CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208603	Submission Date(s): 12/14/2015
Brand Name	Arymo
Generic Name	Morphine Sulfate Extended Release Tablet
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	Egalet Corporation
Relevant IND(s)	117317
Submission Type; Code	Original; 505(b)(2)
Formulation; Strength(s)	Tablet; 15, 30 and 60 mg
Indication	Chronic pain management
Proposed Dosage Regimen	Titrate to effect using a twice daily regimen.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submission is acceptable from clinical pharmacology perspective provided that mutually acceptable labeling is agreed between the sponsor and the Agency.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Egalet Corporation (also referred to as Egalet or Sponsor) has submitted a 505(b)(2) NDA 208603 for marketing Arymo (also referred to as EG-001) morphine sulfate extended-release tablets for the management of chronic pain. Arymo is a polymer matrix tablet that utilizes a plastic injection molding with controlled-release properties as well as physical and chemical features that have been demonstrated to resist intravenous, intranasal and oral routes of abuse following rigorous methods of product manipulation. Egalet indicates that the ingredients in the tablet resist chewing, particle size reduction and chemical extraction of morphine. Egalet also indicates that contact with liquid results in a viscous hydrogel making syringeability difficult.

Egalet has developed Arymo tablet strengths of 15, 30 and 60 mg. This 505(b)(2) NDA relies on the Agency's previous findings of safety and efficacy from NDA 019516 for MS Contin. Clinical bioequivalence data was provided comparing the to-be-marketed product of Arymo tablets and MS Contin tablets (see Table below) at all strengths. Arymo 60 mg and 30 mg were bioequivalent to MS Contin with respect to both Cmax and AUC. Arymo 15 mg was bioequivalent to MS Contin 15 mg with regard to AUC, but Cmax was only slightly lower. Based on team discussion, it is agreed that considering the titration to effect regimen employed for morphine extended release formulations, this slightly lower Cmax for 15 mg is not considered clinically significant and will not prevent approval of the product.

Food-Effect on EG-001 60 mg was assessed. Food delayed median Tmax by 2 hr (6.5 hr vs. 4.5 hr). The Cmax and AUC values met the bioequivalence criteria. The food-effect on EG-001 is not considered clinically significant.

Table : EG-001 Oral Tablet Formulations used in Clinical Studies

Study No.	Study Title	Description of Dosage Strength, and Formulation	Lot Number(s) used in Clinical Trial
067-EG-006	A Randomized, Open-Label, 2-Way Crossover Study to Determine the Bioequivalence of the Egalet® Morphine PR 15-mg Tablet versus MS Contin® Under Fasting Conditions in Healthy Subjects	15 mg Formulation C (to-be-marketed product)	SB69400301
067-EG-011	A Randomized, Open-Label, 2-Cohort, Crossover Design Study to Determine the Bioequivalence of Egalet® Morphine PR 60-mg Tablets versus MS Contin® 60-mg Tablets and to Evaluate the Effect of Food on Egalet® Morphine PR 60-mg Tablets in Healthy Subjects with Naltrexone Blockade	60 mg Formulation C (to-be-marketed product)	SB69300201
067-EG-012	A Randomized, Open-Label, 3-Way Crossover Study to Evaluate the Bioequivalence of Egalet® Morphine PR 30 mg to MS Contin® 30 mg and Egalet® Morphine PR 2 × 15 mg to MS Contin® 30 mg Under Fasting Conditions in Healthy Subjects Under Naltrexone Blockade	15 mg 30 mg Formulation C (to-be-marketed product)	SB69400101 SB69200101

OSIS audit was satisfactory for the BE study site and bioanalytical facilities (b) (4) . *In vitro* alcohol studies did not show dose-dumping and hence *in vivo* alcohol interaction studies were not conducted. Since the BE studies established a satisfactory bridge between Arymo and MS Contin, the sponsor did not conduct any special population studies and would like to rely on the MS Contin product label.

While no efficacy studies were conducted, Egalet conducted two abuse liability studies to support safety of Arymo following oral and intranasal abuse (See Table below). Pharmacokinetics of morphine after intact product administration and after manipulation was reviewed to support the controlled substances staff (CSS) conclusions. Pharmacodynamic endpoints (Drug liking) were reviewed by Dr. James Tolliver of CSS.

Study No.	Study Title	Description of Dosage Strength, and Formulation	Lot Number(s) used in Clinical Trial
067-EG-008	A Randomized, Double-Blind, Triple-Dummy, Active and Placebo-Controlled, Four-Way Crossover Study with an Exploratory Fifth Arm Comparing the Abuse Potential of Manipulated and Intact Egalet® PR Morphine Tablets versus Manipulated MS CONTIN Following Oral Administration in Nondependent Recreational Opioid Users	60 mg Formulation C (to-be-marketed product)	SB69300301
067-EG-009	A Randomized, Double-Blind, Double-Dummy, Active and Placebo-Controlled, Crossover Study Comparing the Abuse Potential of Manipulated and Manipulated/Sieved Egalet® PR Morphine Tablets versus Manipulated MS CONTIN following Intranasal Administration in Nondependent Recreational Opioid Users	60 mg Formulation C (to-be-marketed product)	SB69300301

PR = prolonged-release
Egalet® PR Morphine = EG-001

While the intranasal abuse liability study indicates that Arymo may be less susceptible to intranasal abuse, the oral abuse liability study was not conclusive in showing oral abuse deterrence of Arymo.

Developmental formulations have been investigated in two additional Phase 1 clinical trials investigating the bioavailability and bioequivalence of EG-001 compared to MS Contin in healthy adult subjects (067-EG-001, 067-EG-002). These two studies support the *in vitro in vivo correlation* developed by the sponsor and reviewed by the biopharmaceutics reviewer.

Bioequivalence of Arymo with MS Contin:

The sponsor conducted three separate studies to establish bioequivalence of Arymo to MS Contin at 15 mg, 30 and 60 mg strengths. These studies were all randomized open-label, crossover, single-dose, bioequivalence studies conducted in approximately 60 - 65 healthy adult subjects under naltrexone block.

Study 067-EG-011 was conducted to establish bioequivalence of Formulation C (to-be-marketed product) of EG-001 60 mg Versus MS Contin 60 mg in fasted healthy subjects (n=65). Additionally, Food-Effect on EG-001 60 mg was assessed in this study in a separate cohort.

Table : Study Design (067-EG-011)

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

Treatment A: EG-001 60 mg tablet, fasted conditions.

Treatment B: MS Contin 60 mg tablet, fasted conditions.

Treatment C: EG-001 60 mg tablet, fed conditions. (Food-effect results will be discussed on page 8)

Table: Descriptive Statistics of morphine PK in Study 067-EG-011.

	Morphine	
	EG-001 60 mg Tablet Fasting Conditions Treatment A (n=60)	**MS Contin 60 mg Tablet Fasting Conditions Treatment B (n=60)**
AUC_∞ (ng•h/mL)	196.6 (27.3)	200.5 (26.8)
AUC_t (ng•h/mL)	189.1 (27.3)	192.8 (26.3)
C_{max} (ng/mL)	21.6 (35.6)	22.7 (36.5)
t_{max} (h)	4.50 (1.00, 6.00)	2.50 (0.67, 4.52)
$t_{½}$ (h)	9.57 (26.3)	9.94 (28.5)

The summary data for the PK parameters for morphine are provided in the table above. The 90% CIs of the geometric LS mean ratios for Cmax, AUCt, and AUC∞ of morphine were all contained within the 80% to 125% bioequivalence interval (See Table below). Although there is an apparent difference in Tmax (median) 4.5 h for Arymo vs. 2.5 h for MS Contin 60 mg, this is not considered clinically significant by DAAAP, considering the titration to effect regimen employed for morphine extended release formulations.

Table : Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine (Pharmacokinetic Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	59	59	188.0	192.2	97.79 (95.07, 100.59)
AUC_t (ng•h/mL)	60	60	180.3	185.3	97.32 (94.27, 100.47)
C_{max} (ng/mL)	60	60	20.22	21.20	95.35 (89.40, 101.69)

Study 067-EG-012 was conducted to establish bioequivalence of Formulation C of Arymo 30 mg Versus MS Contin 30 mg in fasted healthy volunteers (n=63). Additionally, bioequivalence of two tablets of 15 mg strength Arymo (Formulation C) with one 30 mg strength of MS Contin was also established in this study.

Subjects were randomized to one of six treatment sequences and were given a single dose of each of the following treatments separated by at least 7 days:

Treatment A: EG-001 30 mg tablet, fasting conditions.

Treatment B: MS Contin 30 mg tablet, fasting conditions.

Treatment C: EG-001 2x15 mg tablet, fasting conditions.

Table: Descriptive Statistics of morphine PK in Study 067-EG-012

	Morphine		
	EG-001 30 mg (n=60)	MS Contin 30 mg (n=59)	EG-001 2x15 mg (n=61)
AUC_∞ (ng•h/mL)	115.7 (26.1)	119.2 (29.1)	117.3 (27.1)
AUC_t (ng•h/mL)	111.9 (25.6)	113.9 (29.0)	112.3 (27.1)
C_{max} (ng/mL)	12.0 (33.5)	12.1 (33.3)	10.8 (33.1)
t_{max} (h)	4.50 (0.67, 6.00)	2.00 (0.67, 5.50)	4.50 (1.50, 8.00)
$t_{½}$ (h)	10.03 (23.6)	10.92 (21.2)	10.51 (23.9)

Pharmacokinetics of morphine following the administration of 30 mg dose of EG-001 (one 30 mg tablet or two 15 mg tablets) and MS Contin are described in the table above. The observed median Tmax for 30 mg EG-001 is 4.5 h while 30 mg MS Contin has a Tmax of 2 hours. While comparing EG-001 (A or C) vs. MS Contin (B), the 90% CIs of the geometric LS mean ratios for Cmax, AUCt, and AUC∞ of morphine were all contained within the 80% to 125% bioequivalence interval (See Table below). Similarly, comparing EG-001 one 30 mg tablet (A) vs. two 15 mg tablets (C) the 90% CIs of the geometric LS mean ratios for Cmax, AUCt, and AUC∞ of morphine were all contained within the 80% to 125% bioequivalence interval.

Table : Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine (Pharmacokinetic Analysis Population), Study 067-EG-012

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (A:B) (90% CI)
	Test (Treatment A)	Reference (Treatment B)	Test (Treatment A)	Reference (Treatment B)	
AUC_∞ (ng•h/mL)	58	58	113.2	115.1	98.31 (95.99, 100.69)
AUC_t (ng•h/mL)	60	59	108.8	110.1	98.84 (96.61, 101.11)
C_{max} (ng/mL)	60	59	11.42	11.59	98.61 (93.91, 103.55)
	Test (Treatment C)	**Reference (Treatment B)**	**Test (Treatment C)**	**Reference (Treatment B)**	**Geometric LS Mean Ratio (%) (C:B) (90% CI)**
AUC_∞ (ng•h/mL)	60	58	113.3	115.1	98.42 (96.13, 100.78)
AUC_t (ng•h/mL)	61	59	108.7	110.1	98.66 (96.45, 100.92)
C_{max} (ng/mL)	61	59	10.20	11.59	88.04 (83.87, 92.43)
	Treatment (Treatment A)	**Treatment (Treatment C)**	**Treatment (Treatment A)**	**Treatment (Treatment C)**	**Geometric LS Mean Ratio (%) (A:C) (90% CI)**
AUC_∞ (ng•h/mL)	58	60	113.2	113.3	99.88 (97.54, 102.29)
AUC_t (ng•h/mL)	60	61	108.8	108.7	100.18 (97.94, 102.47)
C_{max} (ng/mL)	60	61	11.42	10.20	112.00 (106.70, 117.57)

CI = confidence interval; LS = least squares
Source: 067-EG-012 Table 14.2.3.1
Treatment A: EG-001 30 mg tablet, fasted conditions
Treatment B: MS Contin 30 mg tablet, fasted conditions
Treatment C: EG-001 2x15 mg tablets, fasted conditions
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Study 067-EG-006 was conducted to establish bioequivalence of Formulation C of Arymo 15 mg Versus MS Contin 15 mg in fasted healthy volunteers (n=64).

Table: Descriptive Statistics of morphine PK in Study 067-EG-006.

	Morphine	
	EG-001 15 mg Tablet Fasting Conditions (n=64)	MS Contin 15 mg Tablet Fasting Conditions (n=63)
AUC_∞ (ng•h/mL)	47.3 (37.5)	48.0 (42.5)
AUC_t (ng•h/mL)	36.2 (34.0)	38.9 (39.0)
C_{max} (ng/mL)	4.41 (33.6)	5.35 (35.0)
t_{max} (h)	3.53 (1.50, 8.00)	2.00 (1.00, 6.00)
$t_{½}$ (h)	10.11 (47.7)	10.05 (50.0)

The summary data for the PK parameters for morphine are provided in the table above. The 90% CIs of the geometric LS mean ratios for AUCt, and AUC∞ of morphine all contained within the 80% to 125% bioequivalence interval, with the exception of Cmax for morphine (See Table below). For Cmax of morphine, the lower limit of the 90% CI of the geometric LS mean ratio was slightly below the 80% to 125% bioequivalence interval (78.99%). DAAAP clinical division does not consider this clinical significant as the product is only initiated on 15 mg, in some cases, and titrated to effect with higher doses, if necessary.

Table : Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine, Study 067-EG-006

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	29	39	42.12	43.00	97.96 (90.73, 105.76)
AUC_t (ng•h/mL)	64	63	34.15	35.90	95.12 (91.01, 99.42)
C_{max} (ng/mL)	64	63	4.193	5.016	83.60 (78.99, 88.47)

CI = confidence interval; LS = least squares
Source: 067-EG-006 Table 14.2.3.1
Test: EG-001, 15 mg tablet, fasted conditions (Treatment A).
Reference: MS Contin, 15 mg tablet, fasted conditions (Treatment B).
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Additional population PK analysis was conducted to simulate multiple dose PK of Arymo. However, since satisfactory bioequivalence results support Arymo 15 mg to 60 mg strengths under single dose, multiple dose PK study or simulations are considered only supportive.

Food-effect on Arymo 60 mg Tablet:

In Study 067-EG-011, an additional treatment arm (C) was employed in a separate cohort to evaluate the effect of high-fat meal on bioavailability of Arymo 60 mg tablet. The descriptive statistics of morphine following fasted and fed treatments are described in the table below.

Table: Morphine PK in food-effect cohort of study 067-EG-011.

