CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206544Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDP BIOPHARMACEUTICS REVIEW

NDA#:	206544/N000
Submission Date:	11/21/14 and 04/29/15
Brand Name:	MorphaBond
Generic Name:	Morphine Sulfate ARER
Formulation:	Extended release (ER) tablet
Strength:	100, 60, 30, and 15 mg (4 strengths)
Applicant:	Inspirion
Type of submission:	Original (N-000)
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Morphine sulfate, a full opioid agonist, is relatively selective for the μ receptor, although it can interact with other opioid receptors at higher doses. NDA 19516 for MS Contin (morphine sulfate) ER tablets (200, 100, 60, 30, and 15 mg) was approved on 05/29/87 indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Inspirion developed an abuse-deterrent formulation of oral, ER morphine sulfate tablets, Morphine ARER which incorporated IDT's proprietary abuse-deterrent technology. The Morphine ARER tablet is reported to be 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.

Current Submission

On 11/21/14, Inspirion submitted an original NDA 206544 seeking approval for Morphine ARER ER tablets with 4 strengths (100, 60, 30, and 15 mg). According to the SUPAC-MR guidance, these four tablet strengths are not considered (b) (4) (b) (4) This is a 505(b)(2) submission referencing MS Contin ER tablets (100, 60, 30, and 15 mg), the RLD (referenced list drug).

Several bioequivalence (BE) studies were conducted between Morphine ARER ER tablet and MS Contin ER tablet in order to bridge to FDA's findings of safety and effectiveness for the RLD (MS Contin), at 100, 30, and 15 mg strength levels. These BE studies are reviewed by the Office Clinical Pharmacology (OCP). The 60 mg tablet strength was used in an *in vivo* study to determine the relative bioavailability, abuse potential and safety of crushed and intact Morphine ARER tablet compared with crushed MS Contin and Placebo in opioid experienced following intranasal administration.

The formulation development and dissolution method development report were submitted for review. To support the biowaiver of Morphine ARER 60 mg strength, comparative dissolution profile data with the highest strength of 100mg ER tablets in three dissolution media were submitted.

In vitro alcohol dose-dumping study for Morphine ARER 100 mg and 15 mg ER tablets in 0, 5, 10, 20, and 40% of alcohol for up to 2 hrs was also conducted using the proposed dissolution method and the results were submitted for review.

Biopharmaceutics Review

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.

Reviewer's Comments:

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.

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.

The following dissolution method and acceptance criteria are acceptable for release and for long-term stability testing, and should be conveyed to the Applicant if this NDA is deemed to be approved.

The Approved Dissolution Method and Acceptance Criteria for Morphine ARER ER Tablets, 100, 60, 30, and 15 mg

Medium	SGF without enzyme
Temperature	37.0± 0.5° C
Volume	900 mL
Apparatus	I (Basket)
Speed	100 rpm
Time	30, 60, 90, 120, 240, 360, and 480 minutes

Acceptance Criteria:

For 100 and 60 mg tablet strengths
0.5 hr: (b) (4) %
2 hr: (b) (4) %
6 hr: NLT (b) (4) %

For 15 and 30 mg tablet strengths
0.5 hr: (b) (4) %
2 hr: (b) (4) %
6 hr: NLT (b) (4) %

Tienmien Chen -A

Digitally signed by Tienmien Chen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tienmien Chen -A, 0.9.2342.19200300.100.1.1=1300073135
Date: 2015.07.17 11:57:41 -04'00'

Tien-Mien Chen, Ph.D.
ONDP Biopharmaceutics Reviewer

07/11/15
Date

John Z. Duan -S

Digitally signed by John Z. Duan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John Z. Duan -S, 0.9.2342.19200300.100.1.1=1300118208
Date: 2015.07.17 12:06:45 -04'00'

John Duan, Ph.D.
ONDP Biopharmaceutics Secondary Reviewer

07/11/15
Date

CC: NDA No.206544/N-000\PSeo

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Morphine sulfate, a full opioid agonist, is relatively selective for the μ receptor, although it can interact with other opioid receptors at higher doses. NDA 19516 for MS Contin (morphine sulfate) ER tablets (200, 100, 60, 30, and 15 mg) was approved on 05/29/87 indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Inspirion developed an abuse-deterrent formulation of oral, ER morphine sulfate tablets, Morphine ARER. Morphine ARER ER tablet incorporated IDT's proprietary abuse-deterrent technology. The Morphine ARER tablet is reported to be 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.

During the IND stage, several IND meetings were held with the Agency regarding the study requirements to support its NDA submission.

CURRENT SUBMISSION:

On 11/21/14, Inspirion submitted an original NDA 206544 seeking approval for Morphine ARER ER tablets with 4 strengths (100, 60, 30, and 15 mg) as 505(b)(2) submission referencing MS Contin ER tablets (100, 60, 30, and 15 mg), the RLD.

Several bioequivalence (BE) studies were conducted between Morphine ARER ER tablet and MS Contin ER tablet in order to bridge to FDA's findings of safety and effectiveness for the RLD (MS Contin), at 100, 30, and 15 mg strength levels. These BE studies are reviewed by OCP. The 60 mg tablet strength was used in an *in vivo* study to determine the relative bioavailability, abuse potential and safety of equivalent doses of crushed and intact Morphine ARER tablet compared with crushed MS Contin and Placebo in opioid experienced, non-dependent subjects following intranasal administration.

The formulation development and dissolution method development reports were submitted for review. Comparative dissolution profile data (including f2 calculation) between Morphine ARER 60 and 100mg ER tablets were submitted to support the biowaiver of Morphine ARER 60 mg strength in three dissolution media.

In vitro alcohol dose-dumping study for Morphine ARER 100 mg and 15 mg ER tablets was conducted using the proposed dissolution method. The dissolution profiles (n = 12 tablets/batch) was evaluated in 0% (as control), 5%, 10%, 20%, and 40% alcohol up to 2 hours. The study results are reviewed here by the Division of Biopharmaceutics.

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

However, granting the biowaiver for this strength (60 mg) 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.

BIOPHARMACEUTICS ISSUES

The proposed product incorporates proprietary abuse-deterrent technology (b) (4) as described below.

(b) (4)

(b) (4)

The formulations for the 4 strengths of Morphine ARER (100, 60, 30, and 15 mg) are (b) (4)

The Applicant reported that

- (b) (4)

(b) (4)

The composition/formulation of the proposed Morphine ARER ER tablets are shown below.

Table 1. Composition/Formulation of the Proposed Morphine ARER ER Tablets of Four Strengths

Table 2.3.P-1. Quantitative Composition of Morphine ARER Tablets										
Component	Quality Standard	Function	15 mg		30 mg		60 mg		100 mg	
			mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w
(b) (4)										
(b) (4)										
Hypromellose (hydroxypropyl methylcellulose (b) (4) (b) (4)	USP									
Xanthan gum (b) (4)	NF									
Microcrystalline cellulose (b) (4)	NF									
Sodium alginate	NF									
Alginic acid	NF									
Mannitol (b) (4)	USP									
Colloidal silicon dioxide (b) (4)	NF									
Magnesium stearate	NF									
(b) (4)	—									
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)	NF									
Lactose monohydrate (b) (4)	NF									
Polysorbate 80 (b) (4)	NF									
(b) (4)	NF									
(b) (4)										

Table 2.3.P-1. Quantitative Composition of Morphine ARER Tablets										
Component	Quality Standard	Function	15 mg		30 mg		60 mg		100 mg	
			mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w
Color coating										
(b) (4)										
(b) (4)										
(b) (4)										
Titanium dioxide, USP										
(b) (4) polyethylene glycol, NF										
FD&C Blue #1/ (b) (4) (b) (4)										
FD&C Blue #2 (b) (4) (b) (4)										
FD&C Red #40/ (b) (4) (b) (4)										
FD&C Yellow #6 (b) (4) (b) (4) (b) (4)										
(b) (4)										

Table 2.3.P-1. Quantitative Composition of Morphine ARER Tablets										
Component	Quality Standard	Function	15 mg		30 mg		60 mg		100 mg	
			mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w	mg/Tablet	% w/w
(b) (4)										
(b) (4)										
Shellac, USP/NF, (b) (4) (b) (4)										
(b) (4) in ethanol (b) (4)										
Isopropyl alcohol, USP (b) (4)										
Black iron oxide, JPE (b) (4)										
n-Butyl alcohol, NF (b) (4)										
Propylene glycol, USP (b) (4)										
Ammonium hydroxide (b) (4) (b) (4)										
(b) (4)										

DMF = drug master file; JPE = Japanese Pharmaceutical Excipients; NF = National Formulary; USP = United States Pharmacopeia; — = not applicable.
[a] = (b) (4)
[b] =

According to the SUPAC-MR guidance, section **IV. COMPONENTS AND COMPOSITION — RELEASE CONTROLLING EXCIPIENT,** a Level 2 change is as stated below:

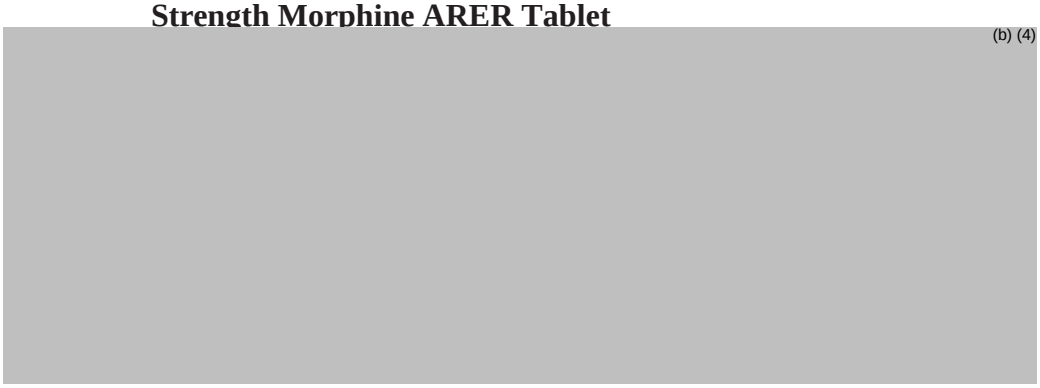
"***Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 1 change, but less than or equal to*** (b) (4) ***% w/w of total release controlling excipient content in the modified release solid oral dosage form***"

(b) (4)

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Figure 14. Comparative Dissolution Profile, With and Without Alcohol, of 100-mg Strength Morphine ARER Tablet

(b) (4)



The Applicant concluded that the comparative dissolution profile curves demonstrate that there is no alcohol-induced dose dumping of morphine within 2 hours in the presence of alcohol up to 40%. At the type C meeting held on 04/10/14, FDA agreed that "no clinical ethanol interaction study is required to support the proposed NDA."

Reviewer's Comments:
The above *in vitro* alcohol dose-dumping study results were reviewed by the Biopharm reviewer and discussed with the Clinpharm reviewer. Both agreed that the *in vitro* alcohol dose-dumping study results are acceptable showing no alcohol dose-dumping potential, therefore, no *in vivo* alcohol dose-dumping study is needed.

VIII. Assay Method Validation Report

The dissolution test method validation report was submitted for review under M32P53 and it was found acceptable. Please see the report in Appendix 3 for details.

(b) (4)

Overall Comments:

1. The dissolution method development in accompany with the formulation development, proposed dissolution acceptance criteria with revisions and submission of updated to specification (M32P51), comparative dissolution data/profiles, and *in vitro* alcohol dose-dumping study were reviewed and found acceptable .

2. 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.

NDA 206544/N000 for Morphine ARER ER Tablets, 15, 30, 60, and 100 mg

Appendix 1

Morphine ARER Stability Study Current Status

The summary of the current status Morphine ARER batches used in the stability studies are provided in the table below.

Table. Morphine ARER Stability Study Current Status

Drug Product Batch Number	Batch Size (Number of Tablets)	Strength	Manufacturing Site	Manufacturing Date	Drug Substance Lot	Storage Conditions	Study Duration	Last Reported Time Point
C003212	(b) (4)	100 mg	Cerovene	(b) (4)	Noramco 11KW200			(b) (4)
C005513		100 mg	Cerovene		Noramco 11KW200			
C005613		100 mg	Cerovene		Noramco 11KW200			
C003512		60 mg	Cerovene		Noramco 11KW200			
C005713		60 mg	Cerovene		Noramco 11KW200			
C005813		60 mg	Cerovene		Noramco			

Drug Product Batch Number		Strength	Manufacturing Site		Drug Substance Lot			
C005913		30 mg	Cerovene		Noramco 12BW523			
C006013		30 mg	Cerovene		Noramco 12BW523			
C006113		30 mg	Cerovene		Noramco 12BW523			
C006213		15 mg	Cerovene		Noramco 11KW200			
C006313		15 mg	Cerovene		Noramco 12BW523			
C006413		15 mg	Cerovene		Noramco 12BW523			

RH – relative humidity; NA – not applicable, [a]– Testing to be performed only if significant change observed at (b) (4)

NDA 206544/N000 for Morphine ARER ER Tablets, 15, 30, 60, and 100 mg

Appendix 2

Revised M32P51 Specifications

3.2.P.5.1 Specification(s) [Morphine ARER 15-mg Tablets, Inspirion Delivery Technologies, LLC]

The proposed specification for Morphine ARER 15-mg tablet is presented in *Table 3.2.P.5.1-1*.

Table 3.2.P.5.1-1. Proposed Specification for Morphine ARER 15-mg Tablets

Test	Acceptance Criterion	Analytical Procedure
Description	A round, blue-colored, coated tablet, ink-printed with IDT/M15 on one side and plain on the other side.	Visual, *3.2.P.5.2*
Identification by IR	Conforms to standard	IR, USP <197K>
Identification by retention time	(b) (4)	HPLC, 3.2.P.5.2
Assay		HPLC, 3.2.P.5.2
Content uniformity		HPLC, 3.2.P.5.2
Dissolution (% amount dissolved):		HPLC, 3.2.P.5.2
0.5 hour	(b) (4) %	
2 hour	(b) (4) %	
6 hour	NLT (b) (4) %	
(b) (4)		

HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia.

3.2.P.5.1 Specification(s) [Morphine ARER 30 mg, Tablets, Inspirion Delivery Technologies, LLC]

The proposed specification for Morphine ARER 30-mg tablet is presented in *Table 3.2.P.5.1-1*.

Table 3.2.P.5.1-1. Proposed Specification for Morphine ARER 30-mg Tablet

Test	Acceptance Criterion	Analytical Procedure
Description	A round, purple-colored, coated tablet, ink-printed with IDT/M30 on one side and plain on the other side.	Visual, *3.2.P.5.2*
Identification by IR	Conforms to standard	IR, USP <197K>
Identification by retention time	(b) (4)	HPLC, 3.2.P.5.2
Assay		HPLC, 3.2.P.5.2
Content uniformity		HPLC, 3.2.P.5.2
Dissolution (% amount dissolved):		HPLC, 3.2.P.5.2
0.5 hour	(b) (4)%	
2 hour	(b) (4)%	
6 hour	NLT (b) (4)%	
(b) (4)		

HPLC = high performance liquid chromatography; IR = infrared spectroscopy; NLT = not less than; NMT = not more than; USP = United States Pharmacopeia.

