CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206544Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206544
Priority or Standard	Standard
Submit Date(s)	November 21, 2014
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PDUFA Goal Date	September 13, 2015
Division / Office	DAAAP/ODE2
Reviewer Name(s)	Timothy T. Jiang, MD, PhD
Review Completion Date	August 18, 2015
Established Name	Morphine Sulfate
(Proposed) Trade Name	Morphabond
Therapeutic Class	Opioid
Applicant	Inspirion Delivery Technologies, LLC
Formulation(s)	Oral
Dosing Regimen	Every (b) (4) 12 hours
Indication(s)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Intended Population(s)	Adults

Timothy Jiang, MD, PhD
NDA 206544
Morphine ARER

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval for Morphine ARER for the indication of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate provided that pre-clinical review team upon completion of their evaluation does not identify any issues that could potentially affect patient safety

This product is an extended-release opioid and formulated with the intention of having abuse- deterrent characteristics through the use of excipients to create physico-chemical barriers to the release of morphine following manipulation.

The Morphine ARER tablet (15, 30, 60, 100 mg) is formulated to deliver the active pharmacological ingredient, morphine sulfate, over (b) (4) 12 hours from a potentially abuse-deterrent oral tablet.

The Applicant has not conducted any clinical studies evaluating or comparing the analgesic effectiveness of Morphine ARER in the target pain population. The Applicant is relying on FDA's previous finding of safety and efficacy for the RLD 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 changes to the approved RLD product labeling 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.

To support a 505(b)(2) application, the Applicant has demonstrated bioequivalence to the 100-mg strength of MS CONTIN, conducted food effect and multiple-dose PK studies using the 100-mg strength tablet, conducted comparative bioavailability studies of the 30- and 15-mg strength tablets, and submitted a biowaiver request for the 60-mg strength tablet. In all of these studies the final formulation was used.

Although C_{max} is lower for both two lower strength Morphine ARER tablets (15 mg with ratio 87.4%, 90% CI, *79.1%* to 96.6% and 30 mg with ratio 80.7%, 90% CI, *76.2%* to 85.3%), this reviewer agrees that not meeting the BE criteria will not affect the efficacy and safety for the following reasons:

- For chronic therapy, BE at steady-state is more relevant to demonstration of similar efficacy (Steady-state PK modeling data from the comparative BA studies predicts BE for both AUC and C_{max}).
- Two lower strengths are mostly used as initiation and titration doses
- Lower C_{max} would not pose a safety concern.

The Applicant has not conducted any clinical studies evaluating or comparing the safety of Morphine ARER in the target pain population. Instead, the Applicant conducted seven BA and PK studies that compared the use of Morphine ARER to MS CONTIN in healthy volunteers between the ages of 18 and 53 years. One of these studies was a human abuse potential study in which the PD parameter of drug liking and PK following intranasal administration was determined in healthy volunteers who were experienced opioid users that were not dependent upon the drug. The profile of adverse events was consistent with a mu-opioid agonist.

The dosing recommendations are the same as reference listed drug MS CONTIN.

1.2 Risk Benefit Assessment

Although C_{max} is lower for both two lower strength Morphine ARER tablets, this reviewer agrees that not meeting the BE criteria will not affect the efficacy and safety for the following reasons as discussed earlier.

From the perspective of risk, the safety data submitted (albeit not in target pain population), were, overall, consistent with those of the opioid class of drugs. There were no deaths or non-fatal SAE reported in the clinical studies, and no unexpected or unusual adverse events of special interest were identified.

All opioids pose the risk of abuse and misuse. The development of abuse-deterrent formulations of opioid analgesics is an important approach to reducing abuse of prescription opioids.

Please see Section 2.6 and Dr. Jim Tolliver's review for detail regarding Agency's findings on abuse-deterrent characteristics. Dr. Tolliver recommended label claims of abuse deterrent properties with the conclusion as follows:

The overall findings of the in vitro studies and the intranasal human abuse potential study suggest a possible intranasal abuse deterrent effect of Morphabond tablets relative to MS Contin. The studies demonstrate that Morphabond tablets retain the extended release properties upon crushing and extraction. Thus, Morphabond tablets resist manipulation for purposes of intravenous abuse.

These risks (including overdose, misuse and abuse), however, appear to be manageable with the labeling with a REMS as discussed in following section.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

In order to satisfy Agency's Risk Evaluation and Mitigation Strategy (REMS) requirement, the Applicant has applied the most recently approved ER/LA REMS obtained from the FDA REMS website.

1.4 Recommendations for Postmarket Requirements and Commitments

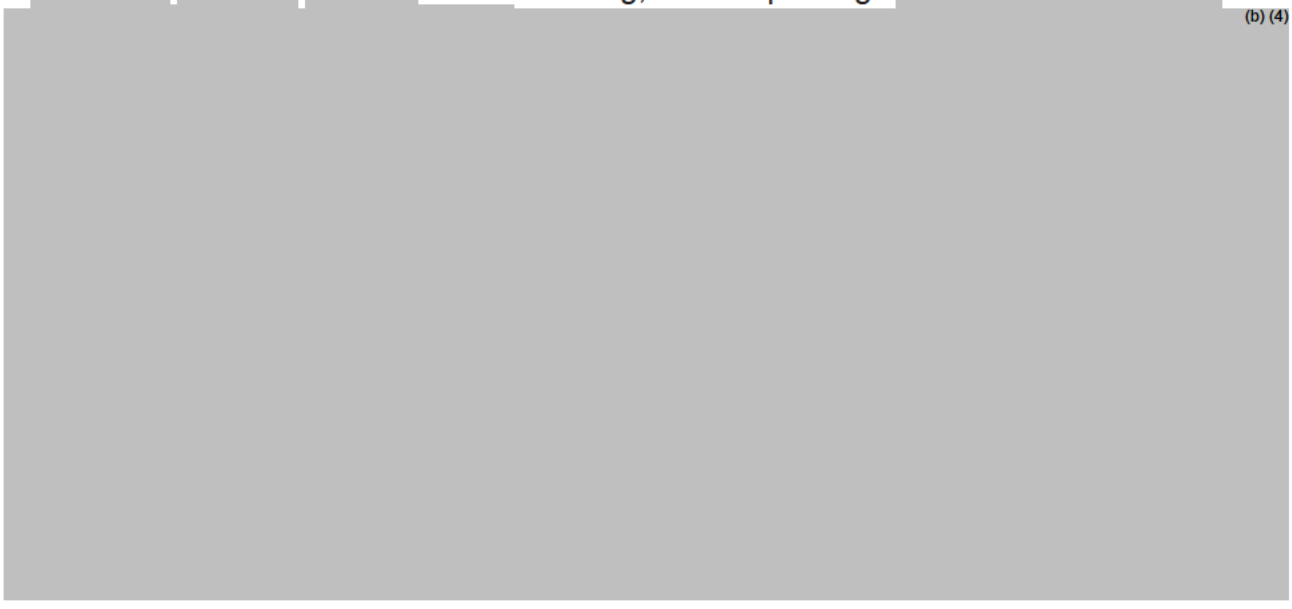
This product does not meet any of the criteria that trigger PREA (new indication, new dosage form, new route of administration, new dosing regimen, new active ingredient).

2 Introduction and Regulatory Background

2.1 Product Information

Morphine ARER tablets incorporate Applicant's abuse-deterrent technology. The Morphine ARER tablets are difficult to manipulate, retain ER characteristics even if the tablet is subjected to physical manipulation and/or chemical extraction, and form a material that resists passage through a needle when subjected to a liquid environment.

According to the Applicant, Morphine ARER tablet comprises (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) a color coating, and ink printing.



(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, including extended-release opioids.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple products with morphine are available. There is also an abuse-deterrent morphine product (EMBEDA containing extended-release morphine pellets and sequestered naltrexone cores at 25:1 ratio).

2.4 Important Safety Issues With Consideration to Related Drugs

Opioids:
The risks associated with the use of Morphine ARER appear similar to the risks of other extended release opioids. These risks would include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdosage (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.

While GI-related adverse events were the most frequently occurring in the Morphine ARER treated subjects, these findings were consistent with those seen in other opioid products and not necessarily a result of the abuse deterrent properties of Morphine ARER.

The combination of the (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) impart the proprietary abuse-deterrent characteristics and the (b) (4) (b) (4) imparts the extended-release characteristics to the product.

From a safety standpoint, abuse deterrent products with polyethylene oxide have been reported to be associated with choking or swallowing difficulties in some postmarketing data for approved products using polyethylene oxide and resulted in labeling of those product(s) regarding the possibility of choking or difficulty swallowing the tablets. No cases of choking or difficulty swallowing the tablets were reported in the Applicant's submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant had several interactions with the Agency during the drug development under IND 115822 as the follows:

- 09/12/2012 IND with questions
  - *"If you demonstrate that Morphine ARER is bioequivalent to the proposed listed drug, MS CONTIN, in your comparative bioavailability studies, and no additional safety concerns arise from your abuse-deterrent formulation, then no efficacy study will be required. However, you must submit additional safety data to ensure that your product does not result in unexpected safety concerns, such as gastrointestinal effects."*
  - Two "likeability" studies were allowed to proceed.

- 07/02/2013 Type C meeting
  - *"The small amount of safety data you have submitted from the pharmacokinetic and liking studies does not show any unexpected adverse GI events."*
  - *"We have reviewed the formulation and it does not appear that there are excipients that would predispose this product to adverse events such as choking, sticking or obstruction. Therefore at this time there is no additional requirement for clinical safety data. If however, safety concerns arise during the continued development of your product, additional clinical safety assessments may be necessary."*

- 04/10/2014 Pre-NDA meeting on topics of:
  - NDA Content and Format
  - Label of abuse-deterrent opioids
  - REMS

2.6 Other Relevant Background Information

The Applicant conducted the following studies to support abuse-deterrent formulation properties of the product:

- In vitro laboratory studies
- Clinical nasal human abuse liability (HAL) study

Dr. Jim Tolliver summarized his findings as follows:

1. *The overall findings of the in vitro studies and the intranasal human abuse potential study suggest a possible intranasal abuse deterrent effect of Morphabond tablets relative to MS Contin. The studies demonstrate that Morphabond tablets retain the extended release properties upon crushing and*

extraction. Morphabond tablets, compared to MS Contin resist manipulation for purposes of intravenous abuse.

2. *Study M-ARER-002 provides evidence that the insufflation of crushed Morphabond 60 mg compared to crushed MS Contin 60 mg is associated with less subjective effects of Drug Liking and High compared to MS Contin.*

3. *With respect to **Drug Liking**, insufflated Morphabond 60 mg compared to MS Contin produced significantly ($p<0.0001$) lower levels of maximum Drug Liking (E_{max}) (LS means of 71.13 mm versus 84.79 mm, respectively) and overall experience of drug liking over first two hours post-dose (AUE_{0-2hrs}) (117.95 h·mm versus 142.6 h·mm, respectively). Likewise, insufflation of crushed Morphabond 60 mg compared to insufflated crushed MS Contin produced significantly lower levels ($p<0001$) of E_{max} for **High** (LS means of 43.0 mm versus 67.7 mm, respectively) and AUE_{0-2hrs} (36.65 h·mm versus 91.63 h·mm, respectively).*

4. ***Intranasal crushed and intact oral Morphabond 60 mg** produced similar E_{max}s of Drug Liking (LS means of 71.13 mm versus 67.03 mm, respectively) and High (LS means of 43.0 mm versus 34.2 mm) that was significantly ($p<0.0001$) greater than the E_{max} produced by intranasal placebo for either **Drug Liking or High**, indicating that both treatments were associated with abuse potential.*

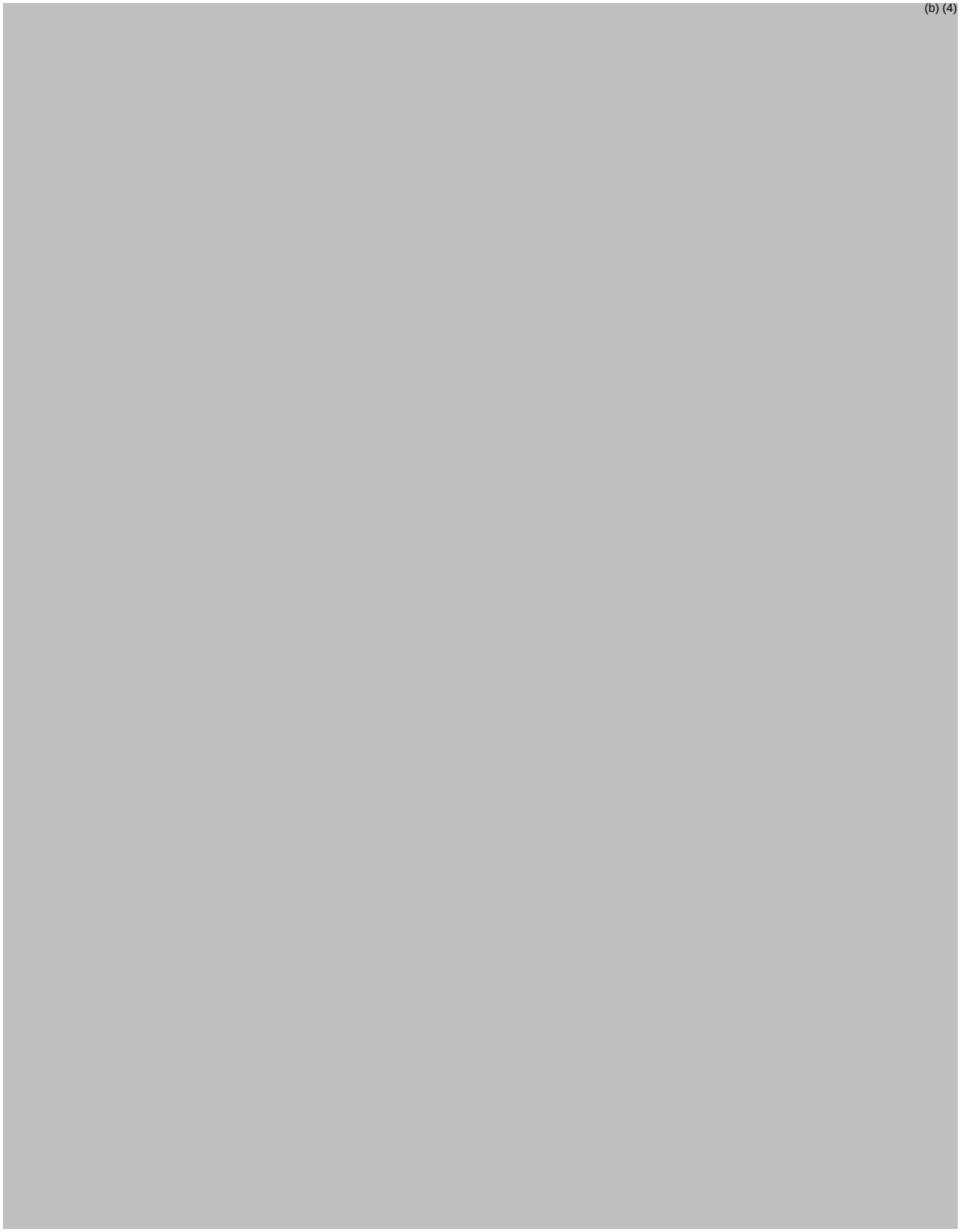
5. *Using bipolar **Take Drug Again** VAS, individuals were more willing ($p=0.0341$) if given the opportunity again to insufflate MS Contin 60 mg (LS mean E_{max} of 76.5 mm) than Morphabond 60 mg (LS mean E_{max} of 66.6 mm).*

6. *Whereas study subjects expressed no interest in insufflating **placebo** again if given the opportunity, they showed some interest in taking again either **intranasal crushed Morphabond 60 mg** (LS means of E_{max} of 66.56 mm versus 49.48 mm, $p=0.0004$)) or **oral intact Morphabond 60 mg** (LS means of E_{max} of 64.33 mm versus 49.48 mm, $p=0.0019$).*

7. *All subjects were able to insufflate the entire amount of crushed Morphabond 60 mg, crushed MS Contin 60 mg, and placebo, all of which consisted of matching weights. In addition, based on the 0-100 point bipolar **Snorting Experience VAS**, subjects recorded a similar overall experience for insufflation of the three treatments. This suggests that the insufflation of crushed Morphabond was not associated with aversive intranasal effects.*

8. *Morphabond tablets, but not MS Contin tablets, demonstrated resistance to **physical manipulation**. using (b) (4) such as (b) (4) (b) (4) Morphabond tablets could be cut*

(b) (4)



(b) (4)

13. *Under the conditions used by the Sponsor, abuse of Morphabond tablets by smoking is not likely.* (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission appeared to be of good quality. It was well organized and easily navigated. Several clinical information requests (IRs) were sent to the Applicant for clarification of safety data. In general, the Applicant responded to the IRs in a timely manner.

3.2 Compliance with Good Clinical Practices

The Applicant reported that all clinical studies in this application were conducted in accordance with applicable regulatory guidances and relevant sections of the International Conference on Harmonization guidelines.

This product is an abuse deterrent formulation of an extended-release opioid. The Division has decided that the HAL study/studies have significant weight in the decision making of a NDA's approval. Therefore, a site should be evaluated where an HAL study was completed.

OSI inspection was consulted for human abuse liability (HAL) study as this application is based on BE studies only (no clinical efficacy study conducted).