	EG-001 60 mg Tablet Fasting Conditions Treatment A (n=14)	EG-001 60 mg Tablet Fed Conditions Treatment C (n=14)
AUC_{∞} (ng•h/mL)	199.9 (23.3)	232.0 (25.1)
AUC_t (ng•h/mL)	192.3 (22.8)	221.4 (25.2)
C_{max} (ng/mL)	23.6 (30.8)	23.8 (35.9)
t_{max} (h)	4.50 (2.00, 5.50)	6.50 (3.50, 10.00)
$t_{½}$ (h)	10.34 (25.7)	10.55 (24.2)

The summary data for the PK parameters for morphine are provided in the table above. The Tmax of EG-001 60 mg under fasting condition is 4.5 h, while Tmax in fed condition is 6.5 hours. Comparison of Fasted (A) vs. Fed (C), the 90% CIs of the geometric LS mean ratios for Cmax, AUCt, and AUC∞ of morphine all contained within the 80% to 125% bioequivalence interval (see table below). Considering this is an extended release product for chronic pain management and the titration to effect regimen employed for morphine extended release formulations, the food-effect on EG-001 is not considered clinically significant.

Table : Bioequivalence Analysis of AUC_t, AUC_{∞}, and C_{max} Parameters of Morphine (Food-Effect Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_{∞} (ng•h/mL)	14	14	194.9	225.3	115.59 (108.35, 123.31)
AUC_t (ng•h/mL)	14	14	187.8	214.9	114.42 (107.04, 122.31)
C_{max} (ng/mL)	14	14	22.71	22.18	97.67 (83.83, 113.79)

CI = confidence interval; LS = least squares
Source: 067-EG-011 Table 14.2.3.1.2
Test: EG-001, 60 mg tablet, fasted conditions (Treatment A).
Reference: EG-001, 60 mg tablet, fed conditions (Treatment C).
A linear mixed-effect model with treatment as a fixed effect and measurements within subject as repeated measures was fitted to the ln-transformed pharmacokinetic parameters.

MS Contin label indicates that no significant differences in Cmax and AUC were noted when the 30 mg tablet was taken while fasting or with high-fat meal.

Oral abuse liability Study 067-EG-008:

The sponsor conducted "A Randomized, Double-Blind, Triple-Dummy, Active and Placebo-Controlled, Four-Way Crossover Study with an Exploratory Fifth Arm Comparing the Abuse Potential of Manipulated and Intact Egalet PR Morphine Tablets versus Manipulated MS CONTIN Following Oral Administration in Nondependent Recreational Opioid Users". After naloxone challenge and drug discrimination phase, non-dependent recreational opioid users (n=38) received the following treatments in a crossover fashion:

Treatment Period:

• Treatment A: Egalet PR morphine, 60 mg oral intact
• Treatment B: Egalet PR morphine, 60 mg oral manipulated
• Treatment C: MS CONTIN, 60 mg oral manipulated
• Treatment D: Placebo

For the manipulated condition, one tablet was manipulated (cut into pieces within three minutes with Tool F) and administered orally directly from the vial and followed by 150 mL Ocean Spray® Diet Cranberry™ juice.

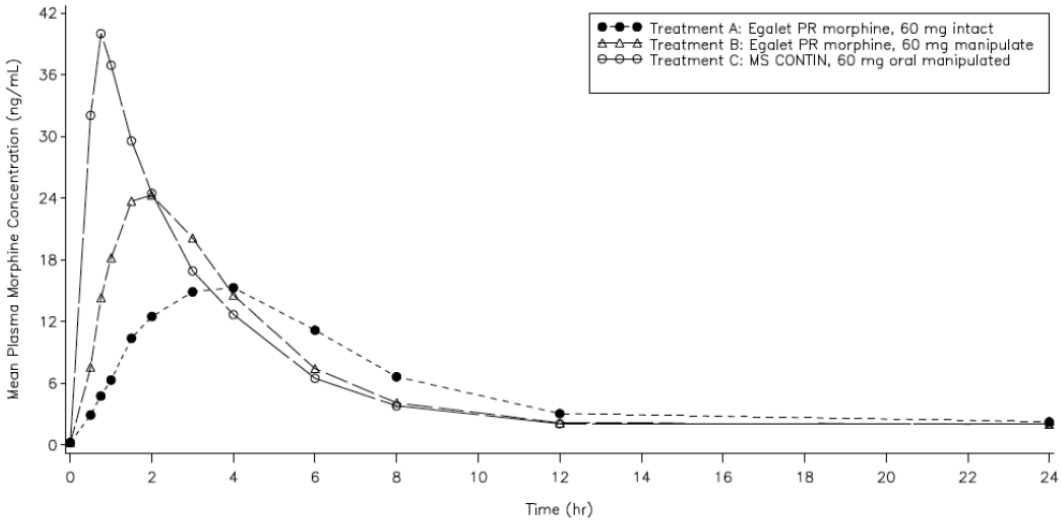
- Exploratory Treatment E: Egalet PR morphine, 60 mg oral manipulated (cut as above) and administered mixed in juice. Twelve subjects received this treatment.

Pharmacokinetic and pharmacodynamic assessments were collected approximately at the same time for several hours after drug administration. Morphine concentration and PK parameters were primary endpoints along with Drug Liking VAS item: "Do you like the drug effect you are feeling now?" where values can range from 0 (strong disliking) to 100 (strong liking) and 50 (neither like nor dislike) is the neutral point.

On August 4, 2016 an FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee was convened to examine the granting of abuse deterrent claims for EG-001 tablets. In this study only Tool F was used for cutting the tablet. It is important to use a manipulation that is relevant to an abuse situation. For example, the study did not employ chewing as a manipulation method. However, as discussed at the advisory committee there may be other methods such as manipulation Tool F followed by J and followed by dissolving for 30 minutes in a solvent that can be easily swallowed by oral route. Sixty to eighty percent Arymo could be extracted for oral consumption, as discussed at the advisory committee meeting. Therefore, the oral abuse methodology used in the study may not have been an optimal oral abuse situation, especially since chewing was excluded.

For the employed method of manipulation (cutting), the morphine peak plasma concentrations of manipulated Arymo 60 mg was 60% higher than intact Arymo treatment. The extended-release characteristics of Arymo are disrupted by cutting the tablet. Even the exploratory treatment arm mimicking crushed product mixed in juice showed 42% higher Cmax compared to intact product. Since MS Contin is not an abuse deterrent product it is not surprising to note the dose-dumping related increase in Cmax by almost 2.3-fold compared to intact Arymo. Earlier Tmax was noted with all manipulated treatments compared to the intact product (see table below).

Figure : Mean Morphine Plasma Concentrations (ng/mL) vs. on Linear Scale- PK Population (N = 39)



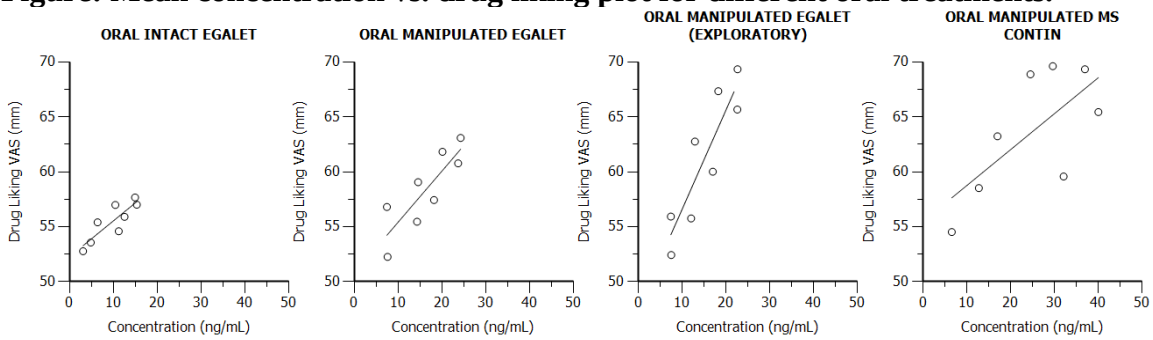
Source: Figure 14.2.7.4.1

Table : Descriptive Statistics for Plasma Morphine Pharmacokinetic Parameters by Treatment - PK Population (N = 39)

Parameter	Statistic	Manipulated MS CONTIN (N=39)	Manipulated Egalet PR Morphine (N=38)	Intact Egalet PR Morphine (N=38)	Manipulated Egalet PR Morphine in Juice (N=12)
C_{max} (ng/mL)	Mean (SD)	42.34 (14.311)	28.74 (9.092)	17.81 (6.596)	25.43 (6.482)
	Median	42.20	29.20	16.70	24.05
	Range	14.2, 79.0	12.5, 47.8	8.5, 32.3	16.4, 36.1
	% CV	33.8	31.6	37.0	25.5
T_{max} (h)	Median	0.880	2.120	4.120	2.140
	Range	0.63, 4.13	0.88, 4.15	1.63, 6.13	1.63, 3.13

Drug Liking: The individual morphine plasma concentration to drug liking VAS was matched by time point and treatment and the relationship of the concentration to drug liking was evaluated. A linear relationship seemed to best fit the individual concentration-response of morphine drug liking following administration of different treatments. For easy representation, mean concentration-response fit is presented below.

Figure: Mean concentration vs. drug liking plot for different oral treatments.



This indicates that the availability of the amount drug at the site of absorption (stomach) will impact the results of the drug liking study. For example, oral route offers significant capacity for administration of abuse-deterrent formulations after extraction. In addition, oral route offers additional physical manipulations to include consumption of solvents/beverages, which is not feasible with the nasal route. For example, as mentioned above, the proceedings of the Advisory Committee recorded methods such as manipulation Tool F followed by J and followed by dissolving for 30 minutes in a solvent that can be easily swallowed by oral route. Sixty to eighty percent Arymo could be extracted for oral consumption, as discussed at the advisory committee meeting. Therefore, the oral abuse methodology used in the study may not have been an optimal oral abuse situation, especially since chewing was excluded.

On the basis of statistical considerations related to drug liking endpoint, the CSS reviewer concluded that the Human abuse potential study 067-EG-008 does not support an abuse deterrent effect of EG-001 tablets to oral abuse. (b) (4)

Intranasal abuse liability Study 067-EG-009

The sponsor conducted "A Randomized, Double-Blind, Double-Dummy, Active and Placebo-Controlled, Crossover Study Comparing the Abuse Potential of Manipulated and Manipulated/Sieved Egalet PR Morphine Tablets versus Manipulated MS CONTIN following Intranasal Administration in Nondependent Recreational Opioid Users". After naloxone challenge and drug discrimination phase, non-dependent recreational opioid users received the following treatments in a crossover fashion:

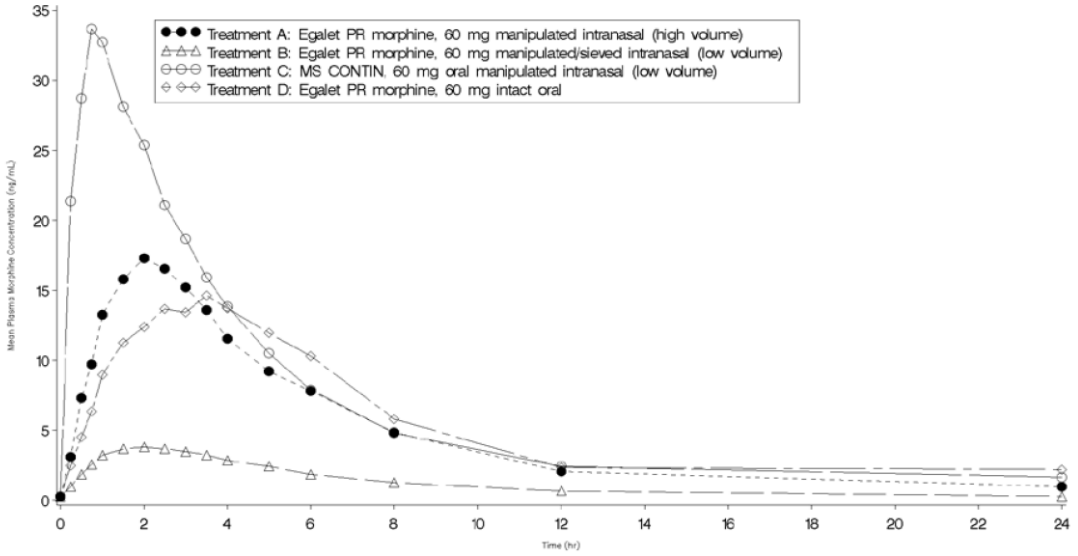
One Egalet PR morphine 60 mg tablet was prepared in a standardized fashion (as detailed in the Pharmacy Manual) by a clinical pharmacist involved in the study. A two-step process was implemented to manipulate Egalet PR morphine which included:
1) a mechanical maneuver using a standard household tool; and
2) an electrical instrument to reduce its particle size.
The full output, which included all particle sizes, was identified as Treatment A, which was of high volume (Lot #SB69300301).
The same process was used for Treatment B, except that the full output was then sieved through a 1000 micron filter to yield particle sizes more amenable to snorting. Treatment B, the manipulated/sieved Egalet PR morphine preparation, was a low volume treatment (Lot #SB69300301).

The low-volume intranasal treatments (active drug or placebo) used in Treatments D (oral Egalet PR morphine; Lot #SB69300301) and E (placebo) matched the volume of Treatment B and Treatment C (manipulated MS CONTIN). The dose of intact oral Egalet PR morphine used was one 60 mg tablet swallowed intact.

Pharmacokinetic and pharmacodynamic assessments were collected approximately at the same time for several hours after drug administration. Morphine concentration and PK parameters were primary endpoints along with Drug Liking VAS item: "Do you like the drug effect you are feeling now?" where values can range from 0 (strong disliking) to 100 (strong liking) and 50 (neither like nor dislike) is the neutral point.

Administration of intact oral tablet of Arymo 60 mg is marked by typical PK profile of an extended-release tablet as shown in other BA/BE studies. Crushing MS Contin 60 mg followed by intranasal administration resulted in very high peak plasma concentrations of morphine up to 35 ng/mL which was twice as much as that noted for intact Arymo 60mg. The relative bioavailability analysis indicates that Treatment A (high volume) is bioequivalent to intact Arymo (Treatment D) with respect to Cmax and exhibited similar Emax (Drug liking). The low volume intranasal treatment (B) has significantly lower bioavailability compared to intact Arymo.