NDA 206544/N000 for Morphine ARER ER Tablets, 15, 30, 60, and 100 mg

Appendix 3

Validation Report for Dissolution Test Method No. ARD98-01 (M32P53)


(b) (4)

CLINICAL PHARMACOLOGY REVIEW

NDA: 206544	Submission Date(s): 11/21/2014
Brand Name	MorphaBond Extended Release Tablets
Generic Name	Morphine Sulfate Extended Release Tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Inspiron Technologies Inc.
Relevant IND(s)	115822
Submission Type; Code	Original NDA; 505(b)(2)
Formulation; Strength(s)	15, 30, 60 and 100 mg Morphine ARER
Indication	Opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Proposed Dosage Regimen	For opioid-naïve and opioid non-tolerant patients, initiate with 15 mg tablets orally every (b) (4) 12 hours.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submission is acceptable from clinical pharmacology perspective provided that a mutually acceptable labeling is agreed by the sponsor.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Inspiron submitted a 505(b)(2) NDA for marketing their morphine sulfate abuse resistant tablets or Morphine ARER or MorphaBond 15, 30, 60 and 100 mg tablets. The application relies on Agency's previous findings of safety and efficacy for MS Contin (NDA 019516). The sponsor relied on a comparative bioavailability program to bridge the proposed product with MS Contin. The Sponsor requested biowaiver for the 60 mg strength, see biopharmaceutics's review regarding the request.

To support the clinical pharmacology and biopharmaceutics program the sponsor conducted bioequivalence studies comparing MorphaBond and MS Contin at each of the 15 mg, 30 mg and 100 mg strength. A food-effect study and a multiple dose PK study also support the biopharmaceutical comparison of MorphaBond with MS Contin. To support the abuse liability claims, the sponsor conducted a clinical study comparing PK and PD of morphine following intranasal administration of crushed MorphaBond with intact MorphaBond and crushed MS Contin.

The topic of bridging all strengths of the proposed product to MS Contin was discussed at several meetings during the clinical development program. The sponsor was provided an opportunity to establish BE of 15 mg (lowest) and 100 mg (highest) strength formulations to MS Contin. The sponsor was able to successfully establish BE at the 100 mg strength. Multiple dose PK study M-ARER-008 compared bioavailability of morphine with five day dosing of MorphaBond 100 mg and MS Contin 100 mg tablets. The results indicate similar exposure in Cmax and AUC of morphine for the two products.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond 100 mg Tablet under fasting condition (Study M-ARER-004)

Parameter	Treatment	Geo. Mean	Ratio	CI	Intra-subject %CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 49) MS CONTIN (N = 49)	372.46 383.28	0.9718	0.9413-1.0022	8.63	0.0117	0.0036
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 47) MS CONTIN (N = 48)	391.92 402.92	0.9721	0.9409-1.0045	8.94	0.0158	0.0084
C_{max} (ng/mL)	Morphine ARER (N = 49) MS CONTIN (N = 49)	34.36 32.78	1.0480	0.9959-1.1000	14.50	0.0139	NA

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. Mean = geometric mean; NA = not available.
Morphine ARER = morphine sulfate pentahydrate extended-release 100-mg tablet.
MS CONTIN = morphine sulfate controlled-release 100-mg tablet).
Data source: *M-ARER-004* in module 5

Based on the results of study M-ARER-007, MorphaBond 15 mg tablets met the 90% CI criterion for natural ln-transformed AUC0-t and AUC0-∞, and statistically met the standards of bioequivalence compared to an equal dosage of MS CONTIN 15 mg tablets, in healthy adult subjects under fasted conditions. Maximum plasma concentration (Cmax) was lower for MorphaBond 15 mg tablet and failed to meet the criterion for bioequivalence on the lower confidence interval at 79.08% instead of the set 80% limit. Results indicate that under fasting conditions, the Cmax of morphine for the MorphaBond 15mg tablet was 13% lower than the mean Cmax obtained for MS CONTIN. Peak plasma concentrations of morphine were observed around Median Tmax of 2.25 hours (Range: 0.5 – 6 hours) for MorphaBond 15 mg tablets and 1.5 hours (Range: 0.5 – 4.5 hours) for MS Contin 15 mg tablets.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond or Morphine ARER 15 mg Tablet under fasting condition (Study M-ARER-007)

Parameter	Treatment	LS Geo. Mean	Mean Ratio (%)	90% CI (%)	%CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 28) MS CONTIN (N = 28)	42.1 43.7	96.35	89.08-104.21	17.3	0.6604	0.1060
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 25) MS CONTIN (N = 22)	49.0 49.7	98.73	90.84-107.30	15.7	0.8503	0.3249
C_{max} (ng/mL)	Morphine ARER (N = 28) MS CONTIN (N = 28)	4.57 5.23	87.38	79.08-96.55	22.1	0.3102	0.8817

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. Mean = geometric mean; LS = least squares.
Morphine ARER = morphine sulfate pentahydrate extended-release 15-mg tablet.
MS CONTIN = morphine sulfate controlled-release 15-mg tablet.
Data source: *M-ARER-007* amendment in module 5

Earlier in the drug development, the division had reviewed the BE data for the 15 mg strength and communicated to the sponsor that "…we do not anticipate that the slightly missed lower limit of the confidence interval for Cmax, nor the slightly longer Tmax, will affect the efficacy of your proposed drug product to a substantial degree." Based on this advice the sponsor discontinued an ongoing, at the time, (b) (4) (b) (4)

The sponsor also conducted a bioequivalence study M-ARER-012 to compare MorphaBond 30 mg tablet with MSContin. MorphaBond 30 mg tablets met the 90% CI criterion for natural ln-transformed AUC0-t and AUC0-∞, and statistically met the standards of bioequivalence compared to an equal dosage of MS CONTIN 30 mg tablets, in healthy adult subjects under fasted conditions. Maximum plasma concentration (Cmax) was lower for MorphaBond 30 mg tablet and failed to meet the criterion for bioequivalence on the lower confidence interval at 76.24% instead of the set 80% limit. Peak plasma concentrations of morphine were observed around Median Tmax of 2 hours (Range: 0.5 – 6 hours) for MorphaBond 30 mg tablets and 2.5 hours (Range: 0.5 – 6 hours) for MS Contin.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond or Morphine ARER 30 mg Tablet under fasting condition (Study M-ARER-012)

Parameter	Treatment	LS Geo. Mean	Mean Ratio (%)	90% CI (%)	%CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	96.5 101.0	95.55	92.12-99.11	9.8	0.4584	0.8512
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 39) MS CONTIN (N = 35)	103.2 106.9	96.61	92.90-100.47	9.6	0.6597	0.5574
C_{max} (ng/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	9.31 11.5	80.65	76.24-85.32	15.2	0.9115	0.4270

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. mean = geometric mean; h = hour; LS = least squares.
Morphine ARER = morphine sulfate pentahydrate extended-release 30-mg tablet.
MS CONTIN = morphine sulfate controlled-release 30-mg tablet.
Data source: *M-ARER-012* in module 5

For both 15 mg and 30 mg MorphaBond tablets, Cmax slightly missed the 80% lower bound. For such extended release product, Tmax and Cmax value will highly depend on PK sampling time, and the observed Tmax and Cmax values may not reflect the real Tmax and Cmax values. Considering the fact that Cmax missed the 80% lower bound slightly and this product will be titrated to effect, this observation may not be clinically significant.

When dosing MorphaBond 100 mg tablets after a high-fat breakfast, morphine Cmax was increased by approximately 33%, and morphine median Tmax was extended by 0.5 hours compared with the fasted state. However, there was no change in overall extent of morphine bioavailability, with the geometric 90% CI for both morphine AUC0-t and AUC0-∞ falling within the range 80% to 125%. Therefore, food does not have a significant effect on MorphaBond tablet and it may be taken regardless of food.

Since the application is solely relying on bioequivalence studies for bridging their product with MS Contin, the clinical site and bioanalytical site require OSIS inspection. An OSIS inspection request was submitted after filing the NDA. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting the data without an on-site inspection. The rationale for this decision was noted as: “The site listed below was inspected within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI)”.

In summary, MorphaBond 100 mg tablet met the bioequivalence criteria for both AUC and Cmax with MSContin. For both 15 mg and 30 mg MorphaBond tablets, bioequivalence criteria were met for AUC, but Cmax slightly missed the 80% lower bound. However, this observation may not be clinically significant. Food does not have a significant effect on MorphaBond tablet so it can be taken regardless of food.

2 QBR

2.1 General Attributes

Inspiron submitted a 505(b)(2) NDA for marketing their morphine sulfate abuse resistant tablets or MorphaBond. The application requests that Agency rely on previous findings of safety and efficacy for MS Contin (NDA 019516). The sponsor relied on a biopharmaceutics program to bridge the proposed product with MS Contin. In addition, the sponsor developed the product with excipients that may impart certain abuse deterrent characteristics.

To support the clinical pharmacology and biopharmaceutics program the sponsor conducted bioequivalence studies comparing MorphaBond and MS Contin at each of the 15 mg, 30 mg and 100 mg strength. A food-effect study and a multiple dose PK study also support the biopharmaceutical comparison of MorphaBond with MS Contin.

To support the abuse liability claims, the sponsor conducted a clinical study comparing PK and PD of morphine following intranasal administration of crushed MorphaBond with intact MorphaBond and crushed MS Contin.

2.2 General Clinical Pharmacology

Is MorphaBond bioequivalent to MS Contin?

MorphaBond 100 mg morphine sulfate extended-release tablets are bioequivalent to the same strength tablet of MS Contin. MorphaBond 15 mg or 30 mg extended-release tablets have similar exposure as the same dose of MS Contin tablets.

Study M-ARER-004 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 MorphaBond 100 mg tablets compared to MS CONTIN 100 mg tablets in healthy adult subjects under fasted conditions. Food and fluid intake were controlled during each confinement period. Serial blood samples for determination of morphine and Morphine-6-glucuronide (M6G) plasma concentrations were measured using a validated analytical procedure. A total of 54 healthy adult subjects were entered into the study, and 49 subjects (43 males, 6 females) completed both periods of the study. Five subjects did not complete both periods of the study, and therefore their plasma samples were not analyzed. To determine relative bioavailability, 90% CIs for the comparison of test and reference area and peak results were constructed to test 2, one-sided hypotheses at the α = 0.05 level of significance for AUC0-t, AUC0-∞, and Cmax. The CIs were determined for the geometric mean ratios (obtained from logarithmic transformed data). Determination of bioequivalence was based on the natural ln-transformed data for morphine. Based on the results of this study, MorphaBond 100 mg tablets met the 90% CI criterion for natural ln-transformed AUC0-t, AUC0-∞, and Cmax, and was therefore considered to have an equivalent bioavailability to an equal dosage of MS CONTIN 100 mg tablets, in healthy adult subjects under fasted conditions. Peak plasma concentrations of morphine were observed around Median Tmax of 3 hours (Range: 0.5 – 5) for MorphaBond 100 tablets and 2.5 (Range: 0.5 – 8) for MS Contin.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond 100 mg Tablet (Study M-ARER-004)

Parameter	Treatment	Geo. Mean	Ratio	CI	Intra-subject %CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 49) MS CONTIN (N = 49)	372.46 383.28	0.9718	0.9413-1.0022	8.63	0.0117	0.0036
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 47) MS CONTIN (N = 48)	391.92 402.92	0.9721	0.9409-1.0045	8.94	0.0158	0.0084
C_{max} (ng/mL)	Morphine ARER (N = 49) MS CONTIN (N = 49)	34.36 32.78	1.0480	0.9959-1.1000	14.50	0.0139	NA

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. Mean = geometric mean; NA = not available.
Morphine ARER = morphine sulfate pentahydrate extended-release 100-mg tablet.
MS CONTIN = morphine sulfate controlled-release 100-mg tablet).
Data source: *M-ARER-004* in module 5

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 MorphaBond 15 mg tablets compared to MS CONTIN 15 mg tablets in healthy adult subjects under fasted conditions. Food and fluid intake were controlled during each confinement period. Serial blood samples for determination of morphine and Morphine-6-glucuronide (M6G) plasma concentrations were measured using a validated analytical procedure. A total of 32 healthy adult subjects were entered into the study, and 28 subjects (28 males) completed both periods of the study. Four subjects did not complete both periods of the study, and therefore their plasma samples were not analyzed.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond 15 mg Tablet (Study M-ARER-007)

Parameter	Treatment	LS Geo. Mean	Mean Ratio (%)	90% CI (%)	%CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 28) MS CONTIN (N = 28)	42.1 43.7	96.35	89.08-104.21	17.3	0.6604	0.1060
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 25) MS CONTIN (N = 22)	49.0 49.7	98.73	90.84-107.30	15.7	0.8503	0.3249
C_{max} (ng/mL)	Morphine ARER (N = 28) MS CONTIN (N = 28)	4.57 5.23	87.38	79.08-96.55	22.1	0.3102	0.8817

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. Mean = geometric mean; LS = least squares.
Morphine ARER = morphine sulfate pentahydrate extended-release 15-mg tablet.
MS CONTIN = morphine sulfate controlled-release 15-mg tablet.
Data source: *M-ARER-007* amendment in module 5

Based on the results of this study, MorphaBond 15 mg tablets met the 90% CI criterion for natural ln-transformed AUC0-t and AUC0-∞, and statistically met the standards of bioequivalence compared to an equal dosage of MS CONTIN 15 mg tablets, in healthy adult subjects under fasted conditions. Maximum plasma concentration (Cmax) was delayed for MorphaBond 15 mg tablet and failed to meet the criterion for bioequivalence

on the lower confidence interval at 79.08% instead of the set 80% limit. Results indicate that under fasting conditions, the Cmax of morphine for the MorphaBond 15mg tablet was 13% lower than the mean Cmax obtained for MS CONTIN. Peak plasma concentrations of morphine were observed around Median Tmax of 2.25 hours (Range: 0.5 – 6 hours) for MorphaBond 15 mg tablets and 1.5 hours (Range: 0.5 – 4.5 hours) for MS Contin 15 mg tablets.

The sponsor conducted two BA/BE studies to compare bioavailability of 30 mg strength of MorphaBond and MS Contin. First study M-ARER-009 had the same study design as M-ARER-012 and was conducted as a relative bioavailability study in twenty healthy subjects (n=15 completed the study). A total of 16 healthy adult subjects were entered into the study, and 15 subjects (10 males, 5 females) completed both periods of the study. One subject did not complete both periods of the study, and therefore their plasma samples were not analyzed.
As indicated in the table below, the sponsor had observed that the 30 mg strength of MorphaBond had comparable Cmax and AUC to MS Contin. Based on results of this study a bioequivalence study (M-ARER-012) was conducted.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond 30 mg Tablet under fasting condition (Study M-ARER-009)

Table	**Summary of Pharmacokinetic and Bioequivalence Parameters for Morphine (Study M-ARER-009)**				
Parameter	**Treatment**	**Geo. Mean**	**Ratio%[a]**	**%CV[b]**	**CI[c]**
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 15) MS CONTIN (N = 15)	79.2 82.3	96.19	10.4	89.91-102.90
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 15) MS CONTIN (N = 15)	85.4 88.2	96.88	11.5	89.94-104.36
C_{max} (ng/mL)	Morphine ARER (N = 15) MS CONTIN (N = 15)	9.8 10.3	95.67	15.6	86.54-105.77

ANOVA = analysis of variance; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. mean = geometric mean; LS = least squares; MSE = mean square error.

[a] = Ratio % calculated as [test LS mean divided by the reference LS mean] x 100. None of the comparisons were detected as statistically significant by ANOVA ($\alpha = 0.05$).

[b] = Estimated intra-subject CV, %CV = 100*SQRT(eMSE-1), where MSE is the mean square error term from ANOVA

[c] = CI on the test-to-reference ratio%.