Study M-ARER-002 was the only clinical study that supported abuse deterrence of Morphine ARER, and the single CI site at which this study was (entirely) conducted was identified for GCP inspection.

Site at CRI Lifetree, 3838 South 700 East Suite 202, Salt Lake City, UT 84106 was identified for GCP inspection based on largest subject enrollment (48 subjects) and contribution to the overall HAL outcome.

Clinical Investigator	Study and Subjects	Inspection Outcome
Lynn R. Webster, M.D. CRI Lifetree, Inc. 3838 South 700 East, Suite 202 Salt Lake City, Utah	Study M-ARER-002 48 enrolled, 27 randomized	July 13 - 21, 2015 Pending, preliminary NAI

NAI = no action indicated (no significant violations)
Pending = preliminary results based on communication with field investigator

Source: Dr. Lee's review.

Dr. Lee made the following general comments:

a. What was inspected:

Records review: institutional review board oversight, sponsor's study monitoring, CI financial disclosure, drug accountability and disposition, and subject records

Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification (randomization, efficacy, AEs, protocol deviations, and subject discontinuations)

b. General observations and comments:

Seventy subjects were screened, 48 were enrolled (qualification phase), 27 were randomized, and 25 completed the study. Records were reviewed for all enrolled subjects, including detailed review for 30 subjects (15 randomized for efficacy, 15 others enrolled for safety).

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, drug accountability, AE monitoring, and reporting of AEs and protocol deviations. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, case report forms (CRFs), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.
Dr. Lee made the OVERALL ASSESSMENT AND RECOMMENDATIONS as follows:
To support the review of this 505 (b)(2) NDA for Morphine ARER, the HAL study M-ARER-002 was audited at GCP inspection of the only site at which this study was entirely conducted. Subject case records were reviewed for all enrolled subjects, including detailed review for 30 subjects: 15 of 27 randomized (56%) for the efficacy audit, and 15 others of 48 enrolled (31%) for the safety audit.

No significant deficiencies were observed and a Form FDA 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 this HAL study appear reliable as reported in the NDA.

3.3 Financial Disclosures

The Applicant's submission included the completed Certification: Financial Interests and Arrangements of Clinical Investigators in compliance with 21CFR part 54. This certified that the Applicant had not entered into any financial arrangements with the listed clinical investigators, that each clinical investigator had no financial interests to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant for studies

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

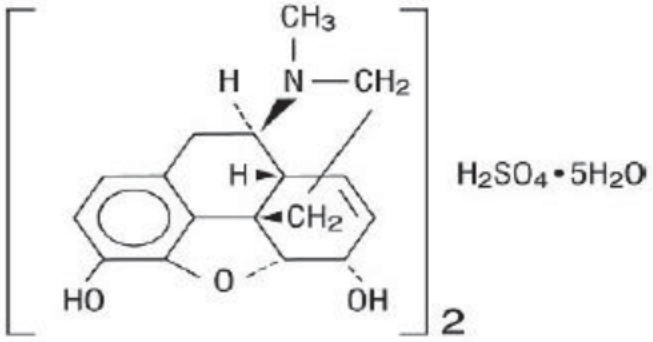
4.1 Chemistry Manufacturing and Controls

Please see Dr. Xiaobin Shen's CMC review for detail. There are no approvability issues identified from CMC perspective.

Dr. Shen Recommends approval with 24 month expiry with the conclusions as follows:

- EES status acceptable.
- DS DMF reviewed and found acceptable.
- DP Specifications acceptable.
- DP stability data support 24 month expiry.
- Carton labeling revised and found acceptable.

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:



4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

Please see Dr. Carlic Huynh's review for detail. There are no approvability issues identified with DS and DP specs. However, the adequacy of Sponsor's justification for (b) (4) and (b) (4) is still to be determined. The review team sent out an IR on July 23, 2015 as follows with pending response:

During review of your NDA submission, we have determined that the level of (b) (4) (b) (4) associated with the maximum theoretical daily dose of 2 g/day of morphine ARER exceeds those levels that are present in approved FDA oral products. As discussed previously, the safety of the (b) (4) polymeric backbone, which consists of ethyl acrylate and methyl methacrylate copolymer, appears to be addressed in your NDA submission. However a safety justification for the (b) (4), cannot be located in your NDA submission. As the levels of (b) (4) exceeds those levels in FDA-approved oral products, submit as soon as possible a comprehensive safety assessment of (b) (4) that supports the safety of this (b) (4) at the level associated with the MTDD of morphine ARER of 2 g/day.

4.4 Clinical Pharmacology

Please see Dr. Srikanth Nallani's review for detail. There are no approvability issues identified from clinical pharmacology perspective. Dr. Nallani summarized his findings as follows:

In summary, Morphine ARER 100-mg tablet met the bioequivalence criteria for both AUC and Cmax with MSContin. For both 15 mg and 30 mg Morphine ARER tablets, bioequivalence criteria were met for AUC, but Cmax slightly missed the 80% lower

bound. However, this observation is not considered clinically significant. Food does not have a significant effect on Morphine ARER tablet so it can be taken regardless of food.

There are no approvability issues identified from biopharmaceutics perspective. Please see Dr. Chen's review for detail. Dr. Chen provided the following comments:

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method development report, comparative dissolution profile data, proposed dissolution method and acceptance criteria, biowaiver request, and the in vitro alcohol dose-dumping study results.

Granting the biowaiver for 60 mg strength is pending successful demonstration of BE in vivo and similar in vitro dissolution profile comparison (f2 value >50) between Morphine ARER ER tablets (Test) and the MS Contin tablets (RLD) for both the 100 mg and 15 mg strengths.

Dr. Chen made additional comments as follows:

1. The dissolution method development in accompany with the formulation development and the in vitro alcohol dose-dumping study were reviewed and found acceptable.

2. The Applicant accepted the Agency's 04/29/15 recommendation for dissolution acceptance criteria and submitted the updated Specification (M32P51) and other related sections to the Agency.

3. Per discussions with the Clinpharm reviewer, based on the Agency's BE acceptance criteria, the highest strength 100 mg did demonstrate BE between the Morphine ARER and MS Contin, however, the lowest strength 15 mg missed slightly the lower boundary of BE assessment when compared to MS Contin 15 mg. Additional BE analysis by Clinpharm reviewer is needed and/or Medical Division will make final decision on the acceptance of both BE studies. Therefore, granting the biowaiver for the 60 mg tablet strength is therefore pending the Clinpharm and/or Medical Division's final decision.

Dr. Chen made the following final recommendation:

From the Biopharmaceutics perspectives, the recommendation for this NDA is pending final decision on the acceptance of the two BE studies by Clinpharm and/or Medical Division.

4.4.1 Mechanism of Action

Morphine sulfate, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include analgesia, 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 produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. 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.

4.4.2 Pharmacodynamics

The Applicant conducted PK studies to bridge to the listed drugs with no pharmcodynamic data collected.

4.4.3 Pharmacokinetics

Morphine ARER is an extended-release tablet containing morphine sulfate. Morphine is released from Morphine ARER somewhat more slowly than from immediate-release oral preparations. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is Morphine ARER or an immediate-release formulation. Because of pre-systemic elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Absorption
The oral bioavailability of morphine is approximately 20 to 40%. When Morphine ARER is given on a fixed dosing regimen, steady-state is achieved in about a day.

Food Effect
Administration of a single dose of Morphine ARER with a standardized high-fat meal (b) (4)
(b) (4)
(b) (4)

Distribution
Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. 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
The major pathways of morphine metabolism include glucuronidation to produce metabolites including morphine-3-glucuronide, M3G (about 50%) and morphine-6-glucuronide, M6G (about 5 to 15%) and sulfation in the liver to produce morphine-3-etheral sulfate. A small fraction (less than 5%) of morphine is demethylated. M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.

Excretion
The elimination of morphine occurs primarily as renal excretion of M3G and its effective half-life after intravenous administration is normally 2 to 4 hours. Approximately 10% of the dose is excreted unchanged in urine. In some studies involving longer periods of plasma sampling, a longer terminal half-life of about 15 hours was reported. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant conducted six comparative bioavailability studies to provide a “bridge” to the efficacy and safety of the LD, both single-dose and multiple-dose in healthy naltrexone-blocked subjects, and one HAL in healthy subjects who were opioid-experienced, recreational drug users

Table 1 Table of Clinical Studies

Table 1. Overview of Studies Conducted with Morphine ARER					
Study Number/ Status	**Study Design**	**Objective**	**Baseline Demographics Total Subjects Enrolled[a] Total Subjects Analyzed/Mean Age/(range)/Race**	**Patient Population**	**Morphine ARER and MS CONTIN: Dose Regimen/Route of Administration**
Single-dose Studies					
M-ARER-004[b] (P-ARER-45-04; 11249801)/ Completed	Single-center, randomized, open-label, single-dose, 2-treatment, 2-period, 2-sequence, crossover	Bioavailability of Morphine ARER 100 mg tablets compared to MS CONTIN 100 mg tablets	Total subjects: N = 54 47 males, 7 females Mean age: 34.1 ± 7.0 years Range: 23 to 45 years Black/white/other: 28/19/7	Healthy males or nonpregnant females between 18 and 45 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 100 mg tablet/oral, fasted MS CONTIN 100 mg tablet/oral, fasted
M-ARER-005 (11249802)/ Completed	Single-center, randomized, open-label, single-dose, 2-treatment, 2-period, 2-sequence, crossover	Effect of food on bioavailability of Morphine ARER 100 mg tablets	Total subjects: N = 28 28 males, 0 females Mean age: 33.0 ± 5.8 years Range: 22 to 43 years Black/white/other: 13/11/4	Healthy males or nonpregnant females between 18 and 45 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 100 mg tablet/oral, fasted Morphine ARER 100 mg tablet/oral, fed
M-ARER-007 (11249803)/ Completed	Single-center, randomized, open-label, single-dose, 2-treatment, 2-period, 2-sequence, crossover	Bioavailability of Morphine ARER 15 mg tablets compared with MS CONTIN 15 mg tablets under fasted conditions	Total subjects: N = 32 32 males, 0 females 28 analyzed Mean age: 29.5 ± 8.8 years Range: 18 to 45 years Black/white/other: 16/8/8	Healthy males or nonpregnant females between 18 and 45 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 15 mg tablet/oral, fasted MS CONTIN 15 mg tablet/oral, fasted

Table 1. Overview of Studies Conducted with Morphine ARER					
Study Number/ Status	**Study Design**	**Objective**	**Baseline Demographics Total Subjects Enrolled[a] Total Subjects Analyzed/Mean Age/(range)/Race**	**Patient Population**	**Morphine ARER and MS CONTIN: Dose Regimen/Route of Administration**
M-ARER-012[c]/ (11449801)/ Completed	Single-center, randomized, single-dose, open-label, 2-treatment, 2-period, 2-sequence, crossover	Bioavailability of Morphine ARER 30 mg tablets compared to MS CONTIN 30 mg tablets	Total subjects enrolled:: N=42 36 males, 6 females Mean age: 31.8 ± 6.6 years Range: 20 to 44 years Black/white//other: 14/21/7	Healthy adult males or nonpregnant females between 18 and 55 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 30 mg tablet/oral, fasted MS CONTIN 30 mg tablet/oral, fasted
M-ARER-002/ Completed	Single-center, randomized, single-dose, double-blind, double-dummy, placebo-controlled, 4-way, crossover	Abuse potential (PD) and bioavailability of crushed or intact Morphine ARER 60 mg versus crushed or intact MS CONTIN 60 mg versus placebo. Investigational products were administered intranasally or orally, in a fasted state	Total subjects enrolled: N = 48 42 males, 6 females Total subjects who were randomized to treatment and analyzed[d]: 27 23 males, 4 females Mean age: 25.4 ± 6.6 years Range: 19 to 53 years Black/white: 1/26	Healthy, experienced opioid users (not opioid-dependent) either male or nonpregnant female between 18 and 55 years of age	Crushed placebo ARER/ insufflated and intact placebo ARER tablet/oral Crushed MS CONTIN 60 mg/insufflated and intact placebo ARER tablet/oral Crushed Morphine ARER 60 mg/insufflated and intact placebo ARER tablet/oral Crushed ARER placebo ARER/ insufflated and intact Morphine ARER 60 mg tablet/oral

Table 1. Overview of Studies Conducted with Morphine ARER					
Study Number/ Status	Study Design	Objective	Baseline Demographics Total Subjects Enrolled[a] Total Subjects Analyzed/Mean Age/(range)/Race	Patient Population	Morphine ARER and MS CONTIN: Dose Regimen/Route of Administration
Multiple-dose Studies					
M-ARER-006/ Completed	Single-center, randomized, multiple-dose, open-label, 2-treatment, 2-period, crossover	Bioequivalence of Morphine ARER 100 mg tablets and MS CONTIN 100 mg tablets at steady-state	Total subjects: N = 45 40 males, 5 females Mean age: 34.2 ± 6.9 years Range: 20 to 45 years Black/white/other: 29/10/6	Healthy males or nonpregnant females between 18 and 45 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 100 mg tablet, twice daily/oral, fasted) MS CONTIN 100 mg tablet, twice daily/oral, fasted
M-ARER-008/ Completed	Single-center, randomized, multiple-dose, open-label, 2-treatment, 2-period, crossover	Bioequivalence of Morphine ARER 100 mg tablets and MS CONTIN 100 mg tablets at steady-state	Total subjects: N = 37 31 males, 6 females Mean age: 25.8 ± 5.4 years Range: 18 to 40 years Black/white/other: 1/34/2	Healthy males or nonpregnant females between 18 and 45 years of age. Naltrexone was used to block the effects of morphine	Morphine ARER 100 mg tablet, twice daily/oral, fasted MS CONTIN 100 mg tablet, twice-daily/ oral, fasted

Source: Applicant's submission (ISS, Pages12-13)

5.2 Review Strategy

The Applicant did not conduct efficacy study; the review is focused on the safety based on the comparative bioavailability studies in healthy naltrexone-blocked subjects and abuse HAL study in healthy subjects who were opioid-experienced, recreational drug users.

5.3 Discussion of Individual Studies/Clinical Trials

See Section 7.1.1.

6 Review of Efficacy

Efficacy Summary

The Applicant has not conducted any clinical studies evaluating or comparing the analgesic effectiveness of Morphine ARER in the target pain population. The Applicant is relying on FDA's previous finding of safety and efficacy for the RLD 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 changes to the approved RLD product labeling 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 Morphine ARER to the proposed RLD, MS CONTIN, was demonstrated in the comparative BA studies.

The Applicant has evaluated the comparative BA of Morphine ARER versus MS CONTIN following single administration of 100, 30, and 15 mg, and 5-day (steady-state) administration of 100 mg. In these studies, all subjects were naltrexone-blocked to minimize the PD effects of treatment with an opioid in healthy volunteers.

100-mg Single-dose Bioavailability and Bioequivalence

Study M-ARER-004 was conducted to determine BE of the highest strength tablets (Morphine ARER 100-mg tablets) with the RLD (MS CONTIN 100-mg tablets) and to establish a scientifically valid bridge to FDA's prior finding of safety and efficacy for the RLD. This was a single-center, open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study in healthy adult subjects. A single oral dose of the Morphine ARER 100-mg tablet or MS CONTIN 100-mg tablet was administered to subjects on 2 separate occasions under fasted conditions (at least 10 hours) with a 7-day washout between doses. Each subject received naltrexone 50-mg oral tablet at approximately 12 and 1.5 hours prior to and 12 hours after receiving study treatments

The 90% CI of the Morphine ARER to MS CONTIN ratio was entirely contained within the 80% to 125% BE range for C_{max}, AUC. Thus, the results of this comparative BA study supported the BE of single doses of Morphine ARER 100 mg to MS CONTIN 100 mg.

60-mg Biowaiver Request
Based in part on these PK data, a biowaiver for the 60-mg strength tablet was requested. In a type C meeting held on April 10, 2014 (Reference ID 3504688), The Division agreed that the 60-mg strength meets all the conditions for the BA/BE waiver for the following reasons:

1. The 60-mg strength and 100-mg strength product have the same dosage form.

2. There appear to be acceptable BA/BE data for the 100-mg strength.

3. The 60-mg strength product is (b) (4) (b) (4) in its active and inactive ingredients to the 100-mg strength product.

4. Dissolution profile comparisons between the 60- and 100-mg strengths in 3 different media meet the f2 similarity requirements.

30- and 15-mg Single-dose Bioavailability and Bioequivalence

To support marketing of the lower strength titration dose tablets, the Applicant evaluated the comparative BA of Morphine ARER 30- and 15-mg tablets with MS CONTIN 30- and 15-mg controlled-release tablets in separate single-dose, 2-way, crossover design clinical studies.

Study M-ARER-007 was a single-center, open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study designed to evaluate the relative BA of equal doses of Morphine ARER 15-mg tablets compared to MS CONTIN 15-mg tablets in healthy adult subjects under fasted conditions. Subjects were administered naltrexone 50-mg oral tablet at approximately 12 and 1.5 hours prior to receiving morphine and 12 hours after morphine dosing. Each drug administration was separated by a 7-day washout period.

Morphine ARER 15-mg tablets met the 90% CI criterion for ln-transformed AUC_{0-t} and $AUC_{0-\infty}$, and statistically met the standards of BE compared to an equal dosage of the RLD, MS CONTIN 15-mg tablets, in healthy adult subjects under fasted conditions. For Morphine ARER 15 mg, the C_{max} was lower compared to MS CONTIN 15 mg (ratio 87.4%, 90% CI, 79.1% to 96.6%). Results for the metabolite, M6G, were similar to those of morphine.

