ORIGINAL ARTICLE

Clinical relevance of the pharmacokinetic characteristics of an abuse-deterrent, extended-release, injection-molded morphine tablet

Jeffrey M. Dayno, MD; Gwendolyn Niebler, DO; John Lawler, BS; Torben Elhauge, MSc; Karsten Lindhardt, MSc, PhD, DBE

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ABSTRACT

Objective: *To characterize the pharmacokinetics (PK) and in vitro alcohol dissolution characteristics of extended-release (ER), injection-molded (IM) morphine tablets with abuse-deterrent (AD) features (morphine-ADER-IMT).*

Design: *In vivo, in vitro, and in silico studies were conducted. A randomized, two-cohort study evaluated the bioequivalence of morphine-ADER-IMT (60 mg) to morphine ER (60 mg; MS Contin®; Purdue Pharma LP, Stamford, CT) and characterized the effect of food on the PK profile of morphine-ADER-IMT. A three-treatment, three-period crossover study assessed the bioequivalence of morphine-ADER-IMT (30 and 2 × 15 mg) to morphine ER (30 mg). Bioequivalence studies were performed in healthy male and female subjects (18-55 y of age) in the presence of naltrexone blockade. PK modeling was performed to assess steady-state bioequivalence for morphine-ADER-IMT 60 mg compared with morphine ER 60 mg. In vitro alcohol dissolution studies were performed with morphine-ADER-IMT (15 and 60 mg).*

Results: *Fifty-nine and 56 subjects completed the 60-mg bioequivalence/food effect study and 30-mg bioequivalence study, respectively. Bioequivalence of morphine-ADER-IMT 60, 30, and 2 × 15 mg and morphine ER was demonstrated to comparable doses of morphine ER. No clinically significant food effect was observed with morphine-ADER-IMT. Treatment-emergent adverse events were similar among all treatment groups. Steady-state modeling indicated bioequivalence between morphine-ADER-IMT 60 mg and morphine ER 60 mg when administered every 8 or 12 hours. No evidence of alcohol dose-dumping was observed with morphine-ADER-IMT.*

Conclusions: *Morphine-ADER-IMT, an ER morphine formulation with robust AD features, has a clinical PK profile that is well suited for patients with chronic pain.*

INTRODUCTION

Approximately 25 million people in the United States suffer with chronic pain (defined as daily pain for ≥3 months), which is associated with significant costs to society.[1,2] Unfortunately, pharmacologic treatment options for moderate to severe pain are limited. Opioids offer an option for people experiencing moderate to severe chronic pain when other treatment options are inadequate. Recent guidelines for prescribing opioids for the treatment of chronic pain recommend that opioid therapy should only be continued if clinically meaningful improvements in pain and function are observed and if the improvements outweigh the risks of continued opioid treatment.[3] However, it has long been recognized that opioids can produce positive psychoactive effects, which can contribute to their misuse and abuse.[4,5]

The development of oral, extended-release (ER) opioid formulations designed to produce consistent analgesia over prolonged dosing intervals has benefited patients with chronic pain; however, some of these ER formulations carry a higher amount of drug than more rapidly released opioid products containing the same opioid moiety, also called short-acting opioids. As such, manipulation of ER opioids may alter the pharmacokinetics (PK) of the drug and increase the risk of serious adverse effects.[6] ER opioid formulations can be manipulated by abusers via physical or chemical means to defeat the product's controlled-release features to extract the active ingredient and get it into an abusable form. Through this process, an ER opioid can be converted into one with a more rapidly released profile that can then be administered via alternative routes such as snorting, injecting, or smoking to achieve a faster concentration in the brain than that achieved by oral consumption.[7] While manipulation is usually undertaken with tools, chewing is also an approach used to manipulate opioids.[8] For many years, it was believed that patients with pain were less likely to undertake nonmedical use of opioids; however, observed rates of opioid misuse, abuse, and addiction-related aberrant behaviors in pain patients range from 15 to 26 percent.[9] Furthermore, there is a growing appreciation that misuse and abuse of prescription opioids is a risk not only for patients but also for their circle of friends and family. Approximately 70 percent of abused opioids are obtained from friends and family.[10] Vulnerable populations in this circle include teenagers in the home, who are at a higher risk of developing opioid addiction than older adults.[9]

The US Food and Drug Administration (FDA) has responded to the prescription opioid abuse epidemic by acknowledging the importance of striking a balance between adequate access to opioid pain medication for patients while protecting individuals and society from the effects of opioid misuse and abuse.[11] Healthcare providers are attempting to find this balance through a combination of thoughtful prescribing, use of prescription drug monitoring programs, and patient education. An additional approach to achieving this balance of access and abuse risk reduction is through the prescribing of opioids with abuse-deterrent (AD) features. AD technology may help to prevent misuse and abuse of ER opioids by making manipulation more difficult and time consuming, and the resulting product of any manipulation less suitable for alternative routes of administration—all of which decrease the desirability of the drug for misuse and abuse.[12] There is an ongoing, national effort supported by the White House Office of National Drug Control Policy, FDA, National Institute of Drug Abuse, and Drug Enforcement Administration to support the development and use of AD formulations of opioids as an integral component of a comprehensive prescription opioid misuse and abuse prevention plan.[7,12,13] The FDA issued a final guidance in 2015 on the development of AD opioid formulations titled *Abuse-Deterrent Opioids—Evaluation and Labeling*.[12]

As of January 1, 2017, seven opioid formulations have received labeling claims indicating that the product has properties that are expected to reduce abuse by specific routes of administration. However, it is important to understand that products that receive specific AD claims are not abuse proof. Two of these formulations contain morphine, Embeda® (Pfizer, New York, NY) and MorphaBond™ ER (Inspirion Delivery Sciences, Valley Cottage, NY) and deter abuse by using agonist/antagonist (morphine and sequestered naltrexone ER) and physical/chemical barrier approaches, respectively.[14,15]

Egalet Corporation (Wayne, PA) has developed Guardian™ Technology, a novel drug delivery platform that utilizes a unique combination of a polymer-based matrix in combination with the process of injection molding to produce a hard tablet. Egalet is a pioneer in the process of injection molding used for the manufacturing of pharmaceutical tablets and ultimately for the development of a commercial product. Guardian Technology allows for customization of tablet design and release profile and results in tablets that are very hard and resistant to particle size reduction and chemical extraction. The tablets possess robust physical and chemical barriers that result in a broad AD profile to help reduce the potential for abuse through all alternative routes. This technology was used to manufacture morphine AD, ER, injection-molded tablets (morphine-ADER-IMT), an ER morphine formulation with AD properties.