Figure : Mean Morphine Plasma Concentrations (ng/mL) versus Time on Linear Scale- PK Population (N = 46)



Source: Figure 14.2.10.4.1

Table : Descriptive Statistics for Plasma Morphine Pharmacokinetic Parameters by Treatment - PK Population (N = 46)

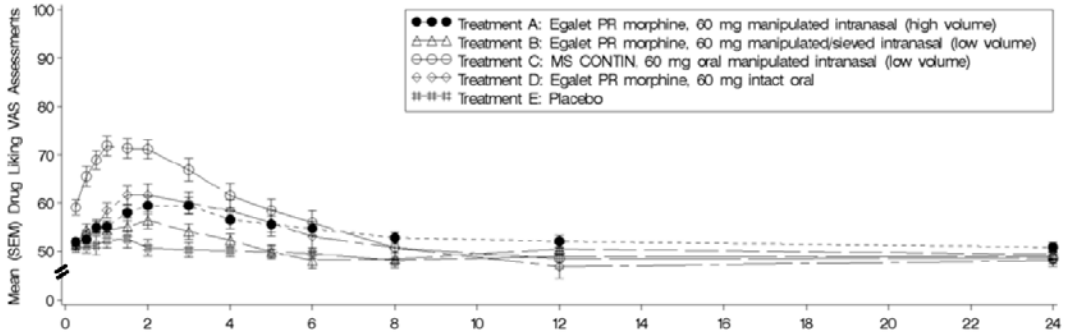
Parameter	Statistic	Manipulated Intranasal MS CONTIN (n=37)[a]	Manipulated Intranasal Egalet PR Morphine (n=45)[b]	Manipulated/ Sieved Intranasal Egalet PR Morphine (n=46)[c]	Intact Oral Egalet PR Morphine (n=39)[d]
C_{max} (ng/mL)	Mean (SD)	36.33 (12.896)	19.02 (9.556)	4.47 (2.254)	17.20 (4.263)
	Median	34.60	19.80	4.08	18.10
	Range	6.5 – 62.3	4.2 – 40.1	1.0 – 11.3	9.3 – 24.8
	% CV	35.5	50.2	50.4	24.8
T_{max} (h)	Median	1.130	2.170	2.660	3.650
	Range	0.42 – 2.67	1.13 – 6.13	0.85 – 6.10	1.13 – 6.17

As described above, a linear concentration-response describes the morphine drug liking. This indicates that the availability of the amount drug at the site of absorption will impact the results of the drug liking study. For example, oral route offers significant capacity for administration of abuse-deterrent formulations after extraction. However, nasal cavity is limited by its size and capacity to hold manipulated abuse-deterrent products. In

addition, oral route offers additional physical manipulations to include consumption of solvents/beverages, which is not feasible with the nasal route.

The drug liking profiles and the descriptive statistics of the pharmacodynamics of morphine following different intranasal treatments are presented in the figure and table below. In comparison with the intact oral Arymo tablet, manipulated Arymo tablet administered intranasally did not show substantial increase in Emax drug liking. Upon sieving the manipulated product, intranasal Arymo treatment showed lower Emax of drug liking compared to intact product; this is perhaps due to loss of bigger particles during sieving. Since MS Contin is not an abuse-deterrent formulation, Emax of drug liking is highest with it.

Figure: Mean ± SEM Drug Liking Scores over Time – Completers Population (N = 46)



Source: Figure 14.2.1.6
hr=hour; PR=prolonged-release; SEM=standard error of the mean; VAS=visual analog scale
Drug Liking VAS item: "Do you like the drug effect you are feeling now?" where values can range from 0 (strong disliking) to 100 (strong liking) and 50 (neither like nor dislike) is the neutral point.

Table : Descriptive Statistics for PD Parameters for Drug Liking VAS – Completers Population (N = 46)

Parameter	Statistic	Manipulated Intranasal MS CONTIN (N=46)	Manipulated Intranasal Egalet PR Morphine (N=46)	Manipulated/Sieved Intranasal Egalet PR Morphine (N=46)	Intact Oral Egalet PR Morphine (N=46)	Placebo (N=46)
E_{max}	Mean (SD)	77.7 (11.69)	65.5 (14.29)	59.6 (12.52)	68.5 (13.57)	54.7 (10.60)
	Median	77.5	62.0	52.5	68.0	51.0
AUE_{0-8}	Mean (SD)	91.963 (101.5344)	46.729 (63.9948)	13.492 (57.0461)	49.397 (95.8341)	0.908 (65.1065)
	Median	87.388	19.913	2.938	51.175	0.000
TE_{max} (h)	Median	1.01	1.75	1.01	2.00	0.63
	Range	0.2 – 8.0	0.2 – 24.0	0.2 – 24.0	0.3 – 8.0	0.2 – 6.0

Source: Table 14.2.1.2
AUE = area under the effect curve; E_{max} = maximum (peak) effect; h = hour; N = number of subjects; PD = pharmacodynamic; PR=prolonged-release; TE_{max} = time to maximum (peak) effect; VAS = visual analog scale

Conclusions:

The sponsor indicates [redacted] (b) (4) The sponsor also indicated that the dissolution rate of Arymo in presence of alcohol is reduced *in vitro* and therefore *in vivo* studies were not conducted. These two studies are reviewed by Biopharmaceutics reviewer Dr. An-Chi Lu and see biopharms's review for details.

- EG-001 tablets in strengths of 30 and 60 mg are bioequivalent to the listed drug, MS Contin tablets in strengths of 30 and 60 mg. Slightly lower Cmax was observed for 15 mg strength to MS Contin, but it is not considered clinically significant and will not prevent approval of the product
- Two EG-001 15 mg tablets are bioequivalent to one MS Contin 30 mg tablet as well as to one EG-001 30 mg tablet.
- There is no clinically relevant food effect on the rate or extent of absorption of morphine from EG-001 tablets.
- Because bioequivalence studies established a bridge between MS Contin and Arymo, no additional special population studies were conducted. The Sponsor may rely on Agency's previous findings in MS Contin labeling regarding special population to support this product.

1.4 General Biopharmaceutics

Arymo is a polymer matrix tablet that utilizes a plastic injection molding with controlled-release properties as well as physical and chemical features that have been demonstrated to resist intravenous, intranasal and oral routes of abuse following rigorous methods of product manipulation. Egalet indicates that the ingredients in the tablet resist chewing, particle size reduction and chemical extraction of morphine. Egalet also indicates that contact with liquid results in a viscous hydrogel making syringeability difficult.

Composition of Commercial Formulations of EG-001

Strength	**15 mg**	**30 mg**	**60 mg**
Ingredient	**Amount per Tablet (%)**		
Morphine sulfate	1.976	3.939	7.828
Polyethylene Oxide 400,000 (b) (4) (b) (4)	(b) (4)		
Butylated hydroxytoluene (b) (4			
Total	100.0	100.0	100.0

NA = not applicable

1.5 Analytical

The analytes and matrix used to evaluate the bioavailability/bioequivalence of EG-001 in the Phase 1 clinical program are listed in the Table below. Pharmacokinetic samples were analyzed using two validated liquid chromatography (LC) with tandem mass spectrometry (MS/MS) assays for morphine, morphine-6-glucuronide [M6G] (equivalent to morphine-6-βD-glucuronide), and morphine-3-glucuronide [M3G] (equivalent to morphine-3-βD-glucuronide) in human plasma. An ultra-performance liquid chromatography (UPLC) method with MS/MS detection was also validated. The bioanalysis included incurred sample reanalysis testing for each method. A summary of the validation parameters and the results of the bioanalytical validations are Appended to the review. OSIS recommended accepting data without an on-site inspection as the site listed ((b) (4)) was recently inspected and the inspectional outcome was "No Action Indicated".

Table: Bioanalytical method and validation reports used to support different PK studies.

Study No.	Bioanalytical Method (Bioanalytical Method Validation Report)
067-EG-001 067-EG-002	Validation of a High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Morphine, Morphine-3-Beta-D-Glucuronide and Morphine-6-Beta-D-Glucuronide in Human EDTA Plasma (87126TEA)
067-EG-006 067-EG-008	Quantitation of Morphine, Morphine-3β-glucuronide, and Morphine-6β-glucuronide in Human Plasma via HPLC with MS/MS Detection (LCMS454)
067-EG-011 067-EG-012	Quantitation of Morphine, Morphine-3β-D-glucuronide, and Morphine-6β-D-glucuronide in Human Plasma via UPLC® with MS/MS Detection (AHUB2)
067-EG-009	Quantitation of Morphine, Morphine-3β-glucuronide, and Morphine-6β-glucuronide in Human Plasma via HPLC with MS/MS Detection (LCMS454)

2 Labeling

The sponsor proposed text is in regular font, reviewer recommended changes are in bold and strikethrough text.

The NDA relies on Agency's previous findings of safety and efficacy of MS Contin. Hence, most of the product label is reflects approved MS Contin product label.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

Note: (b) (4)

(b) (4)

12.3 Pharmacokinetics

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

A Table describing PK of morphine (such as Cmax, AUC, Tmax) following administration of 15 mg, 30 mg and 60 mg Arymo should be included in the product label.

Food Effect

The effect of food upon the systemic bioavailability of ARYMO ER has been evaluated. In a food effect study with ARYMO ER 60 mg, there was no significant difference in peak plasma concentration (C_{max}), ~~or~~ overall exposure (AUC_{0-24h})**. There was a 2-hour delay in median Tmax value (6.5 hour with food compared to 4.5 hour without food)** when ARYMO ER was administered with a high fat meal compared to the fasted state. **The extent of food effect is not considered clinically significant so ARYMO ER can be taken without regard to food.** (b) (4)

Distribution

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

Metabolism

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

Excretion

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

Specific Populations

A (b) (4) 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.

37 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

4.1 Individual Study Reviews

4.1.1 Synopsis of Bioequivalence and Food-effect study of 60 mg Arymo.

Protocol No. 067-EG-011 Clinical Study Report

2. SYNOPSIS

Name of Sponsor/Company: Egalet Ltd	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: Egalet® Morphine PR		
Name of Active Ingredient: Morphine sulfate		

Title of study: A Randomized, Open-Label, 2-Cohort, Crossover Design Study to Determine the Bioequivalence of Egalet® Morphine PR 60-mg Tablets Versus MS CONTIN® 60-mg Tablets and to Evaluate the Effect of Food on Egalet® Morphine PR 60-mg Tablets in Healthy Subjects With Naltrexone Blockade

Investigator: Rebecca Wood-Horrall, MD

Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744

Publication (reference): None

Studied period (years): 16 March 2015 13 May 2015	**Phase of development**: 1

Objectives:

The primary objective of the study was:

- To assess the bioequivalence (BE) of Egalet® morphine prolonged-release (PR) 60-mg tablets (test) relative to MS CONTIN 60-mg tablets (reference) in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.

The secondary objectives of the study were:

- To characterize the effect of food on Egalet® morphine PR 60-mg tablets, and
- To assess the safety and tolerability of Egalet® morphine PR 60-mg tablets in healthy subjects following single-dose oral administration under fasting and fed conditions and naltrexone blockade.

Methodology: This was a Phase 1, single-center, randomized, open-label, 2-cohort, crossover, single-dose study in healthy subjects. The study consisted of a screening period (Days −28 through −2), 2 treatment periods (2-period cohort) or 3 treatment periods (3-period cohort) with confinement (Days −1 through 3 of each period), and an end-of-study/early termination visit (within 4 to 14 days of the last dose of study drug). There was a washout interval of at least 7 days between doses of any 2 consecutive treatment periods.

Reference ID: 3983722

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

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

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

On Day 1 of Periods 1 and 2, each subject received 1 of 2 study drug treatments as follows:

- Treatment A: Egalet® morphine PR, 60-mg tablet, fasting conditions
- Treatment B: MS CONTIN, 60-mg tablet, fasting conditions

In the 3-period cohort, subjects received the following study drug treatment on Day 1 of Period 3:

- Treatment C: Egalet® morphine PR, 60-mg tablet, fed conditions

Subjects also received naltrexone 50 mg orally approximately –15 and –3 hours before each study drug administration and approximately 9 and 21 hours after each study drug administration.

For Periods 1 and 2, subjects in both cohorts fasted overnight for at least 10 hours before each dose of study drug. All treatments were administered with 240 mL of water on the morning of Day 1 of each period. Subjects fasted for 4 hours after dosing. For Period 3, subjects in the 3-period cohort received study drug 30 minutes after starting a standard Food and Drug Administration high-fat breakfast (consumed within 30 minutes).

Serial blood samples for the pharmacokinetic (PK) analysis of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide were collected up to 48 hours after each dose of study drug.

Number of subjects (planned and analyzed): A total of 65 subjects were enrolled and 59 subjects completed the study. All 65 subjects were included in the safety analysis, 61 subjects were included in the PK analysis, and 14 subjects were included in the food-effect (FE) analysis.

Diagnosis and main criteria for inclusion: Subjects were male and female subjects between 18 and 55 years of age, inclusive, with a body mass index of 18.5 to 32 kg/m^2, inclusive, and were willing and able to provide written consent for participation. Healthy subjects had no clinically significant abnormalities as determined by the investigator.

Test product, dose and mode of administration, batch number:

- Egalet® morphine PR, 60-mg tablet, administered orally, lot number SB69300201.

Duration of treatment: Subjects received a single oral dose of 60-mg Egalet® morphine PR or 60-mg MS CONTIN on Day 1 of each period according to the randomization schedule. Subjects received study drug under fasting conditions, with the exception of Day 1 of Period 3 (3-period cohort) when subjects received 60-mg Egalet® morphine PR under fed conditions.

Reference therapy, dose and mode of administration, batch number:

- MS CONTIN, 60-mg tablet, administered orally, lot number WTB11.

All doses of study drug were administered orally and under naltrexone blockade.

- Naltrexone, 50-mg tablet, administered orally, lot number 1170U82358.

Criteria for evaluation:

Pharmacokinetics:

Serial blood samples for the determination of plasma concentrations of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide were collected on Day 1 of each period before dosing (0 minutes) and at 20 minutes, 40 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, and 48 hours after each study drug administration.

The following PK parameters were determined from plasma concentration and actual time data using noncompartmental methods:

- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), calculated by the linear trapezoidal rule
- Area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{0-inf})
- Percentage of AUC extrapolated between AUC_{0-t} and AUC_{0-inf} ($\%AUC_{exp}$)
- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Terminal phase half-life ($t_{1/2}$)
- Terminal elimination rate constant (K_{el})

Reference ID: 3983722

Statistical methods:

Pharmacokinetics:

The PK analysis population included all subjects who received at least 1 dose of study drug and had sufficient concentration data to support accurate estimation of at least 1 PK parameter for PK analysis. Subjects who experienced vomiting within 8 hours after study drug dosing were excluded from the PK analysis. If any subject had a predose value greater than 5% of C_{max}, the subject was excluded from PK analysis.