Morphine ARER 30 mg, Study M-ARER-012 was conducted to evaluate the comparative BA Morphine ARER 30 mg to MS CONTIN 30 mg. This was a single-center, open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study in which healthy adult subjects were administered equal doses of Morphine ARER 30-mg tablets and MS CONTIN 30-mg tablets under fasted conditions. Subjects were administered a naltrexone 50-mg oral tablet at approximately 12 and 1.5 hours prior to receiving morphine and 12 hours after morphine dosing. Each drug administration was separated by a 7-day washout period.

Morphine ARER 30-mg tablet met the 90% CI criterion for ln-transformed $AUC0_{0-t}$ and $AUC_{0-\infty,}$ and statistically met the standards of BE compared to an equal dosage of the RLD, MS CONTIN 30-mg tablets, in healthy adult subjects under fasted conditions. For Morphine ARER 30 mg, the C_{max} was lower compared to MS CONTIN 30 mg (ratio 80.7%, 90% CI, 76.2% to 85.3%). The Division indicated that adequate justification that not meeting the BE criteria will not affect the efficacy and safety would be needed to support approval of the 30- and 15-mg strengths without an additional clinical study.

Although C_{max} was lower for the lower strength Morphine ARER tablets, the Applicant believes that these studies are acceptable for bridging to FDA's finding of safety and efficacy for the same tablet strength of MS CONTIN for the following two main reasons: Bioequivalence at Steady-state Predicted by PK Modeling: Morphine ARER is indicated for chronic therapy; therefore, BE at steady-state is more relevant to demonstration of similar efficacy. Steady-state PK modeling (simulations of repeated administration) data from the comparative BA studies predicts that the 80% to 125% CI for BE for both AUC

and C_{max} will be met for Morphine ARER 30 and 15 mg to MS CONTIN 30 and 15 mg, respectively.

Titration Doses: The 15- and 30-mg strengths are regarded as initiation and titration doses, and given the large variability with respect to pain response versus plasma levels among patients; prescribers will adjust the dose to the individual requirements of each patient as they titrate to effective pain relief.

Reviewer's efficacy conclusion:
Although C_{max} is lower for both two lower strength Morphine ARER tablets (15 mg with ratio 87.4%, 90% CI, 79.1% to 96.6% and 30 mg with ratio 80.7%, 90% CI, 76.2% to 85.3%), the reviewer agrees that not meeting the BE criteria will not affect the efficacy and safety for the following reasons:

- For chronic therapy, BE at steady-state is more relevant to demonstration of similar efficacy (Steady-state PK modeling data from the comparative BA studies predicts BE for both AUC and C_{max}).
- Two lower strengths are mostly used as initiation and titration doses
- Lower C_{max} would not pose a safety concern.

6.1 Indication

The product is indicated for pain severe enough to require daily around the clock, long-term opioid treatment and for which alternative treatment options are inadequate.

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There will be no changes to the approved RLD product labeling including dosing recommendations with respect to effectiveness in the management the proposed indication.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects is not studied.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The Applicant has not conducted any clinical studies evaluating or comparing the safety of Morphine ARER in the target pain population. Instead, the Applicant conducted seven BA and PK studies that compared the use of Morphine ARER to MS CONTIN in healthy volunteers between the ages of 18 and 53 years. One of these studies was a human abuse potential study in which the PD parameter of drug liking and PK following intranasal administration was determined in healthy volunteers who were experienced opioid users that were not dependent upon the drug.

In the PK studies in healthy volunteers (M- ARER-004, M-ARER-005, M-ARER-006, M-ARER-007, M-ARER-008, and M-ARER-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 human abuse potential study (M-ARER-002), the subject population (recreational drug users) was not naltrexone-blocked and adverse events (AEs) reported following oral administration in this study are confounded

by the co- administration of insufflated placebo using the Applicant's abuse-deterrent technology. Adverse events reported in this study are further confounded by the unintended route of administration (intranasal), which limits direct comparison.

The Applicant is relying on FDA's previous finding of safety and efficacy 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.

A total of 241 healthy adult subjects from seven studies were exposed to oral Morphine ARER: 152 subjects received one single-dose and 89 subjects received between two and nine doses. This database is adequate to assess any formulation-related safety concerns with respect to passage through the GI tract

In all studies, subjects were exposed to between 15 and 900 mg of Morphine ARER or MS CONTIN. In the single-dose studies, subjects received one dose of Morphine ARER or MS CONTIN at 15, 30, or 100 mg in Studies M-ARER-007, M-ARER-012, and M-ARER-004, respectively. In two additional single-dose studies, subjects received two doses of Morphine ARER: in Study M-ARER-005, 100 mg was administered in a fed and fasted state, and in Study M-ARER-002, 60 mg was administered orally and insufflated. Subjects in Study M-ARER-005 did not receive MS CONTIN, and subjects in Study M-ARER-002 also received one dose of insufflated, 60-mg MS CONTIN, but no oral MS CONTIN and one treatment period was placebo. M-ARER-002 was the only study that utilized placebo in the study design. In the multiple-dose studies, subjects were randomized to receive nine doses each of 100-mg Morphine ARER and MS CONTIN administered twice daily.

There were no deaths, and no SAE, although one subject who received one single dose of study drug (15 mg) developed abdominal pain, subsequently evaluated and treated in hospital emergency room, but not admitted to hospital in Study M-ARER-007.

The common AEs were consistent with expected opioid AEs related to GI and nervous systems such as nausea, vomiting, somnolence, and headache.

There was no signal for TEAEs from the GI SOC that were associated with choking, sticking, or obstruction, in the clinical studies or demonstration of tablet stickiness in the in vitro physical characteristics testing.

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, were generally consistent with those of the known safety profile of the opioid.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A series of in vitro tests of the physical characteristics of the Morphine ARER tablets was performed to evaluate tablet properties of swelling and stickiness, change in tablet size, and level of intactness of the tablet (b) (4) (b) (4) in the presence of (b) (4) (b) (4) simulated gastric fluid over 24 hours. Morphine ARER tablets did not increase appreciably in weight or thickness for up to 24 hours after incubation in (b) (4) at pH (b) (4) (data not shown) or in simulated gastric fluid as presented in the Figure below.

Figure 1 Assessment of Morphine ARER Tablet Swelling

(b) (4)

Source: Applicant's submission (ISS, Page 8)

Table of All Investigations Pertinent to Safety is presented in Section 5.1. The Table 1 Table of Clinical Studies presents summary information by study type for all completed clinical studies included in this NDA. The Morphine ARER development program is composed of seven clinical studies in healthy volunteers, including one study conducted in subjects who were opioid-experienced, nontherapeutic, recreational opioid users.

The clinical studies were conducted to determine the PK of Morphine ARER and the relative bioavailability and the human abuse potential of Morphine ARER versus MS CONTIN. The studies were randomized, crossover studies designed to determine the bioavailability of Morphine ARER (test product) versus MS CONTIN (reference product). The GI safety of Morphine ARER tablet formulation is examined across Applicant's studies.

Morphine ARER and MS CONTIN were administered to subjects in a fasted condition in all studies and, in the food effect Study M-ARER-005,subjects also received test and reference product after a high-calorie meal (subjects in this study only received Morphine ARER, not MS CONTIN).

Six studies—M-ARER-004, M-ARER-005, M-ARER-006, M-ARER -007, M-ARER-008, and M-ARER-012—were conducted as randomized, open-label, 2-way, 2-period, crossover designs in healthy, adult subjects. With the exception of Study M-ARER-005, the objective of each study was to compare the bioavailability and safety of Morphine ARER to MS CONTIN. The effects of the active pharmaceutical ingredient (API), morphine, in Morphine ARER and MS CONTIN were mitigated by naltrexone, which was administered orally before and after Morphine ARER or MS CONTIN were ingested within study periods. Hence, naltrexone was considered to be a study medication in addition to the Morphine ARER and MS CONTIN. Both agents were administered at 15 mg (Study M-ARER-007), 30 mg (Study M-ARER-012), and 100 mg (Study M-ARER-004, M-ARER-005, M-ARER-006, and M-ARER-008) per dose. In the multiple-dose studies (M-ARER-006 and M-ARER-008), subjects received Morphine ARER and MS CONTIN twice daily (bid) for 4.5 days, with a maximum of nine doses administered for each treatment group.

One additional clinical study was conducted, M-ARER-002, a double-blind, double-dummy randomized 4-way crossover study that was conducted as a PK and PD study in healthy subjects who were also experienced, nontherapeutic, recreational opioid users that were not opioid dependent. The design and subject population differed from all other studies, and the objective was to determine the human abuse potential of Morphine ARER versus MS CONTIN as evaluated by drug-liking after intranasal and oral administration and comparative PK after intranasal administration. Morphine ARER 60 mg or MS CONTIN 60 mg were crushed in order to mimic known conditions of abuse. Crushed intranasal and intact oral Morphine ARER were compared with the equivalent doses of crushed intranasal MS CONTIN and crushed intranasal placebo ARER tablet. The placebo ARER tablet had the same physical and chemical properties of the Morphine ARER tablets, but without the API. Thus, subjects received both oral and insufflated products during each of the four periods, as indicated in Table 1 Table of Clinical Studies.

The effects of tampering with Morphine ARER and MS CONTIN were evaluated with subjective drug measures such as the drug-liking and snorting experience. Each treatment period was separated by at least seven days. In order to determine the drug-liking effects of Morphine ARER, the effects of morphine were not mitigated by naltrexone in this study as in all the other studies that were conducted. Rather, subjects received naloxone, an opioid antagonist that was administered as an IV bolus in a challenge test to determine whether a subject exhibited signs of withdrawal after naloxone was administered (ie, opioid-dependence). Subjects who did not exhibit symptoms of withdrawal proceeded to a drug discrimination crossover test in which subjects received a single intranasal dose of morphine sulfate immediate-release or placebo. Each dose was separated by a 24-hour period. In the qualification stage of the study, subjects were required to distinguish immediate-release morphine sulfate from placebo before being randomized to treatment.

Integrated Data

The statistical analysis plan for the ISS summarizes studies by single-dose and multiple-dose, all active oral doses and active dosage forms as presented in table below.

Table 2 Safety Data Sets by Single-dose and Multiple-dose

Table 2. Summary of Studies in the Data Sets by Single-dose and Multiple-dose				
Treatment	**Single-dose Studies[a]**	**Multiple-dose 100-mg Studies[b]**	**All Active Oral Doses[c]**	**Active Dosage Forms[d]**
Morphine ARER	M-ARER-004 100 mg M-ARER-007 15 mg M-ARER-012 30 mg M-ARER-002 60 mg oral only	M-ARER-006 (9 doses) M-ARER-008 (9 doses)	M-ARER-004 100 mg M-ARER-005 100 mg (fasted, fed) M-ARER-007 15 mg M-ARER-012 30 mg M-ARER-002 60 mg (oral only) M-ARER-006 100 mg M-ARER-008 100 mg	M-ARER-004 100 mg M-ARER-005 100 mg (fasted, fed) M-ARER-007 15 mg M-ARER-012 30 mg M-ARER-002 60 mg (oral, insufflated) M-ARER-006 100 mg M-ARER-008 100 mg
MS CONTIN	M-ARER-004 100 mg M-ARER-007 15 mg M-ARER-012 30 mg	M-ARER-006 (9 doses) M-ARER-008 (9 doses)	M-ARER-004 100 mg M-ARER-007 15 mg M-ARER-012 30 mg M-ARER-006 100 mg M-ARER-008 100 mg	M-ARER-004 100 mg M-ARER-007 15 mg M-ARER-012 30 mg M-ARER-002 60 mg (insufflated) M-ARER-006 100 mg M-ARER-008 100 mg
Placebo	M-ARER-002	Not applicable	M-ARER-002	M-ARER-002

[a] = The study design included treatment with 1 dose of oral Morphine ARER (test) or MS CONTIN (reference) in Studies M-ARER-004, M-ARER-007, and M-ARER-012 and oral Morphine ARER only for M-ARER-002 and M-ARER-005.
[b] = The study design included treatment with up to 9 doses of oral Morphine ARER and MS CONTIN administered twice daily for 4.5 days in Studies M-ARER-006 and M-ARER-008.
[c] = All studies conducted with a single-dose, oral formulation of Morphine ARER or MS CONTIN.
[d] = All studies conducted with Morphine ARER or MS CONTIN product administered orally and intranasally.
Source: *ISS Statistical Analysis Plan.*

Source: Applicant's submission (ISS, Page 15)

In the single-dose studies, subjects received one dose of Morphine ARER or MS CONTIN at 15, 30, or 100 mg. Studies M-ARER-004, M-ARER-007, and M-ARER-012 are exclusively single-dose studies. In two additional single-dose studies, subjects received two doses of Morphine ARER, Study M-ARER-005 100 mg (administered in a fed and fasted state) and Study M-ARER-002 60 mg (oral and insufflated). Subjects in Study M-ARER-005 did not receive MS CONTIN and subjects in Study M-ARER-002 received one dose of insufflated, 60-mg MS CONTIN, one dose of insufflated 60-mg Morphine ARER, and one dose of oral 60-mg Morphine ARER. A placebo arm was also used in Study M-ARER-002, the only study with a placebo group, and subjects received crushed and insufflated placebo and oral placebo ARER. No oral MS CONTIN was administered in that study. One concentration of Morphine ARER or MS CONTIN, 100 mg bid, was used in the multiple-dose studies. A total of up to nine doses of each product were administered.

Standard evaluations were performed in all studies (ie, demographics and baseline characteristics, extent of exposure, concomitant medications, treatment-emergent AEs [TEAEs]). In Study M-ARER-002, all three treatment arms including placebo are presented in the summary table of AEs.

For the ISS, the safety population was defined as all enrolled and randomized subjects who received at least one dose of Morphine ARER or MS CONTIN. In Study M-ARER-002, the effects of morphine were not blocked with naltrexone before the administration of Morphine ARER or MS CONTIN; thus, the safety data, in which subjects were administered morphine ARER orally, were also considered relevant with respect to GI effects from the intended oral route of administration. In contrast, the safety population in all other clinical studies was defined as all subjects who received at least one dose of naltrexone. Consequently, the safety population in the individual clinical studies differed from that of the ISS population and the AEs in these studies were confounded by the presence of naltrexone. The AEs in M-ARER-002 were also confounded by the fact that in order to maintain the blind, subjects received both an oral and insufflated dose, such that in the oral Morphine ARER arm, subjects also insufflated a placebo that incorporated Applicant's abuse-deterrent technology. This addition most likely caused the high rate of nasal congestion associated with the oral administration of Morphine ARER seen in that study that was not noted in other trials. Moreover, AEs reported in this study are further confounded by the unintended route of administration (intranasal), which limits direct comparison.

7.1.2 Categorization of Adverse Events

The safety assessments in the Morphine ARER clinical development program includes physical examinations, vital signs, pulse oximetry, 12-lead ECGs, clinical laboratory tests (chemistry, hematology, and urinalysis), pregnancy tests, and AEs.

Adverse Events

An AE was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment.

An SAE was defined as any untoward medical occurrence that at any dose resulted in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This summary of safety presents the following information for the specified integration sets:

Table 3 Safety Populations

Table 2.7.4-4.	Safety Populations Used in Clinical Studies and the Integrated Summary of Safety
Study Number	**Definition**
M-ARER-004 M-ARER-005 M-ARER-006 M-ARER-007 M-ARER-008 M-ARER-012	Subjects who received at least 1 dose of naltrexone. If the subject vomited after naltrexone administration, they were withdrawn from the study and not randomized to Morphine ARER or MS CONTIN but are included in the safety population.
M-ARER-002	Subjects who received at least 1 dose of Morphine ARER or MS CONTIN. Naltrexone was not administered in this study.
Integrated Summary of Safety	Subjects who received naltrexone and at least 1 dose of Morphine ARER or MS CONTIN.
Source: Individual study reports.	

Source: Applicant's submission (Summary of Clinical Studies, Page 15)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

A total of 241 healthy adult subjects from six PK studies and one PD study were exposed to single (177 subjects) or multiple (64 subjects) doses of Morphine ARER, and 220 subjects were exposed to single (150 subjects) or multiple (70 subjects) doses of MS CONTIN.

After being randomized and treated, 39 subjects withdrew from treatment prematurely: 15 after treatment with Morphine ARER and 24 after treatment with MS CONTIN. In the single-dose studies, a total of 13 subjects withdrew; whereas, in the multiple-dose studies, 26 withdrew. The most common reasons for withdrawal (20 subjects) were TEAEs: seven treated with Morphine ARER and 13 treated with MS CONTIN. The second most common reason for withdrawal (nine subjects) was subject withdrawal consent: four subjects treated with Morphine ARER and five subjects treated with MS CONTIN. Other reasons for withdrawal were lost to follow-up (n = 5 subjects; two treated with MS CONTIN and three treated with Morphine ARER), protocol violations (n = 2; one withdrawn from each treatment group), and other (n = 3 treated with MS CONTIN [one subject was considered lost to follow-up in the individual study report]). No withdrawals for noncompliance were reported.

Of the 15 subjects treated with Morphine ARER who prematurely discontinued treatment, six withdrew from single-dose studies and nine withdrew from multiple-dose studies. The reasons for withdrawal included AE (seven subjects), subject withdrawal (four subjects), lost to follow-up (three subjects), and protocol violation (one subject with positive drug screen). For the two most common reasons for withdrawal, five of the seven subjects with AEs were treated with multiple doses of Morphine ARER. In contrast, three of the four subjects who voluntarily withdrew received single doses of Morphine ARER.