Data from the 2015 IMS National Prescription Audits show that morphine is the most commonly prescribed ER opioid, and the majority of these products do not possess any AD properties. Morphine is abused through many routes of administration (eg, oral, intranasal, intravenous, and inhalation), but the most common nonoral route of morphine abuse is via intravenous injection.[8,16] Morphine-ADER-IMT has undergone a robust development program that includes a full battery of AD studies consistent with

the FDA's final AD opioid guidance.[12] Morphine-ADER-IMT resists rigorous physical manipulation and chemical extraction intended to alter the tablet to make it suitable for abuse by all of the major routes of administration used to abuse morphine.[17,18] In vitro studies have demonstrated that morphine-ADER-IMT is resistant to rigorous, multistep attempts at manipulation to reduce particle size, and, because of the gelling properties, it is difficult to draw up into a syringe for injection.[17,18] Clinical abuse potential studies have demonstrated a significant reduction in maximal drug liking after oral or intranasal administration of manipulated morphine-ADER-IMT compared with a marketed non-AD ER morphine product that was easily crushed. These findings and others from the clinical abuse potential studies indicate a lower potential for abuse with morphine-ADER-IMT relative to non-AD ER morphine through both the manipulated oral and intranasal routes.[19,20]

The development of a new opioid formulation requires characterization of the PK profile of the product, including assessment of the drug absorption in the presence of food. The release profile of an ER opioid is important because a sustained blood level is needed to deliver adequate relief of daily baseline pain levels over time without causing high concentrations of opioid in the blood that could lead to a safety risk. Evaluation of food effects can identify interactions that may lead to reduced efficacy (decreased drug levels) or an increased risk of toxicity (increased drug levels).[21]

From a safety perspective, ER opioid products must be assessed for a potential interaction with alcohol to determine whether there is any evidence of alcohol dose-dumping (ie, rapid release of drug). The risks of respiratory depression, coma, and death are increased when morphine or other μ-opioids are used in conjunction with alcohol or other drugs that cause central nervous system depression.[22] Alcohol is a solvent that has been shown to cause a very fast release of the active substance from ER opioid formulations (dose-dumping), which can lead to high concentrations of drug in a short period of time and pose a significant risk to patient safety.[23,24] In 2005, an ER formulation of hydromorphone was withdrawn from the market because of alcohol dose-dumping.[25] A currently marketed ER morphine combination product with sequestered naltrexone hydrochloride (Embeda®, Pfizer, New York, NY) has a boxed warning indicating that coingestion of alcohol may result in an increase of plasma levels and a potentially fatal morphine overdose.[14]

We undertook a series of in vivo, in vitro, and in silico studies for morphine-ADER-IMT to (1) demonstrate the single-dose PK profile and bioequivalence of morphine-ADER-IMT compared with MS Contin® (morphine sulfate tablet, film coated, ER; Purdue Pharma LP, Stamford, CT), an ER morphine without AD features[22]; (2) determine the PK profile of morphine-ADER-IMT under fed and fasted conditions; (3) demonstrate the steady-state PK profile; and (4) characterize tablet dissolution in the presence of alcohol. The results from all of these studies contribute to key components of an ER opioid's product profile, all of which have clinical relevance for a physician prescribing these products for patients with chronic pain.

METHODS

Studies

Two clinical PK studies were performed to assess the bioequivalence of morphine-ADER-IMT at doses comparable to a morphine sulfate ER tablet (MS Contin®), which served as the reference drug. In the first study, bioequivalence was tested by comparing the PK profile of 60-mg morphine-ADER-IMT with the PK profile of the reference drug under fasted conditions. In an additional treatment period, one of the cohorts in this study was administered 60-mg morphine-ADER-IMT in the fed state to conduct a fed/fasted analysis. No morphine ER comparator was assessed during the fed state portion of the study. The prescribing information for the morphine ER comparator states that systematic evaluation of the effects of food on systemic bioavailability is lacking.[22] The second study assessed the bioequivalence of 30- and 2×15-mg morphine-ADER-IMT compared with 30-mg morphine ER. In silico modeling using data from the 60-mg bioequivalence study was performed to assess the steady-state PK profile and multiple-dose bioequivalence to morphine ER. In vitro alcohol dissolution was performed with 15-mg (lowest strength) and 60-mg (highest strength) morphine-ADER-IMT (Table 1).

In vivo bioequivalence and food effect studies. The bioequivalence and food effect studies were single-center, phase 1, randomized, open-label, single-dose crossover studies in healthy volunteers. Oral naltrexone 50 mg was administered approximately 3

Table 1. Clinical, PK, in silico, and in vitro studies performed for morphine-ADER-IMT

Study	Type	Objective
60-mg bioequivalence, fasted	In vivo	Determine single-dose (60 mg) bioequivalence to 60-mg morphine ER
60-mg food effect	In vivo	Determine effects of food on PK profile of morphine-ADER-IMT
30-mg bioequivalence, fasted	In vivo	Determine single-dose (30 mg) bioequivalence to 30-mg morphine ER
2×15-mg bioequivalence, fasted	In vivo	Determine single-dose (2×15 mg) bioequivalence to 30-mg morphine ER and to 30-mg morphine-ADER-IMT
Steady-state modeling	In silico	Determine probability of bioequivalence following multiple dosing
Alcohol dissolution	In vitro	Determine drug release in the presence of alcohol

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ER, extended release; PK, pharmacokinetic.

and 15 hours before and approximately 9 and 21 hours after administration of study medications. Serial blood samples for analysis of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide levels were collected up to 48 hours after each dose of study medication. Subjects were confined to the clinical unit until discharge on day 3 of each treatment period after the 48-hour PK sample collection.

Institutional review board approval was obtained before the studies began, and written informed consent was obtained from the volunteers.

Morphine-ADER-IMT 60 mg. This was a randomized, open-label, two-period crossover study to assess bioequivalence of morphine-ADER-IMT 60 mg with morphine ER 60 mg when administered in the fasted state. One of the cohorts underwent an additional treatment, during which they were dosed with morphine-ADER-IMT 60 mg in the fed state. All subjects were randomized to one of two treatment sequences before initial treatment. Treatments included single-dose morphine-ADER-IMT 60 mg or morphine ER 60 mg, administered under fasted conditions (overnight for approximately 10 h, with only water to drink). Subjects in the food effect cohort received morphine-ADER-IMT 60 mg 30 minutes after starting a standard high-fat breakfast as defined by the FDA (approximately 50 percent of total caloric content; total meal, 800-1,000 calories) in the third period.[26] There was a washout interval of ≥7 days between all treatments.

Morphine-ADER-IMT 30 and 2×15 mg. This was a randomized, open-label, three-period crossover study design with subjects randomly assigned to receive three treatments in one of six different treatment sequences. The three treatments were morphine-ADER-IMT 30 mg, morphine-ADER-IMT 2×15 mg, and morphine ER 30 mg, each administered under fasted conditions (overnight for approximately 10 h, with only water to drink). There was a washout interval of ≥7 days between doses of any two consecutive treatment periods.