Morphine ARER = morphine sulfate pentahydrate extended-release 30-mg tablet.
MS CONTIN = morphine sulfate controlled-release 30-mg tablet.
Data source: *M-ARER-009* in module 5

M-ARER-012 was a single-center, open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study designed to compare the bioavailability of MorphaBond 30 mg tablets to MS CONTIN 30 mg tablets under fasted conditions in healthy adult subjects.

Forty-two (42) subjects were enrolled in the study, and all subjects were healthy adults. Forty-two (42) subjects were dosed in Period I, and forty-one (41) subjects completed the clinical portion of the study. Subject 30 did not complete both periods of the study; therefore, plasma samples from this participant were not sent for bioanalysis. Based on the results of this study, MorphaBond 30 mg tablets met the 90% CI criterion for natural ln-transformed AUC0-t and AUC0-∞, and statistically met the standards of bioequivalence compared to an equal dosage of MS CONTIN 30 mg tablets, in healthy adult subjects under fasted conditions. Maximum plasma concentration (Cmax) was delayed for MorphaBond 30 mg tablet and failed to meet the criterion for bioequivalence on the lower confidence interval at 76.24% instead of the set 80% limit. Results indicate that under fasting conditions, the Cmax of morphine for the MorphaBond 30 mg tablet was 13% lower than the mean Cmax obtained for MS CONTIN. Peak plasma concentrations of morphine were observed around Median Tmax of 2 hours (Range: 0.5 – 6 hours) for MorphaBond 30 mg tablets and 2.5 hours (Range: 0.5 – 6 hours) for MS Contin.

Table: Summary of Pharmacokinetic and Bioequivalence Parameters – MorphaBond 30 mg Tablet under fasting condition (Study M-ARER-012)

Parameter	Treatment	LS Geo. Mean	Mean Ratio (%)	90% CI (%)	%CV	*P*-value Period	*P*-value Sequence
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	96.5 101.0	95.55	92.12-99.11	9.8	0.4584	0.8512
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 39) MS CONTIN (N = 35)	103.2 106.9	96.61	92.90-100.47	9.6	0.6597	0.5574
C_{max} (ng/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	9.31 11.5	80.65	76.24-85.32	15.2	0.9115	0.4270

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. mean = geometric mean; h = hour; LS = least squares.
Morphine ARER = morphine sulfate pentahydrate extended-release 30-mg tablet.
MS CONTIN = morphine sulfate controlled-release 30-mg tablet.
Data source: *M-ARER-012* in module 5

Reviewer's comments: For both 15 mg and 30 mg MorphaBond tablets, Cmax slightly missed the 80% lower bound. For such extended release product, Tmax and Cmax value will highly depends on PK sampling time, and the observed Tmax and Cmax values may not reflect the real Tmax and Cmax values. Considering the fact that Cmax missed the 80% lower bound slightly and this product will be titrated to effect, this observation may not be clinically significant.

Multiple-Dose PK of MorphaBond:M-ARER-008 was a single-center, open-label, multiple-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study designed to compare the bioavailability of MorphaBond 100 mg tablets to MS CONTIN 100 mg tablets in healthy adult subjects. Subjects were randomly assigned to 1 of 2 treatment sequences (sequence 1 = AB; sequence 2 = BA) of the following products: test treatment (A) (MorphaBond or Morphine ARER [morphine sulfate pentahydrate extended-release] 100 mg tablet; lot number C003212) or reference treatment (B) (MS CONTIN [morphine sulfate] 100 mg controlled-release tablet; lot number WJM31).

The morning dose of study drug was administered in the morning on days 1 to 5 in each period, and the evening dose of study drug was administered 12 hours (± 15 minutes) following the morning dose on days 1 to 4. Following a 7-day washout period, subjects received the alternate treatment during the second treatment visit. In order to minimize opioid side effects, subjects received a standard dose of naltrexone.

A summary of the mean (SD) concentrations for morphine, by treatment (MorphaBond and MS CONTIN) and time point, are presented in Tables below.

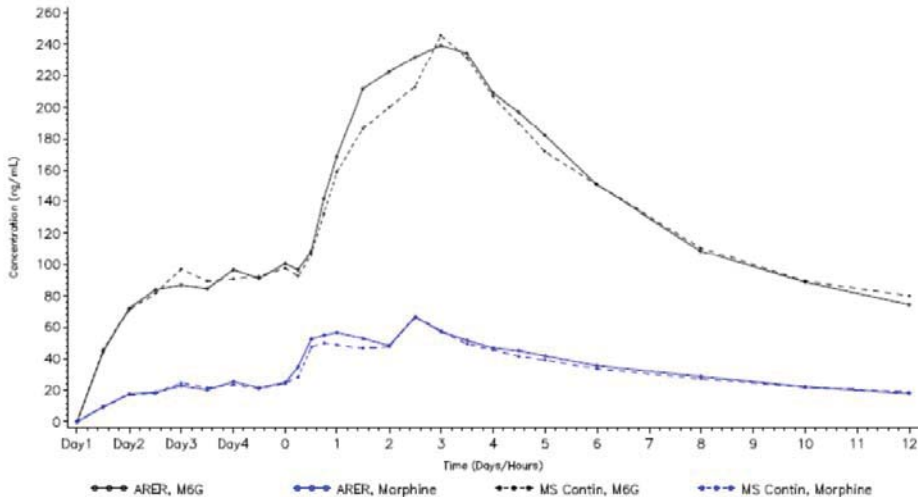
Table Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment - Evaluable Population (N = 25)

Parameter	Treatment	Mean	± SD	%CV	Median	Range
C_{max} (ng/mL)	Morphine ARER	77.3	± 24.62	31.9	75.0	36.9-146.0
	MS CONTIN	72.7	± 23.64	32.5	69.4	38.9-164.0
T_{max} (h)	Morphine ARER	2.15	± 1.04	-	2.50	0.25-4.50
	MS CONTIN	2.18	± 1.04	-	2.50	0.50-5.00
C_{min} (ng/mL)	Morphine ARER	17.9	± 5.58	31.2	17.1	11.2-36.6
	MS CONTIN	18.0	± 5.09	28.2	16.8	8.5-28.7
T_{min} (h)	Morphine ARER	11.7	± 0.95	-	12.0	8.0-12.0
	MS CONTIN	11.0	± 2.59	-	12.0	0-12.0
$AUC_{0\text{-}tau}$ (ng•h/mL)	Morphine ARER	448.4	± 132.06	29.4	431.0	261.0-852.0
	MS CONTIN	427.6	± 102.33	23.9	405.0	237.0-610.0
$AUC_{0\text{-}Tmax}$ (ng•h/mL)	Morphine ARER	126.9	± 38.56	30.4	123.0	74.0-253.0
	MS CONTIN	116.6	± 26.57	22.8	120.0	63.0-171.0
C_{avg} (ng/mL)	Morphine ARER	37.4	± 11.00	29.4	35.9	21.8-71.0
	MS CONTIN	35.6	± 8.52	23.9	33.8	19.8-50.9
Fluctuation (%)	Morphine ARER	159.2	± 38.65	-	153.0	91.8-283.0
	MS CONTIN	154.1	± 46.07	-	151.0	90.9-319.0
Swing (%)	Morphine ARER	343.3	± 121.70	-	330.0	162.0-760.0
	MS CONTIN	325.5	± 163.72	-	285.0	151.0-938.0

AUC = area under the concentration-time curve; C_{avg} = average measured plasma concentration; C_{max} = maximum plasma concentration; C_{min} = minimum measured plasma concentration; CV = coefficient of variation; h = hour; SD = standard deviation; T_{max} = time of maximum plasma concentration; T_{min} = time associated with C_{min}; - = not applicable.
Data source: *Table 14.2.2-1.* Study M-ARER-008

The mean plasma morphine and M6G concentration-time profiles by treatment is presented in the Figure below.

Figure: Mean Plasma Morphine and M6G Concentrations (ng/mL) vs. Time Profile by Treatment (N = 25) Over Five Days of BID Administration of MorphaBond (Morphine ARER) or MS Contin 100 mg.



For the measures of bioequivalence, Cmax and AUC0-tau, there were no statistically significant treatment differences (P > 0.05) and the 90% CIs for the ratios were within the 80% to 125% range, indicating that MorphaBond (Morphine ARER) and MS CONTIN were bioequivalent. For morphine, the Morphine ARER/MS CONTIN ratios for Cmax and AUC0-tau were 106% (CI: 97% to 115%) and 104% (CI: 99.6% to 108%), respectively. For M6G (data is not described in detail), the Morphine ARER/MS CONTIN ratios for Cmax and AUC0-tau were 103% (CI: 98.3% to 108%) and 103% (CI: 98.8% to 107%), respectively.

Table	**Bioequivalence Summary for Morphine by Pharmacokinetic Parameter (Evaluable Population, N = 25)**									
	Least Squares Means (Back-transformed)		**Ratio (%)**	**90% Confidence Interval**		***P*-value**			**%CV**	
Parameter	**Morphine ARER (Test)**	**MS CONTIN (Ref)**	**(Test: Ref)**	**Lower**	**Upper**	**Formulation Difference**	**Sequence Difference**	**Period Difference**	**Inter-Subject**	**Intra-Subject**
C_{max} (ng/mL)	73.79	69.84	105.66	97.08	115.00	0.2765	0.9639	0.6240	24.74	17.59
$AUC_{0\text{-}tau}$ (ng•h/mL)	431.58	415.36	103.90	99.63	108.36	0.1315	0.7378	0.2394	25.51	8.67
$AUC_{0\text{-}Tmax}$ (ng•h/mL)	121.96	113.75	107.22	101.12	113.69	0.0529	0.8903	0.1500	23.78	12.11
C_{min} (ng/mL)	17.19	17.32	99.29	92.17	106.96	0.8717	0.8902	0.6682	25.34	15.43
Ranked T_{max} (h)	1.7308	1.8798	0.00[a]	-	-	0.5059	0.2948	0.3147	-	-
Ranked fluctuation	3.3622	2.9054	0.00[a]	-	-	0.1105	0.5002	0.7722	-	-
Ranked swing	3.3558	2.6827	0.00[a]	-	-	0.0200	0.8911	0.5386	-	-

ANOVA = analysis of variance; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; C_{min} = minimum measured plasma concentration; CV = coefficient of variation; h = hour; Ln = logarithm-transformed; Ref = reference; T_{max} = time of maximum plasma concentration; - = not applicable.
[a] = median of differences
Data source: *Table 14.2.3-3* Study M-ARER-008

Prior to the above described multiple dose PK study, the sponsor had conducted a different multiple dose PK study of similar study design M-ARER-006. Due to the irregularities in the PK profiles of 8 of the 28 completers and the inability to assign the cause to either induction of the metabolism of morphine or subject compliance, the study was repeated (i.e., study M-ARER-008). Study M-ARER-006 is not being relied on for demonstration of BE to MS Contin and hence it was not reviewed in detail.

(b) (4)

2.3 Extrinsic Factors

What extrinsic factors were evaluated? What is the impact of the extrinsic factors on MorphaBond PK/PD?

The sponsor conducted in vitro studies on MorphaBond and concluded that the product is not susceptible to alcohol dose dumping. The sponsor conducted a clinical abuse potential study to conclude that MorphaBond may not be abused to the same extent as MS Contin via intranasal route after crushing.

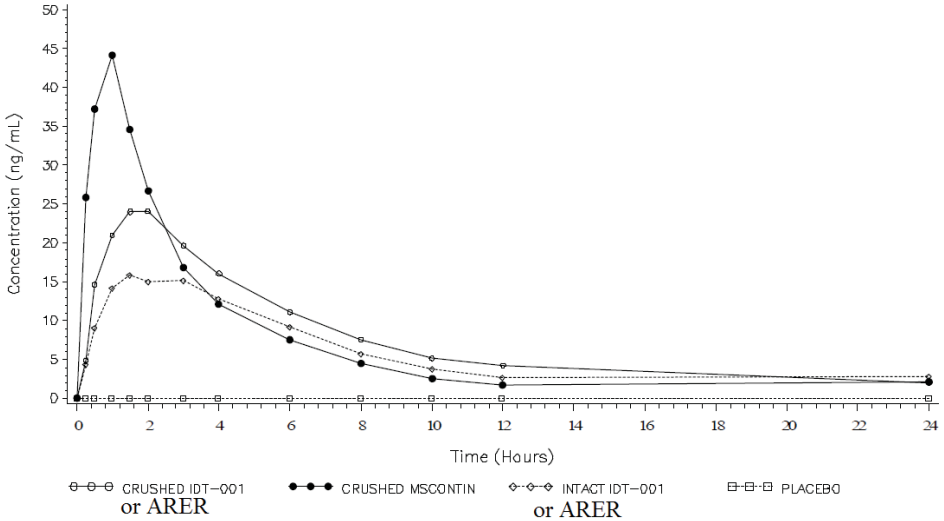
The sponsor conducted in vitro alcohol interaction study to assess risk of accidental dose dumping if MorphaBond were consumed with alcohol. Based on the in vitro study results the sponsor has not conducted in vivo alcohol interaction study. Biopharmaceutics reviewer will evaluate the results of the in vitro alcohol interaction.

The Sponsor developed the morphine extended release product to have certain abuse deterrent characteristics. The sponsor conducted a clinical abuse potential study M-ARER-002 to assess intranasal abuse liability of MorphaBond in opioid-experienced subjects. Study M-ARER-002 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover, single-center study. The purpose of this study was to determine the relative PK, PD effects (ie, drug liking), and safety of MorphaBond or Morphine ARER when crushed (tampered) and administered intranasally. After a screening and qualification phase, experienced but not dependent opioid abusers (N = 27) were randomized to receive 1 of 4 treatments. Each drug administration was separated by a 7-day washout period.

The four treatments were prepared and administered as indicated below:
• Treatment A: crushed intranasal IDT-00l placebo plus intact oral IDT-001 placebo.
• Treatment B: crushed intranasal MS Contin 60 mg (with crushed Placebo Tablet for Reference Product added for volume) plus intact oral IDT-001 placebo.
• Treatment C: crushed intranasal IDT-001 60 mg plus intact oral IDT-001 placebo.
• Treatment D: crushed intranasal IDT-001 placebo plus intact oral IDT-001 60 mg.

The majority of subjects were male (85% and 84%), White (96% and 100%), and not Hispanic or Latino (78% and 76%) for the safety/PK populations and PD population, respectively. Ages ranged from 19 to 53 years for the safety/PK populations and from 19 to 31 years for the PD population.
The morphine maximum concentration of drug (Cmax) was 49% lower and the M6G Cmax was 68% lower for crushed intranasal MorphaBond or Morphine ARER than for crushed intranasal MS CONTIN. Similarly, for crushed intranasal MorphaBond or Morphine ARER, the values for area under the time curve (AUC)0-0.5h were 75% and 68% lower for morphine and M6G, respectively, than for crushed intranasal MS CONTIN. Thus, the short-term exposure to pharmacologically active morphine and M6G were substantially lower for crushed intranasal MorphaBond or Morphine ARER than crushed intranasal MS CONTIN.