The FE analysis population included subjects in the 3-period cohort who received at least 1 dose of study drug for Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) or Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions) and had sufficient concentration data to support accurate estimation of at least 1 PK parameter for FE analysis. Subjects who experienced emesis within 8 hours after study drug dosing were excluded from the FE analysis. If any subject had a predose value greater than 5% of C_{max}, the subject was excluded from FE analysis. Subjects who did not consume the entire meal before dosing of Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions) were excluded from the FE analysis and calculation of summary statistics, while all data were presented in the data listings.

Pharmacokinetic parameters derived for concentrations of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide in plasma samples were listed and summaries by time point for each treatment were presented. The individual PK parameters were presented in a data listing and summarized by treatment using descriptive statistics: number of subjects, mean, standard deviation (SD), percent coefficient of variation (CV%), median, minimum, and maximum. Geometric mean was also included only for AUC_{0-t}, AUC_{0-inf}, and C_{max}. The plasma concentration data were summarized by time point and treatment using descriptive statistics: number of subjects, mean, SD, CV%, geometric mean, median, minimum, and maximum. Individual and mean plasma concentration versus time profiles were presented graphically on linear and semilogarithmic scales. In addition, mean plasma concentration versus time profiles over 0 to 8 hours postdose were presented in linear scale.

A linear mixed-effect model (SAS PROC MIXED) with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect was fitted to the natural log-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} for use in estimation of effects and construction of confidence intervals (CIs) for:

- Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) compared with Treatment B (MS CONTIN, 60-mg tablet, fasting conditions)

Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means and respective 90% CIs on the original scale. Intersubject and intrasubject variability were also estimated. All available Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) and Treatment B (MS CONTIN,

Reference ID: 3983722

60-mg tablet, fasting conditions) PK parameter data obtained from subjects in the PK analysis population were used for this analysis.

Additionally for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment B (MS CONTIN, 60-mg tablet, fasting conditions), the statistical analysis of AUC_{0-t}, AUC_{0-inf}, and C_{max} was repeated adjusting for actual drug content as described in "Comparative Bioavailability Standards: Formulations Used for Systemic Effects" (Health Canada 2012).

The same model was applied to the untransformed $t_{1/2}$ and K_{el} parameters for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment B (MS CONTIN, 60-mg tablet, fasting conditions).

For T_{max}, the Wilcoxon signed rank test was performed for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment B (MS CONTIN, 60-mg tablet, fasting conditions). A *P* value ≤0.05 was considered a statistically significant difference between treatments.

Bioequivalence was concluded if the 90% CIs for the ratios (Egalet® morphine PR 60-mg tablet/MS CONTIN 60-mg tablet) of the geometric means were entirely contained within the equivalence interval of 80.00% to 125.00% for AUC_{0-t}, AUC_{0-inf}, and C_{max} of morphine.

To evaluate the effect of food on Egalet® morphine PR 60-mg tablets, a linear mixed-effects model (SAS PROC MIXED) with treatment as a fixed effect and measurements within subject as repeated measures was fitted to the natural log-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} for use in estimation of effects and construction of CIs for:

- Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions) compared with Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions)

Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for the ratios of geometric means and respective 90% CIs on the original scale. Intersubject and intrasubject variability were also estimated. Only available Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) or Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions) PK parameter data obtained from subjects in the FE analysis population were used for this analysis. For subjects who did not consume the entire meal before dosing of Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions), their Treatment C PK parameter data were excluded from the FE analysis and calculation of summary statistics, while all data were presented in the data listings.

Additionally for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions), the statistical analysis of AUC_{0-t}, AUC_{0-inf}, and C_{max} was repeated adjusting for actual drug content as described in "Comparative Bioavailability Standards: Formulations Used for Systemic Effects" (Health Canada 2012).

The same model applied to the untransformed $t_{1/2}$ and K_{el} parameters for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions).

For T_{max}, the Wilcoxon signed rank test was performed for the comparison of Treatment A (Egalet® morphine PR, 60-mg tablet, fasting conditions) with Treatment C (Egalet® morphine PR, 60-mg tablet, fed conditions). A *P* value of ≤0.05 was considered a statistically significant difference between treatments.

BE results of morphine are discussed in the summary of clinical pharmacology findings.

Table 26: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-6-Glucuronide (Pharmacokinetic Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	59	60	1097	1146	95.69 (93.63, 97.79)
AUC_t (ng•h/mL)	60	60	1062	1111	95.54 (93.38, 97.75)
C_{max} (ng/mL)	60	60	129.0	143.9	89.66 (86.42, 93.02)

CI = confidence interval; LS = least squares
Source: 067-EG-011 Table 14.2.3.2.1
Test: EG-001 60 mg tablet, fasted conditions (Treatment A).
Reference: MS Contin 60 mg tablet, fasted conditions (Treatment B).
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Table 27: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-3-Glucuronide (Pharmacokinetic Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	59	60	7347	7702	95.39 (93.22, 97.61)
AUC_t (ng•h/mL)	60	60	7124	7460	95.49 (93.29, 97.75)
C_{max} (ng/mL)	60	60	772.7	855.6	90.32 (86.96, 93.80)

CI = confidence interval; LS = least squares
Source: 067-EG-011 Table 14.2.3.3.1
Test: EG-001 60 mg tablet, fasted conditions (Treatment A).
Reference: MS Contin 60 mg tablet, fasted conditions (Treatment B).
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Table 29: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-6-Glucuronide (Food-Effect Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	14	14	1063	1149	108.06 (103.26, 113.09)
AUC_t (ng•h/mL)	14	14	1032	1101	106.65 (102.04, 111.46)
C_{max} (ng/mL)	14	14	130.7	116.0	88.73 (79.79, 98.67)

CI = confidence interval; LS = least squares
Source: 067-EG-011 Table 14.2.3.2.2
Test: EG-001 60 mg tablet, fasted conditions (Treatment A).
Reference: EG-001 60 mg tablet, fed conditions (Treatment C).
A linear mixed-effect model with treatment as a fixed effect and measurements within subject as repeated measures was fitted to the ln-transformed pharmacokinetic parameters.

Table 30: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-3-Glucuronide (Food-Effect Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	14	14	6853	7477	109.11 (102.97, 115.61)
AUC_t (ng•h/mL)	14	14	6652	7165	107.71 (101.74, 114.03)
C_{max} (ng/mL)	14	14	747.0	695.3	93.07 (83.13, 104.21)

CI = confidence interval; LS = least squares
Source: 067-EG-011 Table 14.2.3.3.2
Test: EG-001 60 mg tablet, fasted conditions (Treatment A).
Reference: EG-001 60 mg tablet, fed conditions (Treatment C).
A linear mixed-effect model with treatment as a fixed effect and measurements within subject as repeated measures was fitted to the ln-transformed pharmacokinetic parameters.

Reference ID: 3983722

4.1.2 Synopsis of Bioequivalence study of 30 mg Arymo.

Egalet Ltd
Protocol No. 067-EG-012 Clinical Study Report

2. SYNOPSIS

Name of Sponsor/Company: Egalet Ltd	**Individual Study Table Referring to Part of the Dossier** **Volume**:	**(For National Authority Use Only)**
Name of Finished Product: Egalet® morphine PR		
Name of Active Ingredient: Morphine sulfate	**Page**:	
Title of study: A Randomized, Open-Label, 3-Way Crossover Study to Evaluate the Bioequivalence of Egalet® Morphine PR 30 mg to MS CONTIN® 30 mg and Egalet® Morphine PR 2 × 15 mg to MS CONTIN® 30 mg Under Fasting Conditions in Healthy Subjects Under Naltrexone Blockade		
Investigator: Rebecca Wood-Horrall, MD		
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744		
Publication (reference): None		
Studied period (years): 12 November 2014 27 January 2015	**Phase of development**: 1	

Objectives:

The primary objective of the study was:

- To assess the bioequivalence of the Egalet® morphine prolonged-release (PR) 30-mg tablet versus the MS CONTIN® 30-mg tablet in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.

The secondary objectives of the study were:

- To assess the bioequivalence of the Egalet® morphine PR 2 × 15-mg tablets versus the MS CONTIN 30-mg tablet.
- To assess the safety and tolerability of the Egalet® morphine PR 15- and 30-mg tablets in healthy subjects following single-dose oral administration under fasting conditions and naltrexone blockade.

Reference ID: 3983722

Methodology: This was a Phase 1, single-center, randomized, open-label, 3-treatment, 3-period, 6-sequence, crossover, single-dose, bioequivalence study in healthy subjects. The study consisted of a screening period (Days –28 through –2), 3 treatment periods with confinement (Days –1 through 3 of each period), and an end-of-study/early termination visit (within 4 to 14 days of the last dose of study drug). There was a washout interval of at least 7 days between doses of any 2 consecutive treatment periods.

Before dosing on Day 1 of Period 1, subjects were randomly assigned to receive study drug according to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, and CBA).

On Day 1 of each period, each subject received 1 of 3 study drug treatments as follows:

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

Subjects also received naltrexone 50 mg orally approximately –15 and –3 hours before each study drug administration and approximately 9 and 21 hours after each study drug administration.

All subjects fasted overnight for at least 10 hours before each dose of study drug. All treatments were administered with 240 mL of water on the morning of Day 1 of each period. All subjects fasted for 4 hours after each dosing.

Serial blood samples for the pharmacokinetic (PK) analysis of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide were collected up to 48 hours after each dose of study drug.

Number of subjects (planned and analyzed): A total of 66 subjects were enrolled and 56 subjects completed the study. All 66 subjects were included in the safety analysis and 63 subjects were included in the PK analysis.

Diagnosis and main criteria for inclusion: Subjects were male and female subjects between 18 and 55 years of age, inclusive, with a body mass index of 18.5 to 32 kg/m^2, inclusive, and were willing and able to provide written consent for participation. Healthy subjects had no clinically significant abnormalities as determined by the investigator.

Test product, dose and mode of administration, batch number:

- Egalet® morphine PR, 30-mg tablet, administered orally, lot number SB69200101
- Egalet® morphine PR, 2 × 15-mg tablets, administered orally, lot number SB69400101

Duration of treatment: Subjects received a single oral dose of Egalet® morphine PR 30 mg, Egalet® morphine PR 2 × 15 mg, or MS CONTIN 30 mg under fasting conditions and naltrexone blockade on Day 1 of each period according to the randomization schedule.

Reference therapy, dose and mode of administration, batch number:

- MS CONTIN, 30-mg tablet, administered orally, lot number WPG51

All doses of study drug were administered orally and under naltrexone blockade.

- Naltrexone, 50-mg tablet, administered orally, lot number 1170X91151

Statistical methods:

Pharmacokinetics:

The PK population included all subjects who received at least 1 dose of study drug and had sufficient concentration data to support accurate estimation of at least 1 PK parameter. Subjects who experienced emesis within 8 hours after study drug dosing were excluded from the PK analysis. Also, if any subject had a predose value greater than 5% of C_{max}, the subject was excluded from the PK analysis. Pharmacokinetic parameters derived from concentrations of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide in plasma samples were listed and a summary by treatment was presented. The summary statistics consisted of the number of subjects, mean, standard deviation, coefficient of variation, median, minimum, and maximum. Geometric mean was included for all PK parameters except for T_{max}. Individual and mean plasma concentration versus time profiles were presented graphically on both linear and semilogarithmic scales.

A linear mixed-effect model with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect was fitted to the natural log-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} for use in estimation of effects and construction of confidence intervals (CIs) for:

- Treatment A (Egalet® morphine PR 30 mg, fasting conditions) compared with Treatment B (MS CONTIN 30 mg, fasting conditions)
- Treatment C (Egalet® morphine PR 2 × 15 mg, fasting conditions) compared with Treatment B (MS CONTIN 30 mg, fasting conditions)
- Treatment A (Egalet® morphine PR 30 mg, fasting conditions) compared with Treatment C (Egalet® morphine PR 2 × 15 mg, fasting conditions)

Point estimates and 90% CIs for differences on the natural-log scale were exponentiated to obtain estimates for the ratios of geometric least squares (LS) means and respective 90% CIs on the original scale. Intersubject and intrasubject variability were also estimated. No adjustment was made for multiplicity. The same model was applied to the untransformed $t_{1/2}$ and K_{el} parameters. For T_{max}, the Wilcoxon signed rank test was performed. A *P* value ≤0.05 was considered a statistically significant difference between treatments.

Bioequivalence was concluded if the 90% CIs for the ratios (Egalet® morphine PR 30 mg/MS CONTIN 30 mg or Egalet® morphine PR 2 × 15 mg/MS CONTIN 30 mg or Egalet® morphine PR 30 mg/Egalet® morphine PR 2 × 15 mg) of the geometric LS means were entirely contained within the equivalence interval of 80.00% to 125.00% for AUC_{0-t}, AUC_{0-inf}, and C_{max} of morphine. Additionally, the statistical analysis of AUC_{0-t}, AUC_{0-inf}, and C_{max} was repeated by adjusting for actual drug content as described in "Comparative Bioavailability Standards: Formulations Used for Systemic Effects" (Health Canada 2012).

See summary of clinical pharmacology findings for conclusions on this study.