Safety. Adverse events (AEs) were monitored and recorded during the course of the studies. AEs were coded using the Medical Dictionary for Regulatory Activities, version 17.1, by preferred term and system organ class. Treatment-emergent AEs (TEAEs), defined as AEs that were not present prior to initiation of treatment or if present, worsened in intensity or frequency after initiation of treatment, were summarized by treatment, severity, and relationship to study drug.

Steady-state modeling. PK models describing morphine plasma concentration versus time for morphine-ADER-IMT 60 mg or morphine ER 60 mg were developed. The steady-state model and simulations were developed and performed because morphine-ADER-IMT is intended to be dosed chronically to steady state, while the pivotal PK studies described herein were all single dose. The compartmental models were simulated to predict steady-state morphine plasma concentration versus time profiles and to determine the probability of bioequivalence of the multiple-dose PK parameters. The model engine (estimation method) used in PK modeling was the quasi-random parametric expectation maximization (QRPEM) method. The results from the QRPEM estimation method

were compared with two other nonlinear mixed-effects modeling estimation methods: the first-order conditional estimation-extended least squares and the iterative two-stage expectation-maximization models.

In vitro alcohol dissolution study. Testing was conducted using intact 15- and 60-mg tablets, reflecting the lowest and highest doses of the product dosage range of morphine-ADER-IMT. Evaluation was done by using conventional, standardized conditions at 37 °C ± 0.5 °C in 900 mL of 0.1 N HCl (pH 1.2; reflecting gastric pH) or buffer (pH 6.8; reflecting intestinal pH) media in the presence of 0, 5, 10, 20, and 40 percent ethanol. Aliquots were sampled at 15-minute intervals from 15 minutes to 2 hours, and morphine concentrations were measured using high-performance liquid chromatography with an ultraviolet detector (285 nm).

Statistics

Statistical analysis for bioequivalence and food effect studies. A linear mixed-effect model (SAS PROC MIXED; SAS Institute, Cary, NC), with treatment, sequence, and period as fixed effects and subjects nested within the sequence as a random effect, was fit using the natural log-transformed parameters of maximum observed plasma concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time 0 extrapolated to infinity ($AUC_{0-\infty}$), and AUC from time 0 to the time of the last quantifiable concentration (AUC_{0-t}) for use in the estimation of effects and construction of confidence intervals (CIs). Point estimates and 90% CIs for the differences on the log scale were exponentiated to obtain estimates for the ratios of the geometric means and respective 90% CIs. Bioequivalence was concluded if the 90% CIs for the ratios (treatment A [test drug]/treatment B [reference drug]) of the geometric means were entirely contained within the equivalence interval of 80.00-125.00 percent for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} of morphine.

Statistical analysis for alcohol dissolution study. Comparisons of morphine levels in 0 percent ethanol (aqueous medium) and ethanolic media were made for each of the dosage strengths of morphine-ADER-IMT using the f2 profile comparison test. The f2 (similarity factor) predicts similarity from dissolution studies indicating potential similarity between profiles if tested in a human PK study.[27]

RESULTS

Bioequivalence studies

Subjects. Demographics and baseline characteristics for all randomized subjects in the 60-mg bioequivalence and food effects study and the 30- and 2×15-mg bioequivalence study are shown in Table 2. The majority of subjects in the 60-mg study were men, whereas the percentage of men and women was approximately equal in the 30- and 2×15-mg study. The majority of subjects in both studies were white, with a mean age of 30.8 years in the 60-mg study and 33.3 years in the 30- and 2×15-mg study. Other baseline characteristics were generally similar among patients in each of the treatment sequences of the respective bioequivalence studies.

Six subjects discontinued from the 60-mg bioequivalence study: five because of AEs and one by choice (Figure 1A). Ten subjects discontinued from the 30- and 2×15-mg bioequivalence study; the majority discontinued because of AEs (n = 4) or because an exclusion criteria was met (n = 3; Figure 1B). Vomiting was the primary TEAE leading to discontinuation, causing 80.0 percent (4/5) and 100 percent (4/4) of discontinuations in the 60-mg bioequivalence and food effect study and in the 30- and 2×15-mg bioequivalence study, respectively.

PK analyses. Morphine plasma PK parameters are provided in Table 3. The point estimate and 90% CIs of the geometric least squares mean ratio comparison between morphine-ADER-IMT 60 mg and morphine ER 60 mg under fasted conditions for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} were all contained within the 80-125 percent bioequivalence interval (Table 4), demonstrating bioequivalence between morphine-ADER-IMT 60 mg and morphine ER 60 mg. The mean plasma concentrations of morphine versus time after treatment with morphine-ADER-IMT 60 mg and morphine ER 60 mg under fasted conditions are shown in Figure 2. A delay in the time to C_{max} (t_{max}) for morphine-ADER-IMT compared with morphine ER of approximately 2 hours was observed (Table 3); this reflects the ER design of morphine-ADER-IMT but does not impact the finding of bioequivalence to the reference product.

The point estimate and 90% CIs of the geometric least squares mean ratio comparison between morphine-ADER-IMT in the fed and fasted conditions for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} were all contained

Table 2. Demographics and baseline characteristics in the bioequivalence studies

60-mg bioequivalence study*					
Characteristic	**Two-period cohort**		**Three-period cohort**		**Overall (N = 65)**
	AB (n = 20)	**BA (n = 20)**	**ABC (n = 12)**	**BAC (n = 13)**	
Mean (SD) age, y	31.3 (10.2)	32.2 (9.7)	30.3 (6.8)	28.6 (9.7)	30.8 (9.3)
Sex, n (percent)					
Female	7 (35.0)	8 (40.0)	5 (41.7)	7 (53.8)	27 (41.5)
Male	13 (65.0)	12 (60.0)	7 (58.3)	6 (46.2)	38 (58.5)
Race, n (percent)					
White	13 (65.0)	12 (60.0)	8 (66.7)	10 (76.9)	43 (66.2)
Black	6 (30.0)	7 (35.0)	4 (33.3)	2 (15.4)	19 (29.2)
American Indian or Alaska Native	1 (5.0)	0	0	0	1 (1.5)
Multiracial	0	1 (5.0)	0	1 (7.7)	2 (3.1)
Mean (SD) weight, kg	77.4 (14.6)	76.0 (16.4)	83.8 (11.8)	79.2 (13.9)	78.5 (14.5)
Mean (SD) BMI, kg/m^2	26.7 (3.3)	26.0 (3.2)	28.1 (3.3)	26.6 (2.8)	26.7 (3.2)