Figure: Pharmacokinetic profile of morphine following intranasal abuse of 60 mg MorphaBond or MS Contin compared to intact MorphaBond taken orally.



or ARER
or MorphaBond

or ARER
or MorphaBond

Table : Pharmacokinetic Parameters for Morphine after Administration of Crushed Intranasal IDT-001, Crushed Intranasal MS Contin, and Intact Oral IDT-001 (PK Population, N = 27)

Parameter	Analyte	Crushed Intranasal IDT-001 Mean ± SD	Crushed Intranasal MS Contin Mean ± SD	Intact Oral IDT-001 Mean ± SD
C_{max}	Morphine	26.2 ± 11.2	49.5 ± 17.3	18.6 ± 5.7
(ng/mL)	M6G	58.2 ± 30.7	169.0 ± 55.0	108.2 ± 18.2
T_{max}	Morphine	1.6 (1.0-3.1)	1.1 (0.2-1.6)	1.6 (0.5-3.1)
(hr)	M6G	3.1 (2.1-10.0)	1.6 (1.1-10.1)	2.1 (1.6-4.1)
$AUC_{0-0.5h}$	Morphine	2.8 ± 1.2	10.9 ± 5.2	2.1 ± 1.3
(ng•hr/mL)	M6G	0.4 ± 0.5	1.9 ± 1.3	2.2 ± 1.3
AUC_{0-t}	Morphine	178.5 ± 77.7	171.6 ± 55.2	139.4 ± 40.1
(ng•hr/mL)	M6G	441.8 ± 202.0	777.9 ± 156.9	844.4 ± 146.5
$AUC_{0-\infty}$	Morphine	219.8 ± 97.4[a]	188.0 ± 51.5[b]	158.0 ± 21.9[c]
(ng•hr/mL)	M6G	575.1 ± 263.5[d]	907.7 ± 158.6[e]	1,054.7 ± 154.5[f]
k_e	Morphine	0.0997 ± 0.0649[g]	0.0684 ± 0.0583[c]	0.0688 ± 0.0399[h]
(hr^{-1})	M6G	0.0768 ± 0.0448[a]	0.0761 ± 0.0384[e]	0.0720 ± 0.0365[i]
$t_{1/2}$	Morphine	10.8 ± 8.3[g]	21.0 ± 20.9[c]	18.4 ± 20.0[h]
(hr)	M6G	11.9 ± 6.1[a]	11.5 ± 6.2[e]	14.0 ± 11.4[i]
AUC_{0-1}	Morphine	11.2 ± 4.8	30.8 ± 12.1	7.5 ± 3.2
(ng•hr/mL)	M6G	4.8 ± 3.1	26.9 ± 13.3	18.3 ± 6.5
AUC_{0-2h}	Morphine	34.2 ± 13.7	67.0 ± 22.9	22.6 ± 7.5
(ng•hr/mL)	M6G	35.8 ± 18.9	161.4 ± 68.5	96.6 ± 20.3
AUC_{0-8h}	Morphine	120.9 ± 48.2	136.5 ± 43.4	89.3 ± 25.4
(ng•hr/mL)	M6G	266.6 ± 124.2	588.3 ± 151.5	545.2 ± 90.1
AUC_{0-12h}	Morphine	143.2 ± 57.8	148.1 ± 47.4	105.6 ± 29.5
(ng•hr/mL)	M6G	331.8 ± 149.8	660.3 ± 145.7	659.7 ± 116.5
AUC_{0-24h}	Morphine	181.1 ± 75.9	171.6 ± 55.2	139.4 ± 40.1
(ng•hr/mL)	M6G	446.8 ± 196.5	777.9 ± 156.9	844.4 ± 146.5

Values for T_{max} are medians and ranges.
n = 27 for Crushed intranasal MS Contin and n = 26 for both IDT-001 treatments, except as noted.
[a] n = 19 [b] n = 4 [c] n = 5 [d] n = 14 [e] n = 6 [f] n = 11
[g] n = 22 [h] n = 7 [i] n = 13
Source: Table 14.2.9-1, Table 14.2.9-2, Table 14.2.9-3, Table 14.2.9-4, Table 14.2.11-3, and Table 14.2.11-4.

The primary PD end point was drug liking, assessed according to a 100-point bipolar VAS for drug liking where a 0 to 100 point bipolar VAS was anchored on the left with

"strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100). In the clinical study report, the area under the effect (AUE) curve for the primary end point of drug liking VAS was calculated using raw scores from the bipolar scale. However, this makes interpretation of a neutral response difficult. Therefore, to account for the collection of data using a bipolar scale and to aid in interpretation of neutral responses, this end point was normalized by subtracting 50 mm from each time point and then recalculating key parameters (ie, AUE end points). By normalizing the data in this manner, neutral-responses would be approximately 0, negative results would correlate to drug disliking, and positive results would correlate to drug liking.

The study validity was confirmed by comparing crushed intranasal MS CONTIN versus intranasal placebo ARER. The least square (LS) mean for Emax for drug liking was significantly higher for crushed intranasal MS CONTIN than intranasal/oral placebo ARER (84.79 vs 54.22, $p < 0.0001$). The difference of LS means between the crushed intranasal MS CONTIN and intranasal/oral placebo ARER were also statistically significantly higher ($p < 0.0001$) for AUE0-1h, AUE0-2h, AUE0-8h, AUE0-12h, and AUE0-24h.

Table	**Overall Summary of Statistical Comparisons of Pharmacodynamic Parameters for the Primary End Point, Drug Liking (Pharmacodynamic Population, N = 25)**		
	LS Means; p-value[a]		
	Crushed Intranasal MS CONTIN vs Crushed Intranasal Morphine ARER[b]	**Intact Oral Morphine ARER vs Crushed Intranasal Morphine ARER[c]**	**Crushed Intranasal MS CONTIN vs Intact Oral Morphine ARER[d]**
E_{max} (mm)	84.79 vs 71.13; < 0.0001	67.03 vs 71.13; 0.1675	84.79 vs 67.03; < 0.0001
$AUE_{0\text{-}0.5h}$ (h•mm)	4.41 vs 1.41; 0.0002	0.28 vs 1.41; 0.1450	4.41 vs 0.28; < 0.0001
$AUE_{0\text{-}1h}$ (h•mm)	15.75 vs 6.15; < 0.0001	1.81 vs 6.15; 0.0571	15.75 vs 1.81; < 0.0001
$AUE_{0\text{-}2h}$ (h•mm)	44.55 vs 19.84; < 0.0001	11.79 vs 19.84; 0.0831	44.55 vs 11.79; < 0.0001
$AUE_{0\text{-}8h}$ (h•mm)	137.61 vs 89.28; 0.0193	58.91 vs 89.28; 0.1382	137.61 vs 58.91; 0.0002
$AUE_{0\text{-}24h}$ (h•mm)	181.81 vs 99.91; 0.0421	56.53 vs 99.91; 0.2782	181.81 vs 56.53; 0.0024
TE_{max} (h)	1.84 vs 2.33; 0.2579	2.41 vs 2.33; 0.8598	1.84 vs 2.41 0.1931
	% Subjects		
Reduction in E_{max}[e]	76%	33%	84%

AUE = area under the effect curve; E_{max} = maximum effect; LS = least square; TE_{max} = time of peak effect.

[a] = Unadjusted p-value.

[b] = 76% of subjects had a reduction in E_{max} with crushed intranasal Morphine ARER vs crushed intranasal MS CONTIN. Source for E_{max} and TE_{max} LS means is Study M-ARER-002 *Table 14.2.1-5*; source for AUE interval LS mean is Study M-ARER-002 *Table 14.2.13-3* Addendum.

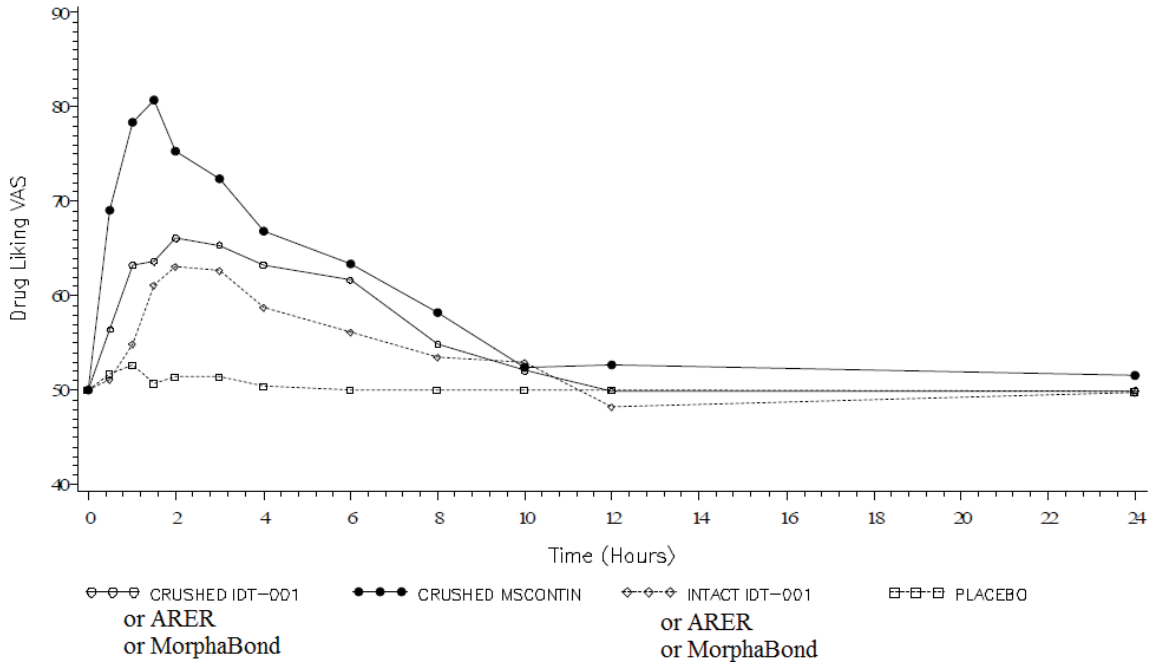
[c] = 33% of subjects had a reduction in E_{max} with crushed intranasal Morphine ARER compared with intact oral Morphine ARER. Source for E_{max} and TE_{max} LS mean is Study M-ARER-002 *Table 14.2.1-5*; AUE interval LS mean is from Study M-ARER-002 *Table 14.2.13-3* Addendum

[d] = 84% of subjects had a reduction in E_{max} with intact oral Morphine ARER vs crushed intranasal MS CONTIN. Source for E_{max} and TE_{max} LS mean is Study M-ARER-002 *Table 14.2.1-5*; AUE interval LS mean is from Study M-ARER-002 *Table 14.2.13-3* Addendum.

[e] = Source: Study M-ARER-002 *Table 11.4.2.5-1*.

Pharmacodynamic profile of drug liking (VAS scores) over time following different treatments is described in the figure below.

Figure: Mean Drug Liking Scores Over Time (Pharmacodynamic Population N = 25)



IDT-001 = MorphaBond or Morphine ARER; VAS = Visual analogue scale.

2.4 General Biopharmaceutics

The four different strengths of MorphaBond or Morphine ARER (15, 30, 60, or 100 mg) contain the described amount of morphine per tablet as the pentahydrated sulfate salt (morphine sulfate, USP). The sponsor attempted to make the product abuse-resistant, extended-release morphine tablet using a combination of excipients as presented in Table below.

Table	Excipients in Morphine ARER		
Hypromellose	(b) (4)	Colloidal silicon dioxide	Microcrystalline cellulose
Xanthan gum		(b) (4) gray, purple, orange, and blue	Lactose monohydrate
Sodium alginate	Magnesium stearate	(b) (4) black	Alginic acid
Mannitol	Polysorbate 80	--	--
ARER = abuse-resistant extended-release; -- = not applicable.			

What is the effect of food on PK of MorphaBond?

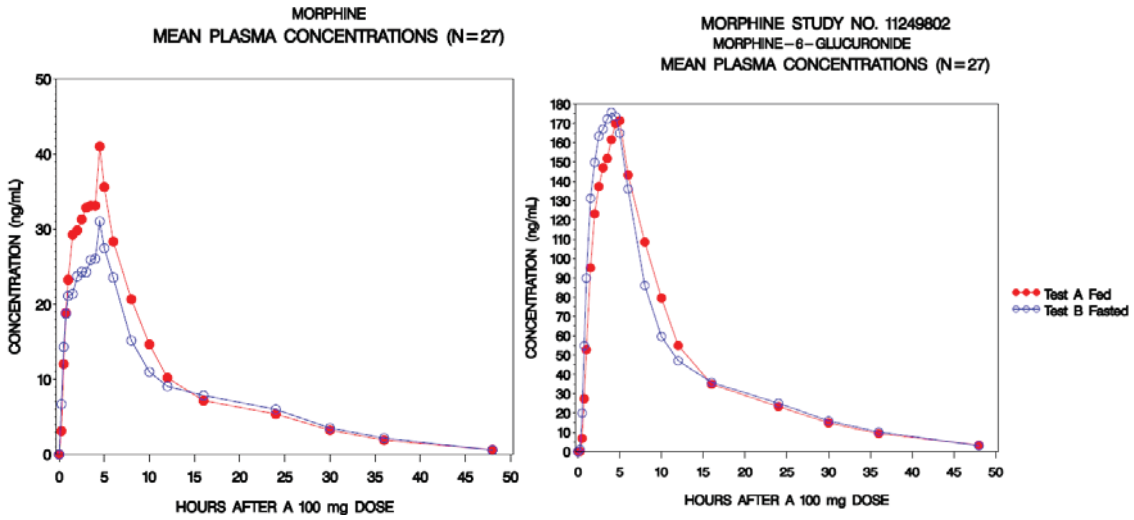
Taking MorphaBond with FDA high-fat meal increases Cmax of morphine by 33% without any effect on AUC.

Food effect study M-ARER-005: This was a single center, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study designed to evaluate the effect of food on the bioavailability of MorphaBond or Morphine ARER 100 mg tablets when dosed following a high-fat, high-calorie breakfast compared to when dosed after an overnight fast. Subjects were randomly assigned to 1 of 2 treatment sequences (sequence 1 = AB; sequence 2 = BA) of the following products: treatment (A) (MorphaBond or Morphine ARER [morphine sulfate pentahydrate extended-release] 100 mg tablet [lot number C003212] following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours) or treatment (B) (MorphaBond or Morphine ARER [morphine sulfate pentahydrate extended-release] 100 mg tablet [lot number C003212] following an overnight fast of at least 10 hours).

A single oral dose was administered to subjects on 2 separate occasions under fed or fasted conditions with a 7-day washout between doses. In order to minimize opioid side effects, subjects were administered naltrexone (1 x 50-mg tablet) with 240 mL of water at 12 hours (± 30 minutes) and 1.5 hours (± 30 minutes) prior to receiving each dose of study drug, and 12 hours (± 30 minutes) following each dose of study drug. Serial blood samples for determination of morphine and M6G plasma concentrations were collected on day 1 of each period. Plasma concentrations were measured using a validated analytical procedure.

A total of 28 healthy adult subjects were entered into the study, and 27 subjects (27 males) completed both periods of the study. One subject did not complete both periods of the study, and therefore their plasma samples were not analyzed

Figure: Pharmacokinetic Profile of Morphine (Left) and M6G (Right) Following Administration of MorphaBond 100 mg Tablet Under Fed (Filled circle) or Fasted (open circles) State.



Summaries of the effect of food on the PK bioavailability of MorphaBond or Morphine ARER and its metabolite, M6G, under fed and fasted conditions following oral administration of MorphaBond or Morphine ARER 100 mg tablet are presented in Table below.