In all studies, subjects were exposed to between 15 and 900 mg of Morphine ARER or MS CONTIN. The extent of exposure to Morphine ARER or MS CONTIN in the pooled safety population for the integrated analysis is presented in the table below.

Table 4 Summary of Extent of Exposure

Table 4.	**Summary of Extent of Exposure to Morphine ARER and MS CONTIN (ISS, Safety Analysis Set)**					
	Multiple 100 mg Doses[a]		**All Active Oral Doses[b]**		**All Active Dosage Forms[c]**	
Dose	**MS CONTIN N = 70**	**Morphine ARER N = 64**	**MS CONTIN N = 193**	**Morphine ARER N = 241**	**MS CONTIN N = 220**	**Morphine ARER N = 241**
Mean ± SD (mg)	797.1 ± 241.96	840.6 ± 191.67	324.8 ± 386.75	280.7 ± 355.23	292.3 ± 372.45	287.2 ± 351.66
Min, Max (mg)	100, 900	100, 900	15, 900	15, 900	15, 900	15, 900

ISS = integrated summary of safety; max = maximum; min = minimum; SD = standard deviation.
[a] = Subjects were enrolled in two multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Morphine ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral or insufflated Morphine ARER and MS CONTIN.
Source: *Table ex_t001m*.

Source: Applicant's submission (ISS, Page 18)

In all studies, the mean Morphine ARER exposure for oral doses (281 mg) and for all formulations (287 mg) was slightly lower than the mean MS CONTIN exposure for oral doses (325 mg) and for all formulations (292 mg). In the multiple-dose studies, mean exposure for Morphine ARER (797 mg) and MS CONTIN (841 mg) was near the total administered doses possible (900 mg for nine doses). The number of subjects who were included in the safety population was higher for Morphine ARER than MS CONTIN

in the single-dose studies (177 vs 150) and lower in the multiple-dose studies (64 vs 70).

Naltrexone 50 mg was administered in all studies, with the exception of Study M-ARER-002, and was considered to be a study medication for the safety population of these clinical studies.

In single-dose studies, naltrexone 50 mg was administered approximately 12 hours and one hour before Morphine ARER or MS CONTIN and then again approximately 12 hours after administration of the Morphine ARER or MS CONTIN. In the multiple-dose studies, naltrexone 50 mg was administered approximately 12 hours before the first dose of test or reference product and then every 12 hours, until 12 hours after the last dose of Morphine ARER or MS CONTIN.

In all studies, the mean exposure for naltrexone was 498 mg in the Morphine ARER group and 524 mg in the MS CONTIN group. In the multiple-dose studies, mean exposure for naltrexone was 982 mg in the Morphine ARER group and 929 mg in the MS CONTIN group.

The number of subjects randomized to single- and multiple-doses of Morphine ARER and MS CONTIN by dose is presented in the table below.

Table 5 Summary of Subjects Randomized to Single-dose or Multiple-dose Morphine ARER or MS CONTIN by Dose

Table 6.	**Summary of Subjects Randomized to Single-dose or Multiple-dose Morphine ARER or MS CONTIN by Dose (ISS, Safety Analysis Set)**					
	Multiple 100-mg Doses[a]		**Active Oral Doses[b]**		**Active Dosage Forms[c]**	
Dose	**MS CONTIN N = 70 n (%)**	**Morphine ARER N = 64 n (%)**	**MS CONTIN N = 193 n (%)**	**Morphine ARER N = 241 n (%)**	**MS CONTIN N = 220 n (%)**	**Morphine ARER N = 241 n (%)**
Single-dose 1 Tablet						
15 mg	0	0	29 (15.0)	31 (12.9)	29 (13.2)	31 (12.9)
30 mg	0	0	42 (21.8)	41 (17.0)	42 (19.1)	41 (17.0)
60 mg	0	0	0	26 (10.8)	27 (12.3)	0
100 mg	1 (1.4)	2 (3.1)	53 (27.5)	54 (22.4)	53 (24.1)	54 (22.4)
Total	1 (1.4)	2 (3.1)	124 (64.2)	152 (63.1)	151 (68.6)	126 (52.3)
Multiple-dose Between 2 and 9 Tablets[d]						
120 mg	0	0	0	0	0	26 (10.8)

200 mg	5 (7.1)	1 (1.6)	5 (2.6)	28 (11.6)	5 (2.3)	28 (11.6)
300 mg	4 (5.7)	1 (1.6)	4 (2.1)	1 (0.4)	4 (1.8)	1 (0.4)
400 mg	1 (1.4)	1 (1.6)	1 (0.5)	1 (0.4)	1 (0.5)	1 (0.4)
500 mg	0	1 (1.6)	0	1 (0.4)	0	1 (0.4)
600 mg	0	0	0	0	0	0
700 mg	0	0	0	0	0	0
800 mg	0	0	0	0	0	0
900 mg	59 (84.3)	58 (90.6)	59 (30.6)	58 (24.1)	59 (26.8)	58 (24.1)

ISS = integrated summary of safety.
[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Study M-ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.
[d] = Subjects received 2 to 9 tablets in 100 mg in dose increments between 200 and 900 mg in Studies M-ARER-006 and M-ARER-008. In Study M-ARER-002, 26 subjects who received 120 mg received 2 doses of 60 mg of MS CONTIN, 1 ingested orally and 1 insufflated. In Study M-ARER-005, 27 subjects received 2 doses of 100 mg Morphine ARER in a fed and fasted state.
Source: *Table ex_t1001m* and *Table pa_t0001*.

Source: Applicant's submission (ISS, Page 20)

The total numbers from the single-dose studies included three additional subjects from the multiple-dose studies: two subjects treated with Morphine ARER and one subject treated with MS CONTIN, who withdrew after receiving one dose of Morphine ARER or MS CONTIN as indicated. Only one subject from Study M-ARER-005, who withdrew after one dose of MS CONTIN, is included in the single-dose section of the table above. The remaining subjects from Study M-ARER-005 each received a total of 200 mg of Morphine ARER, 100 mg after fasting and 100 mg after ingestion of a high-calorie meal, and are included in the multiple-dose portion of the table. Moreover, subjects inStudy M-ARER-002 received two doses of 60-mg Morphine ARER, one oral dose and one insufflated dose, and also appear in the multiple-dose section under active dosage forms of the table above. However, subjects from this study also appear in the single-dose section of the table under oral doses for Morphine ARER. Subjects treated with insufflated MS CONTIN appear in the single-dose section under active dosage forms.

In the multiple-dose studies, 64 subjects were treated with 100-mg Morphine ARER and 70 subjects were treated with 100-mg MS CONTIN; 53 subjects completed the studies. Fifty-eight subjects completed treatment with nine doses of Morphine ARER, and 59 subjects completed treatment with nine doses of MS CONTIN. Twenty-six subjects

withdrew before study completion. Of those that withdrew, six subjects withdrew from the study after receiving one to five doses of Morphine ARER, and 11 subjects withdrew after receiving one to four doses of MS CONTIN. An additional nine subjects withdrew after treatment completion with Morphine ARER or MS CONTIN. Reasons for withdrawal are presented in the subject disposition earlier.

Demographics

A summary of demographic characteristics for single-dose studies and multiple-dose and pooled data (safety population) are presented in the two tables below, respectively.

Table 6 Demographic by Dose in Single-dose Studies

Table 7. Summary of Demographic Characteristics by Dose in Single-dose Studies (ISS, Safety Analysis Set)

Variable Statistic/ Category	Placebo[a] N = 26 n (%)	MS CONTIN Oral Doses 15 mg N = 29 n (%)	MS CONTIN Oral Doses 30 mg N = 42 n (%)	MS CONTIN Oral Doses 100 mg N = 52 n (%)	MorphineARER Oral Doses 15 mg N = 31 n (%)	MorphineARER Oral Doses 30 mg N = 41 n (%)	MorphineARER Oral Doses 60 mg N = 26 n (%)	MorphineARER Oral Doses 100 mg N = 79 n (%)
Age (years)								
Mean ± SD	25.6 ± 6.66	30.3 ± 8.78	31.8 ± 6.76	34.1 ± 7.05	29.8 ± 8.74	32.0 ± 6.62	24.4 ± 3.66	33.9 ± 6.68
min, max	19, 53	19, 45	20, 44	23, 45	18, 45	20, 44	19, 31	22, 45
Sex n (%)								
Female	4 (15.4)	0	6 (14.3)	6 (11.5)	0	6 (14.6)	4 (15.4)	7 (8.9)
Male	22 (84.6)	29 (100)	36 (85.7)	46 (88.5)	31 (100)	35 (85.4)	22 (84.6)	72 (91.1)
Race n (%)								
American Indian/ Alaskan Native	0	1 (3.4)	0	0	1 (3.2)	0	0	1 (1.3)
Asian	0	1 (3.4)	1 (2.4)	0	1 (3.2)	1 (2.4)	0	1 (1.3)
Black/African American	0	13 (44.8)	14 (33.3)	27 (51.9)	15 (48.4)	14 (34.1)	1 (3.8)	40 (50.6)
Hawaiian/Pacific Islander	0	1 (3.4)	1 (2.4)	2 (3.8)	1 (3.2)	1 (2.4)	0	1 (1.3)
White	26 (100)	8 (27.6)	20 (47.6)	19 (36.5)	8 (25.8)	19 (46.3)	25 (96.2)	30 (38.0)
Other	0	5 (17.2)	6 (14.3)	4 (7.7)	5 (16.1)	6 (14.6)	0	6 (7.6)
Ethnicity n (%)								
Hispanic/Latino	6 (23.1)	5 (17.2)	3 (7.1)	4 (7.7)	5 (16.1)	3 (7.3)	6 (23.1)	4 (5.1)
Non-Hispanic/Latino	20 (76.9)	24 (82.8)	39 (92.9)	48 (92.3)	26 (83.9)	38 (92.7)	20 (76.9)	75 (94.9)

Source: Applicant's submission (ISS, Page 22)

Table 7 Demographic of Multiple-dose and Pooled Data

Table 8. Summary of Demographic Characteristics From Multiple-dose and Pooled Data (ISS, Safety Analysis Set)						
Variable Statistic/Category	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)	MS CONTIN N = 220 n (%)	Morphine ARER N = 241n (%)
	Multiple 100 mg Doses[a]		All Active Oral Doses[b]		All Active Dosage Forms[c]	
Age (years)						
Mean ± SD	30.2 ± 7.42	30.7 ± 7.27	31.6 ± 7.53	31.2 ± 7.38	30.8 ± 7.67	31.2 ± 7.38
min, max	18, 45	18, 45	18, 45	18, 45	18, 53	18, 45
Sex n (%)						
Female	9 (12.9)	8 (12.5)	21 (10.9)	25 (10.4)	25 (11.4)	25 (10.4)
Male	61 (87.1)	56 (87.5)	172 (89.1)	216 (89.6)	195 (88.6)	216 (89.6)
Race n (%)						
American Indian/ Alaskan Native	1 (1.4)	1 (1.6)	2 (1.0)	3 (1.2)	2 (0.9)	3 (1.2)
Asian	3 (4.3)	3 (4.7)	5 (2.6)	6 (2.5)	5 (2.3)	6 (2.5)
Black/African American	24 (34.3)	23 (35.9)	78 (40.4)	93 (38.6)	79 (35.9)	93 (38.6)
Hawaiian/ Pacific Islander	1 (1.4)	0	5 (2.6)	3 (1.2)	5 (2.3)	3 (1.2)
White	38 (54.3)	35 (54.7)	85 (44.0)	117 (48.5)	111 (50.5)	117 (48.5)
Other	0	0	15 (7.8)	17 (7.1)	15 (6.8)	17 (7.1)
Multiple	1 (1.4)	1 (1.6)	1 (0.5)	1 (0.4)	1 (0.5)	1 (0.4)
Missing	2 (2.9)	1 (1.6)	2 (1.0)	1 (0.4)	2 (0.9)	1 (0.4)
Ethnicity						
Hispanic/ Latino	10 (14.3)	9 (14.1)	22 (11.4)	27 (11.2)	28 (12.7)	27 (11.2)
Non-Hispanic/ Latino	60 (85.7)	55 (85.9)	171 (88.6)	214 (88.8)	192 (87.3)	214 (88.8)

ISS = integrated summary of safety; max = maximum; min = minimum; SD = standard deviation.
[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Morphine ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.
Source: *Table bc_t001m.*

Source: Applicant's submission (ISS, Page 23)

For all active dosage formulations in the pooled data, the mean (± SD) age of subjects who received Morphine ARER was 31.2 years and MS CONTIN was 30.8 years with a maximum age of 45 years for the Morphine ARER group and 53 years for the MS CONTIN group. In both the Morphine ARER and MS CONTIN groups, the majority of subjects were male (89.6% and 88.6%, respectively), white (48.5% and 50.5%,

respectively) or black (38.6% and 35.9%, respectively), and non-Hispanic or Latino (88.8% and 87.3%, respectively).

Baseline characteristics of height, weight, and body mass index values were similar between subjects treated with Morphine ARER and MS CONTIN in the single- and multiple-dose studies.

A summary of demographic characteristics for the safety population by healthy subjects versus opioid-experienced subjects is presented the table below.

Table 8 Demographic by Healthy and Opioid-Experienced Subjects

Table 9. Summary of Demographic Characteristics by Healthy and Opioid-Experienced Subjects (ISS, Safety Analysis Set)

	Healthy Subjects[a]			Opioid-Experienced Subjects[b]			Total
Variable Statistic/ Category	MS CONTIN N = 193	Morphine ARER N = 215	Total N = 235	MS CONTIN N = 27	Morphine ARER N = 26	Total N = 27	Total N = 262
Age (years)							
Mean ± SD	31.6 ± 7.53	32.0 ± 7.30	31.7 ± 7.41	25.4 ± 6.57	24.4 ± 3.66	25.4 ± 6.57	31.0 ± 7.56
min, max	18, 45	18, 45	18, 45	19, 53	19, 31	19, 53	18, 53
Sex n (%)							
Female	21 (10.9)	21 (9.8)	23 (9.8)	4 (14.8)	4 (15.4)	4 (14.8)	27 (10.3)
Male	172 (89.1)	194 (90.2)	212 (90.2)	23 (85.2)	22 (84.6)	23 (85.2)	235 (89.7)
Race n (%)							
American Indian/Alaskan Native	2 (1.0)	3 (1.4)	3 (1.3)	0	0	0	3 (1.1)
Asian	5 (2.6)	6 (2.8)	6 (2.6)	0	0	0	6 (2.3)
Black/African American	78 (40.4)	92 (42.8)	100 (42.6)	1 (3.7)	1 (3.8)	1 (3.7)	101 (38.5)
Hawaiian/Pacific Islander	5 (2.6)	3 (1.4)	5 (2.1)	0	0	0	5 (1.9)
White	85 (44.0	92 (42.8)	100 (42.6)	26 (96.3)	25 (96.2)	26 (96.3)	126 (48.1)
Other	15 (7.8)	17 (7.9)	18 (7.7)	0	0	0	18 (6.9)
Multiple	1 (0.5)	1 (0.5)	1 (0.4)	0	0	0	1 (0.4)
Missing	2 (1.0)	1 (0.5)	2 (0.9)	0	0	0	2 (0.8)
Ethnicity							
Hispanic/Latino	22 (11.4)	21 (9.8)	24 (10.2)	6 (22.2)	6 (23.1)	6 (22.2)	30 (11.5)
Non-Hispanic/Latino	171 (88.6)	194 (90.2)	211 (89.8)	21 (77.8)	20 (76.9)	21 (77.8)	232 (88.5)

ISS = integrated summary of safety; max = maximum; min = minimum; SD = standard deviation.
[a] = Healthy subjects were enrolled in all clinical studies. Subjects from M-ARER-002 were opioid-experienced subjects and are not included in this category.
[b] = Subjects in Study M-ARER-002 were opioid-experienced but not opioid-dependent.
Source: *Table bc_t001r.*

Source: Applicant's submission (ISS, Page 25)

7.2.2 Explorations for Dose Response

There were no specific studies designed to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology and Toxicology review by Dr. Carlic Huynh, PhD.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of Morphine ARER appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology review by Dr. Srikanth Nallani, PhD.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Study drug is a mu-opioid receptor agonist. Expected adverse events for the opioid component of the drug include those related to the central nervous system (i.e., sedation, dizziness, somnolence, headache, and respiratory depression), the gastrointestinal system (i.e. nausea, vomiting, and constipation) and other AEs such as pruritus and fatigue.

In general, the data collected allowed for adequate evaluation of the potential adverse events noted for similar drug classes.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died in the clinical development program for Morphine ARER.