30- and 2×15-mg bioequivalence study							
Treatment sequence†							
	DEF (n = 11)	**EFD (n = 11)**	**FDE (n = 11)**	**DFE (n = 11)**	**EDF (n = 11)**	**FED (n = 11)**	**Overall (N = 66)**
Mean (SD) age, y	31.6 (10.6)	32.5 (6.9)	33.3 (12.2)	35.0 (6.7)	31.6 (6.3)	35.5 (9.6)	33.3 (8.8)
Sex, n (percent)							
Female	3 (27.3)	7 (63.6)	5 (45.5)	8 (72.7)	6 (54.5)	6 (54.5)	35 (53.0)
Male	8 (72.7)	4 (36.4)	6 (54.5)	3 (27.3)	5 (45.5)	5 (45.5)	31 (47.0)
Race, n (percent)							
White	8 (72.7)	5 (45.5)	9 (81.8)	9 (81.8)	10 (90.9)	7 (63.6)	48 (72.7)
Black	3 (27.3)	6 (54.5)	1 (9.1)	2 (18.2)	1 (9.1)	3 (27.3)	16 (24.2)
Multiracial	0	0	1 (9.1)	0	0	1 (9.1)	2 (3.0)
Mean (SD) weight, kg	73.2 (11.1)	67.0 (13.0)	73.9 (11.2)	74.3 (15.2)	75.2 (9.1)	72.3 (11.7)	72.6 (11.9)
Mean (SD) BMI, kg/m^2	25.3 (2.9)	25.1 (3.7)	25.5 (2.8)	27.1 (2.5)	27.1 (2.8)	26.8 (3.3)	26.2 (3.0)

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; BMI, body mass index; ER, extended release.
*A = morphine-ADER-IMT 60 mg, fasted; B = morphine ER 60 mg, fasted; C = morphine-ADER-IMT 60 mg, fed.
†D = morphine-ADER-IMT 30 mg, fasted; E = morphine ER 30 mg, fasted; F = morphine-ADER-IMT 2×15 mg, fasted.

within the 80-125 percent bioequivalence interval (Table 4), demonstrating bioequivalence of morphine-ADER-IMT 60 mg under fed versus fasted state. The mean plasma concentrations of morphine versus time under fed and fasted conditions after treatment with morphine-ADER-IMT 60 mg are shown in Figure 3. t_{max} was delayed by 2 hours for morphine-ADER-IMT in the presence of food (Table 3). The plasma PK parameters for morphine metabolites (ie, morphine-3β-glucuronide and morphine-6β-glucuronide) were consistent with those for morphine.

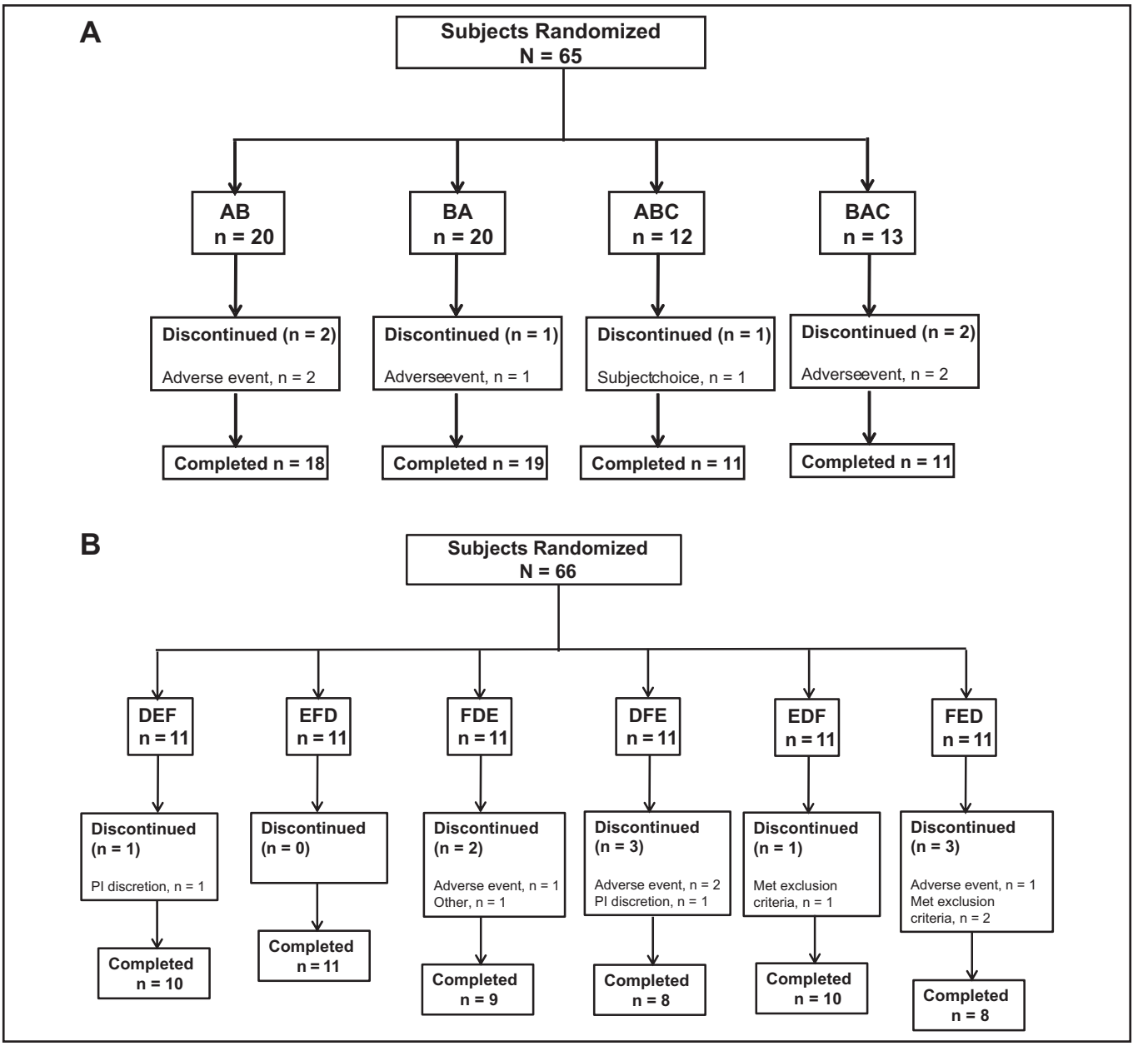

Figure 1. Study disposition. (A) Sixty-milligram bioequivalence and food effect study. (B) Thirty-milligram and 2×15-mg bioequivalence study. A, morphine-ADER-IMT 60 mg, fasted; ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; B, morphine ER 60 mg, fasted; C, morphine-ADER-IMT 60 mg, fed; D, morphine-ADER-IMT 30 mg, fasted; E, morphine ER 30 mg, fasted; ER, extended release; F, morphine-ADER-IMT 2×15 mg, fasted. PI, principal investigator.