Table	**Summary of Food Effect on Morphine: Mean (SD) Pharmacokinetic Parameters Following a Single Oral Dose of Morphine M-ARER 100-mg Tablet (Study M-ARER-005)**			
	Morphine ARER (Fed) (N = 27)		**Morphine ARER (Fasted) (N = 27)**	
Parameter	**Arithmetic Mean (SD)**	**%CV**	**Arithmetic Mean (SD)**	**%CV**
AUC_{0-t} (ng•h/mL)	419.12 (105.80)	25.24	367.69 (99.11)	26.95
$AUC_{0-\infty}$ (ng•h/mL)	440.61 (108.44)	24.61	395.06 (103.62)	26.23
$AUC_{0-t}/AUC_{0-\infty}$	0.9505 (0.0262)	2.76	0.9299 (0.0363)	3.91
C_{max} (ng/mL)	44.78 (11.78)	26.31	33.39 (7.79)	23.32
T_{max} (h)	3.60 (1.64)	45.40	3.76 (1.09)	28.91
T_{max} (h) Median (min-max)	4.50 (0.50-8.00)	--	4.00 (1.50-6.00)	--
K_{el} (l/h)	0.0740 (0.0175)	23.69	0.0711 (0.0176)	24.73
$t_{½}$ (h)	9.91 (2.49)	25.08	10.32 (2.56)	24.76

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point; C_{max} = maximum plasma concentration; CV = coefficient of variation; h = hour; K_{el} = elimination rate constant; max = maximum; min = minimum; SD = standard deviation; $t_{½}$ = half-life; T_{max} = time to peak concentration; -- = not applicable.
Morphine ARER (Fed) = morphine sulfate pentahydrate extended-release 100-mg tablet following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.
Morphine ARER (Fasted) = morphine sulfate pentahydrate extended-release 100-mg tablet following an overnight fast of at least 10 hours.
Data source: *M-ARER-005* in module 5

When dosing MorphaBond 100 mg tablets after a high-fat breakfast, morphine Cmax was increased by approximately 33%, and morphine median Tmax was extended by 0.5 hours compared with the fasted state. However, there was no change in overall extent of

morphine bioavailability, with the geometric 90% CI for both morphine AUC0-t and AUC0-∞ falling within the range 80% to 125%. Food does not have a significant effect on MorphaBond or Morphine ARER tablet so it can be taken regardless of food.

Table	**Summary of Food Effect on Morphine: Bioequivalence Parameters and Statistics (Geometric Mean) Based on ANOVA of Log-Transformed Data (N = 27) (Study M-ARER-005)**				
Parameter	**Morphine ARER (Fed)** [a]	**Morphine ARER (Fasted)** [a]	**Ratio of Means**	**90% CI** [b]	**Intra-subject %CV**
AUC_{0-t} (ng•h/mL)	408.25	356.53	1.1451	1.0963-1.1960	9.3696
$AUC_{0-\infty}$ (ng•h/mL)	429.78	383.62	1.1203	1.0701-1.1729	9.8784
C_{max} (ng/mL)	43.40	32.58	1.3324	1.2090-1.4684	21.1228

ANOVA = analysis of variance; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point; C_{max} = maximum plasma concentration; CI = confidence interval; CV = coefficient of variation; h = hour.

[a] = N = number of subjects with evaluable data for both the fed and fasted treatment arms.

[b] = Equivalent if CIs are within 0.8000-1.2500 (80.00% to 125.00%) limits.

Morphine ARER (Fed) = morphine sulfate pentahydrate extended-release 100-mg tablet following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.
Morphine ARER (Fasted) = morphine sulfate pentahydrate extended-release 100-mg tablet following an overnight fast of at least 10 hours.
Data source: *M-ARER-005* in module 5

Morphine ARER (Fed) = morphine sulfate pentahydrate extended-release 100-mg tablet following a standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.
Morphine ARER (Fasted) = morphine sulfate pentahydrate extended-release 100-mg tablet following an overnight fast of at least 10 hours.
Data source: *M-ARER-005* in module 5

2.5 Analytical

A liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method for the determination of morphine and its metabolite, morphine-6-glucuronide (M6G), was adopted and validated to support the human PK studies for MorphaBond or Morphine ARER. This method was determined to be sensitive and selective for the determination of morphine and M6G in human plasma. This method was utilized in studies M-ARER-002, M-ARER-004, M-ARER-005, M-ARER-006, M-ARER-007, M-ARER-008, M-ARER-009, and M-ARER-012. A summary of the bioanalytical and validation reports for the human studies in this submission is presented in the Table below.

Table Bioanalytical and Analytical Method Reports for Human Studies

Analytical Report Number/Study Number	Site of Sample Analysis	Bioanalytical Matrix	Bioanalytical Method Type	Analyte(s) Measured	Assay Range	Study Report Location
(b) (4) *VR11180-02*	(b) (4)	Plasma	LC-MS/MS	Morphine Metabolite M6G	0.725-145.0 ng/mL 2.5-500.0 ng/mL	module 5.3.1.4.1
(b) (4) *1211205/ M-ARER-002/*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.746-149.148 ng/mL 2.5-500.0 ng/mL	module 5.3.4.1.1
(b) (4) *1206133/ M-ARER-004*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.749-149.797 ng/mL 2.5-500.0 ng/mL	module 5.3.1.2.3
(b) (4) *1208162/ M-ARER-005*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.751-150.192 ng/mL 2.5-500.0 ng/mL	module 5.3.1.1.1
(b) (4) *1307288/ M-ARER-007*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.247-150.699 ng/mL 0.819-500.0 ng/mL	module 5.3.1.2.6
(b) (4) *1211207/ M-ARER-006*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.746-149.148 ng/mL 2.5-500.0 ng/mL	module 5.3.1.2.9
(b) (4) *1311357/ M-ARER-008*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.766-153.238 ng/mL 2.5-500.0 ng/mL	module 5.3.1.2.8
(b) (4) *1405470/ M-ARER-009*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.245-149.797 ng/mL 0.819-500.0 ng/mL	module 5.3.1.2.8
(b) (4) *1406486/ M-ARER-012*		Plasma	LC-MS/MS	Morphine Metabolite M6G	0.245-149.797 ng/mL 0.819-500.0 ng/mL	module 5.3.1.2.5

LC-MS/MS = liquid chromatography coupled to tandem mass spectrometry; M6G = morphine-6-glucuronide; USA = United States of America.

Since the application is solely relying on bioequivalence study M-ARER-004 (100 mg BE study) for bridging MorphaBond with MS Contin, an OSIS inspection of the clinical site and bioanalytical site inspection was requested after filing the NDA. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) declined to inspect the facilities and recommended accepting the data without an on-site inspection (See memo dated 4/7/2015 by Dr. Shila S. Nkah). The rationale for this decision was noted as: "The site listed below was inspected within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI)".

3 Labeling

Proposed labeling for MorphaBond relies on previously approved labeling for MS Contin. Clinical Pharmacology related labeling that is unique for the proposed product is described in this section. Sponsor proposed text appears as regular text, reviewer proposed changes appear as bold text for additions and strikethrough text for deletions.

12.3 Pharmacokinetics

BRAND NAME is an extended-release tablet containing morphine sulfate. Morphine is released from **BRAND NAME** 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 **BRAND NAME** 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 **BRAND NAME** is given on a fixed dosing regimen, steady-state is achieved in about a day.

(b) (4)

[redacted]

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Food Effect

The effect of food upon the systemic bioavailability of **BRAND NAME** has not been systematically evaluated for all strengths. Administration of a single dose of **BRAND NAME** with a standardized high-fat meal **resulted in a 33% increase in morphine peak plasma concentrations and no change in AUC compared to fasted state**. (b) (4)

(b) (4)

[redacted]

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.

Special Populations

Geriatric Patients

The pharmacokinetics of **BRAND NAME** have not been studied in elderly patients.

Pediatric Patients

The pharmacokinetics of **BRAND NAME** have not been studied in pediatric patients below the age of 18.

Gender

A gender analysis of pharmacokinetic data from healthy subjects taking morphine sulfate extended-release indicated that morphine concentrations were similar in males and females.

Race

Chinese subjects given intravenous morphine had a higher clearance when compared to Caucasian subjects (1852 +/- 116 ml/min compared to 1495 +/-80 ml/min).

Hepatic Impairment

Morphine pharmacokinetics are altered in individuals with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these subjects, indicating diminished metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. The AUC is increased and clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

4.2 Individual Study Reviews

4.2.1 Synopsis and additional PK analysis from Study M-ARER-004

STUDY TITLE: A Study to Evaluate the Relative Bioavailability of a Formulation of MorphaBond or Morphine ARER Tablets CII 100 mg (Morphine Sulfate Pentahydrate Extended Release Tablets) (Manufactured By: Cerovene, Inc.) compared to MS Contin® (morphine sulfate controlled-release) 100 mg Tablets CII (Purdue Pharma L.P.) in Healthy Volunteers under Fasted Conditions.

STUDY TYPE: Single-dose, randomized, two-treatment, two-period, two-sequence, crossover study, under fasted conditions.

OBJECTIVE: The purpose of this study was to evaluate the relative bioavailability of a test formulation of morphine sulfate pentahydrate extended release tablets CII 100 mg (manufactured by: Cerovene, Inc.) with the FDA Orange Book listed reference formulation, MS Contin® (morphine sulfate controlled-release) 100 mg tablets CII (Purdue Pharma L.P.) under fasted conditions, in healthy, adult subjects.

METHODOLOGY: This was a randomized, single-dose, two-treatment, two-period, two-sequence, crossover study under fasting conditions comparing equal doses of the test and reference products. The study was conducted with 54 (49 completing) healthy, adult subjects in accordance with Protocol No. P-ARER-45-04 (Revision 0). A single morphine sulfate modified release 100 mg tablet CII was administered to subjects following an overnight fast of at least 10 hours in each study period. The test formulation was MorphaBond or Morphine ARER 100 mg tablets CII (morphine sulfate pentahydrate extended release tablet) (manufactured by: Cerovene, Inc.) and the reference formulation was MS Contin® (morphine sulfate controlled-release) 100 mg tablets CII (Purdue Pharma L.P.). Subjects received the test product in one of the study periods and the reference product in the other study period according to the two-sequence randomization schedule. Blood samples were collected at pre-dose and at intervals over 48 hours after dosing each period. Subjects were confined at the clinical facility from 13 hours before dosing until after the 36-hour blood collection and returned to the clinical facility for the 48-hour blood pharmacokinetic sample. The interval between doses was 7 days. In order to minimize opioid side effects, all subjects were given a 50 mg oral naltrexone tablet with 240 mL of water at 12 hours (±30 minutes) and 1.5 hours (±30 minutes) before dosing with morphine and 12 hours (±30 minutes) after dosing with morphine.

Blood samples were collected at pre-dose and at intervals over 48 hours after dosing in each period. The plasma samples from all subjects who completed the study were shipped to the attention of (b) (4), (b) (4) for measurement of morphine and morphine-6-glucuronide (M6G) concentrations.

Pharmacostatistical analysis using average bioequivalence methodology was performed to evaluate the relative bioavailability of the test formulation to that of the reference product under fasted conditions. Equivalence was evaluated by a statistical comparison of the natural log-transformed data for the pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax for morphine. Analysis of M6G is presented as supportive information.

NUMBER OF SUBJECTS: A total of 54 healthy, adult subjects were enrolled, and 49 subjects completed the study. In order to ensure that up to 54 healthy adult subjects would be entered into the study, 58 subjects were pre-treated with naltrexone before initial morphine dosing in the first study period.

TEST PRODUCT A: MorphaBond or Morphine ARER (morphine sulfate pentahydrate extended release tablet), CII 100 mg Extended Release Tablet
Manufactured by: Cerovene, Inc.
Lot No.: C003212
Manufacture Date: 4/4/2012

REFERENCE PRODUCT B: MS Contin® (morphine sulfate controlled-release) CII 100 mg Controlled-Release Tablet
Purdue Pharma L.P.
Lot No.: W7G41
Expiration Date: DEC 12

NALTREXONE: Naltrexone Hydrochloride, USP
50 mg Tablet
Manufactured for: Accord Healthcare, Inc.;
Manufactured by: Intas Pharmaceuticals Limited
Lot No.: N01661
Expiration Date: JAN 2014

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, two-treatment, two-period, two-sequence crossover study. In each study period, a single morphine sulfate modified release tablet, 100 mg was administered to subjects following an overnight fast of at least 10 hours. Subjects received the test product in one study period and the reference product in the other study period. The order of treatment administration was according to the dosing randomization schedule. Each dose was separated by a 7 day interval. The study began dosing on 06/03/12 and was completed on 06/12/12.

STATISTICAL METHODS: Twenty-one (21) blood samples were collected from each subject during each period of the study: before dosing, then at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 30, 36 and 48* hours post-dose (* return sample) for analysis of plasma morphine and M6G concentrations. The analytical data were used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T½. The t in AUC0-t is the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS, Version 9.2) was used for all pharmacokinetic and statistical calculations.

Analyses of Variance (ANOVA) were performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment, and period. Sequence effects were tested against the Type III mean square term for subjects within sequence. All other main effects were tested against the mean squared error term.

Least squares means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were calculated. Confidence intervals (90%) for the comparison

of test and reference area and peak results were constructed to test two, one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals are presented for the ratio of the test-to-reference treatment means and the geometric mean ratios (obtained from logarithmic transformation). Determination of equivalence was based on the log-transformed data for plasma morphine. If the 90% confidence intervals for the pharmacokinetic parameters, AUC0-t, AUC0-inf, and Cmax, for morphine all fell within the range of 80.00-125.00%, then equivalence between the two formulations was considered to have been demonstrated. Analyses of the M6G results are presented as supportive information.

SUMMARY OF RESULTS: Mean plasma concentration versus time plots (linear) are presented in Figures 1 for morphine. Tables summarizing geometric means, ratio of means, and their associated 90% confidence intervals based on ANOVA (ln-transformed) are also provided in Tables 1 and 2.

A total of 54 subjects were entered into this study, and 49 subjects completed both periods of the study. Subjects 11, 15, 16, 30, and 45 did not complete both periods of the study, and therefore their plasma samples were not sent for bioanalysis. Three subjects, Subject 01, Period I, Test A, Subject 29, Period II, Reference B, and Subject 32, Period II, Test A, had an observed Cmax for morphine that was at the first post-dose pharmacokinetic sample point (0.5 hours). Originally these subjects were excluded from the statistical analysis; however, an additional analysis was performed including these subjects as per FDA guidance (Type C guidance meeting minutes dated 5/12/2014). The original study report incorrectly indicates that "As per FDA Guidance, these subjects were excluded from the statistical analysis; however, an additional analysis (for informational purposes) was performed including these subjects." The sponsor rectified the approach towards exclusion of selective blood sample data and submitted an Addendum to Study report (for studies M-ARER-004 amd M-ARER-007). The purpose of this addendum was to present the conclusions from the additional PK analysis including all subjects from the original study report (P-ARER-45-04) as the primary analysis based on clarifications provided by FDA to IDT. The PK analysis in the original clinical study report was conducted by both excluding and including 3 subjects (01, 29, and 32) who had an observed Cmax for morphine that was at the first postdose PK sample point (0.5 hours) in the respective period of the study (periods 1 or 2). Because it could not be determined for these 3 subjects whether this first time point was a valid reflection of Cmax, these 3 subjects were excluded from the primary statistical PK analysis. FDA's response to this approach to the PK analysis was that exclusion of data points from any study in the manner proposed was not acceptable without specific explanation provided. Thus, the PK analysis performed that was inclusive of all evaluable subjects located in appendix 16.1.9 of the original clinical study report P-ARER-45-04, is summarized in this addendum as the primary PK analysis for clinical study report P-ARER-45-04.

