Original Research Article

Human Abuse Potential of an Abuse-Deterrent (AD), Extended-Release (ER) Morphine Product Candidate (Morphine-ADER Injection-Molded Tablets) versus Extended-Release Morphine Administered Orally in Nondependent Recreational Opioid Users

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Abstract

Objective. To compare the relative human abuse potential of intact and manipulated morphine abuse-deterrent, extended-release injection-molded tablets (morphine-ADER-IMT) with that of marketed morphine sulfate ER tablets

Methods. This randomized, double-blind, triple-dummy, active- and placebo-controlled, 4-way crossover, single-center study included adult volunteers who were experienced, nondependent, recreational opioid users. Participants were randomized 1:1:1:1 to placebo, morphine-ADER-IMT (60 mg, intact), morphine-ADER-IMT (60 mg, manipulated), and morphine ER (60 mg, manipulated) and received 1 dose of each oral agent in crossover fashion, separated by ≥5 days. Pharmacodynamic and pharmacokinetic endpoints were assessed, including the primary endpoint of peak effect of Drug Liking (E_{max}) via Drug Liking Visual Analog Scale (VAS) score and the secondary endpoints of time to E_{max} (TE_{max}) and mean abuse quotient (AQ; a pharmacokinetic parameter associated with drug liking).

Results. Thirty-eight participants completed the study. Median Drug Liking VAS E_{max} was
Introduction

Prescription opioid abuse is a major public health problem, with a reported 4.3 million Americans abusing prescription opioids in 2014 [1]. In a nationwide surveillance system of prescription opioids in the US, 11.5% of patients entering a substance abuse treatment facility indicated misuse of an opioid within the previous 30 days, compared to 6% who used heroin, 29% who reported alcohol intoxication, and 13% who used cocaine [2]. Ingestion is the most frequent route of opioid abuse, following by inhalation and injection [3]. Extended-release (ER) opioids are frequently manipulated to hasten opioid release and facilitate alternate routes of administration with the intent of heightening positive subjective effects or, in other words, “getting high” [4]. Manipulation of ER opioid formulations allows more opioid to be available, essentially changing ER formulations into immediate-release formulations. Abuse-deterrent (AD) technology that presents physical and chemical barriers aims to deter drug abuse by making it harder to defeat the tablet, thus blunting the euphoria that is experienced when opioids are misused or abused after attempted manipulation. This misuse and abuse can result in heightened positive subjective effects that may lead to addiction, overdose, or death [4]. Use of AD formulations can serve as one method to reduce the misuse and abuse of prescription opioids while maintaining treatment options for patients with pain [5–8]. Significant decreases in all exposures, abuse, unintentional therapeutic errors, unintentional general/accidental exposures, suspected suicides, and adverse reactions were observed following reformulation of ER oxycodone to an AD formulation [5]. An examination of the annual medical costs and indirect costs (eg, criminal justice, lost workplace productivity, excess medical costs) suggested that savings of $430 million in annual medical costs and $605 million in indirect costs were associated with reformulation of ER oxycodone to an AD formulation [6,8].

In a survey of recreational drug users, more abusers tampered with morphine ER (72%) than oxycodone ER (63%) and oral hydrocodone with acetaminophen (31%), indicating AD formulations of morphine ER are needed [3]. The morphine AD, ER injection-molded tablet (morphineADER-IMT) is a unique AD, ER morphine product that is the result of the combination of a polymer matrix formulation and a novel manufacturing process for the production of pharmaceutical tablets that involves injection molding. The tablets are produced using a proprietary technology (Guardian™; Egalet Corporation, Wayne, PA) that results in tablets with controlled-release properties as well as physical and chemical features that have been demonstrated to resist both common and rigorous methods of manipulation, therefore limiting particle size reduction and chemical extraction. In addition, the tablets form a viscous hydrogel on contact with liquid, limiting the ability to get the contents of a manipulated tablet into a syringe.

This study compared the relative human abuse potential (HAP) of intact and manipulated morphine-ADER-IMT (EG-001; Egalet Corporation, Wayne, PA) with that of morphine sulfate ER tablets (MS Contin®; Purdue Pharma LP, Stamford, CT) and placebo.

Methods

Study Design and Participants

This was a single-center (United States), randomized, double-blind, triple-dummy, active- and placebo-controlled, 4-way crossover study (Figure 1). The protocol was approved by the New England Institutional Review Board. All participants provided written informed consent.