Reference ID: 3983722

Table 31: Summary of Pharmacokinetic Parameters for Morphine, Morphine-6-Glucuronide, and Morphine-3-Glucuronide (Pharmacokinetic Analysis Population), Study 067-EG-012

	Pharmacokinetic Parameters, Mean (CV%)								
	Morphine			M6G			M3G		
	EG-001 30 mg (n=60)	MS Contin 30 mg (n=59)	EG-001 2x15 mg (n=61)	EG-001 30 mg (n=60)	MS Contin 30 mg (n=59)	EG-001 2x15 mg (n=61)	EG-001 30 mg (n=60)	MS Contin 30 mg (n=59)	EG-001 2x15 mg (n=61)
AUC_∞ (ng•h/mL)	115.7[1] (26.1)	119.2[1] (29.1)	117.3[2] (27.1)	609.1 (16.6)	628.4[1] (16.9)	604.8 (15.6)	4134.0[3] (17.9)	4294.9[1] (16.6)	4086.5 (16.1)
AUC_t (ng•h/mL)	111.9 (25.6)	113.9 (29.0)	112.3 (27.1)	588.8 (16.7)	608.2 (16.7)	582.9 (15.5)	4005.2 (18.2)	4160.4 (16.9)	3937.6 (16.4)
C_{max} (ng/mL)	12.0 (33.5)	12.1 (33.3)	10.8 (33.1)	67.1 (21.8)	73.4 (19.6)	60.7 (21.2)	413 (24.8)	440 (21.1)	369 (24.3)
t_{max}[4] (h)	4.50 (0.67, 6.00)	2.00 (0.67, 5.50)	4.50 (1.50, 8.00)	4.00 (1.50, 5.50)	2.50 (1.00, 4.50)	4.00 (2.00, 8.00)	4.01 (1.00, 5.50)	3.00 (1.50, 6.00)	4.50 (2.00, 8.00)
$t_{½}$ (h)	10.03[1] (23.6)	10.92[1] (21.2)	10.51[2] (23.9)	9.98 (33.5)	10.60[1] (24.3)	10.52 (29.5)	9.66[3] (26.2)	10.63[1] (23.2)	10.40 (24.7)

CV = coefficient of variation; M3G = morphine-3β-glucuronide; M6G = morphine-6β-glucuronide
Source: 067-EG-012: Table 14.2.2.1; Table 14.2.2.2; Table 14.2.2.3
[1] n=58
[2] n=60
[3] n=59
[4] Median (minimum, maximum)

Reference ID: 3983722

Table 33: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-6-Glucuronide (Pharmacokinetic Analysis Population), Study 067-EG-012

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (A:B) (90% CI)
	Test (Treatment A)	Reference (Treatment B)	Test (Treatment A)	Reference (Treatment B)	
AUC_∞ (ng•h/mL)	60	58	602.1	623.1	96.63 (95.23, 98.06)
AUC_t (ng•h/mL)	60	59	581.2	601.1	96.70 (95.32, 98.11)
C_{max} (ng/mL)	60	59	66.01	72.57	90.95 (87.60, 94.44)
	Test (Treatment C)	**Reference (Treatment B)**	**Test (Treatment C)**	**Reference (Treatment B)**	**Geometric LS Mean Ratio (%) (C:B) (90% CI)**
AUC_∞ (ng•h/mL)	61	58	598.2	623.1	96.02 (94.63, 97.42)
AUC_t (ng•h/mL)	61	59	576.5	601.1	95.91 (94.55, 97.30)
C_{max} (ng/mL)	61	59	59.30	72.57	81.71 (78.72, 84.83)
	Treatment (Treatment A)	**Treatment (Treatment C)**	**Treatment (Treatment A)**	**Treatment (Treatment C)**	**Geometric LS Mean Ratio (%) (A:C) (90% CI)**
AUC_∞ (ng•h/mL)	60	61	602.1	598.2	100.64 (99.20, 102.11)
AUC_t (ng•h/mL)	60	61	581.2	576.5	100.82 (99.39, 102.27)
C_{max} (ng/mL)	60	61	66.01	59.30	111.31 (107.23, 115.54)

CI = confidence interval; LS = least squares
Source: 067-EG-012 Table 14.2.3.2
Treatment A: EG-001 30 mg tablet, fasted conditions
Treatment B: MS Contin 30 mg tablet, fasted conditions
Treatment C: EG-001 2x15 mg tablets, fasted conditions
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Reference ID: 3983722

Table 34: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-3-Glucuronide (Pharmacokinetic Analysis Population), Study 067-EG-012

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (A:B) (90% CI)
	Test (Treatment A)	Reference (Treatment B)	Test (Treatment A)	Reference (Treatment B)	
AUC_∞ (ng•h/mL)	59	58	4100	4258	96.29 (95.09, 97.50)
AUC_t (ng•h/mL)	60	59	3967	4109	96.54 (95.35, 97.76)
C_{max} (ng/mL)	60	59	405.2	433.0	93.59 (90.12, 97.19)
	Test (Treatment C)	**Reference (Treatment B)**	**Test (Treatment C)**	**Reference (Treatment B)**	**Geometric LS Mean Ratio (%) (C:B) (90% CI)**
AUC_∞ (ng•h/mL)	61	58	4037	4258	94.81 (93.65, 95.99)
AUC_t (ng•h/mL)	61	59	3889	4109	94.65 (93.49, 95.84)
C_{max} (ng/mL)	61	59	358.4	433.0	82.78 (79.73, 85.95)
	Treatment (Treatment A)	**Treatment (Treatment C)**	**Treatment (Treatment A)**	**Treatment (Treatment C)**	**Geometric LS Mean Ratio (%) (A:C) (90% CI)**
AUC_∞ (ng•h/mL)	59	61	4100	4037	101.56 (100.31, 102.82)
AUC_t (ng•h/mL)	60	61	3967	3889	101.99 (100.74, 103.27)
C_{max} (ng/mL)	60	61	405.2	358.4	113.05 (108.90, 117.37)

CI = confidence interval; LS = least squares
Source: 067-EG-012 Table 14.2.3.3
Treatment A: EG-001 30 mg tablet, fasted conditions
Treatment B: MS Contin 30 mg tablet, fasted conditions
Treatment C: EG-001 2x15 mg tablets, fasted conditions
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequences as a random effect.

Reference ID: 3983722

4.1.3 Synopsis of Bioequivalence study of 15 mg Arymo.

SYNOPSIS

Name of Sponsor/Company: Egalet Corporation	**Individual Study Table Referring to Part of the Dossier** **Volume**: **Page**:	**(For National Authority Use Only)**
Name of Finished Product: Egalet® morphine PR		
Name of Active Ingredient: Egalet® morphine PR		
Title of study: A Randomized, Open-Label, 2-Way Crossover Study to Determine the Bioequivalence of the Egalet® Morphine PR 15-mg Tablet Versus MS CONTIN® Under Fasting Conditions in Healthy Subjects		
Investigator: Aziz L. Laurent, MD		
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744		
Publication (reference): None		
Studied period (years): 28 May 2014 04 August 2014	**Phase of development**: 1	
Objectives: The primary objective of the study was to assess the bioequivalence of the Egalet® morphine prolonged-release (PR) 15-mg tablet (test) relative to the MS CONTIN® 15-mg tablet (reference) in healthy subjects following single-dose oral administration under fasting conditions. The secondary objective of the study was to assess the safety and tolerability of the Egalet® morphine PR 15-mg tablet in healthy subjects.		
Methodology: This was a Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose, bioequivalence study in healthy subjects. The study consisted of a screening period (Days –28 through –2), 2 treatment periods with confinement (Days –1 through 3 of each period), and an end-of-study/early termination visit (within 4 to 14 days of the last dose of study drug). There was a washout interval of at least 5 days between doses in each period. On Day 1 of each period, each subject received 1 of 2 study drug treatments as follows: • Treatment A: Egalet® morphine PR, 15-mg tablet, fasting conditions • Treatment B: MS CONTIN, 15-mg tablet, fasting conditions Before dosing on Day 1 of Period 1, subjects were randomly assigned to receive study drug according to 1 of 2 treatment sequences (AB or BA). All subjects fasted overnight for at least 10 hours. Both treatments were administered with 240 mL of water on the morning of Day 1 of each period. All subjects continued fasting for 4 hours after dosing.		

Reference ID: 3983722

Serial blood samples for the pharmacokinetic (PK) analysis of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide were collected up to 48 hours after each dose of study drug.

Safety assessments included monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examination findings, and 12-lead electrocardiogram (ECG) results. On Day −1 of Period 1 only, continuous cardiac telemetry monitoring was performed for approximately 8 hours. Continuous cardiac telemetry and pulse oximetry monitoring were performed for 24 hours after each study drug administration.

Subjects were confined to the clinical unit until discharge on Day 3 of each period after the 48-hour PK blood sample was collected. Subjects returned to the clinical unit 4 to 14 days after the last dose of study drug for an end-of-study/early termination visit. The duration of the study, including screening, was approximately 55 days.

Number of subjects (planned and analyzed): A total of 65 subjects were enrolled and 63 subjects completed the study. All 65 subjects were included in the safety analysis and 64 subjects were included in the PK analysis.

Diagnosis and main criteria for inclusion: Subjects were male and female subjects between 18 and 55 years of age, inclusive, with a body mass index of 18.5 to 32 kg/m^2, inclusive, and were willing and able to provide written consent for participation. Healthy subjects had no clinically significant abnormalities as determined by the investigator.

Test product, dose and mode of administration, batch number:

- Egalet® morphine PR, 15-mg tablet, administered orally, lot number SB69400301

Duration of treatment: Subjects received a single oral dose of 15 mg Egalet® morphine PR or 15 mg MS CONTIN tablet under fasting conditions on Day 1 of each period according to the randomization schedule.

Reference therapy, dose and mode of administration, batch number:

- MS CONTIN, 15-mg tablet, administered orally, lot number WKG71

Criteria for evaluation:

Pharmacokinetics:

Serial blood samples for the determination of plasma concentrations of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide were collected before dosing (0 minutes) and at 20 minutes, 40 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, 36, and 48 hours after each study drug administration on Day 1 of each period.

The following PK parameters were determined from plasma concentration and actual time data using noncompartmental methods:

- Area under the plasma concentration versus time curve from time 0 to the time of the last quantifiable concentration (AUC_{0-t})
- Area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{0-inf})
- Percentage of AUC extrapolated between AUC_{0-t} and AUC_{0-inf} ($\%AUC_{exp}$)
- Maximum observed plasma concentration (C_{max})
- Time to reach maximum observed plasma concentration (T_{max})
- Terminal phase half-life ($t_{1/2}$)
- Terminal elimination rate constant (K_{el})

Reference ID: 3983722

Statistical methods:

Pharmacokinetics:

The PK population included all subjects who received at least 1 dose of study drug and had sufficient concentration data to support accurate estimation of at least 1 PK parameter. Subjects who experienced vomiting within 8 hours after study drug dosing were excluded from the PK analysis. Also, if any subject had a predose value greater than 5% of C_{max}, the subject was excluded from PK analysis. Pharmacokinetic parameters derived for concentrations of morphine, morphine-6β-glucuronide, and morphine-3β-glucuronide in plasma samples were listed and a summary by time point for each treatment was presented. The summary consisted of the number of subjects, mean, standard deviation, geometric mean, coefficient of variation, median, minimum, and maximum. Individual and mean plasma concentration versus time profiles were presented graphically on linear and semilogarithmic scales.

A linear mixed-effect model (SAS PROC MIXED) with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect was fitted to the natural log-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} for use in estimation of effects and construction of confidence intervals (CIs) for the test treatment (Egalet® morphine PR, fasted, Treatment A) compared with the reference treatment (MS CONTIN, fasted, Treatment B). Point estimates and 90% CIs for differences on the natural log scale were exponentiated to obtain estimates for the ratios of the geometric least squares (LS) means and respective 90% CIs on the original scale. Intersubject and intrasubject variability were also estimated. No adjustment was made for multiplicity. The same model was applied to the untransformed $t_{1/2}$ and K_{el} parameters. For T_{max}, the Wilcoxon signed rank test was performed. A *P* value of ≤0.05 was considered a statistically significant difference between treatments. The statistical analysis of AUC_{0-t}, AUC_{0-inf}, and C_{max} was repeated adjusting for actual drug content. Bioequivalence was concluded if the 90% CIs for the ratios (Egalet® morphine PR 15-mg tablet/MS CONTIN 15-mg tablet) of the geometric means were entirely contained within the equivalence interval of 80% to 125% for AUC_{0-t}, AUC_{0-inf}, and C_{max}.

See summary of clinical pharmacology findings for conclusions of this study.

Table 18: Summary of Pharmacokinetic Parameters for Morphine, Morphine-6-Glucuronide, and Morphine-3-Glucuronide, Study 067-EG-006

	Pharmacokinetic Parameters, Mean (CV%)					
	Morphine		M6G		M3G	
	EG-001 15 mg Tablet Fasting Conditions (n=64)	MS Contin 15 mg Tablet Fasting Conditions (n=63)	EG-001 15 mg Tablet Fasting Conditions (n=64)	MS Contin 15 mg Tablet Fasting Conditions (n=63)	EG-001 15 mg Tablet Fasting Conditions (n=64)	MS Contin 15 mg Tablet Fasting Conditions (n=63)
AUC_{∞} (ng•h/mL)	47.3 (37.5)[1]	48.0 (42.5)[2]	326.2 (13.9)[3]	338.0 (15.7)[4]	2185.4 (16.1)[5]	2246.6 (15.5)[6]
AUC_t (ng•h/mL)	36.2 (34.0)	38.9 (39.0)	282.5 (17.3)	294.4 (18.2)	1972.7 (17.4)	2028.0 (16.9)
C_{max} (ng/mL)	4.41 (33.6)	5.35 (35.0)	37.0 (21.2)	42.4 (18.9)	221 (23.8)	246 (20.0)
t_{max}[7] (h)	3.53 (1.50, 8.00)	2.00 (1.00, 6.00)	3.50 (1.50, 6.00)	2.50 (2.00, 5.00)	3.51 (1.50, 6.02)	2.50 (1.50, 5.00)
$t_{½}$ (h)	10.11 (47.7)[1]	10.05 (50.0)[2]	11.24 (37.3)[3]	11.10 (33.8)[4]	11.38 (31.1)[5]	11.31 (31.2)[6]

CV = coefficient of variation; M3G = morphine-3β-glucuronide; M6G = morphine-6β-glucuronide
Source: 067-EG-006: Table 14.2.2.1, Table 14.2.2.2, and Table 14.2.2.3
[1] n=29
[2] n=39
[3] n=49
[4] n=50
[5] n=62
[6] n=59
[7] Median (minimum, maximum)

Reference ID: 3983722

Table 20: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-6-Glucuronide, Study 067-EG-006

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	49	50	318.7	335.4	95.02 (92.72, 97.37)
AUC_t (ng•h/mL)	64	63	278.4	290.3	95.91 (94.06, 97.80)
C_{max} (ng/mL)	64	63	36.20	41.70	86.81 (83.71, 90.01)

CI = confidence interval; LS = least squares
Source: 067-EG-006 Table 14.2.3.2
Test: EG-001, 15 mg tablet, fasted conditions (Treatment A).
Reference: MS Contin, 15 mg tablet, fasted conditions (Treatment B).
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

Table 21: Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine-3-Glucuronide, Study 067-EG-006

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	62	59	2151	2231	96.44 (95.09, 97.82)
AUC_t (ng•h/mL)	64	63	1944	2010	96.72 (95.27, 98.20)
C_{max} (ng/mL)	64	63	214.8	241.8	88.84 (85.62, 92.17)

CI = confidence interval; LS = least squares
Source: 067-EG-006 Table 14.2.3.3
Test: EG-001, 15 mg tablet, fasted conditions (Treatment A).
Reference: MS Contin, 15 mg tablet, fasted conditions (Treatment B).
A linear mixed-effect model was performed with the ln-transformed pharmacokinetic parameters as the dependent variable and sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect.