7.3.2 Nonfatal Serious Adverse Events

No subject had nonfatal SAE except one subject who was treated with 15 mg study drug visited hospital ER with GI symptoms but not admitted as described follows:

Listing ae_d0003 Severe Treatment-Emergent Adverse Events: Safety Population

Subject ID	Treatment Group	Period	Coded Preferred Term Verbatim Term from CRF	Start Date/Time Day	Stop Date/Time Day	SAE	Sev	TEAE	Disc	Related	Outcome
M-ARER-007-20	15mg M-ARER	1	Abdominal pain ABDOMINAL CRAMPS (INTERMITTENT) (PAIN)	13:03 1	(b) (6) 09:00 6	Yes	Sev	Yes	No	Related	Comp Recovery

Note: CRF = case report form. insf = insufflated adminstration. M-ARER = morphine sulfate, abuse-resistant, extended-release (test product). MS Contin = morphine sulfate, controlled-release tablets (reference product). po = oral administration. SAE = serious adverse event. TEAE = treatment emergent adverse events. Disc = resulted in discontinuation of study medication. Start and Stop Day are calculated relative to the Date of First Dose in the Period (Day 1). Severity (Sev) is mild, moderate or severe. Outcome is completely recovered, recovered with sequelae, not recovered or death.

Source: Applicant's submission (ISS, Data Page 1)

In section 12.3.2, Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events, of the clinical study report for Study M-ARER-007,

information was provided on this subject. This and additional information on the subject from the subject's case report form and study listings are provided in the table below:

Subject: 20 (b) (6)
Treatment period: 1 (15 mg Morphine ARER)
Subject details: 27 years, male, Black, 71 inches, 172 pounds

Table 9 AEs for Subject 20 in Study M-ARER-007

Table 1.11.3-1. Adverse Events for Subject 20 in Study M-ARER-007						
Adverse Event (MedDRA Preferred Term)	**Onset**	**Severity**	**Relationship to Study Drug**	**Outcome**	**Action Taken**	**Serious Adverse Event?**
Abdominal cramps	(b) (6)	Severe	Remote	Resolved	Concomitant medication administered	Yes
Vomiting		Moderate	Probable	Resolved	Concomitant medication administered	Yes
Diarrhea		Moderate	Probable	Resolved	None	Yes
Nausea		Moderate	Probable	Resolved	Concomitant medication administered	Yes
Headache		Mild	Possible	Resolved	None	No
MedDRA = Medical Dictionary of Regulatory Activities.						
Source: *Listing 16.2.7 in Appendix 16.2.7 of Study M-ARER-007.*						

Source: Applicant's submission (Response to Request for Clinical Information)

The Applicant provided the narrative of the case as follows:

About 5.5 hours after dosing in period 1 with the test product, Subject 20 (b) (6) developed acute onset of abdominal pain, associated with nausea, vomiting, and diarrhea. As the abdominal cramping worsened, the subject became incontinent and soiled his clothing due to diarrhea. While being attended to by clinical staff, the subject independently contacted 911. EMS staff arrived and, simultaneously with the investigator, evaluated the subject. The subject desired further evaluation at the emergency room, and the subject was transported to the local emergency room.

The emergency room attending physician ordered hematology, general chemistry, urinalysis labs, and CT scan of abdomen/pelvis. Isovue (iopamidol) 100 mL IV was used as contrast agent for the CT scan. On this day, the subject was also given IV sodium chloride 0.9%, pantoprazole, morphine, ondansetron, and oral and IV

potassium. Via a telephone call, the emergency room physician reported to the investigator "normal" findings for the CT scan and low potassium in the laboratory tests. Final report findings on the CT scan were "nonspecific findings". The subject was discharged later the same day, about 8 hours after the onset of symptoms, with a diagnosis of nausea and abdominal pain. No clear etiology was determined. The subject was given dietary instructions and prescriptions for ondansetron and pantoprazole, which he reportedly did not take.

Three days later, the subject returned to the clinical facility for follow-up evaluation by the investigator. During this visit, the subject completed end-of-study laboratory and vital sign evaluations with no clinically significant findings. The adverse events (AE) of nausea, vomiting, and diarrhea had resolved, though mild abdominal pain reportedly persisted for an additional 2 days. All AEs had resolved by 5 days after dosing.

The Serious Adverse Experience Report was forwarded to the Chairman of the (b) (6) *and the sponsor within 24 hours of the reporting of the adverse events. A copy of the serious (SAE) report and follow-up is provided in the case report form for subject 20 (crf-* (b) (6) *in appendix 16.3) located in section 5.3.1.2.*

The subject was discontinued per protocol due to emesis within 12 hours of dosing. No pharmacokinetic blood samples were reported. Abdominal pain was the Medical Dictionary of Regulatory Activities (MedDRA) preferred term used in the listing of AEs by subject; however, the case report form included the descriptors "intermittent" and "pain". The subject had aspartate aminotransferase (AST; serum glutamic oxalo-acetic transaminase [SGOT]) value (51 IU/L) and white blood cell count (3.5 k/µL) that were out of range at screening on July 2, 2013, and blood urea nitrogen (BUN) value (6 mg/dL), red blood cell count (4.18 k/µL), hemoglobin (13.1 g/dL), and monocyte count (14.0 %) at early termination that were out of range; none of these were considered clinically significant.

Reviewer's comments:
This is a young man who developed GI symptoms and headache shortly after taking a 15 mg study product, and treated in hospital's emergency room, but not admitted to hospital. While the GI symptoms such as abdominal cramp, nausea, vomiting, and diarrhea may related to study product, the totality of presentation and imaging in emergency room don't suggest GI obstruction.

7.3.3 Dropouts and/or Discontinuations

In all studies, subjects were exposed to between 15 and 900 mg of Morphine ARER or MS CONTIN. In the single-dose studies, subjects received one dose of Morphine ARER or MS CONTIN at 15, 30, or 100 mg in Studies M-ARER-007, M-ARER-012, and M-ARER-004, respectively. In two additional single-dose studies, subjects received two

doses of Morphine ARER. In Study M-ARER-005, 100 mg was administered in a fed and fasted state, and in Study M-ARER-002, 60 mg was administered orally and intranasally. Subjects in Study M-ARER-005 did not receive MS CONTIN, and subjects in Study M-ARER-002 also received one dose of insufflated, 60 mg MS CONTIN but no oral MS CONTIN. In the multiple-dose studies, subjects were randomized to receive nine doses each of 100 mg Morphine ARER and MS CONTIN. Subject disposition for the safety population is presented in the table below.

Table 10 Subject Disposition

Table 3. Summary of Subject Disposition (ISS, Safety Analysis Set)

	Multiple 100-mg Doses[a]		All Active Oral Doses[b]		All Active Dosage Forms[c]	
Reasons for Withdrawal	**MS CONTIN N = 70 n (%)**	**Morphine ARER N = 64 n (%)**	**MS CONTIN N = 193 n (%)**	**Morphine ARER N = 241 n (%)**	**MS CONTIN N = 220 n (%)**	**Morphine ARER N = 241 n (%)**
Number (%) of subjects who withdrew from the study	17 (24.3)	9 (14.1)	22 (11.4)	15 (6.2)	24 (10.9)	15 (6.2)
AEs that led to withdrawal from the study[d]	11 (15.7)	5 (7.8)	13 (6.7)	7 (2.9)	13 (5.9)	7 (2.9)
TEAEs that led to withdrawal of study medication[d]	8 (11.4)	3 (4.7)	8 (4.1)	3 (1.2)	8 (3.6)	3 (1.2)
Protocol violation	1 (1.4)	1 (1.6)	1 (0.5)	1 (0.4)	1 (0.5)	1 (0.4)
Subject withdrawal	3 (4.3)	1 (1.6)	5 (2.6)	4 (1.7)	5 (2.3)	4 (1.7)
Lost to follow-up	2 (2.9)	2 (3.1)	2 (1.0)	3 (1.2)	2 (0.9)	3 (1.2)
Other	0	0	1 (0.5)	0	3 (1.4)	0

AE = adverse event; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.

[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.

[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Morphine ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.

[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.

[d] = Six subjects withdrew from a study but did not have study medication withdrawn recorded in the AE listing: 4 subjects in the single-dose studies (2 in Study M-ARER-004 and 2 in Study M-ARER-007) and 2 in the multiple-dose Study M-ARER-006. Three additional subjects in Study M-ARER-008 had AEs that occurred before the first dose of study drug was administered that led to withdrawal that were not considered to be treatment-emergent. These 9 subjects were counted in the AEs that led to withdrawal of the study but were not included in the TEAEs that led to withdrawal of study medication.

Source: *Table ds_t001s*, *Table ds_t001m*, *Table ae_t001s*, *Table ae_t001m*, *Listing ae_d0001*, *Listing ae_d0004*.

7.3.4 Significant Adverse Events

The Applicant presented safety data for TEAEs of special interest as discussed below in Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

Standardised MedDRA Queries (SMQ) Terms of Special Interest
Gastrointestinal side effects are a well-known and common adverse reaction to opioid drugs. Data from approved oral, ER, opioids suggests that the tablets may be associated with sticking to the esophageal mucosa and may result in GI obstruction, particularly in patients with GI abnormalities or previous GI surgery that may cause difficulty swallowing tablets, intestinal obstructions, or exacerbation of diverticulitis. Extended-release medications may also have an obstructive capability and are often contraindicated in patients with gastric disorders.

To capture events possibly associated with tablet stickiness, a search criterion from SMQs was used by the Sponsor. TEAEs belonging to the following sets of PTs were reported:

- GI hemorrhage SMQ
- GI obstruction SMQ
- GI perforation SMQ
- GI ulceration SMQ
- GI perforation, ulcer, hemorrhage, obstruction, nonspecific findings/procedures SMQ, plus
- Difficulty/pain with swallowing (any PT containing dysphagia or ondynophagia)
- Any other PT belonging to GI disorders SOC

The five SMQs define the higher level SMQ GI perforation, ulcer, hemorrhage, or obstruction. Summaries for TEAEs possibly associated with tablet stickiness were prepared and presented for single-dose; and multiple-dose and pooled studies in the tables below respectively.

Table 11 TEAES Possibly Associated with Tablet Stickiness in Single-dose Studies

Table 18. Summary of Treatment-emergent Adverse Events Possibly Associated with Table Stickiness in Single-dose Studies (ISS, Safety Analysis Set)								
		MS CONTIN Oral Doses			Morphine ARER Oral Doses			
System Organ Class Preferred Term	Placebo[a] N = 26 n (%)	15 mg N = 29 n (%)	30 mg N = 42 n (%)	100 mg N = 52 n (%)	15 mg N = 31 n (%)	30 mg N = 41 n (%)	60 mg N = 26 n (%)	100 mg N = 79 n (%)
Any subjects (%) with TEAEs in GI disorders SOC	2 (7.7)	3 (10.3)	4 (9.5)	7 (13.8)	5 (16.1)	5 (12.2)	8 (30.8)	8 (10.1)
GI perforation, ulcer, haemorrhage, obstruction, nonspecific findings procedures SMQ	0	0	0	1 (1.9)	0	0	0	1 (1.3)
Abdominal discomfort	0	0	0	1 (1.9)	0	0	0	1 (1.3)
Any TEAEs possibly associated with tablet stickiness[b]	2 (7.7)	3 (10.3)	4 (9.5)	8 (15.4)	5 (16.1)	5 (12.2)	8 (30.8)	9 (11.4)

Source: Applicant's submission (ISS, page 48)

Table 12 TEAEs Possibly Associated with Tablet Stickiness in Multiple-dose Studies and Pooled Data

Table 19. Summary of Treatment-emergent Adverse Events Possibly Associated with Table Stickiness in Multiple-dose Studies and Pooled Data (ISS, Safety Analysis Set)				
	Multiple 100-mg Doses[a]		All Active Oral Doses[b]	
System Organ Class Preferred Term	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)
All subjects (%) with TEAEs in GI disorders SOC	16 (22.9)	13 (20.3)	31 (16.1)	40 (16.6)
GI perforation, ulcer, haemorrhage, obstruction, nonspecific findings procedures SMQ	0	0	1 (0.5)	1 (0.4)
Abdominal discomfort	0	0	1 (0.5)	1 (0.4)
Any TEAEs possibly associated with tablet stickiness[c]	16 (22.9)	13 (20.3)	31 (16.1)	40 (16.6)

Source: Applicant's submission (ISS, page 49)

In the single-dose studies, two subjects, one treated with Morphine ARER (Study M-ARER-005) and one treated with MS CONTIN (Study M-ARER-004), had one event each of abdominal discomfort that was associated with the SMQ perforation, ulcer hemorrhage, obstruction, nonspecific findings/procedures in the SOC for GI disorders. The investigator considered both events to be related to treatment with naltrexone, not Morphine ARER or MS CONTIN. In the multiple-dose studies, no AEs under that SMQ were reported.

On the basis of the low number of TEAEs in the GI disorders SOC and the five SMQs defining GI perforation, ulcer, hemorrhage, or obstruction; the known relationship of the observed TEAEs to morphine sulfate; and the completed in vitro evaluation of physical characteristics of the tablet formulation, the Applicant believes that Morphine ARER will not have the same issues with tablet stickiness as seen by DAAAP for other products with similar types of excipients.

At the request of the Division, the Applicant provided the narrative of the case of abdominal pain treated with study drug as follows:

Subject 27 (b) (6) participated in Study M-ARER-005, a food-effect bioavailability study. The subject was naltrexone-blocked prior to receiving a single 100-mg M-ARER tablet during period 1 (fasted; August 17, 2012) of the study and a single 100-mg M-ARER tablet during period 2 (fed; August 24, 2012) of the study.
The timing of study medication administrations in period 1 (fasted) and period 2 (fed) were as follows:

	Dose Period 1	*Period 2*
First dose of naltrexone	*20:26 hour*	*20:26 hour*
Second dose of naltrexone	*06:56 hour*	*06:56 hour*
Randomization	*(B) Test = fasted*	*(A) Test = fed*
Morphine ARER dose	*08:26 hour*	*08:26 hour*
Post dose naltrexone	*20:26 hour*	*20:26 hour*

Source: 16.3 Case Report Forms in CSR Study M-ARER-005

The subject reported a single TEAE of upset stomach, which was assigned the MedDRA preferred term of abdominal discomfort, (08:43 hour) during period 2 of the study after receiving the second 100-mg Morphine ARER tablet at 08:26 hour. The upset stomach was resolved by 11:09 hour. This TEAE was not serious, mild in severity, and considered possibly related to the study drug, which could have included either naltrexone or Morphine ARER. No action was taken, a completed recovery was made, and the subject completed the study.
No TEAEs were reported during period 1 of the study. Period 2 of the study for this subject was the fed period. In the fed period of the study, starting approximately 30 minutes prior to administration of the test drug, the subject was required to consume a

standardized high fat (500 fat calories), high calorie (900 total calories) breakfast prior to dosing which consisted of:

- *2 eggs fried in butter, 2 strips of bacon*
- *2 slices of toast with butter*
- *4 oz of hash brown potatoes*
- *8 oz of whole milk*

Given the close association of the TEAE in occurrence to dosing in the fed arm of the study and that no TEAEs were reported for this subject in the fasted arm of the study it is considered that the AE of "upset stomach" (MedDRA preferred term of abdominal pain) was due to a combination of the known effects of the study treatments on the gastrointestinal tract and the nausea (upset stomach) associated with opioids and naltrexone, particularly when taken with food.
There were no protocol deviations with respect to subject 27. The subject had an out-of-range fasting glucose (58 mg/dL) at end-of-study that was not clinically significant. The test was not repeated. There were no clinically significant out-of-range vital signs. No rescue medications were administered and no concomitant medications were reported for this subject.

Finally, the Applicant made one correction as follows:

An error occurred in the body of the ISS report that was carried over to section 2.5 of the NDA. The sentence on page 50, second paragraph stating, "(t)he investigator considered both events to be related to treatment with naltrexone…" should have been omitted. The tables and listing included in the ISS (including Table 18), correctly associated the event with the appropriate study treatment (eg, Morphine ARER or MS CONTIN).

Reviewer's comments on TEAEs and SMQ Terms of Special Interest:
In single dose studies, one subject treated with study drug and one with MS Contin developed abdominal discomfort that fit SMQ terms. While both considered to be related to study drug or MS Contin, the overall clinical presentation in the case treated with the study drug does not suggest GI obstruction.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events for all clinical studies was GI, which have been discussed in Section 7.3.5.

<u>Overall TEAEs:</u>

Table 13 TEAEs by Dose in Single-Dose Studies

Table 10. Summary of Treatment-emergent Adverse Events by Dose in Single-Dose Studies (ISS, Safety Analysis Set)

Subjects	Placebo[a] N = 26 n (%)	MS CONTIN Oral Doses 15 mg N = 29 n (%)	MS CONTIN Oral Doses 30 mg N = 42 n (%)	MS CONTIN Oral Doses 100 mg N = 52 n (%)	Morphine ARER Oral Doses 15 mg N = 31 n (%)	Morphine ARER Oral Doses 30 mg N = 41 n (%)	Morphine ARER Oral Doses 60 mg N = 26 n (%)	Morphine ARER Oral Doses 100 mg N = 79 n (%)
TEAEs	11 (42.3)	7 (24.1)	9 (21.4)	17 (32.7)	7 (22.6)	6 (14.6)	18 (69.2)	22 (27.8)
Drug-related TEAEs	11 (42.3)	5 (17.2)	8 (19.0)	16 (30.8)	7 (22.6)	6 (14.6)	17 (65.4)	18 (22.8)
Severe AEs	0	0	0	0	1 (3.2)	0	0	0
Serious AEs	0	0	0	0	1 (3.2)	0	0	0
AEs that led to withdrawal from the study[b]	0	1 (3.4)	0	1 (1.9)	1 (3.2)	0	0	1 (1.3)
TEAEs that led to withdrawal of study medication[b]	0	0	0	0	0	0	0	0

AE = adverse event; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.
[a] = Placebo refers to oral placebo/insufflated placebo treatment in M-ARER-002.
[b] = Four subjects withdrew from a study but did not have study medication withdrawn recorded in the AE listing: 4 subjects in the single-dose studies (2 in Study M-ARER-004 and 2 in Study M-ARER-007). These subjects were counted in the AEs that led to withdrawal of the study but were not included in the TEAEs that led to withdrawal of the study medication.
Source: *Table ae_t001s*, *Table ds_t001s*, *Listing ae_d0001*, *Listing ae_d0002*, *Listing ae_d0003*, *Listing ae_d0004*.