Adult volunteers 18 to 55 years of age who were experienced, nondependent, recreational opioid users were eligible for inclusion in the study. A recreational user was defined as a user with a history of nonmedical use of opioids, with ≥10 occasions within the past year and ≥1 in the 12 weeks before screening. Volunteers were recruited from individuals already in the PRA Health Sciences database and from responses to print and radio ads in the surrounding community. Key exclusion criteria included a history of substance and/or alcohol dependence (excluding caffeine and nicotine), as assessed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria; any condition in which an opioid is contraindicated (eg, significant respiratory depression, acute or severe bronchial asthma or hypercarbia, suspected paralytic ileus); presence of hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus at screening; and a history of sleep apnea in the past 5 years that has not resolved or been corrected.
Study Phases

The qualification phase consisted of a naloxone challenge test to exclude participants who were opioid dependent, and a drug discrimination test to exclude participants who could not tolerate 30 mg morphine or distinguish its positive subjective effects from placebo when crushed and taken orally. During the treatment phase, participants were randomized in a 1:1:1:1 ratio to the treatment groups, with each participant receiving each treatment taken orally and separated by a 5-day washout period. The study included the following treatment groups: placebo, morphine-ADER-IMT (60-mg intact tablet), morphine-ADER-IMT (60-mg manipulated tablet), and morphine sulfate ER tablets (morphine ER; 60-mg manipulated tablet). During the treatment phase, participants were confined to the clinic from the time of dosing until completion of the 24-hour postdose assessment. Participants returned to the clinic 7 to 14 days after the final treatment for physical and laboratory examinations and to report any adverse events (AEs).

Study Medication Preparation

Because of the hardness of the tablet, manipulation of morphine-ADER-IMT required significant time and effort to prepare the treatment for oral administration. Morphine-ADER-IMT (60-mg manipulated tablet) was prepared by cutting the tablet into small chunks using a knife for 3 minutes. This method of manipulation was chosen based on the results of a Category 1 study [9,10], where cutting the morphine-ADER-IMT with a knife reduced the particle size sufficiently to allow the tablet to be put in the mouth and taken with liquid. Morphine-ADER-IMT tablets are very hard because of the injection-molding manufacturing process. Cutting the tablets is very challenging, with the risk of injury to the fingers increasing as the pieces become smaller. Therefore, a much higher level of effort (force and time) is required to cut the tablets into sufficiently small chunks. Morphine ER (60-mg manipulated tablet) was prepared by crushing the tablet with a mortar and pestle to produce a fine powder (achieved within 1 minute, with no risk of injury), requiring a much lower level of effort and shorter amount of time compared with the time and effort needed to prepare morphine-ADER-IMT. Placebo preparations matched both the intact and manipulated active drugs.

Assessments

Pharmacodynamic Endpoints

The primary pharmacodynamic (PD) endpoint was the peak effect (E_max) of Drug Liking using the 0 to 100 bipolar Drug Liking Visual Analog Scale (VAS; 0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking). Secondary PD endpoints included time to E_max (T_E_max) of Drug Liking; E_max and T_E_max for changes in pupil diameter as measured with a NeurOptics VRP™ 200 Pupillometer (NeurOptics, Irvine, CA); response to the Take Drug Again VAS using the 0 to 100 bipolar VAS (0 = definitely would not; 50 = do not care; 100 = definitely would); response to the Overall Drug Liking VAS using the 0 to 100 bipolar VAS (0 = strongly dislike; 50 = neither like nor dislike; 100 = strongly like); and responses to the Drug Effects Questionnaire (DEQ) using a 0 to 100 unipolar VAS (0 = not at all; 100 = extremely) for each statement. PD endpoints were measured predose, at 30 and 45 minutes postdose, and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose, except for the Overall Drug Liking and Take Drug Again VASs, which were measured at 12 and 24 hours postdose.

Pharmacokinetic Endpoints

Blood samples were collected predose, at 30 and 45 minutes postdose, and at 1, 1.5, 2, 3, 4, 6, 8, 12,
and 24 hours postdose. Multiple pharmacokinetic (PK) parameters were calculated for plasma morphine, including maximum plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration versus time curve extrapolated to infinity (AUC0–∞), apparent first-order terminal elimination half-life (t1/2), and Abuse Quotient (AQ; Cmax/tmax). The AQ reflects the rate and extent of increase in plasma morphine concentration from dosing to tmax and is a PK parameter that has been associated with drug liking and abuse potential [11,12].