4.1.4 Oral abuse liability study 067-EG-008

2. SYNOPSIS

Name of Company: Egalet Ltd	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Egalet PR Morphine	**Volume:**	
Name of Active Ingredient: Morphine Sulfate	**Page:**	
Title of Study: A Randomized, Double-Blind, Triple-Dummy, Active and Placebo-Controlled, Four-Way Crossover Study With an Exploratory Fifth Arm Comparing the Abuse Potential of Manipulated and Intact Egalet® PR Morphine Tablets versus Manipulated MS CONTIN Following Oral Administration in Nondependent Recreational Opioid Users		
Investigator and Study Center: This study was conducted at a single site in the United States of America (USA): Lynn R. Webster, MD, PRA Health Sciences, Salt Lake City, Utah.		
Publication (reference): None		
Study Start Date: 15JUL2014 **Study Completion Date**: 18NOV2014	**Phase of Development:** 1	
Objectives: The primary objective was to compare the relative abuse potential of oral intact and oral manipulated formulations of Egalet Prolonged Release (PR) morphine vs. oral manipulated MS CONTIN. Secondary Objectives: The secondary objectives were: • to determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of oral manipulated Egalet PR morphine; and • to assess the safety and pharmacokinetics of intact and manipulated formulations of Egalet PR morphine following oral administration. Exploratory Objective: An exploratory objective was to evaluate the relative abuse potential of oral Egalet PR morphine when manipulated and administered mixed in juice.		
Methodology: This was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of Egalet PR morphine vs. MS CONTIN in nondependent recreational opioid users. Subjects were randomized to treatment sequence in a 1:1:1:1 ratio. The study included a Screening Visit, a Qualification Phase, a Treatment Phase (comprising 4 treatment periods, each of which included a 3 day/2 night in-clinic visit), and a Follow-up Visit. Subjects who initially satisfied the inclusion and exclusion criteria during the Screening Visit were eligible for the Qualification Phase. Within 28 days after the Screening Visit, subjects reported to the study center for the Qualification Phase. During the Qualification Phase, subjects underwent a Naloxone Challenge Test to ensure that they were not physically dependent on opioids and a Drug Discrimination Test to ensure that they could differentiate between the effects of 30 mg immediate release oral morphine from placebo. Subjects who successfully completed the Screening Visit, Naloxone Challenge Test, and Drug Discrimination Test remained in the clinic and began Treatment Period 1 following a minimum 48-hour washout period. To		

Reference ID: 3983722

facilitate subject schedules and clinic availability, eligible subjects could be discharged following the Qualification Phase and return for Treatment Period 1 within 30 days. During Treatment Period 1, subjects could remain in the clinic through the 24-hour assessments for Treatment Day 2. For the remaining Treatment Periods (i.e., Treatment Periods 2 through 4) subjects checked in to the clinic on Day 0, at least 12 hours prior to study drug administration on Day 1, and fasted for at least 8 hours prior to receiving their study treatment. Subjects were discharged from the inpatient facility on Treatment Day 2 following the 24-hour study assessments. Following a washout period of at least 5 days between dosing, subjects reported to the study center to complete subsequent Treatment Periods. During the 4 Treatment Periods, subjects received each of the 4 treatments using a computer-generated randomization scheme based on a William's design. Approximately 7 to 14 days after their final treatment dose in Treatment Period 4, subjects reported to the inpatient facility for a Follow-up Visit. Subjects who were prematurely discontinued from the study completed an Early Termination evaluation upon discharge.

Subjects who completed the study were invited to participate in an additional exploratory treatment arm during which they received a fifth treatment of Egalet PR morphine, 60 mg oral manipulated and administered mixed in juice. Subjects returned to the clinic for a 3 day/2 night in-clinic visit and underwent the same study procedures as for the previous treatment arms except that fewer pharmacodynamic assessments were administered. Approximately 3 to 7 days after completion of the fifth treatment arm, subjects completed a follow-up telephone call.

Number of Subjects (Planned and Analyzed):

Planned: Sample size calculations were generated for the original 4-arm crossover component of the study. A sample size of 36 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥11.2 points in peak effect (E_{max}) for the bipolar Drug Liking visual analog scale (VAS), at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 20 points.

Analyzed: A total of 78 subjects entered the Qualification Phase and underwent the Naloxone Challenge Test; 78 subjects passed the test. Of the 78 subjects who participated in the Drug Discrimination Test, 34 failed the Drug Discrimination Test (i.e., they were unable to discriminate between opioid and placebo based on Drug Liking scores); 5 withdrew (i.e., they no longer wanted to participate, withdrew for personal reasons, or withdrew consent); and 1 was discontinued due to an Adverse Event (AE). Of the 39 subjects who entered the Treatment Phase, 38 completed the study.

Test Product, Dose and Mode of Administration:

Naloxone Challenge Test: An initial dose of naloxone hydrochloride (HCl) 0.2 mg was administered by intravenous (IV) bolus followed by an additional 0.6 mg of IV naloxone HCl if no evidence of withdrawal occurred within 30 seconds.

- Naloxone HCl Injection, USP, 0.4 mg/1 mL multidose vial (Hospira, Lake Forrest, Il): NDC # 00409-1219-01, Lot # 00409-1219-01, Expiry date: 01JUN2015

Drug Discrimination Test: Single dose of 30 mg oral immediate-release morphine in solution and matching placebo solution administered orally with doses separated by 24 hours.

- Immediate-release morphine, USP, 30 mg (Roxane Labs, Columbus, Ohio): NDC # 00054-0236-25, Lot #464022A, Expiry 31OCT2015. One 30 mg tablet crushed and administered in 150 mL Ocean Spray® Diet Cranberry™ juice.
- Avicel PH-102 powder (FMC Biopolymer, Philadelphia, PA): Lot # P213825558, Expiry date: 02APR2017. 200 mg of powder administered in 150 mL Ocean Spray® Diet Cranberry™ juice.

Treatment Period: Single doses of Egalet PR morphine were provided at a tablet dose strength of 60 mg.

- Egalet PR morphine, 60 mg tablets. Lot # SB69300301, Retest date: (b) (4). Egalet PR morphine was administered orally intact and manipulated. The manipulated product was administered directly from the vial with 150 mL Ocean Spray Diet Cranberry juice. For the exploratory treatment, Egalet PR morphine was manipulated and mixed into 150 mL of Ocean Spray Diet Cranberry juice. This was followed by additional 50 mL rinses with the cranberry juice.

Duration of Treatment: Subjects completed an initial Screening Visit to determine eligibility for the study. Eligible subjects completed a 3-day Qualification Phase and 4 Treatment Periods (each of which included a 3 day/2 night in-clinic visit) with each treatment separated by a washout period of at least 5 days. Overall study duration was approximately 11 weeks, depending on the length of time between study visits. Subjects who agreed to participate in the fifth treatment arm returned to the clinic for one additional 3 day/2 night in-clinic visit.

Reference Therapy, Dose and Mode of Administration:

Treatment Period:

- MS CONTIN, USP, 60 mg (Purdue Pharma, Stamford, CT) is an extended-release oral formulation of morphine NDC # 59011-0262-10, Lot # WTB11, Expiry date: 31DEC2016. MS CONTIN was crushed with a mortar and pestle and mixed into 150 mL Ocean Spray® Diet Cranberry™ juice.
- Matching Egalet PR placebo was provided as identical to the Egalet PR morphine investigational product Lot # SB72100101, Retest date: (b) (4). The method of administration and amount was also identical for placebo treatment. For the manipulated condition, one placebo tablet was manipulated and administered orally directly from the vial with 150 mL Ocean Spray® Diet Cranberry™ juice.
- Placebo powder (Avicel PH-102 powder) (Biopolymer, Philadelphia PA) was used to match MS CONTIN: Lot # P213825558.

Criteria for Evaluation:

Pharmacodynamic Assessments:

- Drug Liking: 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose using a bipolar 0-100 point VAS.

The following PD parameters were calculated:

- E_{max}: Peak effect over the 24 hours of collection.
- TE_{max}: Time to peak effect.
- AUE_{0-x}: area under the efficacy curve from time zero to x hours, where x is 0.5 hours ($AUE_{0-0.5}$), 1 hour (AUE_{0-1}), 2 hours (AUE_{0-2}), 4 hours (AUE_{0-4}), 8 hours (AUE_{0-8}), 12 hours (AUE_{0-12}), and 24 hours (AUE_{0-24}).
- $AUE_{0-TEmax}$: Area under the effect-time curve from 0 to TE_{max}.
- Percent reduction: The percent reduction in E_{max} (calculated for Drug Liking only).

Reference ID: 3983722

Pharmacokinetic Assessments: On dosing days during each Treatment Period, blood samples were collected in 6 mL sodium heparin tubes at predose, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose for morphine and morphine-6-glucuronide determinations. The plasma pharmacokinetic parameters include, but were not limited to, the following:

- T_{max}: The time to maximum observed plasma concentration for each subject.
- C_{max}: The maximum observed plasma concentration for each subject.
- $AUC_{0\text{-last}}$: Area under the plasma concentration vs. time curve from 0 to last measurable concentration.
- $AUC_{0\text{-INF}}$: Area under the plasma concentration vs. time curve from time zero extrapolated to infinity.
- Abuse Quotient (AQ): ratio of C_{max}/T_{max}.
- $AUC_{0\text{-x}}$: Area under the plasma concentration vs. time curve from 0 to x, where x is 0.5 hours ($AUC_{0\text{-}0.5}$), 1 hour ($AUC_{0\text{-}1}$), 2 hours ($AUC_{0\text{-}2}$), 4 hours ($AUC_{0\text{-}4}$), 8 hours ($AUC_{0\text{-}8}$), 12 hours ($AUC_{0\text{-}12}$), and 24 hours ($AUC_{0\text{-}24}$).

Statistical Methods:

Sample Size Determination: Sample size calculations were generated for the original 4-arm crossover study component of the study. The proposed sample size of 36 completed subjects was expected to provide at least 90% power to detect treatment differences of ≥11.2 points in peak effect (E_{max}) for the bipolar Drug Liking VAS, at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming a standard deviation of differences of 20 points.

No formal sample size calculation was made for the exploratory arm.

Pharmacodynamic Evaluation:

The primary PD endpoint of interest is the Drug Liking VAS E_{max}.

Pharmacokinetic Evaluations

The plasma PK parameters were estimated from the concentration-time profiles for the PK population. In estimating the PK parameters, below the quantifiable limit (BQL) values at the beginning of the profile were set to zero. Actual sampling times, rather than scheduled sampling times, were used in all computations involving sampling times. Descriptive statistics (n, mean, geometric mean, SD, CV, median, minimum, and maximum) were used to summarize the calculated PK parameters by treatment.

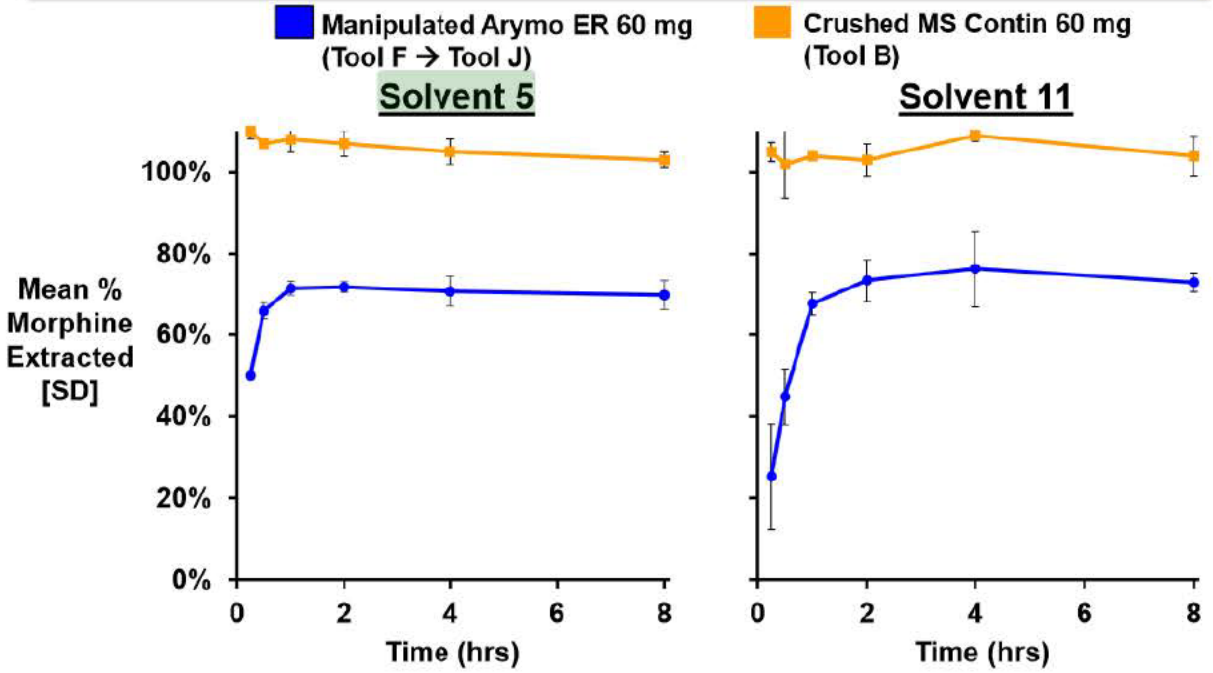
Relative bioavailability of morphine was calculated using the ratio and 90% Confidence Interval (CI) of geometric means for area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-inf}}$), area under the plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$), and C_{max}. Analyses of C_{max} and AUCs used the natural log-transformed C_{max} and AUCs. The SAS mixed effect linear model procedure (PROC MIXED) was used to construct the analysis of variance (ANOVA) model for the PK population. The model included terms for sequence, period, and treatment as fixed effects and subject nested within sequences as a random effect. Least-squares geometric means for C_{max} and AUCs along with 90% CIs are provided for each treatment. The comparisons include manipulated Egalet PR morphine vs. manipulated MS CONTIN (Treatment B to Treatment C), intact Egalet PR morphine vs. manipulated MS CONTIN (Treatment A to Treatment C), and manipulated Egalet PR morphine vs. intact Egalet PR (Treatment B to Treatment A).