The point estimate and 90% CIs of the geometric least squares mean ratio comparison between morphine-ADER-IMT 30 mg and morphine ER 30 mg, as well as between morphine-ADER-IMT 2×15 mg and morphine ER 30 mg, under fasted conditions for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} were all contained within the 80-125 percent bioequivalence interval (Table 4), demonstrating bioequivalence between morphine-ADER-IMT 30 mg and morphine ER 30 mg, as well as morphine-ADER-IMT 2×15 mg and morphine ER 30 mg. The data also demonstrated bioequivalence between morphine-ADER-IMT 30 mg and morphine-ADER-IMT 2×15 mg. t_{max} was delayed by approximately 2.5 hours for morphine-ADER-IMT 30 mg compared with morphine ER 30 mg in this study (Table 3). The mean plasma concentration curves are shown in Figure 4.

Safety. Approximately one third of the subjects reported TEAEs in the bioequivalence studies (Table 5). In each of the bioequivalence studies, the

Table 3. Morphine plasma PK parameters*

Parameter			
60-mg bioequivalence study	**Morphine-ADER-IMT, fasted (n = 60)**	**Morphine ER, fasted (n = 60)**	
C_{max}, ng/mL	21.6 (35.6)	22.7 (36.5)	
$AUC_{0-\infty}$, ng h/mL	196.6 (27.3)†	200.5 (26.8)†	
AUC_{0-t}, ng h/mL	189.1 (27.3)	192.8 (26.3)	
t_{max}, h	4.5 (1.0, 6.0)	2.5 (0.7, 4.5)	
$t_{½}$, h	9.57 (26.3)†	9.94 (28.5)†	
60-mg food effect study	**Morphine-ADER-IMT, fasted (n = 14)**	**Morphine-ADER-IMT, fed (n = 14)**	
C_{max}, ng/mL	23.6 (30.8)	23.8 (35.9)	
$AUC_{0-\infty}$, ng h/mL	199.9 (23.3)	232.0 (25.1)	
AUC_{0-t}, ng h/mL	192.3 (22.8)	221.4 (25.2)	
t_{max}, h	4.5 (2.0, 5.5)	6.5 (3.5, 10.0)	
$t_{½}$, h	10.34 (25.7)	10.55 (24.2)	
30- and 2×15-mg study	**Morphine-ADER-IMT 30 mg, fasted (n = 60)**	**Morphine ER 30 mg, fasted (n = 59)**	**Morphine-ADER-IMT 2×15 mg, fasted (n = 61)**
C_{max}, ng/mL	12.0 (33.5)	12.1 (33.3)	10.8 (33.1)
$AUC_{0-\infty}$, ng h/mL	115.7 (26.1)‡	119.2 (29.1)‡	117.3 (27.1)§
AUC_{0-t}, ng h/mL	111.9 (25.6)	113.9 (29.0)	112.3 (27.1)
t_{max}, h	4.5 (0.7, 6.0)	2.0 (0.7, 5.5)	4.5 (1.5, 8.0)
$t_{½}$, h	10.03 (23.6)‡	10.92 (21.2)‡	10.51 (23.9)§

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; CV percent, percentage coefficient of variation; ER, extended release; PK, pharmacokinetics; $t_{½}$, half life; t_{max}, time to maximum plasma concentration.
*All data are mean (CV percent) except t_{max}, which is median (min, max).
†n = 59.
‡n = 58.
§n = 60.

percentage of subjects reporting TEAEs was similar between treatment groups and similar between the two studies. Overall, the most commonly reported TEAEs were gastrointestinal disorders (eg, nausea and vomiting) and nervous system disorders (eg, headache and dizziness), consistent with common opioid-related AEs.

Steady-state modeling. The mean ratios and 90% CIs for C_{max} and AUC for morphine-ADER-IMT 60 mg and morphine ER 60 mg from all 100 replicates in the population simulations fell within the 80-125 percent bioequivalence bounds (Table 6). The multiple-dose steady-state simulations predicted bioequivalence between morphine-ADER-IMT 60 mg and morphine ER 60 mg when administered either every 8 hours or every 12 hours.

Alcohol dissolution study. The dissolution profiles of 15- and 60-mg morphine-ADER-IMT complied with f2 test criteria for similarity at both pH conditions at all ethanol concentrations. Morphine release from morphine-ADER-IMT 15 and 60 mg at pH 1.2 and pH 6.8 is shown in Figures 5 and 6. For both dosage strengths of morphine-ADER-IMT, release was slowed with increasing alcohol concentrations and no evidence of alcohol dose-dumping was observed.

Table 4. Plasma PK parameters for assessment of bioequivalence

Parameter	Geometric mean		Geometric LS mean		Geometric LS mean ratio, percent (90% CI)
60-mg bioequivalence study	**Morphine-ADER-IMT, fasted**	**Morphine ER, fasted**	**Morphine-ADER-IMT, fasted**	**Morphine ER, fasted**	**Morphine-ADER-IMT:morphine ER**
C_{max}, ng/mL	20.4*	21.3*	20.22*	21.2*	95.35 (89.40-101.69)
$AUC_{0-\infty}$, ng h/mL	189.0†	193.1†	188.0†	192.2†	97.79 (95.07-100.59)
AUC_{0-t}, ng h/mL	181.8*	186.0*	180.3*	185.3*	97.32 (94.27-100.47)
60-mg food effect study	**Morphine-ADER-IMT, fasted**	**Morphine-ADER-IMT, fed**	**Morphine-ADER-IMT, fasted**	**Morphine-ADER-IMT, fed**	**Morphine-ADER-IMT:morphine ER**
C_{max}, ng/mL	22.7‡	22.2‡	22.71‡	22.18‡	97.67 (83.83-113.79)
$AUC_{0-\infty}$, ng h/mL	194.9‡	225.3‡	194.9‡	225.3‡	115.59 (108.35-123.31)
AUC_{0-t}, ng h/mL	187.8‡	214.9‡	187.8‡	214.9‡	114.42 (107.04-122.31)
30-mg bioequivalence study	**Morphine-ADER-IMT 30 mg, fasted**	**Morphine ER 30 mg, fasted**	**Morphine-ADER-IMT 30 mg, fasted**	**Morphine ER 30 mg, fasted**	**Morphine-ADER-IMT:morphine ER**
C_{max}, ng/mL	11.4*	11.5†	11.42*	11.59†	98.61 (93.91-103.55)
$AUC_{0-\infty}$, ng h/mL	112.1§	115.1§	113.2§	115.1§	98.31 (95.99-100.69)
AUC_{0-t}, ng h/mL	108.6*	110.0†	108.8*	110.1†	98.84 (96.61-101.11)
2×15-mg bioequivalence study	**Morphine-ADER-IMT 2×15 mg, fasted**	**Morphine ER 30 mg, fasted**	**Morphine-ADER-IMT 2×15 mg, fasted**	**Morphine ER 30 mg, fasted**	**Morphine-ADER-IMT:morphine ER**
C_{max}, ng/mL	10.2¶	11.5†	10.20¶	11.59†	88.04 (83.87-92.43)
$AUC_{0-\infty}$, ng h/mL	113.6*	115.1§	113.3*	115.1§	98.42 (96.13-100.78)
AUC_{0-t}, ng h/mL	108.9¶	110.0†	108.7¶	110.1†	98.66 (96.45-100.92)
2×15-mg bioequivalence study	**Morphine-ADER-IMT 30 mg, fasted**	**Morphine-ADER-IMT 2×15 mg, fasted**	**Morphine-ADER-IMT 30 mg, fasted**	**Morphine-ADER-IMT 2×15 mg, fasted**	**Morphine-ADER-IMT:morphine ER**
C_{max}, ng/mL	11.4*	10.2¶	11.42*	10.20¶	112.00 (106.70-117.57)
$AUC_{0-\infty}$, ng h/mL	112.1§	113.6*	113.2§	113.3*	99.88 (97.54-102.29)
AUC_{0-t}, ng h/mL	108.6*	108.9¶	108.8*	108.7¶	100.18 (97.94-102.47)