Safety

Adverse events were assessed in the qualification and treatment phases and at the follow-up visit for all participants who received ≥1 dose of study medication during the treatment phase (safety population).

Statistical Analyses

Outcomes were assessed for participants who received all 4 treatments (completer population). PD outcomes were analyzed using a linear mixed-effects model with fixed effects for sequence, period, and treatment, and a random effect for participant nested in sequence. PK outcomes were analyzed using descriptive statistics (median and 95% CI).

Results

Participants

Thirty-eight of the 78 participants (48.7%) passed the qualification phase of the study. Failure in the drug discrimination test was the primary reason for not completing the qualification phase, with 85% (34/40) of all discontinuations during this phase because of a failed drug discrimination test. The disposition of participants in the study is shown in Figure 1. One participant withdrew consent before completion of the treatment phase. Of the 38 study completers, the majority were white men; the mean (SD) age of the completer population was 24.3 (4.2) years (Table 1). Baseline demographics were similar among participants randomized to each of the study treatment sequences.

Pharmacodynamic Endpoints

Drug Liking VAS

Mean Drug Liking VAS scores were lower after treatment with manipulated or intact morphine-ADER-IMT compared with manipulated morphine ER from 30 minutes to 3 hours postdose (Figure 2A). Median Peak Drug Liking VAS (Emax) was significantly lower after treatment with manipulated morphine-ADER-IMT (67) compared with manipulated morphine ER (74; P = 0.007; Figure 2B). No significant differences in Emax were reported between treatment with intact and manipulated morphine-ADER-IMT. Tmax was significantly shorter after treatment with manipulated morphine ER compared with intact (P < 0.0001) or manipulated (P = 0.004) morphine-ADER-IMT (Figure 2C).

Pupillary Miosis

Peak pupillary miosis occurred between 1.5 and 6 hours after treatment with manipulated morphine ER and peaked at 6 hours after treatment with manipulated or intact morphine-ADER-IMT (Figure 3). The median pupillary miosis Emax values after treatment with manipulated morphine ER and manipulated morphine-ADER-IMT

| Table 1  | Demographics and characteristics of the completer population |
|---------|---------------------------------------------------------------|
|         | Treatment Sequence*                                          |
|         | ABCD (n = 10) BDAC (n = 10) CADB (n = 8) DCBA (n = 10) Overall (N = 38) |
| Male, n (%) | 7 (70.0) | 9 (90.0) | 5 (62.5) | 7 (70.0) | 28 (73.7) |
| Female, n (%) | 3 (30.0) | 1 (10.0) | 3 (37.5) | 3 (30.0) | 10 (26.3) |
| Race, n (%) | 9 (90.0) | 9 (90.0) | 8 (100)  | 9 (90.0) | 35 (92.1) |
| White | 0 | 0 | 0 | 1 (10.0) | 1 (2.6) |
| Black | 1 (10.0) | 0 | 0 | 0 | 1 (2.6) |
| Native Hawaiian or other Pacific Islander | 1 (10.0) | 1 (10.0) | 1 (10.0) | 1 (10.0) | 1 (2.6) |
| Other | 22.7 (3.7) | 24.6 (4.3) | 24.8 (5.3) | 25.2 (3.7) | 24.3 (4.2) |
| Weight, lb, mean (SD) | 159.2 (22.9) | 171.6 (28.9) | 141.9 (15.1) | 163.4 (32.5) | 159.9 (27.2) |
| BMI, kg/m², mean (SD) | 24.2 (3.6) | 25.8 (4.2) | 22.0 (1.8) | 24.7 (4.6) | 24.3 (3.9) |

ADER-IMT = abuse-deterrent, extended-release injection-molded tablets; BMI = body mass index; ER = extended release.
*Treatment sequence consisted of treatments A = intact morphine-ADER-IMT (60 mg); B = manipulated morphine-ADER-IMT (60 mg); C = manipulated morphine ER (60 mg); and D = placebo.
were the same, but pupillary miosis TE\text{max} was significantly shorter after manipulated morphine ER versus intact and manipulated morphine-ADER-IMT (\(P < 0.0001\); data not shown).