Based on this statistical PK analysis including all subjects, the test formulation of MorphaBond or Morphine ARER 100 mg tablets (morphine sulfate pentahydrate extended-release tablet) (manufactured by Cerovene, Inc.) met the 90% confidence interval criterion for natural logtransformed AUC0-t, AUC0-inf, and Cmax, and was therefore considered bioequivalent to an equal dosage of the reference formulation, MS CONTIN 100 mg tablets (morphine sulfate controlled-release tablet) (manufactured by

Purdue Pharma L.P.), in healthy adult subjects under fasted conditions (See Table 1 next page).
Peak plasma concentrations of morphine were observed around Median Tmax of 3 hours (Range: 0.5 – 5) for MorphaBond 100 tablets and 2.5 (Range: 0.5 – 8) for MS Contin.

Figure 1: Mean Morphine Plasma Concentration versus Time Plot (Linear) following administration of MorphaBond or MS Contin 100 mg (N = 49). Inset with expansion of the profile over first six hours.

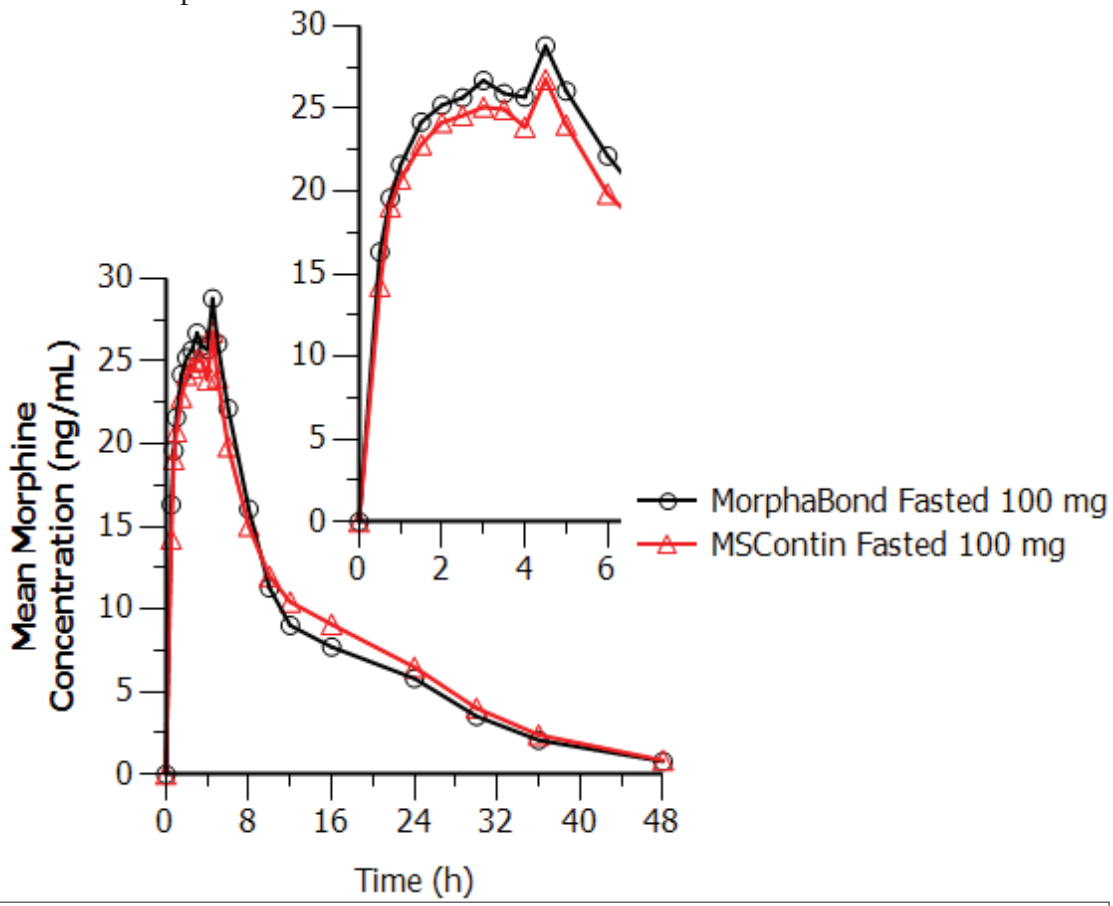


Table 1 Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Log-Transformed Data – Morphine

Parameter	Treatment (N)	Geometric Mean	Ratio	CI	Intra-subject % CV	P-value Period	P-value Sequence
AUC_{0-t} (ng·h/mL)	A (N = 49) B (N = 49)	372.46 383.28	0.9718	0.9413- 1.0022	8.6254	0.0117	0.0036
$AUC_{0-\infty}$ (ng·h/mL)	A (N = 47) B (N = 48)	391.92 402.92	0.9721	0.9409- 1.0045	8.9395	0.0158	0.0084
C_{max} (ng/mL)	A (N = 49) B (N = 49)	34.36 32.78	1.0480	0.9959- 1.1000	14.4977	0.0139	NC

ANOVA = analysis of variance; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak plasma concentration; CV = coefficient of variation; NC = not calculated.
Treatment A = Morphine ARER 100-mg tablets C-II (morphine sulfate pentahydrate extended-release tablet)
Treatment B = MS CONTIN® 100-mg tablets C-II (morphine sulfate controlled-release tablet)

Table 1.1: Summary of Morphine PK Parameters M-ARER-004 (n=49).						
PK Parameter	TRT	N	NMiss	NObs	Mean	SD
AUC0-1	A	49	0	49	13.7	5.3
AUC0-1	B	49	0	49	12.7	6.5
AUC0-2	A	49	0	49	37.5	11.8
AUC0-2	B	49	0	49	35.3	14.7
AUC0-3	A	49	0	49	63.3	18.7
AUC0-3	B	49	0	49	59.9	21.8
AUC0-4	A	49	0	49	89.3	25.7
AUC0-4	B	49	0	49	84.6	28.7
AUC0-5	A	49	0	49	116.6	32.6
AUC0-5	B	49	0	49	110.0	35.5
AUC0-6	A	49	0	49	140.7	39.1
AUC0-6	B	49	0	49	131.9	42.6
AUC0-7	A	49	0	49	161.3	44.7
AUC0-7	B	49	0	49	150.5	48.5
AUC0-8	A	49	0	49	178.9	49.2
AUC0-8	B	49	0	49	166.7	53.4
AUC0-12	A	49	0	49	226.5	58.8
AUC0-12	B	49	0	49	216.1	64.7
AUC0-24	A	49	0	49	313.9	79.3
AUC0-24	B	49	0	49	317.3	86.2
AUCall	A	49	0	49	375.7	99.5
AUCall	B	49	0	49	387.2	109.5
AUCINF_obs	A	49	0	49	392.2	105.0
AUCINF_obs	B	49	0	49	404.2	110.4
AUClast	A	49	0	49	372.1	100.6
AUClast	B	49	0	49	383.9	111.7
Cmax	A	49	0	49	34.3	10.7
Cmax	B	49	0	49	32.8	10.7
Tmax	A	49	0	49	3	(0.5 -5)
Tmax	B	49	0	49	2.5	(0.5 - 8)

Treatment A = Morphine ARER 100-mg tablets C-II (morphine sulfate pentahydrate extended-release tablet)
Treatment B = MS CONTIN® 100-mg tablets C-II (morphine sulfate controlled-release tablet)

Table 2	Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Log-Transformed Data – M6G						
Parameter	**Treatment (N)**	**Geometric Mean**	**Ratio**	**CI**	**Intra-subject % CV**	**P-value Period**	**P-value Sequence/Treatment**
AUC_{0-t} (ng·h/mL)	A (N = 49) B (N = 49)	1896.95 1934.91	0.9804	0.9589-1.0019	6.4589	NC	NC
$AUC_{0-\infty}$ (ng·h/mL)	A (N = 48) B (N = 49)	1975.65 2015.63	0.9802	0.9564-1.0039	7.0887	NC	NC
C_{max} (ng/mL)	A (N = 49) B (N = 49)	200.87 189.61	1.0594	1.0253-1.0935	9.8212	NC	0.0054[a]

ANOVA = analysis of variance; AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak plasma concentration; CV = coefficient of variation; NC = not calculated.
Treatment A = Morphine ARER 100-mg tablets C-II (morphine sulfate pentahydrate extended-release tablet)
Treatment B = MS CONTIN® 100-mg tablets C-II (morphine sulfate controlled-release tablet)
[a] = P-value treatment effect.

Table 2.1 Summary of Pharmacokinetic Parameters of Untransformed Data: M6G

Pharmacokinetic Parameter	**Arithmetic mean ± SD (%CV)**	
	Test A (N = 49*)	**Reference B (N = 49)**
AUC0-t (ng·hr/mL)	1896.7086 ± 390.8925 (20.6090)	1934.5068 ± 432.9830 (22.3821)
AUC0-inf (ng·hr/mL)	1974.7812 ± 408.4288 (20.6822)	2015.3448 ± 446.3187 (22.1460)
AUC0-t/AUC0-inf	0.9602 ± 0.0236 (2.4624)	0.9599 ± 0.0270 (2.8109)
Cmax (ng/mL)	200.7965 ± 42.0637 (20.9484)	189.5687 ± 44.5668 (23.5096)
Tmax (hr)	3.0922 ± 1.0336 (33.4276)	3.2245 ± 1.0003 (31.0225)
Tmax (hr) Median (Min – Max)	3.00 (1.5000 – 6.0000)	3.00 (1.5000 – 5.0000)
Kel (1/hr)	0.0818 ± 0.0305 (37.2330)	0.0803 ± 0.0205 (25.5560)
T½ (hr)	9.5039 ± 3.2315 (34.0015)	9.1372 ± 2.1278 (23.2869)

*N=48 for AUC0-inf, AUC0-t/AUC0-inf, Kel, and T½ for Test Product A.

4.2.2 Synopsis and additional PK analysis from Study M-ARER-007

STUDY TITLE: A Study to Evaluate the Relative Bioavailability of a Test Formulation of MorphaBond or Morphine ARER (Morphine Sulfate Pentahydrate Extended-Release) Tablets CII, 15 mg (Cerovene, Inc.) compared to MS Contin® (morphine sulfate controlled-release) Tablets CII, 15 mg (Purdue Pharma L.P.) in Healthy Volunteers under Fasted Conditions.

STUDY TYPE: Single-dose, randomized, two-treatment, two-period, two-sequence, crossover study under fasted conditions.

OBJECTIVE: The objective of this study was to evaluate the relative bioavailability of a test formulation of MorphaBond or Morphine ARER (morphine sulfate pentahydrate extended-release) tablets CII, 15 mg (Cerovene, Inc.) compared to MS Contin® (morphine sulfate controlled-release) Tablets CII, 15 mg (Purdue Pharma L.P.) in healthy adult subjects under fasted conditions.

METHODOLOGY: This was a randomized, single-dose, two-treatment, two-period, two-sequence, crossover study under fasting conditions comparing equal doses of the test and reference products. The study was conducted with 32 (28 completing) healthy, adult subjects in accordance with Protocol No. M-ARER-007 (Revision 0). A single morphine sulfate modified-release 15 mg tablet CII was administered to subjects following an overnight fast of at least 10 hours in each study period. The test formulation was MorphaBond or Morphine ARER 15 mg tablets CII (morphine sulfate pentahydrate extended-release tablet) (Cerovene, Inc.) and the reference formulation was MS Contin® (morphine sulfate controlled-release) 15 mg tablets CII (Purdue Pharma L.P.). Subjects received the test product in one of the study periods and the reference product in the other study period according to the two-treatment, two-sequence randomization schedule. Blood samples were collected at pre-dose and at intervals over 48 hours after dosing each period.

Subjects were confined at the clinical facility from 13 hours before dosing until after the 36-hour blood collection and returned to the clinical facility for the 48-hour blood pharmacokinetic sample. The interval between doses was 7 days.

To minimize opioid side effects, a 50 mg oral naltrexone tablet with 240 mL of room temperature water was given to all subjects at 12 hours (±30 minutes) and 1.25 hours (±15 minutes) before study drug dosing and 12 hours (±30 minutes) after study drug dosing in each study period.

Blood samples were collected at pre-dose and at intervals over 48 hours after dosing in each period. The plasma samples from all subjects who completed the study were shipped to the attention of (b) (4) (b) (4) (b) (4) for measurement of morphine and morphine-6-glucuronide (M6G) concentrations.

Pharmacokinetic and statistical analyses using average bioequivalence methodology was performed to evaluate the relative bioavailability of the test product to that of the reference product under fasted conditions. Bioequivalence was evaluated by a statistical

comparison of the natural log-transformed data for the pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax for morphine. Analysis of M6G is presented as supportive information.

NUMBER OF SUBJECTS: A total of 32 healthy, adult subjects were enrolled, and 28 subjects completed the study. To ensure that 32 healthy adult subjects would be entered into the study, 36 subjects were pre-treated with naltrexone before morphine dosing in the first study period.

TEST PRODUCT A:	Morphine ARER (morphine sulfate pentahydrate extended-release tablet), CII 15 mg Extended Release Tablet Cerovene, Inc. Lot No.: C006413
REFERENCE PRODUCT B:	MS Contin® (morphine sulfate controlled-release), CII 15 mg Controlled-Release Tablet Purdue Pharma L.P. Lot No.: WFF31 Expiration Date: MAR 14
NALTREXONE:	Naltrexone Hydrochloride, USP 50 mg Tablet Mallinckrodt Inc.; (b) (4) Lot No.: 1170W86216 Expiration Date: 11/2017

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, two-treatment, two-period, two-sequence crossover study. In each study period, a single morphine sulfate modified-release tablet, 15 mg was administered to subjects following an overnight fast of at least 10 hours. Subjects received the test product in one study period and the reference product in the other study period. The order of treatment administration was according to the dosing randomization schedule. Each dose was separated by a 7 day interval. The study began dosing on 07/09/13 and was completed on 07/18/13.

STATISTICAL METHODS: Twenty-one (21) blood samples were collected from each subject during each period of the study: before dosing, then at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 30, 36 and 48* hours post-dose (* return sample) for analysis of plasma morphine and M6G concentrations. The analytical data were used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T½. The t in AUC0-t is the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS, Version 9.3) was used for all pharmacokinetic and statistical calculations. Analyses of Variance (ANOVA) were performed using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of sequence, subject within sequence, treatment, and period. Sequence effects were tested against the Type III mean square term for subjects within sequence. All other main effects were tested against

the mean squared error term. Least squares means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were calculated.

For morphine, the 90% confidence intervals for the comparison of the test to the reference AUC0-t, AUC0-inf, and Cmax were constructed to test two, one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals are presented for the geometric mean ratios (obtained from logarithmic transformed data).

Evaluation of bioequivalence was based on the ln-transformed data for morphine. If the 90% confidence intervals for natural log-transformed AUC0t, AUC0inf, and Cmax fell within the range of 80.00-125.00%, then the test formulation was considered bioequivalent to the reference formulation. M6G data are provided for informational purposes only.

SUMMARY OF RESULTS: Mean plasma concentration versus time plots (linear) are presented in Figures 1 for morphine. The mean test-to-reference ratios and their associated 90% confidence intervals are also provided in Table 1 for morphine and Table 2 for M6G. Thirty-two (32) subjects were dosed with study drug in Period I, and twenty-eight (28) subjects completed the clinical portion of the study. Subjects 04, 20, 21, and 32 did not complete both periods of the study; therefore, plasma samples from these participants were not sent for bioanalysis. The plasma samples from 28 subjects were assayed for morphine and M6G. There are 56 sets of data (28 test and 28 reference datasets) from 28 subjects eligible for pharmacokinetic and statistical analyses of morphine and M6G (informational purposes) for this study.