Source: Applicant's submission (ISS, page 28)

Table 14 TEAEs in Multiple-dose and Pooled Data

Table 11. Summary of Treatment-emergent Adverse Events in Multiple-dose and Pooled Data (ISS, Safety Analysis Set)						
	Multiple 100-mg Doses[a]		**All Active Oral Doses[b]**		**All Active Dosage Forms[c]**	
Subjects	**MS CONTIN N = 70 n (%)**	**Morphine ARER N = 64 n (%)**	**MS CONTIN N = 193 n (%)**	**Morphine ARER N = 241 n (%)**	**MS CONTIN N = 220 n (%)**	**Morphine ARER N = 241 n (%)**
TEAEs	20 (28.6)	17 (26.6)	53 (27.5)	70 (29.0)	66 (30.0)	74 (30.7)
Drug-related TEAEs	18 (25.7)	13 (20.3)	47 (24.4)	61 (25.3)	60 (27.3)	65 (27.0)
Severe AEs	0	0	0	1 (0.4)	0	1 (0.4)
Serious AEs	0	0	0	1 (0.4)	0	1 (0.4)
Drug-related severe, AEs	0	0	0	1 (0.4)	0	1 (0.4)
Drug-related, serious, AEs	0	0	0	1 (0.4)	0	1 (0.4)
AEs that led to withdrawal from the study[d]	11 (15.7)	5 (7.8)	13 (6.7)	7 (2.9)	13 (5.9)	7 (2.9)
TEAEs that led to withdrawal of study medication[d]	8 (11.4)	3 (4.7)	8 (4.1)	3 (1.2)	8 (3.6)	3 (1.2)
Drug-related TEAEs that led to withdrawal of study medication	7 (10.0)	3 (4.7)	7 (3.6)	3 (1.2)	7 (3.2)	3 (1.2)

AE = adverse event; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.
[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Study M-ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.
[d] = Six subjects withdrew from a study but did not have study medication withdrawn recorded in the AE listing: 4 subjects in the single-dose studies (2 in Study M-ARER-004 and 2 in Study M-ARER-007) and 2 in the multiple-dose study M-ARER-006. Three additional subjects in Study M-ARER-008 had AEs that led to withdrawal that occurred before the first dose of study drug was administered that were not considered to be treatment-emergent. These 9 subjects were counted in the AEs that led to withdrawal of the study but were not included in the TEAEs that led to withdrawal of study medication.
Sources: *Table ae_t001m*, *Table ds_t001m*, *Listing ae_d0001*, *Listing ae_d0002*, *Listing ae_d0003*, *Listing ae_d0004* .

Source: Applicant's submission (ISS, page 29)

SOC and PT

Summaries of TEAEs by SOC and PT that occurred in more than one subject per category for the single-dose studies and for the multiple-dose and pooled studies are presented in next two tables.

If an SOC had more than one subject per category but no individual PT occurred in more than one subject, it was not included in these tables.

Table 15 TEAEs by SOC and PT in Single-dose Studies

Table 12. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term that Occurred in More than 1 Subject in Single-dose Studies (ISS, Safety Analysis Set)

System Organ Class Preferred Term	Placebo[a] N = 26 n (%)	MS CONTIN Oral Doses 15 mg N = 29 n (%)	 30 mg N = 42 n (%)	 100 mg N = 52 n (%)	Morphine ARER Oral Doses 15 mg N = 31 n (%)	 30 mg N = 41 n (%)	 60 mg N = 26 n (%)	 100 mg N = 79 n (%)
Number (%) of subjects with a TEAE	11 (42.3)	7 (24.1)	9 (21.4)	17 (32.7)	7 (22.6)	6 (14.6)	18 (69.2)	22 (27.8)
Gastrointestinal disorders	2 (7.7)	3 (10.3)	4 (9.5)	8 (15.4)	5 (16.1)	5 (12.2)	8 (30.8)	9 (11.4)
Nausea	2 (7.7)	1 (3.4)	2 (4.8)	4 (7.7)	5 (16.1)	4 (9.8)	8 (30.8)	6 (7.6)
Vomiting	0	2 (6.9)	0	1 (1.9)	1 (3.2)	0	2 (7.7)	2 (2.5)
Abdominal pain	0	1 (3.4)	2 (4.8)	1 (1.9)	1 (3.2)	0	0	0
General disorders and administration site conditions	0	0	3 (7.1)	1 (1.9)	0	0	0	2 (2.5)
Fatigue	0	0	3 (7.1)	0	0	0	0	1 (1.3)
Investigations	0	1 (3.4)	2 (4.8)	4 (7.7)	0	0	0	7 (8.9)
Blood glucose increased	0	0	0	0	0	0	0	3 (3.8)
Blood pressure decreased	0	0	0	2 (3.8)	0	0	0	2 (2.5)
Nervous system disorders	1 (3.8)	3 (10.3)	1 (2.4)	5 (9.6)	3 (9.7)	3 (7.3)	0	9 (11.4)
Somnolence	0	2 (6.9)	0	3 (5.8)	0	0	0	7 (8.9)
Dizziness	0	0	0	1 (1.9)	0	2 (4.9)	0	2 (2.5)
Headache	1 (3.8)	1 (3.4)	1 (2.4)	0	2 (6.5)	0	0	2 (2.5)
Renal and urinary disorders	0	2 (6.9)	0	0	0	0	0	0
Pollakiuria	0	2 (6.9)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	9 (34.6)	0	0	0	0	0	12 (46.2)	0
Nasal congestion	8 (30.8)	0	0	0	0	0	9 (34.6)	0
Nasal discharge discolouration	1 (3.8)	0	0	0	0	0	2 (7.7)	0
Rhinorrhoea	0	0	0	0	0	0	3 (11.5)	0
Skin and subcutaneous tissue disorder	0	0	0	0	1 (3.2)	0	3 (11.5)	1 (1.3)
Pruritus generalized	0	0	0	0	0	0	2 (7.7)	0

ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.
[a] = Placebo refers to oral placebo/insufflated placebo treatment in M-ARER-002.
Source: *Table ae_t002s.*

Source: Applicant's submission (ISS, page 31)

Table 16 TEAEs by SOC and PT in Multiple Dose Studies and Pooled Data

Table 13. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term that Occurred in More Than 1 Subject in Multiple-dose and Pooled Data (ISS, Safety Analysis Set)

	Multiple 100-mg Doses[a]	All Active Oral Doses[b]	All Active Dosage Forms[c]

System Organ Class Preferred Term	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)	MS CONTIN N = 220 n (%)	Morphine ARER N = 241 n (%)
Number (%) of subjects with a TEAE	20 (28.6)	17 (26.6)	53 (27.5)	70 (29.0)	66 (30.0)	74 (30.7)
Eye disorders	1 (1.4)	1 (1.6)	1 (0.5)	2 (0.8)	1 (0.5)	2 (0.8)
Vision blurred	1 (1.4)	1 (1.6)	1 (0.5)	2 (0.8)	1 (0.5)	2 (0.8)
Gastrointestinal disorders	16 (22.9)	13 (20.3)	31 (16.1)	40 (16.6)	39 (17.7)	44 (18.3)
Nausea	13 (18.6)	11 (17.2)	20 (10.4)	34 (14.1)	27 (12.3)	37 (15.4)
Vomiting	6 (8.6)	2 (3.1)	9 (4.7)	7 (2.9)	14 (6.4)	9 (3.7)
Constipation	3 (4.3)	2 (3.1)	4 (2.1)	2 (0.8)	4 (1.8)	2 (0.8)
Dyspepsia	1 (1.4)	1 (1.6)	1 (0.5)	2 (0.8)	2 (0.9)	2 (0.8)
Abdominal pain	0	0	4 (2.1)	1 (0.4)	4 (1.8)	1 (0.4)
Abdominal pain upper	0	0	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)
General disorders and administration site conditions	1 (1.4)	1 (1.6)	5 (2.6)	3 (1.2)	6 (2.7)	3 (1.2)
Fatigue	0	0	3 (1.6)	1 (0.4)	3 (1.4)	1 (0.4)
Investigations	0	0	7 (3.6)	7 (2.9)	7 (3.2)	7 (2.9)
Blood glucose increased	0	0	0	3 (1.2)	0	3 (1.2)
Blood pressure decreased	0	0	2 (1.0)	2 (0.8)	2 (0.9)	2 (0.8)
Metabolism and nutrition disorders	1 (1.4)	0	2 (1.0)	0	2 (0.9)	0
Decreased appetite	1 (1.4)	0	2 (1.0)	0	2 (0.9)	0
Nervous system disorder	7 (10.0)	7 (10.9)	16 (8.3)	22 (9.1)	18 (8.2)	23 (9.5)
Headache	4 (5.7)	5 (7.8)	6 (3.1)	9 (3.7)	7 (3.2)	9 (3.7)
Somnolence	0	1 (1.6)	5 (2.6)	8 (3.3)	5 (2.3)	8 (3.3)
Dizziness	3 (4.3)	0	4 (2.1)	4 (1.7)	4 (1.8)	4 (1.7)
Tremor	0	0	0	2 (0.8)	0	2 (0.8)

Table 13. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term that Occurred in More Than 1 Subject in Multiple-dose and Pooled Data (ISS, Safety Analysis Set)

	Multiple 100-mg Doses[a]	All Active Oral Doses[b]	All Active Dosage Forms[c]

System Organ Class Preferred Term	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)	MS CONTIN N = 220 n (%)	Morphine ARER N = 241 n (%)
Psychiatric disorders	3 (4.3)	0	4 (2.1)	2 (0.8)	5 (2.3)	2 (0.8)
Insomnia	2 (2.9)	0	2 (1.0)	0	2 (0.9)	0
Renal and urinary disorders	1 (1.4)	0	3 (1.6)	0	3 (1.4)	0
Pollakiuria	0	0	2 (1.0)	0	2 (0.9)	0
Respiratory, thoracic, and mediastinal disorders	0	2 (3.1)	0	14 (5.8)	1 (0.5)	22 (9.1)
Nasal congestion	0	0	0	9 (3.7)	1 (0.5)	16 (6.6)
Epistaxis	0	1 (1.6)	0	1 (0.4)	0	4 (1.7)
Rhinorrhoea	0	0	0	3 (1.2)	0	3 (1.2)
Nasal discharge discolouration	0	0	0	2 (0.8)	0	2 (0.8)
Skin and subcutaneous tissue disorder	1 (1.4)	0	1 (0.5)	5 (2.1)	6 (2.7)	6 (2.5)
Pruritus generalized	0	0	0	2 (0.8)	4 (1.8)	3 (1.2)
Pruritus	1 (1.4)	0	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)

AE = adverse event; ISS = integrated summary of safety; TEAE = treatment-emergent adverse event.
[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Morphine ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.
Source: *Table ae_t002m*.

Source: Applicant's submission (ISS, pages 33-34)

Nearly one-third of subjects treated with active oral or insufflated formulations experienced TEAEs: 30.7% (74/241) for Morphine ARER and 30% (66/220) for MS CONTIN. Similar numbers of TEAEs were reported in the oral dose formulations of Morphine ARER and MS CONTIN: 29.0% (70/241) and 27.5% (53/193), respectively. Regardless of whether the studies were single-dose, multiple-dose, or the data from these studies were pooled, the most common SOC was GI disorders, and the most

common AE was nausea. The second most common was nervous system disorders, and the most common AEs were somnolence (single-dose studies), and headache (multiple-dose and pooled studies). Most TEAEs were considered to be related to treatment.

In all single-dose studies, the greatest number of TEAEs occurred in the GI disorders SOC: 15.3% of subjects (27/177) treated with oral Morphine ARER, 12.2% of subjects (15/123) treated with oral MS CONTIN, and 7.7% of subjects (2/26) treated with placebo. Within this SOC, the most common TEAEs by preferred term (PT) were nausea and vomiting experienced by 23 (13.0%) and five (2.8%) subjects treated with Morphine ARER, seven (5.7%) and three (2.4%) subjects treated with MS CONTIN, and two (7.7%) and 0 subjects treated with placebo, respectively. The next most common SOC for TEAEs was nervous system disorders. A total of 15 subjects (8.5%) treated with Morphine ARER and nine subjects (7.3%) treated with MS CONTIN experienced TEAEs in this SOC. The most common AEs by PT were somnolence, dizziness, and headache experienced by seven (4.0%), 4 (2.3%), and four (2.3%) subjects treated with Morphine ARER, respectively; by five (4.1%), one (0.8%), and two (1.6%) subjects treated with MS CONTIN, respectively; and by 0, 0, and one (3.8%) subject treated with placebo, respectively.

In the single-dose studies, subjects enrolled in Study M-ARER-002 experienced the greatest number of TEAEs: 18 subjects (69.2%) treated with oral Morphine ARER 60-mg group followed by 11 subjects (42.3%) from the oral placebo group. However, only oral formulations are reported in Table 12; hence, TEAEs that occurred with insufflated Morphine or MS CONTIN from Study M-ARER-002 were not presented in this table.

In the multiple-dose studies (pooled data), the greatest number of TEAEs also occurred in the GI disorders SOC: 13 subjects (20.3%) treated with Morphine ARER and 16 subjects (22.9%) treated with MS CONTIN. Within this SOC, the most common TEAEs by PT were nausea and vomiting experienced by 11 (17.2%) and two subjects (3.1%) treated with Morphine ARER,13 (18.6%) and six subjects (8.6%) treated with MS CONTIN, respectively. The nervous system disorders SOC also had the next highest number of TEAEs, seven subjects from both treatment groups. The most common TEAE in that SOC was headache with five subjects (7.8%) treated with Morphine ARER and four subjects (5.7%) treated with MS CONTIN.

In the pooled studies for all active and oral dosage forms, over half of all TEAEs were reported in the GI disorders SOC. For all active dosage forms, TEAEs from this SOC were reported for 44 of 241 subjects (18.3%) in the Morphine ARER treatment group and 39 of 220 subjects (17.7%) in the MS CONTIN treatment group. For all active oral dosage forms, TEAEs from the GI disorders SOC were reported for 40 of 241 subjects (16.6%) in the Morphine ARER treatment group and 31 of 193 subjects (16.1%) in the MS CONTIN treatment group. The most common TEAE by PT in this SOC was nausea, which was reported at a similar incidence rate in subjects receiving all active

dosage formulations of Morphine ARER and MS CONTIN (15.4% and 12.3%, respectively) and in all oral formulations (14.1% and 10.4%, respectively). Vomiting was the second most common AE by PT in this SOC in the GI disorders SOC, with a similar incidence rate reported for active dosage formulations of Morphine ARER and MS CONTIN (3.7% and 6.4%, respectively) and in oral formulations (2.9% and 4.7%, respectively). All AEs of vomiting and all but one event of nausea (subject treated with oral Morphine ARER in Study M-ARER-002) were considered to be drug related.

In the pooled studies, the second most common TEAEs were reported in the nervous system disorders SOC. For all active dosage forms, TEAEs in this SOC were reported for 23 subjects (9.5%) in the Morphine ARER treatment group and 18 subjects (8.2%) in the MS CONTIN treatment group. For all active oral dosage forms, TEAEs in this SOC were reported for 22 subjects (9.1%) in the Morphine ARER treatment group and 16 subjects (8.3%) in the MS CONTIN treatment group. The most common TEAE by PT in the nervous system disorders SOC was headache, which was reported at a similar incidence rate in subjects receiving all active dosage formulations of Morphine ARER and MS CONTIN (3.7% and 3.2%, respectively) and in oral formulations (3.7% and 3.1%, respectively). Somnolence was the second most common AE by PT reported in this SOC, with a similar incidence rate reported in subjects receiving all active dosage formulations of Morphine ARER and MS CONTIN (3.3% and 2.3%, respectively) and in oral formulations (3.3% and 2.6%, respectively).

A summary of TEAEs by SOC and PT that occurred in more than one subject per category for healthy subjects and opioid-experienced subjects is presented in table below.