**Take Drug Again and Overall Drug Liking Visual Analog Scales**

The median \(E_{\text{max}}\) value for the Take Drug Again VAS was lower after treatment with manipulated (61.5; \(P = 0.05\)) and intact morphine-ADER-IMT (56.0; \(P < 0.001\)) compared with manipulated morphine ER (68.0). Similarly, the median \(E_{\text{max}}\) value for Overall Drug Liking was lower after treatment with manipulated (63.5; \(P = 0.13\) vs morphine) and intact (57.0; \(P < 0.001\)) morphine-ADER-IMT compared with morphine ER (67.5).

**Drug Effects Questionnaire**

Median scores on the DEQ for “I can feel good drug effects,” “I am feeling high,” and “I can feel a drug effect” were significantly lower after treatment with manipulated or intact morphine-ADER-IMT compared with manipulated morphine ER (Table 2).
Pharmacokinetic Endpoints

Morphine plasma concentrations were higher in participants receiving manipulated morphine ER compared with participants receiving manipulated morphine-ADER-IMT up to 1.5 hours after treatment. From 2 to 12 hours posttreatment, morphine plasma concentrations were similar in participants receiving manipulated morphine ER and those receiving morphine-ADER-IMT (Figure 4). Morphine PK parameters are shown in Table 3. Higher \( C_{\text{max}} \) and shorter \( t_{\text{max}} \) values for plasma morphine were observed in participants receiving manipulated morphine ER compared with those receiving manipulated or intact morphine-ADER-IMT. The mean AQ was lower after treatment with intact (5.7) or manipulated (16.4) morphine-ADER-IMT compared with manipulated morphine ER (45.9; Figure 5).

Safety

Treatment-emergent AEs (TEAEs) with morphine ER and morphine-ADER-IMT were similar and typical of morphine analgesics, with gastrointestinal symptoms (eg, nausea, vomiting) and generalized pruritus being the most frequently reported (Table 4). There were no serious AEs in this study.

Discussion

There were several key findings in this study suggestive of a lower oral abuse potential for morphine-ADER-IMT compared with morphine ER. Drug Liking \( E_{\text{max}} \) was significantly lower after oral administration with manipulated morphine-ADER-IMT compared with manipulated morphine ER. Additionally, no significant differences in \( E_{\text{max}} \)

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Table 2  Median responses to Drug Effects Questionnaire*

| Placebo (n = 38) | Manipulated Morphine ER (n = 38) | Manipulated Morphine-ADER-IMT (n = 38) | \( P \) Values† | Intact Morphine-ADER-IMT (n = 38) | \( P \) Values† |
|------------------|---------------------------------|--------------------------------------|----------------|---------------------------------|----------------|
| Median VAS score, \( E_{\text{max}} \) | | | | | |
| I can feel a drug effect | 0 | 55.5 | 39.0 | 0.001 | 17.5 | <0.0001 |
| I can feel good drug effects | 0 | 52.0 | 25.5 | 0.0025 | 17.5 | <0.0001 |
| I can feel bad drug effects | 0 | 6.0 | 4.0 | NS | 1.0 | NS |
| I am feeling high | 0 | 49.0 | 38.0 | 0.0035 | 18.5 | <0.0001 |
| I am feeling sick | 0 | 0 | 1.0 | NS | 0 | NS |
| I am feeling nauseous | 0 | 1.5 | 0.5 | NS | 0 | NS |
| I am feeling sleepy | 0 | 27.0 | 27.5 | NS | 19.0 | NS |
| I am feeling dizzy | 0 | 1.0 | 0 | NS | 0 | NS |

ADER-IMT = abuse-deterrent, extended-release injection-molded tablets; \( E_{\text{max}} \) = peak effect; ER = extended release; NS = not significant; VAS = visual analog scale.

*0–100 unipolar VAS (0 = not at all; 100 = extremely) for each statement.
†Relative to manipulated morphine ER.

Pharmacokinetic Endpoints

Morphine Plasma Concentrations were higher in participants receiving manipulated morphine ER compared with participants receiving manipulated morphine-ADER-IMT up to 1.5 hours after treatment. From 2 to 12 hours posttreatment, morphine plasma concentrations were similar in participants receiving manipulated morphine ER and those receiving morphine-ADER-IMT (Figure 4). Morphine PK parameters are shown in Table 3. Higher \( C_{\text{max}} \) and shorter \( t_{\text{max}} \) values for plasma morphine were observed in participants receiving manipulated morphine ER compared with those receiving manipulated or intact morphine-ADER-IMT. The mean AQ was lower after treatment with intact (5.7) or manipulated (16.4) morphine-ADER-IMT compared with manipulated morphine ER (45.9; Figure 5).