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; AUC_{0-t}, area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 extrapolated to infinity; C_{max}, maximum observed plasma concentration; ER, extended release; LS, least squares; PK, pharmacokinetics.

*n = 60.

†n = 59.

‡n = 14.

§n = 58.

¶n = 61.

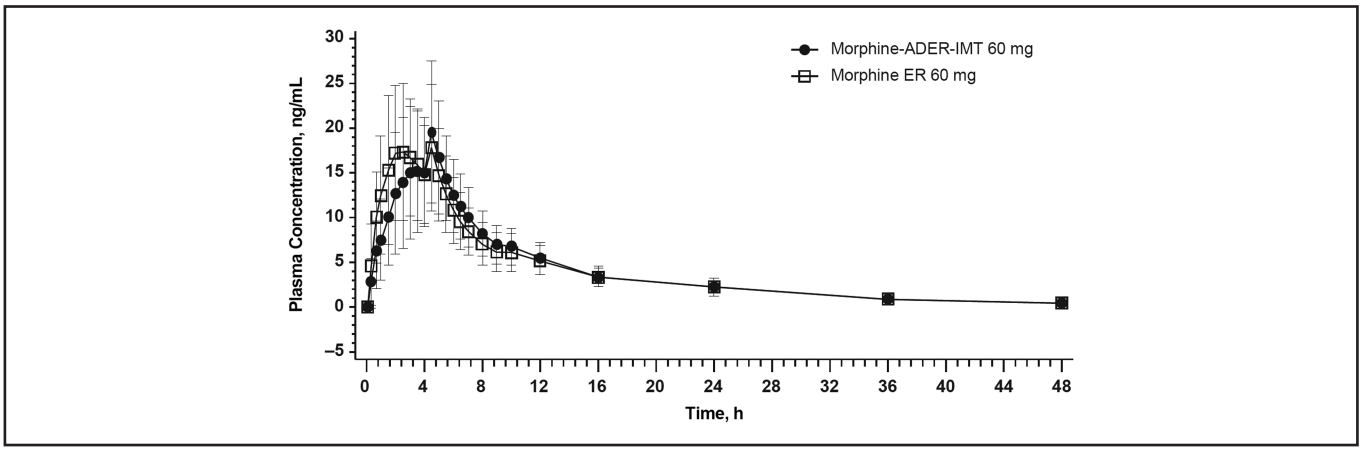

Figure 2. Mean (SD) morphine plasma concentrations versus time following treatment with morphine-ADER-IMT 60 mg and morphine ER 60 mg under fasted conditions. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ER, extended release.

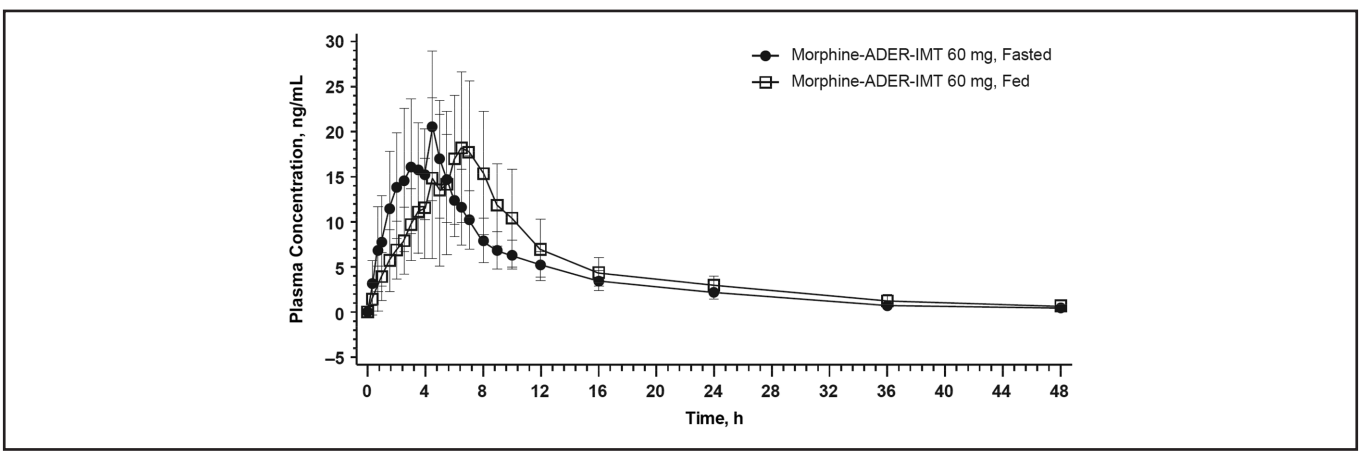

Figure 3. Mean (SD) morphine plasma concentrations versus time following treatment with morphine-ADER-IMT 60 mg under fasted and fed conditions. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets.