Table 17 TEAEs by SOC and PT in Healthy and Opioid-experienced Subjects

Table 14. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term that Occurred in More Than 1 Healthy and Opioid-Experienced Subject (ISS, Safety Analysis Set)

	Healthy Subjects[a]			Opioid-Experienced Subjects[b]			Overall Total
System Organ Class Preferred Term	MS CONTIN N = 193	Morphine ARER N = 215	Total N = 235	MS CONTIN N = 27	Morphine ARER N = 26	Total N = 27	Overall Total N = 262
Number (%) of subjects with a TEAE	53 (27.5)	52 (24.2)	89 (37.9)	13 (48.1)	22 (84.6)	26 (96.3)	115 (43.9)
Eye disorders	1 (0.5)	2 (0.9)	3 (1.3)	0	0	0	3 (1.1)
Vision blurred	1 (0.5)	2 (0.9)	3 (1.3)	0	0	0	3 (1.1)
Gastrointestinal disorders	31 (16.1)	32 (14.9)	55 (23.4)	8 (29.6)	12 (46.2)	16 (59.3)	71 (27.1)
Nausea	20 (10.4)	26 (12.1)	39 (16.6)	7 (25.9)	11 (42.3)	15 (55.6)	54 (20.6)
Vomiting	9 (4.7)	5 (2.3)	14 (6.0)	5 (18.5)	4 (15.4)	6 (22.2)	20 (7.6)
Abdominal pain	4 (2.1)	1 (0.5)	5 (2.1)	0	0	0	5 (1.9)
Constipation	4 (2.1)	2 (0.9)	5 (2.1)	0	0	0	5 (1.9)
Dyspepsia	1 (0.5)	2 (0.9)	3 (1.3)	1 (3.7)	0	1 (3.7)	4 (1.5)
Abdominal discomfort	1 (0.5)	1 (0.5)	2 (0.9)	0	0	0	2 (0.8)
Abdominal pain upper	1 (0.5)	1 (0.5)	1 (0.4)	1 (3.7)	0	1 (3.7)	2 (0.8)
General disorders and administration site conditions	5 (2.6)	3 (1.4)	6 (2.6)	1 (3.7)	0	1 (3.7)	7 (2.7)
Fatigue	3 (1.6)	1 (0.5)	4 (1.7)	0	0	0	4 (1.5)
Investigations	7 (3.6)	7 (3.3)	13 (5.5)	0	0	0	13 (5.0)
Blood glucose increased	0	3 (1.4)	3 (1.3)	0	0	0	3 (1.1)
Blood pressure decreased	2 (1.0)	2 (0.9)	3 (1.3)	0	0	0	3 (1.1)
Blood pressure increased	1 (0.5)	1 (0.5)	2 (0.9)	0	0	0	2 (0.8)
Metabolic and nutrition disorders	2 (1.0)	0	2 (0.9)	0	0	0	2 (0.8)
Decreased appetite	2 (1.0)	0	2 (0.9)	0	0	0	2 (0.8)
Nervous system disorders	16 (8.3)	22 (10.2)	35 (14.9)	2 (7.4)	1 (3.8)	4 (14.8)	39 (14.9)
Headache	6 (3.1)	9 (4.2)	13 (5.5)	1 (3.7)	0	2 (7.4)	15 (5.7)
Somnolence	5 (2.6)	8 (3.7)	13 (5.5)	0	0	0	13 (5.0)

Table 14. Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term that Occurred in More Than 1 Healthy and Opioid-Experienced Subject (ISS, Safety Analysis Set)

	Healthy Subjects[a]			Opioid-Experienced Subjects[b]			Overall Total
System Organ Class Preferred Term	MS CONTIN N = 193	Morphine ARER N = 215	Total N = 235	MS CONTIN N = 27	Morphine ARER N = 26	Total N = 27	Overall Total N = 262
Dizziness	4 (2.1)	4 (1.9)	8 (3.4)	0	0	0	8 (3.1)
Lethargy	1 (0.5)	1 (0.5)	2 (0.9)	0	0	0	2 (0.8)
Sinus headache	0	0	0	1 (3.7)	1 (3.8)	2 (7.4)	2 (0.8)
Tremor	0	2 (0.9)	2 (0.9)	0	0	0	2 (0.8)
Psychiatric disorders	4 (2.1)	2 (0.9)	5 (2.1)	1 (3.7)	0	1 (3.7)	6 (2.3)
Insomnia	2 (1.0)	0	2 (0.9)	0	0	0	2 (0.8)
Renal & urinary disorders	3 (1.6)	0	3 (1.3)	0	0	0	3 (1.1)
Pollakiuria	2 (1.0)	0	2 (0.9)	0	0	0	2 (0.8)
Respiratory, thoracic and mediastinal disorders	0	2 (0.9)	2 (0.9)	1 (3.7)	20 (76.9)	23 (85.2)	25 (9.5)
Nasal congestion	0	0	0	1 (3.7)	16 (61.5)	21 (77.8)	21 (8.0)
Epistaxis	0	1 (0.5)	1 (0.4)	0	3 (11.5)	3 (11.1)	4 (1.5)
Nasal discharge discolouration	0	0	0	0	2 (7.7)	3 (11.1)	3 (1.1)
Rhinorrhoea	0	0	0	0	3 (11.5)	3 (11.1)	3 (1.1)
Skin and subcutaneous tissue disorders	1 (0.5)	2 (0.9)	3 (1.3)	5 (18.5)	4 (15.4)	7 (25.9)	10 (3.8)
Pruritus generalized	0	0	0	4 (14.8)	3 (11.5)	7 (25.9)	7 (2.7)
Pruritus	1 (0.5)	0	1 (0.4)	1 (3.7)	1 (3.8)	2 (7.4)	3 (1.1)

Source: Applicant's submission (ISS, pages 37-38)

Overall, opioid-experienced subjects who were treated with Morphine ARER and MS CONTIN had a TEAE incidence rate of 96.3%, over twice the rate observed in healthy subjects (37.9%), even though healthy subjects also received naltrexone. After Morphine ARER treatment, the incidence rate of TEAEs was 84.6%, and after MS CONTIN, it was 48.1%. This increase in TEAEs was expected because subjects in this study received two doses of Morphine ARER administered both orally and intranasally compared with one dose of MS CONTIN administered intranasally.

Between healthy and opioid-experienced subjects, the incidence rate for TEAEs was similar in most SOCs. However, higher incidence rates in the opioid-experienced group were apparent in three SOCs: GI disorders; respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders. Moreover, higher incidence rates in the respiratory, thoracic, and mediastinal disorders group were more prevalent in the Morphine ARER group than the MS CONTIN group. Incidence rates in the GI disorders SOC for subjects who received Morphine ARER were approximately twice the rate observed for subjects who received MS CONTIN in the opioid-experienced treatment groups. This result is because subjects received two doses of Morphine ARER versus one dose of MS CONTIN. Incidence rates in the skin and subcutaneous tissue disorders SOC were similar even though opioid-experienced subjects received twice as much Morphine ARER.

Unlike the results from the single-dose, multiple-dose, and pooled studies, the highest incidence rate of TEAEs was reported in the respiratory, thoracic, and mediastinal disorders SOC for opioid-experienced subjects. Note that all subjects received insufflated study medication in all four treatment arms and received insufflated ARER (active and placebo) in three groups (Morphine ARER oral and insufflated and placebo) with the highest incidence of TEAEs reported in this SOC. Subjects in other studies only received oral MS CONTIN or Morphine ARER. Overall, 23 of 27 opioid-experienced subjects (85.2%) reported respiratory, thoracic, and mediastinal disorders and all but one AE were attributed to Morphine ARER treatment (76.9%, 20/26). Subjects who received insufflated placebo ARER also reported a higher incidence of TEAEs in this SOC, 34.6%. The most common AE by PT was nasal congestion reported in 16 opioid-experienced subjects (61.5%) treated with Morphine ARER, one subject (3.7%) treated with insufflated MS CONTIN, and eight subjects (30.8%) treated with placebo ARER. Other TEAEs reported in opioid-experienced subjects treated with Morphine ARER were epistaxis (11.5%), nasal discharge discoloration (7.7%), rhinorrhea (11.5%), hiccups (3.8%), and sneezing (3.8%). Placebo ARER-treated subjects also reported nasal discharge discoloration (3.8%). Healthy subjects who received Morphine ARER and MS CONTIN orally and were naltrexone-blocked infrequently reported TEAEs in this SOC: two subjects (0.9%), one each with epistaxis and oropharyngeal pain, both treated with Morphine ARER, and 0 subjects treated with MS CONTIN.

Because the mode of administration for placebo and Morphine ARER in Study M-ARER-002 was a combination of intranasal and oral ingestion, the ARER formulation of inactive excipients may be the cause of the irritation to the nasal passages. This phenomenon was not observed with MS CONTIN; thus, the excipients within MS CONTIN do not seem to cause irritation. This irritant feature may help to serve as a deterrent of nasal manipulation by potential abusers of Morphine ARER.

Gastrointestinal disorders were the next most common SOC in opioid-experienced subjects, with a total of 16 subjects (59.3%) who reported AEs: 12 subjects (46.2%) treated with Morphine ARER and 8 subjects (29.6%) treated with MS CONTIN. Adverse events from this SOC were lower in 55 healthy subjects overall (23.4%) and comparable between treatment groups: 31 subjects treated with Morphine ARER (14.9%) and 32 subjects treated with MS CONTIN (16.1%). Subjects who were opioid-experienced received two doses of Morphine ARER (oral and insufflated) compared with one dose of MS CONTIN (insufflated). This dosing regimen may have accounted for the higher incidence of GI disorders observed with Morphine ARER.

Opioid-experienced subjects also reported a higher incidence rate of AEs in the skin and subcutaneous tissue disorders SOC, with PTs pruritus generalized and pruritus. Overall, seven opioid-experienced subjects (25.9%) reported AEs: four subjects (15.4%) treated with Morphine ARER and 5 subjects (18.5%) treated with MS CONTIN. This incidence rate was higher than the rate observed in healthy subjects overall (1.3%; three subjects), which included two subjects (0.9%) treated with Morphine ARER and one subject (0.5%) treated with MS CONTIN.

TEAEs related to Naltrexone, Morphine ARER and MS Contin:

A summary of related TEAEs by SOC and PT that occurred in more than one subject per category for the single-dose, multiple-dose, and pooled studies are presented in next two tables. These TEAEs were considered to have a possible, probable, or definite relationship to naltrexone, Morphine ARER, or MS CONTIN.

Table 18 TEAEs related to Naltrexone, Morphine ARER or MS Contin by SOC and PT in Single-dose Studies

Table 15. Summary of Treatment-emergent Adverse Events Related to Naltrexone, Morphine ARER or MS CONTIN by System Organ Class and Preferred Term that Occurred in More than 1 Subject in Single-dose Studies (ISS, Safety Analysis Set)

System Organ Class Preferred Term	Placebo[a] N = 26 n (%)	MS CONTIN Oral Doses 15 mg N = 29 n (%)	 30 mg N = 42 n (%)	 100 mg N = 52 n (%)	Morphine ARER Oral Doses 15 mg N = 31 n (%)	 30 mg N =41 n (%)	 60 mg N = 26 n (%)	 100 mg N = 79 n (%)
Number (%) of subjects with a related TEAE	11 (42.3)	5 (17.2)	8 (19.0)	16 (30.8)	7 (22.6)	6 (14.6)	17 (65.4)	18 (22.8)
Gastrointestinal disorders	2 (7.7)	3 (10.3)	4 (9.5)	8 (15.4)	5 (16.1)	5 (12.2)	7 (26.9)	9 (11.4)
Nausea	2 (7.7)	1 (3.4)	2 (4.8)	4 (7.7)	5 (16.1)	4 (9.8)	7 (26.9)	6 (7.6)
Vomiting	0	2 (6.9)	0	1 (1.9)	1 (3.2)	0	2 (7.7)	2 (2.5)
Abdominal pain	0	1 (3.4)	2 (4.8)	1 (1.9)	1 (3.2)	0	0	0
General disorders and administration site conditions	0	0	3 (7.1)	1 (1.9)	0	0	0	2 (2.5)
Fatigue	0	0	3 (7.1)	0	0	0	0	1 (1.3)
Investigations	0	1 (3.4)	1 (2.4)	4 (7.7)	0	0	0	2 (2.5)
Blood pressure decreased	0	0	0	2 (3.8)	0	0	0	2 (2.5)
Nervous system disorders	1 (3.8)	3 (10.3)	1 (2.4)	5 (9.6)	3 (9.7)	3 (7.3)	0	9 (11.4)
Somnolence	0	2 (6.9)	0	3 (5.8)	0	0	0	7 (8.9)
Dizziness	0	0	0	1 (1.9)	0	2 (4.9)	0	2 (2.5)
Headache	1 (3.8)	1 (3.4)	1 (2.4)	0	2 (6.5)	0	0	2 (2.5)
Respiratory, thoracic and mediastinal disorders	9 (34.6)	0	0	0	0	0	12 (46.2)	0
Nasal congestion	8 (30.8)	0	0	0	0	0	9 (34.6)	0
Nasal discharge discolouration	1 (3.8)	0	0	0	0	0	2 (7.7)	0
Rhinorrhoea	0	0	0	0	0	0	3 (11.5)	0
Skin and subcutaneous tissue disorder	0	0	0	0	1 (3.2)	0	3 (11.5)	1 (1.3)
Pruritus generalized	0	0	0	0	0	0	2 (7.7)	0

ISS = integrated summary of safety; N = number of subjects in the safety population; n = number of subjects who had a TEAE; TEAE = treatment-emergent adverse event.
[a] = Placebo refers to oral placebo/insufflated placebo treatment in M-ARER-002.
Note: Related TEAEs were considered by the investigator to have a possible, probable, or definite relationship to naltrexone, Morphine ARER, or MS CONTIN.
Source: *Table ae_t003s*.

Source: Applicant's submission (ISS, pages 41-42)

Table 19 TEAEs related to Naltrexone, Morphine ARER or MS Contin by SOC and PT in Multiple-dose and Pooled Data

Table 16.	Summary of Treatment-emergent Adverse Events Related to Naltrexone, Morphine ARER or MS CONTIN Reference Product by System Organ Class and Preferred Term that Occurred in More Than 1 Subject in Multiple-dose and Pooled Data (ISS, Safety Analysis Set)					
	Multiple 100-mg Doses[a]		All Active Oral Doses[b]		All Active Dosage Forms[c]	
System Organ Class Preferred Term	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)	MS CONTIN N = 220 n (%)	Morphine ARER N = 241 n (%)
Number (%) of subjects with a related TEAE	18 (25.7)	13 (20.3)	47 (24.4)	61 (25.3)	60 (27.3)	65 (27.0)
Gastrointestinal disorders	16 (22.9)	12 (18.8)	31 (16.1)	38 (15.8)	39 (17.7)	41 (17.0)
Nausea	13 (18.6)	11 (17.2)	20 (10.4)	33 (13.7)	27 (12.3)	36 (14.9)
Vomiting	6 (8.6)	2 (3.1)	9 (4.7)	7 (2.9)	14 (6.4)	9 (3.7)
Constipation	3 (4.3)	2 (3.1)	4 (2.1)	2 (0.8)	4 (1.8)	2 (0.8)
Dyspepsia	1 (1.4)	0	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)
Abdominal pain	0	0	4 (2.1)	1 (0.4)	4 (1.8)	1 (0.4)
General disorders and administration site conditions	1 (1.4)	1 (1.6)	5 (2.6)	3 (1.2)	6 (2.7)	3 (1.2)
Fatigue	0	0	3 (1.6)	1 (0.4)	3 (1.4)	1 (0.4)
Investigations	0	0	6 (3.1)	2 (0.8)	6 (2.7)	2 (0.8)
Blood pressure decreased	0	0	2 (1.0)	2 (0.8)	2 (0.9)	2 (0.8)
Metabolism and nutrition disorders	1 (1.4)	0	2 (1.0)	0	2 (0.9)	0
Decreased appetite	1 (1.4)	0	2 (1.0)	0	2 (0.9)	0
Nervous system disorder	6 (8.6)	6 (9.4)	15 (7.8)	21 (8.7)	17 (7.7)	21 (8.7)
Headache	4 (5.7)	4 (6.3)	6 (3.1)	8 (3.3)	7 (3.2)	8 (3.3)
Somnolence	0	1 (1.6)	5 (2.6)	8 (3.3)	5 (2.3)	8 (3.3)
Dizziness	2 (2.9)	0	3 (1.6)	4 (1.7)	3 (1.4)	4 (1.7)
Tremor	0	0	0	2 (0.8)	0	2 (0.8)
Respiratory, thoracic, and mediastinal disorders	0	0	0	12 (5.0)	1 (0.5)	20 (8.3)
Nasal congestion	0	0	0	9 (3.7)	1 (0.5)	16 (6.6)
Rhinorrhoea	0	0	0	3 (1.2)	0	3 (1.2)
Nasal discharge discolouration	0	0	0	2 (0.8)	0	2 (0.8)
Epistaxis	0	0	0	0	0	3 (1.2)

Table 16. Summary of Treatment-emergent Adverse Events Related to Naltrexone, Morphine ARER or MS CONTIN Reference Product by System Organ Class and Preferred Term that Occurred in More Than 1 Subject in Multiple-dose and Pooled Data (ISS, Safety Analysis Set)

	Multiple 100-mg Doses[a]		All Active Oral Doses[b]		All Active Dosage Forms[c]	
System Organ Class Preferred Term	MS CONTIN N = 70 n (%)	Morphine ARER N = 64 n (%)	MS CONTIN N = 193 n (%)	Morphine ARER N = 241 n (%)	MS CONTIN N = 220 n (%)	Morphine ARER N = 241 n (%)
Skin and subcutaneous tissue disorder	1 (1.4)	0	1 (0.5)	5 (2.1)	6 (2.7)	6 (2.5)
Pruritus generalized	0	0	0	2 (0.8)	4 (1.8)	3 (1.2)
Pruritus	1 (1.4)	0	1 (0.5)	1 (0.4)	2 (0.9)	1 (0.4)

ISS = integrated summary of safety; N = number of subjects in the safety population; n = number of subjects who had a TEAE; TEAE = treatment-emergent adverse event.
[a] = Subjects enrolled in 2 multiple-dose studies, M-ARER-006 and M-ARER-008.
[b] = All subjects enrolled in all clinical studies received Morphine ARER and MS CONTIN, with the exception of Studies M-ARER-002 and M-ARER-005. In Study M-ARER-002, only subjects who received oral Morphine ARER (1 arm) were included in this group. In Study M-ARER-005, subjects received oral Morphine ARER in a fed and fasted condition.
[c] = All subjects who received oral and insufflated Morphine ARER and MS CONTIN.
Note: Related TEAEs were considered by the investigator to have a possible, probable, or definite relationship to naltrexone, Morphine ARER, or MS CONTIN.
Source: *Table ae_t003m.*

Source: Applicant's submission (ISS, pages 43-44)

Nearly all TEAEs were considered by the investigator to be related to study medication. In subjects treated with Morphine ARER or MS CONTIN, similar rates of related TEAEs were reported: 27.0% (65/241) for Morphine ARER and 27.3% (60/220) for MS CONTIN. The rates of related TEAEs were higher for placebo ARER patients at 42.3% (11/26). Only nine subjects in the Morphine ARER group, six subjects in the MS CONTIN group and one subject in the placebo ARER group, experienced TEAEs that were considered to be unrelated to treatment. In the Morphine ARER group, the events that were not considered to be drug-related by PT included blood glucose increased, in three subjects, and dyspepsia, nausea, enlarged uvula, blood creatinine increased, blood pressure increased, headache, sinus headache, epistaxis, oropharyngeal pain, lower back pain, neck pain, and vision blurred in one subject each. In the MS CONTIN group, events that were not considered to be drug related by PT included insomnia and pollakiuria, in two subjects each, and blood glucose decreased, tinnitus, white blood cell count abnormal, rash pustular, muscle strain, dizziness, and abdominal pain upper in one subject each. In the placebo group, one event of nasopharyngitis was considered to be drug related. It is important to note that a subject could have had more than one event but was only counted once overall for TEAEs.