Safety

Treatment-emergent AEs (TEAEs) with morphine ER and morphine-ADER-IMT were similar and typical of morphine analgesics, with gastrointestinal symptoms (eg, nausea, vomiting) and generalized pruritus being the most frequently reported (Table 4). There were no serious AEs in this study.

Discussion

There were several key findings in this study suggestive of a lower oral abuse potential for morphine-ADER-IMT compared with morphine ER. Drug Liking \( E_{\text{max}} \) was significantly lower after oral administration with manipulated morphine-ADER-IMT compared with manipulated morphine ER. Additionally, no significant differences in \( E_{\text{max}} \)
were observed after treatment with intact or manipulated morphine-ADER-IMT. These findings occurred after a greater level of effort and time required to manipulate morphine-ADER-IMT compared with the process needed to crush morphine ER. Furthermore, \( T_{\text{E max}} \) was significantly shorter after treatment with manipulated morphine ER compared with intact or manipulated morphine-ADER-IMT. Finally, the mean AQ was lower after treatment with intact or manipulated morphine-ADER-IMT compared with manipulated morphine ER, suggesting that morphine-ADER-IMT maintains some of its ER properties after attempted manipulation. In addition, a higher AQ was observed with manipulated morphine ER compared with intact or manipulated morphine-ADER-IMT, suggesting a greater potential for abuse with manipulated morphine ER because reaching high concentrations in a shorter period of time is associated with rewarding effects [11,12].

It is important to note that the median pupillary miosis \( E_{\text{max}} \) values after treatment with manipulated morphine ER or manipulated morphine-ADER-IMT were the same. However, similar to the \( T_{\text{E max}} \) for Drug Liking, pupillary miosis \( T_{\text{E max}} \) was significantly shorter with manipulated morphine ER versus intact or manipulated morphine-ADER-IMT. Pupillary miosis is a pharmacologic effect of \( \mu \)-opioids [13] and serves as an objective PD endpoint that reflects central \( \mu \)-opioid effects.

Chewing is often the first step in unintentional misuse or intentional abuse of opioids via the oral route of administration. The formulation and novel injection-molding manufacturing process for morphine-ADER-IMT result in hard tablets that are difficult to chew. The combination of the difficulty in chewing and the level of effort needed to manipulate morphine-ADER-IMT, as well as the Drug Liking \( E_{\text{max}} \) and DEQ findings, point to the range of

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**Table 3** Morphine pharmacokinetic parameters

| Parameter, Mean (SD) | Manipulated Morphine ER (n = 39) | Manipulated Morphine-ADER-IMT (n = 38) | Intact Morphine-ADER-IMT (n = 38) |
|----------------------|----------------------------------|--------------------------------------|----------------------------------|
| \( C_{\text{max}}, \text{ng/mL} \) | 42.3 (14.3) | 28.7 (9.1) | 17.8 (6.6) |
| \( t_{\text{max}}, \text{h} \) | 1.1 (0.6) | 2.0 (0.7) | 3.6 (1.1) |
| \( \text{AUC}_{0-\infty}, \text{h} \times \text{ng/mL} \) | 182.1 (49.9)* | 159.3 (36.8)† | 168.0 (53.8)‡ |
| \( t_{1/2}, \text{h} \) | 7.0 (2.0)§ | 9.5 (2.6)¶ | 8.0 (1.5)¶ |
| Abuse Quotient | 45.9 (20.3) | 16.4 (9.4) | 5.7 (3.5) |

ADER-IMT = abuse-deterrent, extended-release injection-molded tablets; \( \text{AUC}_{0-\infty} \) = area under the plasma concentration vs time curve extrapolated to infinity; \( C_{\text{max}} \) = maximum plasma concentration; ER = extended release; \( t_{\text{max}} \) = time to \( C_{\text{max}} \); \( t_{1/2} \) = apparent first-order terminal elimination half-life.

*\( n = 35. \\
†\( n = 28. \\
‡\( n = 19. \\
§\( n = 3. \\
¶\( n = 11. 

