse for Arymo is also justified in Section 9.2 of the label.

Section 17 Patient Counseling Information
The following subsection should replace (b) (4).

Interactions with Benzodiazepines and Other CNS Depressants
Inform patients and caregivers that potentially fatal additive effects may occur if ARYMO ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see Warnings and Precautions (5.4), Drug Interactions (7)].

Reviewer's Comments: *The changes for labelling sections 5, 7, 17, box warnings and medication guide are part of mandatory safety labelling changes submitted by the FDA to the sponsor of MS CONTIN, Purdue Pharma LP, on August 25, 2016. Since this is a class-wide change for all ER/LA opioids, it should apply to Arymo ER as well.*

10.2 Patient Labeling

As with all ER/LA opioids, a medication guide is required. The sponsor has proposed a

medication guide which is appropriate and closely mirrors that for MS CONTIN. Due to a recent change in the safety labelling for all ER/LA opioids regarding concomitant use of opioids and benzodiazepines, the following modification should be made to the proposed medication guide for Arymo ER:
Under **Important information about ARYMO ER**, add the following text as the second bullet:

- Taking ARYMO ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

10.3 Nonprescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

Safety Issue(s) that Warrant Consideration of a REMS

As mentioned previously, due to the inherent risks of the ER/LA opioid class of medications, a REMS is a required part of the approval process. Arymo ER would be required to participate in the current ER/LA REMS program.

11.2 Conditions of Use to Address Safety Issue(s)

The adverse outcomes of concern in ER/LA opioids include addiction, unintentional overdose, and death. The prescriber (physician, nurse practitioner/physician assistant), dispenser and patient all have important roles in preventing and managing the risk of Arymo ER usage. This is illustrated in the relevant sections of the product label and the accompanying medication guide, as well as post marketing requirements spelled out in the current ER/LA REMS program.

11.3 Recommendations on REMS

In accordance with section 505-1 of the Food, Drug and Cosmetic Act, the Agency determined that a REMS is necessary for ER/LA opioids to ensure that the benefits of the drug continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. Additionally, in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, a single, shared system (SSS) was implemented for all members of the class. The ER/LA REMS includes ER/LA opioid brand name and generic products formulated with the active ingredients: buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, ***morphine***, oxycodone, oxymorphone, and tapentadol.
The ER/LA REMS is a SSS and was originally approved on July 9, 2012. The manufacturers of

ER/LA opioids are collectively referred to as the REMS Program Companies (RPC). Multiple modifications to the ER/LA Opioid Analgesic REMS have been approved, most recently on June 26, 2015.
The goal of the ER/LA REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death. The ER/LA REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), and a timetable for submission of assessments of the REMS.
The ETASU includes a training program for prescribers that is not linked to distribution. The tools used to support the ETASU include continuing education (CE) programs by CE providers on the safe use of ER/LA opioids, letters for prescribers and professional organizations to inform them about the program, a patient counseling document, and a REMS website. The timetable for submission of assessments is at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter. For full details, please refer to the ER/LA Opioid Analgesic REMS website at www.ER-LA-opioidREMS.com
I concur with the assessment of FDA's Division of Risk Management (DRISK) that Arymo ER should be required to fully participate and comply with the current ER/LA REMS program.

12 Post-marketing Requirements and Commitments

There will be post-marketing requirements as part of the ER/LA REMS program. For full details, please refer to the ER/LA Opioid Analgesic REMS website at www.ER-LA-opioidREMS.com
The sponsor will also have the standard post-marketing study requirements for new products with abuse-deterrent labeling.

13 Appendices

13.1 References

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13.2 Financial Disclosure

The applicant has attested to the fact that they have not entered into any financial arrangements with their clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR §54.2(a). The applicant also certified that no investigator had a proprietary interest in Arymo ER or a

significant equity in the applicant as defined in 21 CFR §54.2(b), and that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR §54.2(f).

Covered Clinical Studies (Name and/or Number): 067-EG-001, EG-002, EG-004, EG-005, EG-006, EG-008, EG-009, EG-011, EG-012

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Yes (31 investigators in total)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN W HARIADI
09/23/2016

JOHN J FEENEY
09/24/2016