The PK analysis in the original clinical study report was conducted by both excluding and including 5 subjects (07, 10, 12, 14, and 18) who had an observed Cmax for morphine that was at the first post-dose PK sample point (0.5 hours) in the respective period of the study (periods 1 or 2). Because it could not be determined for these 5 subjects whether this first time point was a valid reflection of Cmax, these 5 subjects were excluded from the primary statistical PK analysis. FDA's response to this approach to the PK analysis was that exclusion of data points from any study in the manner proposed was not acceptable without specific explanation provided. Thus, the PK analysis performed that was inclusive of all evaluable subjects located in appendix 16.1.9 of the original clinical study report M-ARER-007, is summarized in this addendum as the primary PK analysis for clinical study report M-ARER-007. Peak plasma concentrations of morphine were observed around Median Tmax of 2.25 hours (Range: 0.5 – 6 hours) for MorphaBond 15 mg tablets and 1.5 hours (Range: 0.5 – 4.5 hours) for MS Contin 15 mg tablets.

Based on the statistical analysis of morphine, the test product of MorphaBond or Morphine ARER 15 mg tablets CII (morphine sulfate pentahydrate extended-release tablet) (Cerovene, Inc.) meets the 90% CI criterion for natural log-transformed AUC0-t, AUC0-inf, and Cmax, and was therefore considered bioequivalent to an equal dosage of the reference formulation, MS CONTIN (morphine sulfate controlled-release) 15 mg tablets CII (Purdue Pharma L.P.) in healthy adult subjects under fasted conditions.

Figure 1: Mean Morphine Concentration Profile following adminsitration of MorphaBond 15 mg or MS Contin 15 mg in fasting subjects (n=28). Inset with expansion of the profile over first six hours.

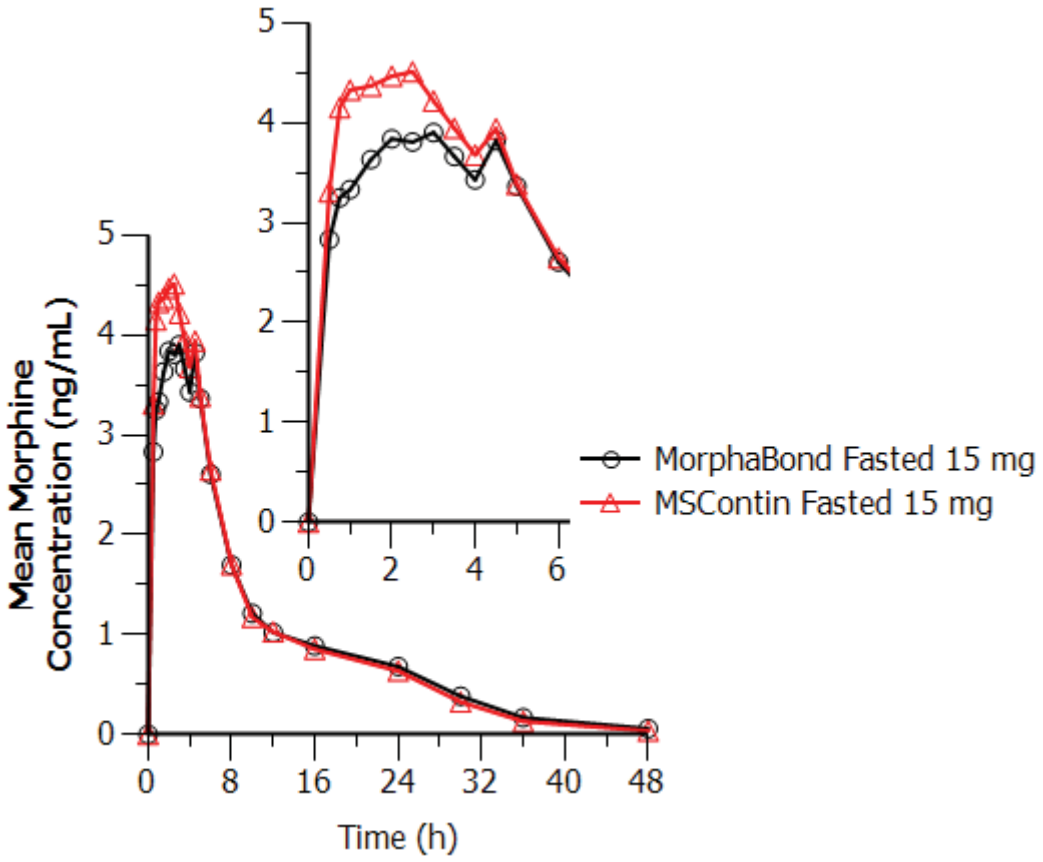


Table 1 Plasma Pharmacokinetic and Bioequivalence Parameters of Morphine

Parameter	Treatment (N)	LS Geometric Mean	Contrast (No. of Subjects)	LS Geometric Mean Ratio (%)	90% CI (%)	CV (%)	P-value Period	P-value Sequence
AUC_{0-t} (ng·h/mL)	A (N = 28) B (N = 28)	42.1 43.7	A vs B (N = 28)	96.35	89.08-104.21	17.3	0.6604	0.1060
$AUC_{0-\infty}$ (ng·h/mL)	A (N = 25) B (N = 22)	49.0 49.7	A vs B (N = 21)	98.73	90.84-107.30	15.7	0.8503	0.3249
C_{max} (ng/mL)	A (N = 28) B (N = 28)	4.57 5.23	A vs B (N = 28)	87.38	79.08-96.55	22.1	0.3102	0.8817

AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = peak plasma concentration; CV = coefficient of variation; LS = least squares.
Treatment A = Morphine ARER 15-mg tablets C-II (morphine sulfate pentahydrate extended-release tablet)
Treatment B = MS CONTIN 15-mg tablets C-II (morphine sulfate controlled-release tablet)

Table 1.1: Summary of Morphine PK Parameters M-ARER-007 (n=28).						
PK Parameter	Treatment	N	NMiss	NObs	Mean	SD
AUC0-1	A	24	4	28	2.3	1.0
AUC0-1	B	24	4	28	2.9	1.2
AUC0-2	A	24	4	28	5.8	2.3
AUC0-2	B	24	4	28	7.3	2.7
AUC0-3	A	24	4	28	9.6	3.7
AUC0-3	B	24	4	28	11.8	4.3
AUC0-4	A	24	4	28	13.2	5.1
AUC0-4	B	24	4	28	15.9	5.6
AUC0-5	A	24	4	28	16.8	6.2
AUC0-5	B	24	4	28	19.7	6.7
AUC0-6	A	24	4	28	19.9	7.1
AUC0-6	B	24	4	28	22.8	7.5
AUC0-7	A	24	4	28	22.3	7.8
AUC0-7	B	24	4	28	25.2	8.2
AUC0-8	A	24	4	28	24.2	8.5
AUC0-8	B	24	4	28	27.3	8.7
AUC0-12	A	24	4	28	29.5	10.4
AUC0-12	B	24	4	28	32.5	10.4
AUC0-24	A	24	4	28	39.7	13.7
AUC0-24	B	24	4	28	42.4	13.6
AUCall	A	28	0	28	45.7	16.5
AUCall	B	28	0	28	46.7	16.0
AUCINF_obs	A	28	0	28	50.2	17.1
AUCINF_obs	B	28	0	28	52.1	16.8
AUClast	A	28	0	28	44.5	16.4
AUClast	B	28	0	28	45.5	16.1
Cmax	A	28	0	28	4.8	1.7
Cmax	B	28	0	28	5.5	1.8
Tmax	A	28	0	28	2.25	(0.5 - 6)
Tmax	B	28	0	28	1.5	(0.5 - 4.5)

*__Treatment A (test):__ 1 x Morphine ARER (morphine sulfate pentahydrate extended-release tablet), CII, 15 mg (Cerovene, Inc.)
__Treatment B (reference):__ 1 x MS Contin® (morphine sulfate controlled-release) tablet, CII, 15 mg (Purdue Pharma L.P.)

Table 2	Plasma Pharmacokinetic and Bioequivalence Parameters of M6G						
Parameter	**Treatment (N)**	**LS Geometric Mean**	**Contrast (No. of Subjects)**	**LS Geometric Mean Ratio (%)**	**CV (%)**	**P-value Period**	**P-value Sequence**
AUC_{0-t} (ng·h/mL)	A (N = 28) B (N = 28)	247.1 259.4	A vs B (N = 28)	95.28	5.2	0.1065	0.7174
$AUC_{0-\infty}$ (ng·h/mL)	A (N = 25) B (N = 26)	271.3 282.4	A vs B (N = 24)	96.05	5.1	0.0106	0.9744
C_{max} (ng/mL)	A (N = 28) B (N = 28)	28.50 33.11	A vs B (N = 28)	86.07	11.9	0.0560	0.6676

AUC_{0-t} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; C_{max} = peak plasma concentration; CV = coefficient of variation; LS = least squares.
Treatment A = Morphine ARER 15-mg tablets C-II (morphine sulfate pentahydrate extended-release tablet)
Treatment B = MS CONTIN 15-mg tablets C-II (morphine sulfate controlled-release tablet

Table 2.1 Summary of Pharmacokinetic Parameters of Untransformed Data: M6G (N = 28)

Pharmacokinetic Parameter	Treatment*	N	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
AUC_{0-t} (ng·hr/mL)	A	28	249.7132 ± 37.4792 (15.0089)	191.5394	243.7711	364.3719
	B	28	261.6829 ± 40.0013 (15.2862)	202.3439	259.6206	391.2521
AUC_{0-inf} (ng·hr /mL)	A	25	274.1441 ± 39.9489 (14.5722)	212.5899	271.6999	400.5341
	B	26	285.6527 ± 41.0107 (14.3569)	219.1517	280.7578	417.4274
AUC_{0-t}/AUC_{0-inf} ratio	A	25	0.9287 ± 0.0298 (3.2086)	0.8633	0.9320	0.9653
	B	26	0.9261 ± 0.0459 (4.9518)	0.7488	0.9364	0.9691
C_{max} (ng /mL)	A	28	29.0223 ± 5.3228 (18.3404)	21.7380	27.5225	43.7420
	B	28	33.4301 ± 5.1175 (15.3079)	24.8730	31.9960	43.8130
T_{max} (hr)	A	28	3.0714 ± 0.8683 (28.2707)	1.5000	3.0000	5.0000
	B	28	2.5018 ± 0.6102 (24.3895)	1.5000	2.5000	3.5000
K_{el} (1/hr)	A	25	0.0745 ± 0.0225 (30.2555)	0.0370	0.0660	0.1238
	B	26	0.0722 ± 0.0252 (34.9272)	0.0269	0.0667	0.1468
T½ (hr)	A	25	10.1544 ± 3.0988 (30.5166)	5.5970	10.5040	18.7440
	B	26	10.8388 ± 4.2973 (39.6476)	4.7190	10.3915	25.7310

***Treatment A (test):** 1 x Morphine ARER (morphine sulfate pentahydrate extended-release tablet), CII, 15 mg (Cerovene, Inc.)
Treatment B (reference): 1 x MS Contin® (morphine sulfate controlled-release) tablet, CII, 15 mg (Purdue Pharma L.P.)

4.2.3 Synopsis and Additional PK analysis from Study M-ARER-012.

STUDY TITLE: A Study to Evaluate the Relative Bioavailability of a Test Formulation of MorphaBond or Morphine ARER (Morphine Sulfate Pentahydrate Extended-Release) Tablets, 30 mg (Inspirion Delivery Technologies LLC) Compared to MS Contin (Morphine Sulfate Extended-Release) Tablets CII, 30 mg (Purdue Pharma L.P.) in Healthy Adult Subjects under Fasted Conditions.

STUDY DURATION: The time from first subject dosed to when the last subject completed was about 9 days.

STUDY TYPE: Open-label, single-dose, randomized, two-treatment, two-period, two sequence, crossover study under fasted conditions.

OBJECTIVE: The objective of this study was to evaluate the relative bioavailability of a test formulation of MorphaBond or Morphine ARER (morphine sulfate pentahydrate extended-release) tablet, 30 mg CII (Cerovene, Inc.) compared to the marketed reference product, MS Contin® (morphine sulfate controlled-release) tablets 30 mg CII (Purdue Pharma L.P.) under fasted conditions in healthy adult subjects.

METHODOLOGY: This was an open-label, randomized, single-dose, two-treatment, two-period, two-sequence, crossover study under fasting conditions comparing equal doses of the test and reference products. The study was conducted with 42 (41 completing) healthy, adult subjects in accordance with Protocol No. M-ARER-012 (Revision 1). A single morphine sulfate extended-release 30 mg tablet CII was administered to subjects following an overnight fast of at least 10 hours in each study period. The test formulation was MorphaBond or Morphine ARER (morphine sulfate pentahydrate extended-release) tablet, 30 mg CII (Cerovene, Inc.) and the reference formulation was MS Contin® (morphine sulfate controlled-release) tablets 30 mg CII (Purdue Pharma L.P.). Subjects received the test product in one of the study periods and the reference product in the other study period according to the two-treatment, two-sequence randomization schedule. Blood samples were collected at pre-dose and at intervals over 48 hours after dosing each period. Subjects were confined at the clinical facility from 13 hours before dosing until after the 36-hour blood collection and returned to the clinical facility for the 48-hour blood pharmacokinetic sample. The interval between morphine doses was 7 days. To minimize opioid side effects, a 50 mg oral naltrexone tablet with 240 mL of room temperature water was given to all subjects at 12 hours (±30 minutes) and 1.25 hours (±15 minutes) before study drug dosing and 12 hours (±30 minutes) after study drug dosing in each study period.

Blood samples were collected at pre-dose and at intervals over 48 hours after dosing in each period. The plasma samples from all subjects who completed the study were shipped to the attention of (b) (4) (b) (4) for measurement of morphine and morphine-6-glucuronide (M6G) concentrations.

Pharmacokinetic and statistical analyses using average bioequivalence methodology were performed to evaluate the bioavailability of the test product relative to that of the reference product under fasted conditions. Bioequivalence was evaluated by a statistical

comparison of the natural log-transformed data for the pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax for morphine. Analysis of M6G is presented as supportive information.

NUMBER OF SUBJECTS: A total of 42 healthy, adult subjects were enrolled, and 41 subjects completed the study. To ensure that 42 healthy adult subjects were entered into the study, 48 subjects were pre-treated with naltrexone before morphine dosing in the first study period.

TEST PRODUCT A:	Morphine ARER Tablet, 30 mg (Morphine Sulfate Pentahydrate Extended-Release Tablet) CII Cerovene, Inc. Lot No.: C006113 Manufacture Date: 04/11/2013
REFERENCE PRODUCT B:	MS Contin® (morphine sulfate controlled-release) Tablets 30 mg CII Purdue Pharma L.P. Lot No.: WHR51 Expiration Date: SEP14
NALTREXONE:	Naltrexone Hydrochloride Tablets USP 50 mg Manufactured By: Barr Laboratories, Inc.; Manufactured For: Teva Pharmaceuticals USA Lot No.: 34007244C Expiration Date: 01/2015

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, two-treatment, two-period, two-sequence crossover study. In each study period, a single morphine sulfate extended-release tablet, 30 mg was administered to subjects following an overnight fast of at least 10 hours. Subjects received the test product in one study period and the reference product in the other study period. The order of treatment administration was according to the dosing randomization schedule. Each dose was separated by a 7 day interval. The study began dosing on 06/10/14 and was completed on 06/19/14.