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**Figure 4** Mean morphine concentrations over time. ADER-IMT = abuse-deterrent, extended-release injection-molded tablets; ER = extended release.
clinically relevant AD features of this product. In addition, to standardize and blind the drug product for these randomized controlled Category 3 HAP studies, they are prepared in a clinical pharmacy and not manipulated by the participants themselves. Therefore, the participants are responding to the PD endpoints without knowledge of the difference in the level of effort needed up front to get the product into an abusable form. Given that the speed and ease with which prescription drugs can be defeated affects their street value [14], this would be another factor that would strengthen the AD profile of morphine-ADER-IMT in the real world.

Following the introduction of an AD formulation of ER oxycodone in 2010, the number of abusers of oxycodone ER decreased significantly [5,15]. However, studies showed migration to other prescription opioids after the introduction of AD oxycodone [4,15]. This migration highlights the need for additional AD formulations of different opioids such as morphine ER. Thus, AD formulations may represent a useful tool as part of a public health strategy to reduce misuse, abuse, and overdose deaths due to prescription opioids [16].

A strength of the current study is that it was conducted in accordance with the final US Food and Drug Administration Guidance on Abuse-Deterrent Opioids – Evaluation and Labeling (April 2015) [17]. Another strength of the study was the rigorous method used to manipulate the morphine-ADER-IMT based on the results of the Category 1 testing [9,10], which was conducted in accordance with FDA guidance on abuse-deterrent opioids [17]. Thus, in addition to the PD and PK results of this study, the considerable level of effort required to try and defeat the AD properties of morphine-ADER-IMT compared with the ease of

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**Figure 5** Mean Abuse Quotient ($C_{\text{max}}/t_{\text{max}}$). ADER-IMT = abuse-deterrent, extended-release injection-molded tablets; $C_{\text{max}}$ = maximum plasma concentration; ER = extended release; $t_{\text{max}}$ = time to $C_{\text{max}}$.

**Table 4** Most frequent* adverse events related to study medication (safety population)

| Preferred Term | Placebo (n = 38) | Manipulated Morphine ER (n = 39) | Manipulated Morphine-ADER-IMT (n = 38) | Intact Morphine-ADER-IMT (n = 38) |
|----------------|------------------|-------------------------------|--------------------------------------|-------------------------------|
| Participants with ≥1 TEAE | 2 (5.3) | 19 (48.7) | 18 (47.4) | 12 (31.6) |
| Nausea | 1 (2.6) | 7 (17.9) | 3 (7.9) | 5 (13.2) |
| Vomiting | 0 | 6 (15.4) | 6 (15.8) | 3 (7.9) |
| Pruritus generalized | 0 | 7 (17.9) | 5 (13.2) | 1 (2.6) |
| Headache | 0 | 2 (5.1) | 4 (10.5) | 2 (5.3) |
| Somnolence | 0 | 5 (12.8) | 2 (5.3) | 1 (2.6) |
| Dizziness | 0 | 3 (7.7) | 2 (5.3) | 0 |

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

*Incidence ≥10% overall.

†Medical Dictionary for Regulatory Activities, version 17.0.
manipulating morphine ER needs to be considered when assessing the overall abuse potential of morphine-ADER-IMT. A potential weakness of the study was a possible unblinding issue because manipulated morphine ER was mixed in juice, but morphine-ADER-IMT was dosed with juice because its gelling properties made it difficult to mix it into a solution. However, the triple-dummy design of this study helped to minimize the risk of unblinding.

In conclusion, although participants of this study were not asked to chew any of the treatments, the hardness of morphine-ADER-IMT would prevent it from being chewed as a method of manipulation. More effort was required to physically manipulate morphine-ADER-IMT compared with morphine ER tablets to reduce particle size for oral abuse. Intact and manipulated morphine-ADER-IMT demonstrated significantly lower Peak Drug Liking \( E_{\text{max}} \) compared with manipulated morphine ER when administered orally. Manipulation of morphine-ADER-IMT did not significantly increase Drug Liking \( E_{\text{max}} \) compared with the intact product, and the AQ for manipulated morphine ER was much higher than the AQ for both manipulated and intact morphine-ADER-IMT. These data suggest that morphine-ADER-IMT would be an important new AD, ER morphine product with lower potential for unintentional misuse by chewing or intentional oral abuse by manipulation of the product than currently available non-AD morphine ER products.

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