See conclusions in the summary of clinical pharmacology findings.

Figure: Slide from sponsor's Advisory Committee presentation representing morphine extraction *in vitro*.

OH-16

Morphine Extraction from Arymo ER and MS Contin Over Time



Category 1

Temperature A, Agitation B, 200 ml, N=3
*FDA has not reviewed MS Contin data

Reference ID: 3983722

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Placebo (manipulated)	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
Emax	n	38	38	38
	Mean	53.3	73.3	68.3
	SD	7.82	9.81	12.28
	SEM	1.27	1.59	1.99
	%CV	14.67	13.39	17.96
	Median(Q1,Q3)	50.0 (50.0,52.0)	74.0 (68.0,79.0)	67.0 (61.0,75.0)
	Min, Max	50, 89	50, 100	50, 100
TEmax (hr)	n	38	38	38
	Mean	1.05	1.45	2.39
	SD	1.484	0.884	1.612
	SEM	0.241	0.143	0.261
	%CV	141.02	60.96	67.45
	Median(Q1,Q3)	0.52 (0.50,0.99)	1.02 (1.00,2.00)	1.99 (1.49,2.99)
	Min, Max	0.5, 8.0	0.5, 4.0	0.5, 8.0
AUE0-0.5	n	38	38	37
	Mean	0.047	2.443	0.562
	SD	0.3345	3.0193	2.5800
	SEM	0.0543	0.4898	0.4241
	%CV	710.10	123.57	458.72
	Median(Q1,Q3)	0.000 (0.000,0.000)	2.020 (0.000,3.750)	0.000 (0.000,1.225)
	Min, Max	-0.25, 2.04	-4.59, 12.25	-12.25, 6.25

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
Emax	n	38	12
	Mean	63.2	72.8
	SD	10.07	7.64
	SEM	1.63	2.20
	%CV	15.94	10.49
	Median(Q1,Q3)	62.0 (56.0,68.0)	70.0 (67.5,78.0)
	Min, Max	50, 91	62, 89
TEmax (hr)	n	38	12
	Mean	3.66	2.25
	SD	4.091	1.032
	SEM	0.664	0.298
	%CV	111.71	45.79
	Median(Q1,Q3)	3.00 (0.75,6.00)	2.01 (1.50,3.00)
	Min, Max	0.5, 24.0	1.0, 4.0
AUE0-0.5	n	38	12
	Mean	0.697	0.604
	SD	1.3490	1.5168
	SEM	0.2188	0.4379
	%CV	193.59	251.06
	Median(Q1,Q3)	0.125 (0.000,0.765)	0.000 (0.000,0.500)
	Min, Max	-0.25, 7.00	-0.25, 5.25

Reference ID: 3983722

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Placebo (manipulated)	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUE0-0.75	n	38	38	38
	Mean	0.326	5.581	1.488
	SD	1.1594	5.6110	4.5152
	SEM	0.1881	0.9102	0.7325
	%CV	355.58	100.53	303.46
	Median(Q1,Q3)	0.000 (0.000,0.120)	4.363 (2.040,8.125)	0.720 (0.000,3.180)
	Min, Max	-0.38, 5.34	-7.23, 25.25	-19.50, 12.01
AUE0-1	n	37	38	38
	Mean	0.657	9.999	3.118
	SD	2.4233	7.6158	5.9538
	SEM	0.3984	1.2354	0.9658
	%CV	368.82	76.17	190.92
	Median(Q1,Q3)	0.000 (0.000,0.250)	9.030 (5.380,14.125)	2.325 (0.000,5.500)
	Min, Max	-0.38, 14.50	-7.36, 37.75	-19.50, 17.22
AUE0-1.5	n	38	38	38
	Mean	2.066	19.732	7.657
	SD	5.6855	11.4419	9.5323
	SEM	0.9223	1.8561	1.5463
	%CV	275.15	57.99	124.49
	Median(Q1,Q3)	0.000 (0.000,0.865)	17.910 (14.630,26.180)	5.293 (1.000,12.250)
	Min, Max	-0.50, 30.75	-5.16, 62.75	-18.75, 29.71

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUE0-0.75	n	38	12
	Mean	1.476	1.629
	SD	2.5459	2.9535
	SEM	0.4130	0.8526
	%CV	172.50	181.29
	Median(Q1,Q3)	0.438 (0.000,1.250)	0.813 (0.000,1.655)
	Min, Max	-0.25, 12.88	0.00, 10.63
AUE0-1	n	38	12
	Mean	2.609	3.620
	SD	3.6328	4.6818
	SEM	0.5893	1.3515
	%CV	139.26	129.32
	Median(Q1,Q3)	0.938 (0.000,4.585)	3.125 (0.640,4.520)
	Min, Max	-0.13, 17.50	0.00, 17.13
AUE0-1.5	n	38	12
	Mean	5.669	9.998
	SD	6.9883	8.0639
	SEM	1.1337	2.3278
	%CV	123.26	80.65
	Median(Q1,Q3)	1.955 (0.000,8.835)	9.003 (4.350,13.385)
	Min, Max	-0.13, 27.30	0.00, 30.85

Reference ID: 3983722

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Placebo (manipulated)	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUE0-2	n	38	38	37
	Mean	3.028	29.298	13.784
	SD	7.8020	15.6875	13.4672
	SEM	1.2657	2.5449	2.2140
	%CV	257.63	53.55	97.70
	Median(Q1,Q3)	0.000 (0.000,1.110)	28.020 (21.180,38.750)	11.860 (3.000,21.250)
	Min, Max	-1.00, 37.50	-2.16, 87.25	-16.75, 42.94
AUE0-3	n	38	38	38
	Mean	3.973	45.012	25.843
	SD	10.1433	25.4156	21.8434
	SEM	1.6455	4.1229	3.5435
	%CV	255.31	56.46	84.52
	Median(Q1,Q3)	0.000 (0.000,1.245)	45.285 (29.760,58.495)	24.615 (12.130,41.230)
	Min, Max	-2.00, 37.50	0.00, 137.75	-15.36, 69.44
AUE0-4	n	38	38	38
	Mean	4.195	55.371	36.301
	SD	11.8561	36.3132	30.3425
	SEM	1.9233	5.8908	4.9222
	%CV	282.62	65.58	83.59
	Median(Q1,Q3)	0.000 (0.000,0.750)	55.248 (36.480,74.270)	30.315 (20.980,58.590)
	Min, Max	-8.14, 44.22	-23.13, 187.25	-24.86, 102.01

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUE0-2	n	38	12
	Mean	8.917	18.772
	SD	10.1502	10.7657
	SEM	1.6466	3.1078
	%CV	113.83	57.35
	Median(Q1,Q3)	4.480 (0.630,16.075)	19.070 (12.370,21.145)
	Min, Max	-0.37, 39.03	1.00, 44.35
AUE0-3	n	38	12
	Mean	15.684	37.032
	SD	15.7310	15.8926
	SEM	2.5519	4.5878
	%CV	100.30	42.92
	Median(Q1,Q3)	10.645 (1.630,26.900)	37.645 (25.530,45.540)
	Min, Max	-0.87, 59.23	10.00, 70.35
AUE0-4	n	38	12
	Mean	23.029	52.166
	SD	21.9099	20.6661
	SEM	3.5543	5.9658
	%CV	95.14	39.62
	Median(Q1,Q3)	18.318 (1.130,34.645)	51.598 (34.790,62.673)
	Min, Max	-0.87, 90.86	26.67, 96.10

Reference ID: 3983722

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Placebo (manipulated)	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUE0-6	n	38	38	38
	Mean	4.121	67.865	52.121
	SD	17.0732	55.9771	49.6973
	SEM	2.7696	9.0807	8.0620
	%CV	414.28	82.48	95.35
	Median(Q1,Q3)	0.000 (0.000,1.630)	64.833 (38.240,94.680)	47.988 (27.310,75.895)
	Min, Max	-46.95, 71.22	-66.13, 286.75	-67.78, 169.34
AUE0-8	n	38	38	38
	Mean	4.018	75.938	61.290
	SD	19.8282	72.4831	68.4464
	SEM	3.2166	11.7583	11.1035
	%CV	493.53	95.45	111.68
	Median(Q1,Q3)	0.000 (0.000,2.000)	77.930 (43.500,109.680)	56.723 (28.310,86.580)
	Min, Max	-60.95, 86.30	-66.13, 385.75	-148.38, 244.34
AUE0-12	n	38	38	38
	Mean	3.806	87.922	61.241
	SD	20.0421	103.3405	106.5644
	SEM	3.2513	16.7640	17.2870
	%CV	526.62	117.54	174.01
	Median(Q1,Q3)	0.000 (0.000,1.750)	84.250 (43.800,123.715)	62.940 (29.650,86.595)
	Min, Max	-60.95, 86.30	-66.13, 577.27	-344.38, 395.96

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUE0-6	n	38	12
	Mean	34.599	70.788
	SD	33.5075	38.8991
	SEM	5.4356	11.2292
	%CV	96.85	54.95
	Median(Q1,Q3)	29.660 (3.510,56.500)	69.793 (56.210,88.120)
	Min, Max	-10.35, 148.86	-14.00, 141.87
AUE0-8	n	38	12
	Mean	39.851	76.603
	SD	45.8591	51.3285
	SEM	7.4393	14.8173
	%CV	115.08	67.01
	Median(Q1,Q3)	32.293 (4.390,54.490)	87.348 (55.740,112.618)
	Min, Max	-34.67, 209.16	-57.00, 128.87
AUE0-12	n	38	12
	Mean	40.020	72.787
	SD	68.0800	67.9880
	SEM	11.0440	19.6264
	%CV	170.11	93.41
	Median(Q1,Q3)	30.900 (3.760,67.150)	97.520 (27.810,111.113)
	Min, Max	-86.67, 303.16	-55.00, 179.63

Reference ID: 3983722

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Placebo (manipulated)	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUE0-24	n	38	38	38
	Mean	3.963	103.869	47.657
	SD	20.8278	144.9556	167.9159
	SEM	3.3787	23.5149	27.2396
	%CV	525.57	139.56	352.34
	Median(Q1,Q3)	0.000 (0.000,2.000)	82.710 (47.230,137.830)	54.945 (17.160,75.050)
	Min, Max	-60.95, 86.30	-66.13, 853.27	-644.38, 575.96
AUEtemax	n	38	38	38
	Mean	1.249	17.648	19.950
	SD	3.9500	14.8202	22.4297
	SEM	0.6408	2.4042	3.6386
	%CV	316.33	83.98	112.43
	Median(Q1,Q3)	0.000 (0.000,0.250)	13.540 (7.280,25.605)	13.810 (4.700,25.125)
	Min, Max	-1.00, 22.42	-5.16, 70.36	0.00, 120.25

Table 14.2.1.2
Summary of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

PD Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUE0-24	n	38	12
	Mean	29.122	63.290
	SD	139.0128	135.7622
	SEM	22.5509	39.1912
	%CV	477.34	214.51
	Median(Q1,Q3)	31.325 (0.000,78.965)	97.560 (24.810,129.025)
	Min, Max	-585.98, 375.10	-293.13, 245.57
AUEtemax	n	38	12
	Mean	24.219	20.655
	SD	47.5145	9.4601
	SEM	7.7079	2.7309
	%CV	196.19	45.80
	Median(Q1,Q3)	8.638 (3.250,28.075)	19.333 (14.710,23.958)
	Min, Max	-0.25, 278.29	5.64, 38.49

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
TEmax (hr)	Intact Egalet PR (A)	3.00			
	Manipulated Egalet PR (B)	1.99			
	Manipulated MS CONTIN (C)	1.02			
	Placebo (D)	0.52			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		<.0001	2.25	(1.24, 3.25)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.0745	-0.76	(-2.00, 0.23)
	Manipulated Egalet PR vs Placebo (B vs D)		<.0001	1.24	(0.85, 1.75)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	-1.75	(-2.61, -0.75)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.0039	-0.74	(-1.25, -0.25)
	Manipulated MS CONTIN vs Placebo (C vs D)		0.0013	0.50	(0.24, 0.76)
Emax	Intact Egalet PR (A)	62.00			
	Manipulated Egalet PR (B)	67.00			
	Manipulated MS CONTIN (C)	74.00			
	Placebo (D)	50.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		<.0001	10.00	(6.50, 14.00)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.0738	4.00	(-0.50, 9.00)
	Manipulated Egalet PR vs Placebo (B vs D)		<.0001	14.50	(10.00, 19.00)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	9.50	(5.50, 14.50)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.0069	4.00	(1.00, 8.00)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	20.50	(16.50, 24.00)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-0.5	Intact Egalet PR (A)	0.13			
	Manipulated Egalet PR (B)	0.00			
	Manipulated MS CONTIN (C)	2.02			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		0.0004	0.26	(0.13, 0.88)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.7170	0.00	(-0.38, 0.43)
	Manipulated Egalet PR vs Placebo (B vs D)		0.0091	0.50	(0.00, 0.99)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	1.38	(0.51, 2.19)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.0028	1.24	(0.24, 2.14)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	2.04	(1.28, 3.19)
AUE0-1	Intact Egalet PR (A)	0.94			
	Manipulated Egalet PR (B)	2.33			
	Manipulated MS CONTIN (C)	9.03			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		0.0013	1.52	(0.19, 2.81)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.7242	0.13	(-0.90, 2.04)
	Manipulated Egalet PR vs Placebo (B vs D)		0.0007	2.17	(0.57, 3.77)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	6.63	(4.57, 8.95)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		<.0001	6.34	(3.74, 8.93)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	9.13	(6.75, 10.88)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-2	Intact Egalet PR (A)	4.48			
	Manipulated Egalet PR (B)	11.86			
	Manipulated MS CONTIN (C)	28.02			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		0.0031	6.09	(1.53, 9.36)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.0959	4.00	(-1.74, 9.06)
	Manipulated Egalet PR vs Placebo (B vs D)		0.0002	10.56	(4.10, 15.05)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	19.24	(14.20, 25.12)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		<.0001	14.37	(7.38, 19.93)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	26.24	(21.61, 30.56)
AUE0-4	Intact Egalet PR (A)	18.32			
	Manipulated Egalet PR (B)	30.32			
	Manipulated MS CONTIN (C)	55.25			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		<.0001	18.48	(10.34, 26.50)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.0497	11.85	(-0.13, 24.40)
	Manipulated Egalet PR vs Placebo (B vs D)		<.0001	31.96	(21.03, 43.30)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		<.0001	29.99	(17.70, 43.06)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.0008	18.26	(7.96, 30.28)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	51.10	(38.99, 62.37)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-8	Intact Egalet PR (A)	32.29			
	Manipulated Egalet PR (B)	56.72			
	Manipulated MS CONTIN (C)	77.93			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		<.0001	34.64	(19.11, 49.86)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.0752	22.16	(-1.54, 42.87)
	Manipulated Egalet PR vs Placebo (B vs D)		<.0001	55.43	(34.93, 79.29)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		0.0008	30.65	(13.88, 48.84)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.2668	9.82	(-7.90, 28.13)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	69.95	(47.92, 90.97)
AUE0-12	Intact Egalet PR (A)	30.90			
	Manipulated Egalet PR (B)	62.94			
	Manipulated MS CONTIN (C)	84.25			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		0.0017	33.79	(15.05, 53.62)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.1100	22.07	(-5.15, 47.51)
	Manipulated Egalet PR vs Placebo (B vs D)		<.0001	57.90	(32.53, 79.92)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		0.0020	39.20	(13.80, 65.16)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.1906	14.83	(-6.41, 36.38)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	76.48	(49.57, 104.33)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=38)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-24	Intact Egalet PR (A)	31.33			
	Manipulated Egalet PR (B)	54.95			
	Manipulated MS CONTIN (C)	82.71			
	Placebo (D)	0.00			
	Differences in Medians				
	Intact Egalet PR vs Placebo (A vs D)		0.0229	34.36	(8.50, 62.09)
	Manipulated Egalet PR vs Intact Egalet PR (B vs A)		0.5353	10.05	(-24.11, 42.36)
	Manipulated Egalet PR vs Placebo (B vs D)		0.0016	46.90	(20.78, 73.10)
	Manipulated MS CONTIN vs Intact Egalet PR (C vs A)		0.0032	42.69	(13.92, 72.78)
	Manipulated MS CONTIN vs Manipulated Egalet PR (C vs B)		0.0376	26.79	(1.55, 75.20)
	Manipulated MS CONTIN vs Placebo (C vs D)		<.0001	84.65	(54.40, 113.69)