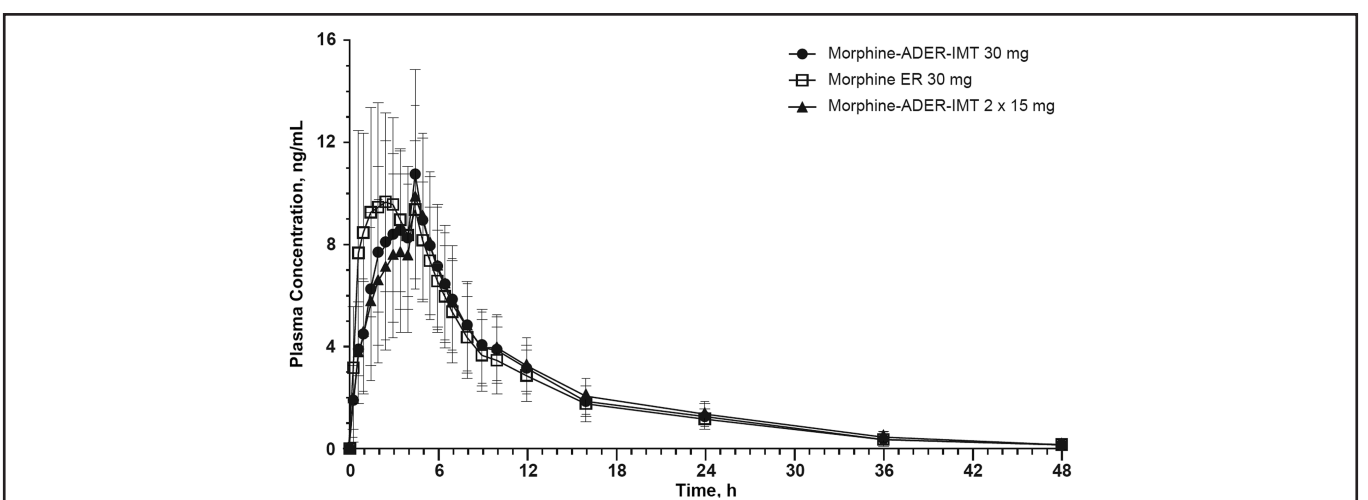

Figure 4. Mean (SD) morphine plasma concentrations versus time following treatment with morphine-ADER-IMT 30 mg, morphine ER 30 mg, and morphine-ADER-IMT 2×15 mg under fasted conditions. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ER, extended release.

Table 5. TEAEs reported by ≥ 2 subjects overall in the bioequivalence studies (safety population)

	60-mg bioequivalence and food effect study			
System organ class preferred term, n (percent)	**Morphine-ADER-IMT 60 mg, fasted (n = 64)**	**Morphine ER 60 mg, fasted (n = 62)**	**Morphine-ADER-IMT 60 mg, fed (n = 22)**	**Overall (N = 65)**
All TEAEs	12 (18.8)	10 (16.1)	4 (18.2)	21 (32.3)
Gastrointestinal disorders	9 (14.1)	5 (8.1)	1 (4.5)	12 (18.5)
Nausea	9 (14.1)	2 (3.2)	1 (4.5)	9 (13.8)
Vomiting	6 (9.4)	1 (1.6)	1 (4.5)	7 (10.8)
Abdominal pain	2 (3.1)	2 (3.2)	0	4 (6.2)
Diarrhea	1 (1.6)	1 (1.6)	0	2 (3.1)
Nervous system disorders	4 (6.3)	3 (4.8)	3 (13.6)	9 (13.8)
Headache	1 (1.6)	2 (3.2)	2 (9.1)	5 (7.7)
Dizziness	1 (1.6)	0	1 (4.5)	2 (3.1)
Somnolence	2 (3.1)	1 (1.6)	0	2 (3.1)
Respiratory, thoracic and mediastinal disorders	1 (1.6)	1 (1.6)	0	2 (3.1)
Cough	1 (1.6)	1 (1.6)	0	2 (3.1)
	30- and 2×15-mg bioequivalence study			
	Morphine-ADER-IMT 30 mg, fasted (n = 62)	**Morphine ER 30 mg, fasted (n = 59)**	**Morphine-ADER-IMT 2×15 mg, fasted (n = 62)**	**Overall (N = 66)**
All TEAEs	7 (11.3)	7 (11.9)	11 (17.7)	20 (30.3)
Gastrointestinal disorders	3 (4.8)	4 (6.8)	4 (6.5)	11 (16.7)
Nausea	0	2 (3.4)	3 (4.8)	5 (7.6)
Vomiting	2 (3.2)	0	2 (3.2)	4 (6.1)
Nervous system disorders	1 (1.6)	3 (5.1)	7 (11.3)	11 (16.7)
Headache	1 (1.6)	1 (1.7)	5 (8.1)	7 (10.6)
Dizziness	1 (1.6)	2 (3.4)	1 (1.6)	4 (6.1)
Respiratory, thoracic, and mediastinal disorders	2 (3.2)	1 (1.7)	0	3 (4.5)
Oropharyngeal pain	2 (3.2)	1 (1.7)	0	3 (4.5)
General disorders and administration site conditions	0	1 (1.7)	1 (1.6)	2 (3.0)
Feeling abnormal	0	1 (1.7)	1 (1.6)	2 (3.0)
Skin and subcutaneous tissue disorders	1 (1.6)	0	1 (1.6)	2 (3.0)
Dermatitis contact	1 (1.6)	0	1 (1.6)	2 (3.0)

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ER, extended release; TEAE, treatment-emergent adverse event.

Table 6. Steady-state PK parameters from population simulations

Parameter	Morphine-ADER-IMT:Morphine ER mean ratio, percent (90% CI)
Single dose	
C_{max}	99.9 (94.2-106.0)
AUC	97.8 (94.3-101.4)
Multiple dose, every 12 h	
C_{maxSS}	95.7 (90.8-100.9)
AUC_{SS}	97.7 (94.4-101.1)
Multiple dose, every 8 h	
C_{maxSS}	93.5 (89.0-98.3)
AUC_{SS}	97.5 (94.3-100.9)

Abbreviations: ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; AUC, area under the plasma concentration versus time curve; C_{max}, maximum observed plasma concentration; ER, extended release; PK, pharmacokinetics; SS, steady state.

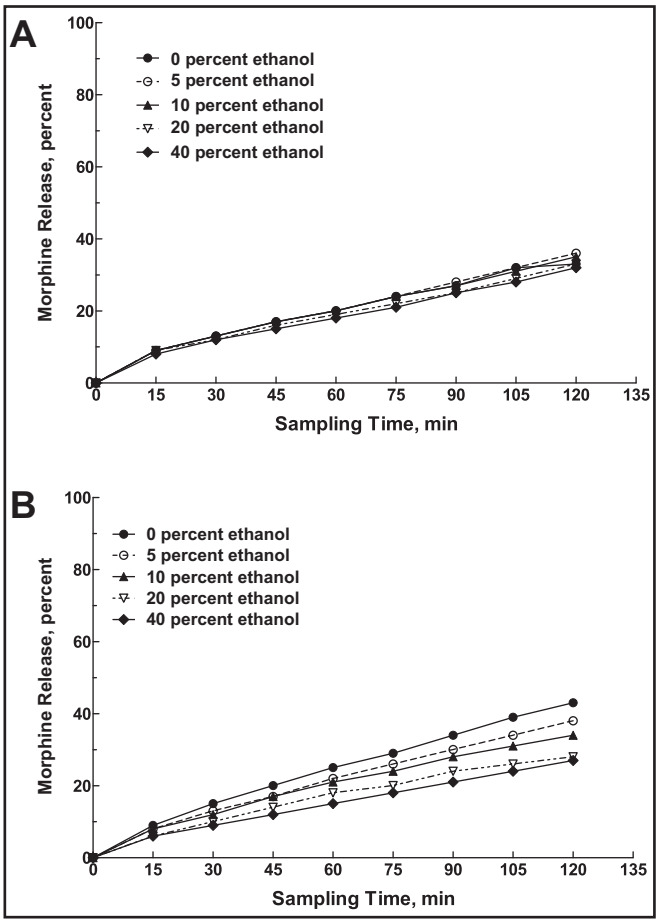

Figure 5. Percentage of morphine released in the presence of different concentrations of ethanol at pH 1.2. (A) Morphine-ADER-IMT 15 mg. (B) Morphine-ADER-IMT 60 mg. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets.