Four events that are usually considered to be related to treatment were considered unrelated to treatment: nausea, headache, sinus headache, and epistaxis, and occurred after Morphine ARER treatment. Descriptions of these AEs are as follows by the Applicant:

- M-ARER-002, subject 070: One subject reported mild nausea seven hours after receiving intact Morphine ARER, which was considered to be unrelated to treatment, and it resolved approximately 0.5 hours later.

- M-ARER-002, subject 065: One subject reported a mild sinus headache 13 hours after receiving insufflated Morphine ARER, and approximately 11 hours before, the subject reported a mild swollen uvula. Both events were considered to be unrelated to treatment and resolved approximately 1.5 days after the sinus headache was reported.

- M-ARER-006, subject 01-054: One subject reported a mild intermittent headache 3.5 hours after receiving Morphine ARER, which was considered to be unrelated to treatment and resolved approximately 29 hours later.

- M-ARER-008, subject 01-134: One subject reported mild epistaxis over 5 hours after the administration of Morphine ARER, which was considered to be unrelated to treatment and resolved approximately 1 hour later.

TEAEs led to withdrawal by SOC and PT:

A total of 20 subjects withdrew from the studies: seven subjects (2.9%) treated with Morphine ARER and 13 subjects (6.7%) treated with MS CONTIN. Four subjects withdrew from the single-dose studies and 16 from the multiple-dose studies. Six subjects who are included in the total number withdrew from a study but did not have study medication withdrawn data recorded (two from Study M-ARER-004, two from Study M-ARER-006, and two from Study M-ARER-007). Three additional subjects in Study M-ARER-008 had AEs that led to withdrawal that occurred before the first dose of study drug was administered that were not considered to be treatment-emergent. All nine subjects were counted in the AEs that led to withdrawal of the study but are not included in the TEAEs that led to withdrawal of study medication. A listing of all subjects who had AEs that led to study withdrawal is presented in table below.

Table 20 List of Subjects who had AEs that Led to Study Withdrawal

Table 17. Listing of Subjects Who Had Adverse Events that Led to Study Withdrawal (ISS, Safety Analysis Set)					
Study Subject Number	Treatment Group	Adverse Events by Preferred Term[a]	Related	Intensity	Treatment-Emergent
Single-dose Studies					
M-ARER-004					
15[b]	MS CONTIN	Vomiting	Yes	Mild	Yes
45[b]	Morphine ARER	Vomiting Abdominal pain upper	Yes Yes	Mild Mild	Yes No
M-ARER-007					
04[b]	MS CONTIN	Vomiting	Yes	Moderate	Yes
20[bc]	Morphine ARER	Abdominal pain Vomiting Diarrhoea Nausea Headache	Yes Yes Yes Yes Yes	Severe Moderate Moderate Moderate Mild	Yes Yes Yes Yes Yes
Multiple-dose Studies					
M-ARER-006					
005	MS CONTIN	Vomiting	Yes	Mild	Yes
008	Morphine ARER	Headache Nausea	Yes Yes	Mild Mild	Yes Yes
009	MS CONTIN	Vomiting	Yes	Mild	Yes
030	MS CONTIN	Insomnia	No	Mild	Yes
036	MSCONTIN	Vomiting	Yes	Mild	Yes
045[b]	Morphine ARER	Headache Nausea	Yes Yes	Mild Mild	Yes Yes
048[b]	MS CONTIN	Hot flush Nausea	Yes Yes	Mild Mild	Yes Yes
M-ARER-008					
106	MS CONTIN	Constipation Nausea	No Yes	Mild Moderate	No[d] No[d]
111	Morphine ARER	Nausea Vomiting	Yes Yes	Moderate Mild	Yes Yes
115	MS CONTIN	Vomiting	Yes	Moderate	Yes
124	MS CONTIN	Nausea	Yes	Mild	No[d]
137	MS CONTIN	Vomiting	Yes	Moderate	Yes
141	MS CONTIN	Nausea	Yes	Moderate	Yes
145	Morphine ARER	Herpes zoster	No	Moderate	No[d]

Table 17. Listing of Subjects Who Had Adverse Events that Led to Study Withdrawal (ISS, Safety Analysis Set)

Study Subject Number	Treatment Group	Adverse Events by Preferred Term[a]	Related	Intensity	Treatment-Emergent
Single-dose Studies					
158	Morphine ARER	Nausea Vomiting	Yes Yes	Moderate Mild	Yes Yes
191	MS CONTIN	Vomiting	Yes	Mild	Yes

ISS = integrated summary of safety.
[a] = Adverse events occurred on the day that study drug was administered.
[b] = Adverse events that led to study withdrawal were not indicated as adverse events that led to withdrawal of study medication. Moreover, Listing ae_d0004 does not indicate under the discontinuation column that these subjects were withdrawn.
[c] = This event was considered to be serious because the subject went to the hospital emergency room for treatment.
[d] = Subjects had an existing adverse event, were given the first dose of Morphine ARER or MS CONTIN, and then withdrew from the study.
Source: *Listing ae_d0004* and individual study reports

Source: Applicant's submission (ISS, pages 46-47)

In the single-dose studies, two subjects treated with Morphine ARER and two subjects MS CONTIN had TEAEs that led to discontinuation. In the multiple-dose studies, five subjects treated with Morphine ARER and 11 subjects treated with MS CONTIN had TEAEs that led to discontinuation. In Studies M-ARER-004, M-ARER-006, and M-ARER-007, two subjects withdrew from each study, but withdrawal from study medication was not reported. In Study M-ARER-008, three subjects had existing AEs at the time the first dose of Morphine ARER or MS CONTIN was administered. Then they withdrew, so the AEs were not considered to be treatment-emergent.

Reviewer's comments:
The common AEs were consistent with expected opioid AEs related to GI and nervous systems such as nausea, vomiting, somnolence (single dose studies), headache (multiple-dose and pooled studies).

7.4.2 Laboratory Findings

Clinical laboratory parameters for hematology, serum chemistry, and urinalysis were collected during screening and at the follow-up visit for each study. Because each subject was treated with both the Morphine ARER and MS CONTIN product, changes from screening to the end of the study could not be reconciled to a specific treatment arm. Instead, treatment-emergent clinical laboratory abnormalities observed by the investigator were reported as TEAEs when the events were associated with signs and symptoms that required treatment or further follow-up. Hence, no summaries of laboratory data were produced.

Seven subjects in four single-dose studies—M-ARER-004, M-ARER-005, M-ARER-007, and M-ARER-012—experienced 8 clinically significant laboratory events. These events are described as follows:

- M-ARER-004, subject 06: blood glucose increased (Morphine ARER)
- M-ARER-004, subject 20: blood alkaline phosphatase increase (MS CONTIN)
- M-ARER-004, subject 34: blood glucose increased (Morphine ARER)
- M-ARER-004, subject 46: blood glucose increased (Morphine ARER)
- M-ARER-005, subject 24: elevated creatinine (Morphine ARER)
- M-ARER-007, subject 04: blood glucose decreased (MS CONTIN)
- M-ARER-007, subject 04: increased bilirubin (MS CONTIN)
- M-ARER-012, subject 10: white blood cell count abnormal (MS CONTIN)

Two events were considered to be related to MS CONTIN treatment: blood alkaline phosphatase increase and increased bilirubin. All other events were not related to Morphine ARER or MS CONTIN.

At the request the Division, the Applicant provided the cases with abnormal laboratory values as follows:

Table 1.11.3-2. Clinical Laboratory Evaluations

Study/Case Report Form	Subject	Lab Finding (MedDRA Preferred Term)	Normal Range	Screening	End of Study Value	Retest Value
M-ARER-004 *crf-11249801-001-06*	06	Blood glucose increased	65-99 mg/dL	89 mg/dL	144 mg/dL	85 mg/dL
M-ARER-004 *crf-11249801-001-20*	20	Blood alkaline phosphatase increased	40-115 IU/L	138 IU/L	144 IU/L	135 IU/L
M-ARER-004 *crf-11249801-001-34*	34	Blood glucose increased	65-99 mg/dL	77 mg/dL	162 mg/dL	146 mg/dL
M-ARER-004 *crf-11249801-001-46*	46	Blood glucose decreased[a]	65-99 mg/dL	83 mg/dL	49 mg/dL	88 mg/dL
M-ARER-005 *crf-11249802-001-24*	24	Elevated creatinine	0.60-1.35 mg/dL	1.41 mg/dL	1.70 mg/dL	1.33 mg/dL
M-ARER-007 *crf-1124903-001-04*	04	Blood glucose decreased	65-99 mg/dL	86 mg/dL	51 mg/dL	107 mg/dL
		Increased bilirubin	0.2-1.1 mg/dL	0.9 mg/dL	2.8 mg/dL	1.0 mg/dL
M-ARER-012 *crf-11449801-001-10*	10	White blood cell count abnormal	3.8-10.8 k/uL	7.6 k/uL	16.5 k/uL	Not available[b]

[a] = Incorrectly coded in the clinical study report as blood glucose increased; see explanation below.
[b] = As noted in *section 10.1* of the clinical study report for M-ARER-012, several attempts to contact this subject in order to schedule repeat analysis were unsuccessful, and this subject is considered lost to follow up.

The Applicant provided additional clinical information regarding two of those subjects as follows:

Regarding subject 34 in Study M-ARER 004, as per the case report form for this subject, the principle investigator noted the following: "If truly fasting needs follow-up with PMD (his primary care doctor). As far as study is concerned this is NCS (not clinically significant) and not related to study participation."

Regarding subject 46 in Study M-ARER 004, in Appendix 16.2.7, Adverse Event Listing of the CSR, the preferred term was incorrectly coded as glucose increased; however, in Appendix 16.2.8, Individual Laboratory Measurements and Other Safety Observations by Subject, the data clearly show that this should have been coded as glucose decreased. This error was carried through the entire clinical study report (CSR) and resulting ISS.

Reviewer's comments:
The subjects who experienced blood glucose increase (#6, #34, and #46) and elevated creatinine (#24) are unlikely related to study drug.

7.4.3 Vital Signs

Seated blood pressure, pulse rate, respiratory rate, oxygen saturation, and temperature were scheduled to be collected before dose administration, at periodic intervals after dose administration, and when subjects were released from the phase 1 testing facility. No summaries of vital sign data were compiled by the Applicant.

Blood pressure and heart rate changes were the only vital signs considered to be clinically significant. Five subjects experienced six clinically significant blood pressure increases or decreases: four events in three subjects of blood pressure decreases and two events in two subjects of blood pressure increases. Moreover, one subject experienced one event of heart rate increased. These abnormalities are presented as follows:

- M-ARER-004, Subject 08 – two related events of decreased blood pressure (Morphine ARER and MS CONTIN)

- M-ARER-004, subject 37: one unrelated event of decreased blood pressure (MS CONTIN)

- M-ARER-004, subject 09: one related event of increased blood pressure (MS CONTIN)

- M-ARER-005, subject 12: one unrelated event of increased blood pressure (Morphine ARER)

- M-ARER-005, subject 15: one related event of decreased blood pressure (MS CONTIN)

- M-ARER-012, subject 20: one related event of heart rate increased (Morphine ARER)

According to the Investigator, five events in four subjects were considered to be related to Morphine ARER or MS CONTIN: three events in two subjects treated with Morphine ARER and two events in two subjects treated with MS CONTIN. The other two events in two subjects were unrelated to Morphine ARER or MS CONTIN.

At the Division's request, the Applicant provided the value of the abnormal vital signs as follows:

In the clinical studies, vital signs were measured predose, 2, 4, 6, 8, 10, 12, 14 (Study M-ARER-012 only), and 24 hours after dosing, and before release from the study site during each study period. Only vital signs that were outside of the normal range and deemed clinically significant by an investigator were reported as an AE. Data on the values for abnormal vital signs and subsequent retests are in the case report form for each subject.

M-ARER-004, subject 08 (crf-11249801-001-08) (screening blood pressure = 111/68 mm Hg):

- *Related decreased blood pressure 24 hours postadministration of Morphine-ARER (period 1)*

  - *95/49 mm Hg*

  - *99/59 mm Hg (retest)*

  - *106/61 mm Hg (retest)*

- *Related decreased blood pressure 6 hours postadministration of MS CONTIN (period 2)*

  - *99/48 mm Hg*

  - *94/58 mm Hg (retest)*

  - *105/53 mm Hg (retest)*

  - *102/64 mm Hg (retest)*

M-ARER-004, subject 09 (crf-11249801-001-09) (screening blood pressure = 126/82 mm Hg):

- *Related increased blood pressure 6 hours postadministration of MS CONTIN (period 2)*

  - *157/111 mm Hg*

  - *146/83 mmHg (retest)*

  - *136/87 mmHg (retest)*

M-ARER-004, subject 37 (crf-11249801-001-37) (screening blood pressure = 102/63 mm Hg):

• *Unrelated decreased blood pressure 10 hours postadministration of MS CONTIN (period 1)*

- *91/45 mm Hg*

- *113/63 mmHg (retest)*

M-ARER-005, subject 12 (crf-11249802-001-12) (screening blood pressure = 123/77 mmHg):

• *Unrelated increased blood pressure 24 hours postadministration of Morphine ARER (period 1)*

- *128/113 mmHg*

- *125/80 mmHg (retest)*

M-ARER-005, subject 15 (crf-11249802-001-15) (screening blood pressure = 122/65 mmHg):

• *Related decreased blood pressure 4 hours postadministration of MS CONTIN (period 1)*

- *88/47 mmHg*

- *105/60 mm Hg (retest)*

M-ARER-012, subject 20 (crf-11449801-001-20) (screening heart rate = 95 beats/minute):

• *Related increased heart rate during release after administration of Morphine ARER (period 1)*

- *110 beats/minute*

- *108 beats/minute (retest)*

- *110 beats/minute (retest)*

- *96 beats/minute (retest)*

Reviewer's comments:
Subjects who experienced hypotension (#08, and #12) and tachycardia (#20) are likely related to study drug which are known AEs to opioids.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed at screening and in a subset of studies at the follow-up visit. According to the Applicant, no clinically significant electrocardiograms were reported.

7.4.5 Special Safety Studies/Clinical Trials

There is one relative abuse liability study (M-ARER-002) in healthy subjects who were opioid-experienced, recreational drug users, which has been incorporated into the overall safety review.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Applicant did not make assessment of dose dependent for AEs.

7.5.2 Time Dependency for Adverse Events

The Applicant did not make assessment of time dependent for AEs.

7.5.3 Drug-Demographic Interactions

The Applicant did not make assessment of drug-demographic interactions.
All studies in the clinical program were conducted in healthy adult.

7.5.4 Drug-Disease Interactions

All studies in the clinical program were conducted in healthy adult.

7.5.5 Drug-Drug Interactions

There was no specific drug-drug interaction study conducted for this submission. The Applicant plans to rely on what is known and labeled for the listed drugs and class of drug as applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See Pharmacology and Toxicology review by Dr. Carliac Huynh.

7.6.2 Human Reproduction and Pregnancy Data

16.6 Pregnancies

Morphine ARER is proposed as Pregnancy Category C. There have been no adequate and well-controlled studies of Morphine ARER in pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

No event of pediatric exposure was reported in the submission. Morphine ARER was not studied in subjects younger than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

See 7.4.5 Special Safety Studies/Clinical Trials for Relative Abuse Liability Study

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

This drug is not currently marketed.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

The labeling review is ongoing. The propriety name of Morphabond was granted by the Division of Medication Error Prevention and Analysis.

9.3 Advisory Committee Meeting

The development program with PK and HAL studies is similar to those of approved abuse deterrent products, and no unexpected issues were identified during the review process. No Advisory Committee meeting is expected for this product.

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/s/

TIMOTHY T JIANG
08/19/2015

JOHN J FEENEY
08/19/2015