STATISTICAL METHODS: Twenty-two (22) blood samples were collected from each subject during each period of the study: up to 60 minutes before dosing (0 hr), then at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48* hours post-dose (* return sample) for measurement of plasma morphine and M6G concentrations. The analytical data were used to calculate the pharmacokinetic parameters: AUC0-t, AUC0-inf, Cmax, Tmax, Kel and T½. The t in AUC0-t is the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS®, Version 9.4) was used for all pharmacokinetic and statistical calculations. Analyses of Variance (ANOVA) were performed on untransformed pharmacokinetic parameters Cmax, AUC0-t, AUC0-inf, T½, Kel, Tmax and ln-transformed Cmax, AUC0-t, AUC0-inf using the General Linear Model (GLM) procedure of SAS with hypothesis testing for treatment effects at $\alpha = 0.05$. The statistical model contained main effects of

sequence, subject within sequence, treatment, and period. Sequence effects were tested at the 0.10 level of significance against the Type III mean square term for subjects within sequence. All other main effects were tested against the mean squared error term. Least squares means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) were estimated. Confidence intervals (90%) for the comparison of the test and reference AUC0-t, AUC0-inf, and Cmax were constructed to test two one-sided hypotheses at the $\alpha = 0.05$ level of significance. The confidence intervals are presented for the geometric mean ratios (obtained from logarithmic transformed data).

Evaluation of bioequivalence was based on the ln-transformed data for morphine. If the 90% confidence intervals on the geometric mean test-to-reference ratio for ln transformed AUC0t, AUC0inf, and Cmax fell within the range of 80.00-125.00%, then the test-formulation was considered bioequivalent to the reference formulation under fasted conditions. M6G data are provided for informational purposes only.

SUMMARY OF RESULTS: Mean plasma concentration versus time plots (linear) are presented in Figure 1 for morphine. The mean test-to-reference ratios and their associated 90% confidence intervals are also provided in Table 1 for morphine and Table 2 for M6G. Forty-two (42) subjects were enrolled in the study, and all subjects were healthy adults. Forty-two (42) subjects were dosed in Period I, forty-one (41) subjects were dosed in Period II, and forty-one (41) subjects completed the clinical portion of the study. Subject 30 did not complete both periods of the study; therefore, plasma samples from this participant were not sent for bioanalysis. The plasma samples from 41 subjects were assayed for morphine and M6G.

There are 82 sets of data (41 Test A and 41 Reference B) from 41 subjects included in the final bioequivalence analysis for morphine and the analysis of M6G (informational purposes). For the natural log-transformed data for morphine with 41 evaluable subjects, the 90% confidence intervals on the least squares geometric mean test-to-reference ratios for AUC0-t and AUC0-inf fall within the standard bioequivalence range of 80.00-125.00%. The geometric mean test-to-reference Cmax ratio for morphine (80.65%) is low and the associated 90% confidence interval on the ratio is not within the standard bioequivalence range of 80.00-125.00%. Results indicate that under fasting conditions, the Cmax of morphine for the MorphaBond or Morphine ARER 30 mg tablet was 13% lower than the mean Cmax obtained for MS CONTIN. Peak plasma concentrations of morphine were observed around Median Tmax of 2 hours (Range: 0.5 – 6 hours) for MorphaBond 30 mg tablets and 2.5 hours (Range: 0.5 – 6 hours) for MS Contin.

Figure 1: Mean Morphine Concentration Profile following adminsitration of MorphaBond 30 mg or MS Contin 30 mg in fasting subjects (n=41). Inset with expansion of the profile over first six hours.

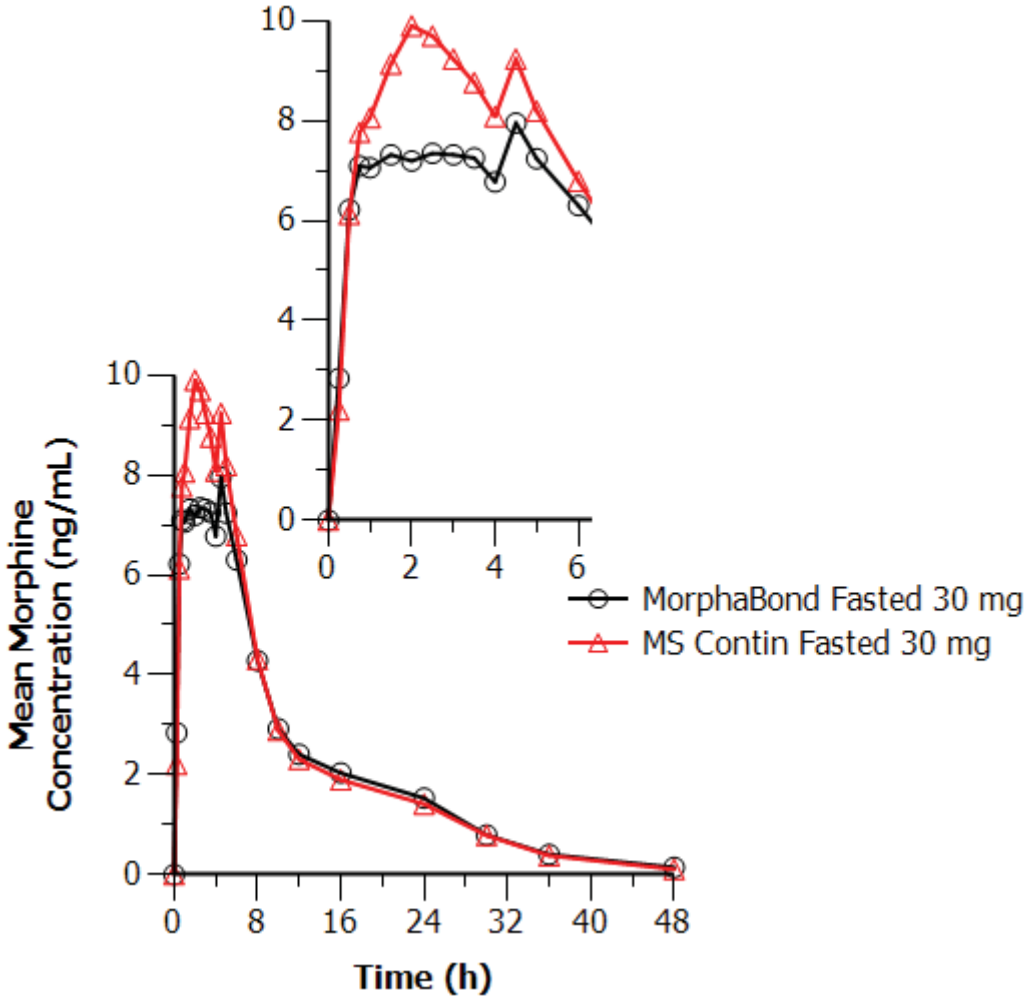


Table 1	Summary of Pharmacokinetic and Bioequivalence Parameters – Morphine ARER 30-mg Tablet (Study M-ARER-012)						
Parameter	**Treatment**	**LS Geo. Mean**	**Mean Ratio (%)**	**90% CI (%)**	**%CV**	***P*-value Period**	***P*-value Sequence**
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	96.5 101.0	95.55	92.12-99.11	9.8	0.4584	0.8512
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 39) MS CONTIN (N = 35)	103.2 106.9	96.61	92.90-100.47	9.6	0.6597	0.5574
C_{max} (ng/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	9.31 11.5	80.65	76.24-85.32	15.2	0.9115	0.4270

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. mean = geometric mean; h = hour; LS = least squares.
Morphine ARER = morphine sulfate pentahydrate extended-release 30-mg tablet.
MS CONTIN = morphine sulfate controlled-release 30-mg tablet.
Data source: *M-ARER-012* in module 5

Table 1.1: Summary of Morphine PK Parameters M-ARER-012 (n=41)						
PK Parameter	TRT	N	NMiss	NObs	Mean	SD
AUC0-1	A	41	0	41	4.9	2.3
AUC0-1	B	41	0	41	5.0	2.6
AUC0-2	A	41	0	41	12.1	4.6
AUC0-2	B	41	0	41	14.1	6.5
AUC0-3	A	41	0	41	19.4	6.7
AUC0-3	B	41	0	41	23.7	9.9
AUC0-4	A	41	0	41	26.6	8.3
AUC0-4	B	41	0	41	32.4	12.5
AUC0-5	A	41	0	41	34.1	9.6
AUC0-5	B	41	0	41	41.1	14.1
AUC0-6	A	41	0	41	40.8	11.0
AUC0-6	B	41	0	41	48.6	15.3
AUC0-7	A	41	0	41	46.6	12.5
AUC0-7	B	41	0	41	54.8	16.6
AUC0-8	A	41	0	41	51.4	13.8
AUC0-8	B	41	0	41	59.7	17.7
AUC0-12	A	41	0	41	64.0	17.6
AUC0-12	B	41	0	41	72.1	20.6
AUC0-24	A	41	0	41	87.1	22.9
AUC0-24	B	41	0	41	93.7	26.4
AUCall	A	41	0	41	100.9	26.6
AUCall	B	41	0	41	106.7	30.7
AUCINF_obs	A	41	0	41	104.7	27.1
AUCINF_obs	B	41	0	41	111.0	31.4
AUClast	A	41	0	41	99.8	27.0
AUClast	B	41	0	41	105.2	30.8
Cmax	A	41	0	41	9.8	3.5
Cmax	B	41	0	41	12.4	5.4
Tmax	A	41	0	41	2	(0.5 - 6)
Tmax	B	41	0	41	2.5	(0.5 - 6)

Treatment A: MorphaBond 30 mg Fasted (Test).

Treatment B: MS Contin 30 mg Fasted (Reference).

Table 2	Summary of Pharmacokinetic and Bioequivalence Parameters – M6G (Study M-ARER-012)						
Parameter	**Treatment**	**LS Geo. Mean**	**Mean Ratio (%)**	**90% CI (%)**	**%CV**	***P*-value Period**	***P*-value Sequence**
AUC_{0-t} (ng•h/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	539.9 580.4	93.03	90.69-95.42	6.8	0.7993	0.8536
$AUC_{0-\infty}$ (ng•h/mL)	Morphine ARER (N = 39) MS CONTIN (N = 41)	568.2 609.7	93.19	90.57-95.89	7.5	0.9005	0.9730
C_{max} (ng/mL)	Morphine ARER (N = 41) MS CONTIN (N = 41)	57.8 72.8	79.35	76.33-82.48	10.4	0.4840	0.0823

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration time point;
CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; Geo. Mean = geometric mean; h = hour; LS = least squares; M6G = morphine-6-glucuronide.
Morphine ARER = morphine sulfate pentahydrate extended-release 30-mg tablet.
MS CONTIN = morphine sulfate controlled-release 30-mg tablet.
Data source: *M-ARER-012* in module 5

Table 2.1 Summary of Pharmacokinetic Parameters of Untransformed Data: M6G (N =41)

Pharmacokinetic Parameter	Treatment*	N	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
AUC_{0-t} (ng·hr/mL)	Test A	41	549.7349 ± 102.9807 (18.7328)	309.9800	549.6119	801.0431
	Reference B	41	592.2130 ± 118.4466 (20.0007)	331.9305	595.3096	935.9960
$AUC_{0-\infty}$ (ng·hr/mL)	Test A	39	576.3805 ± 98.3450 (17.0625)	383.7186	569.8908	811.1959
	Reference B	41	615.3565 ± 119.5025 (19.4200)	347.5277	611.5076	944.4244
AUC_{0-t}/ $AUC_{0-\infty}$	Test A	39	0.9638 ± 0.0244 (2.5351)	0.8812	0.9698	0.9882
	Reference B	41	0.9618 ± 0.0241 (2.5067)	0.8851	0.9702	0.9911
C_{max} (ng/mL)	Test A	41	58.8288 ± 12.1100 (20.5852)	38.3980	58.6060	91.7510
	Reference B	41	74.7985 ± 18.4049 (24.6059)	45.7520	72.1250	129.9400
T_{max} (hr)	Test A	41	3.0366 ± 0.9836 (32.3901)	1.5000	3.0000	6.0000
	Reference B	41	2.8537 ± 0.9236 (32.3657)	1.5000	2.5000	6.0000
K_{el} (hr^{-1})	Test A	39	0.0887 ± 0.0310 (34.9621)	0.0355	0.0848	0.1606
	Reference B	41	0.0822 ± 0.0220 (26.7428)	0.0480	0.0820	0.1349
$T_{½}$ (hr)	Test A	39	8.8363 ± 3.2599 (36.8917)	4.3150	8.1754	19.5425
	Reference B	41	9.0198 ± 2.3670 (26.2426)	5.1371	8.4499	14.4378

*__Treatment A (test):__ 1 x Morphine ARER (morphine sulfate pentahydrate extended-release) tablet, 30 mg CII (Cerovene, Inc.)
__Treatment B (reference):__ 1 x MS Contin® (morphine sulfate controlled-release) tablets 30 mg CII (Purdue Pharma L.P.)

4.2.4 Clinical Pharmacology Filing Memo (Completed)

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	206544	Brand Name	Morphine ARER
OCP Division (I, II, III, IV, V)	DCPII	Generic Name	Morphine Sulfate Extended Release Tablets
Medical Division	DAAAP	Drug Class	Opioid Agonist
OCP Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	Chronic Pain Management
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Tablets
Pharmacometrics Reviewer	-	Dosing Regimen	Twice daily
Date of Submission	11/21/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	8/14/2014	Sponsor	Inspiron Delivery Technologies, LLC
Medical Division Due Date	9/21/2014	Priority Classification	Standard
PDUFA Due Date	9/21/2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	Pilot PK studies 100 mg BA/BE C11-0614 100 mg BA/BE C10-2222 M-ARER-009
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	(b) (4)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	1	1	Intranasal Abuse liability Study 60 mg M-ARER-002
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2	2	BA/BE 15 mg M-ARER-007 BA/BE 30 mg M-ARER-012
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	2	SD 100 mg BE - M-ARER-004 MD 100 mg PK M-ARER-008 ~~MD 100 mg M-ARER-006~~
replicate design; single / multi dose:				
Food-drug interaction studies	X	1	1	100 mg fasted/fed M-ARER-005
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	X	1	-	Sponsor reports absence of alcohol dose dumping.
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		8	8	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			RLD
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	X			
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support	X			RLD

	dose/dosing interval and dose adjustment?				
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	RLD
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	RLD
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	RLD
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and	X			

	exposure-response in the clinical pharmacology section of the label?				
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Inspiron submitted a 505(b)(2) NDA for marketing morphine sulfate abuse resistant tablets. The application requests that Agency rely on previous findings of safety and efficacy for MS Contin. The sponsor relied on a biopharmaceutics program to bridge the proposed product with MS Contin.
The topic of bridging all strengths of the proposed product to MS Contin was discussed at several meetings during the clinical development program. The sponsor was provided an opportunity to establish BE of 15 mg and 100 mg strength formulations to MS Contin. The sponsor indicated being able to successfully establish BE at the 100 mg strength; however, studies trying to establish BE of 15 mg and 30 mg of the proposed product with MSContin failed. The sponsor provided a justification that even though low side Cmax failure was noted with both the 15 mg and 30 mg strength formulations, the steady-state concentrations will be comparable to that of MS Contin. This justification will be considered during the review cycle.

Since the application is solely relying on bioequivalence study M-ARER-004 (100 mg BE study) for bridging their product with MS Contin, the clinical site and bioanalytical site require OSI inspection. An OSI consult form needs to be submitted at filing.

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist Date

Yun Xu, Ph.D.

Team Leader/Supervisor Date

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

/s/

SRIKANTH C NALLANI
07/16/2015

YUN XU
07/16/2015