DISCUSSION

There are several key findings from these studies characterizing the PK profile and features of morphine-ADER-IMT. Despite having physical and chemical properties that present barriers to attempts at abuse, morphine-ADER-IMT with Guardian Technology is bioequivalent to morphine ER across the 15-, 30-, and 60-mg dosage strengths. Steady-state modeling predicted the bioequivalence of morphine-ADER-IMT to morphine ER if administered every 8 or 12 hours. No clinically significant food effect was demonstrated with morphine-ADER-IMT 60 mg following ingestion of a high-fat meal in a fed versus fasted PK study. Last, in vitro dissolution studies of morphine-ADER-IMT showed no evidence of alcohol dose-dumping and, to the contrary, release rates of morphine were progressively slower with higher concentrations of alcohol.

The results of these studies characterizing the in vitro and in vivo PK features of morphine-ADER-IMT demonstrate that this novel AD ER formulation of morphine has the requisite profile for managing patients with chronic pain. Morphine-ADER-IMT demonstrated a PK profile that is bioequivalent to a non-AD ER morphine product that is well known to deliver effective analgesia to patients with chronic pain.[28] The data support that morphine-ADER-IMT can be administered every 8 or 12 hours, which provides for durability of pain relief with flexible dosing. The lack of a clinically relevant food effect also provides flexibility in dosing, allowing the option to administer either with or without a meal. A delay in t_{max} was observed for morphine-ADER-IMT compared with morphine ER. However, when comparing a product that is administered chronically on a regular schedule to that with a drug that is taken intermittently for acute pain, t_{max} is not as clinically relevant a parameter as overall exposure (AUC) at steady state. Finally, no evidence of alcohol dose-dumping was demonstrated in in vitro alcohol interaction studies, which is important from a safety perspective given that patients with chronic pain frequently ingest alcohol while taking opioid medications.[29-31] The lack of accelerated dissolution of morphine-ADER-IMT in alcohol is consistent with other in vitro assessments of

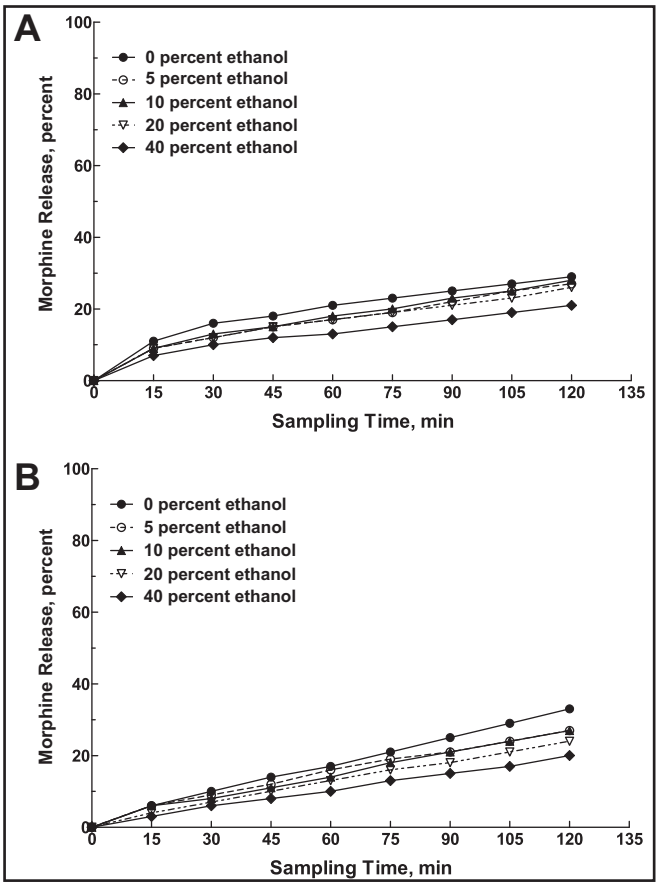

Figure 6. Percentage of morphine released in the presence of different concentrations of ethanol at pH 6.8. (A) Morphine-ADER-IMT 15 mg. (B) Morphine-ADER-IMT 60 mg. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets.

morphine-ADER-IMT that demonstrated the formulation is resistant to chemical extraction with a variety of solvents.[17,18]

Study strengths and limitations

A strength of the current study is that the methodologies used for the bioequivalence and the alcohol interaction studies were performed in a manner consistent with current FDA guidance.[32,33] A limitation of the steady-state data is the use of modeling from the 60-mg bioequivalence study rather than from data obtained from a clinical multiple-dose, steady-state PK study.

CONCLUSIONS

Morphine-ADER-IMT, an ER morphine formulation with robust AD properties designed to deter abuse through all major routes of administration (manipulated oral, intranasal, and intravenous), has a clinical PK profile that is well suited for dosing patients with chronic pain. Morphine-ADER-IMT demonstrated bioequivalence to a non-AD formulation of morphine ER, a treatment for pain with a well-established efficacy profile. In addition, morphine-ADER-IMT was shown to maintain consistent exposures (ie, steady-state AUC and C_{max}) at steady state with simulated 8- or 12-hour dosing in comparison with the single-dose PK profile, does not have a clinically significant interaction with food, and does not exhibit alcohol dose-dumping. Together, this results in a clinically compelling profile for morphine-ADER-IMT, which can provide effective analgesia for patients living with chronic pain while helping to reduce the risk of opioid misuse and abuse. This is especially important because morphine is the most commonly prescribed ER opioid, and the majority of these products can be easily crushed and then swallowed, snorted, or injected intravenously, the latter of which is the most common, and most dangerous, nonoral route of morphine abuse.

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Jeffrey M. Dayno, MD, Chief Medical Officer, Egalet Corporation, Wayne, Pennsylvania.

Gwendolyn Niebler, DO, Senior Vice-President, Clinical Development and Medical Affairs, Egalet Corporation, Wayne, Pennsylvania.

John Lawler, BS, Executive Director, Clinical Operations, Egalet Corporation, Wayne, Pennsylvania.

Torben Elhauge, MSc, Senior Scientist Specialist, Research and Development, Egalet Corporation, Wayne, Pennsylvania.

Karsten Lindhardt, MSc, PhD, DBE, Senior Vice-President, Research and Development, Egalet Corporation, Wayne, Pennsylvania.

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