Table 14.2.1.4
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Exploratory (N=12)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
TEmax (hr)	Intact Egalet PR (A)	2.26			
	Manipulated Egalet PR (B)	2.50			
	Manipulated MS CONTIN (C)	1.02			
	Placebo (D)	0.76			
	Manipulated Egalet PR - Exploratory (E)	2.01			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.0186	-1.00	(-1.75, -0.25)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.8970	-0.07	(-3.00, 1.13)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.3691	-0.50	(-2.00, 0.65)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0024	1.25	(0.51, 2.00)
Emax	Intact Egalet PR (A)	58.00			
	Manipulated Egalet PR (B)	65.00			
	Manipulated MS CONTIN (C)	71.00			
	Placebo (D)	51.50			
	Manipulated Egalet PR - Exploratory (E)	70.00			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.8960	0.50	(-4.00, 6.00)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.0029	13.50	(6.50, 17.50)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.0669	6.50	(-0.50, 10.50)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0015	18.50	(10.50, 26.50)

Reference ID: 3983722

Table 14.2.1.4
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Exploratory (N=12)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-0.5	Intact Egalet PR (A)	0.26			
	Manipulated Egalet PR (B)	0.96			
	Manipulated MS CONTIN (C)	3.03			
	Placebo (D)	0.00			
	Manipulated Egalet PR - Exploratory (E)	0.00			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.0254	1.83	(0.13, 3.50)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.8438	0.00	(-0.77, 0.62)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.4316	-0.50	(-2.67, 2.11)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.1250	0.25	(0.00, 0.88)
AUE0-1	Intact Egalet PR (A)	0.88			
	Manipulated Egalet PR (B)	3.18			
	Manipulated MS CONTIN (C)	10.13			
	Placebo (D)	0.25			
	Manipulated Egalet PR - Exploratory (E)	3.13			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.0010	6.35	(3.39, 9.69)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.2754	1.79	(-0.77, 3.95)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.9097	-0.80	(-4.23, 7.10)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0020	1.71	(0.57, 4.20)

Table 14.2.1.4
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Exploratory (N=12)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-2	Intact Egalet PR (A)	1.13			
	Manipulated Egalet PR (B)	11.42			
	Manipulated MS CONTIN (C)	28.81			
	Placebo (D)	0.68			
	Manipulated Egalet PR - Exploratory (E)	19.07			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.0068	11.77	(4.60, 17.75)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.0068	14.16	(5.54, 19.16)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.3013	5.15	(-5.86, 18.59)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0010	13.98	(7.59, 22.30)
AUE0-4	Intact Egalet PR (A)	6.24			
	Manipulated Egalet PR (B)	26.09			
	Manipulated MS CONTIN (C)	54.44			
	Placebo (D)	0.62			
	Manipulated Egalet PR - Exploratory (E)	51.60			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.3394	6.35	(-6.35, 18.17)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.0034	35.92	(21.99, 46.92)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.0425	17.69	(2.66, 37.96)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0010	44.78	(28.01, 63.24)

Table 14.2.1.4
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Exploratory (N=12)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-8	Intact Egalet PR (A)	19.73			
	Manipulated Egalet PR (B)	55.92			
	Manipulated MS CONTIN (C)	75.88			
	Placebo (D)	1.50			
	Manipulated Egalet PR - Exploratory (E)	87.35			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.7334	-3.75	(-25.19, 13.96)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.0522	45.67	(0.26, 75.93)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.3804	17.02	(-32.37, 48.91)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0342	80.07	(42.73, 105.32)
AUE0-12	Intact Egalet PR (A)	12.52			
	Manipulated Egalet PR (B)	65.32			
	Manipulated MS CONTIN (C)	81.05			
	Placebo (D)	1.50			
	Manipulated Egalet PR - Exploratory (E)	97.52			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.5693	11.15	(-28.44, 28.68)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.3804	31.77	(-36.05, 88.44)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		1.0000	-1.36	(-50.95, 43.57)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.0425	73.41	(6.93, 109.82)

Reference ID: 3983722

Table 14.2.1.4
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Exploratory (N=12)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-24	Intact Egalet PR (A)	6.36			
	Manipulated Egalet PR (B)	54.87			
	Manipulated MS CONTIN (C)	91.84			
	Placebo (D)	4.50			
	Manipulated Egalet PR - Exploratory (E)	97.56			
	Differences in Medians				
	Manipulated MS CONTIN vs Manipulated Egalet PR in juice (C vs E)		0.8501	13.49	(-49.46, 40.96)
	Manipulated Egalet PR in juice vs Intact Egalet PR (E vs A)		0.3394	50.90	(-52.13, 103.35)
	Manipulated Egalet PR in juice vs Manipulated Egalet PR (E vs B)		0.6221	14.25	(-78.65, 60.73)
	Manipulated Egalet PR in juice vs Placebo (E vs D)		0.2036	74.67	(-44.65, 129.03)

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
Tmax (hr)	n	38	12
	Mean	3.593	2.180
	SD	1.0658	0.6166
	SEM	0.1729	0.1780
	%CV	29.7	28.3
	Median(Q1,Q3)	4.120 (3.100,4.130)	2.140 (1.630,2.640)
	Min, Max	1.63, 6.13	1.63, 3.13
Cmax (ng/mL)	n	38	12
	Mean	17.81	25.43
	SD	6.596	6.482
	SEM	1.070	1.871
	%CV	37.0	25.5
	Median(Q1,Q3)	16.70 (12.10,23.00)	24.05 (20.85,30.00)
	Min, Max	8.5, 32.3	16.4, 36.1
AUC0-last (hr*ng/mL)	n	38	12
	Mean	135.57	131.51
	SD	40.258	28.007
	SEM	6.531	8.085
	%CV	29.7	21.3
	Median(Q1,Q3)	124.98 (106.66,161.36)	134.14 (107.53,149.77)
	Min, Max	70.5, 227.4	89.8, 175.7

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUC0-inf (hr*ng/mL)	n	35	28
	Mean	182.10	159.25
	SD	49.905	36.805
	SEM	8.435	6.956
	%CV	27.4	23.1
	Median(Q1,Q3)	185.45 (145.76,203.91)	157.14 (127.28,190.90)
	Min, Max	61.8, 284.1	94.5, 215.3
Abuse Quotient	n	39	38
	Mean	45.88	16.36
	SD	20.306	9.395
	SEM	3.251	1.524
	%CV	44.3	57.4
	Median(Q1,Q3)	46.55 (33.27,61.59)	14.49 (9.77,20.85)
	Min, Max	4.6, 87.8	3.9, 54.3
AUC0-0.5 (hr*ng/mL)	n	39	38
	Mean	10.140	2.419
	SD	4.6175	1.7466
	SEM	0.7394	0.2833
	%CV	45.5	72.2
	Median(Q1,Q3)	9.104 (6.240,14.364)	1.961 (1.132,3.069)
	Min, Max	3.18, 18.99	0.22, 8.35

Reference ID: 3983722

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUC0-inf (hr*ng/mL)	n	19	8
	Mean	167.95	151.48
	SD	53.619	36.726
	SEM	12.301	12.984
	%CV	31.9	24.2
	Median(Q1,Q3)	159.39 (128.88,208.71)	154.49 (118.68,178.65)
	Min, Max	80.9, 274.8	101.6, 206.6
Abuse Quotient	n	38	12
	Mean	5.73	12.73
	SD	3.514	5.256
	SEM	0.570	1.517
	%CV	61.3	41.3
	Median(Q1,Q3)	4.21 (2.93,8.00)	11.50 (8.38,17.03)
	Min, Max	2.1, 15.8	5.5, 22.1
AUC0-0.5 (hr*ng/mL)	n	38	12
	Mean	0.949	2.356
	SD	0.6811	2.1102
	SEM	0.1105	0.6092
	%CV	71.8	89.6
	Median(Q1,Q3)	0.724 (0.484,1.340)	1.622 (1.222,2.701)
	Min, Max	0.00, 3.65	0.63, 8.57

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUC0-0.75 (hr*ng/mL)	n	39	38
	Mean	18.978	5.068
	SD	7.8719	3.5259
	SEM	1.2605	0.5720
	%CV	41.5	69.6
	Median(Q1,Q3)	17.780 (12.618,25.574)	4.164 (2.589,6.418)
	Min, Max	6.12, 35.19	0.51, 15.85
AUC0-1 (hr*ng/mL)	n	39	38
	Mean	28.641	9.241
	SD	10.9669	5.7483
	SEM	1.7561	0.9325
	%CV	38.3	62.2
	Median(Q1,Q3)	29.239 (20.052,35.552)	7.637 (4.631,13.220)
	Min, Max	9.40, 50.61	1.43, 23.98
AUC0-1.5 (hr*ng/mL)	n	39	38
	Mean	45.404	19.642
	SD	15.7229	9.7130
	SEM	2.5177	1.5757
	%CV	34.6	49.4
	Median(Q1,Q3)	44.826 (35.156,55.161)	16.274 (12.344,27.918)
	Min, Max	15.06, 80.02	4.35, 40.76

Reference ID: 3983722

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUC0-0.75 (hr*ng/mL)	n	38	12
	Mean	1.864	4.799
	SD	1.2146	3.9424
	SEM	0.1970	1.1381
	%CV	65.2	82.2
	Median(Q1,Q3)	1.395 (1.041,2.675)	3.376 (2.459,6.273)
	Min, Max	0.07, 6.11	1.23, 15.91
AUC0-1 (hr*ng/mL)	n	38	12
	Mean	3.308	8.447
	SD	2.0040	5.7988
	SEM	0.3251	1.6740
	%CV	60.6	68.6
	Median(Q1,Q3)	2.613 (1.997,4.335)	5.914 (4.159,11.266)
	Min, Max	0.23, 8.63	2.53, 22.34
AUC0-1.5 (hr*ng/mL)	n	38	12
	Mean	7.694	18.496
	SD	4.7200	8.9773
	SEM	0.7657	2.5915
	%CV	61.3	48.5
	Median(Q1,Q3)	6.603 (5.266,8.389)	14.351 (11.835,24.545)
	Min, Max	0.72, 25.23	8.57, 37.79

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUC0-2 (hr*ng/mL)	n	39	38
	Mean	58.869	31.747
	SD	19.2752	13.2648
	SEM	3.0865	2.1518
	%CV	32.7	41.8
	Median(Q1,Q3)	57.019 (47.052,72.302)	27.465 (20.508,42.501)
	Min, Max	19.77, 102.55	9.90, 57.82
AUC0-3 (hr*ng/mL)	n	39	38
	Mean	78.958	53.435
	SD	24.9348	17.9465
	SEM	3.9928	2.9113
	%CV	31.6	33.6
	Median(Q1,Q3)	78.133 (62.319,96.394)	50.215 (39.126,68.979)
	Min, Max	26.28, 136.46	22.15, 83.73
AUC0-4 (hr*ng/mL)	n	39	38
	Mean	93.869	70.865
	SD	28.7532	21.2072
	SEM	4.6042	3.4403
	%CV	30.6	29.9
	Median(Q1,Q3)	93.501 (73.158,113.970)	71.297 (54.039,91.107)
	Min, Max	33.55, 162.04	33.88, 108.33

Reference ID: 3983722

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUC0-2 (hr*ng/mL)	n	38	12
	Mean	13.220	30.001
	SD	6.8010	12.3624
	SEM	1.1033	3.5687
	%CV	51.4	41.2
	Median(Q1,Q3)	11.700 (8.329,15.968)	25.925 (20.926,39.028)
	Min, Max	1.66, 32.00	14.42, 55.42
AUC0-3 (hr*ng/mL)	n	38	12
	Mean	26.796	49.986
	SD	11.6148	15.9973
	SEM	1.8842	4.6180
	%CV	43.3	32.0
	Median(Q1,Q3)	23.765 (17.948,36.168)	47.363 (39.435,61.054)
	Min, Max	5.97, 51.25	29.47, 83.76
AUC0-4 (hr*ng/mL)	n	38	12
	Mean	41.985	65.441
	SD	15.8969	17.6454
	SEM	2.5788	5.0938
	%CV	37.9	27.0
	Median(Q1,Q3)	38.198 (30.832,55.662)	61.406 (52.775,76.658)
	Min, Max	15.07, 75.42	40.74, 100.82

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUC0-6 (hr*ng/mL)	n	39	38
	Mean	112.392	92.083
	SD	32.9297	25.4489
	SEM	5.2730	4.1284
	%CV	29.3	27.6
	Median(Q1,Q3)	110.063 (85.972,135.207)	90.645 (71.479,117.109)
	Min, Max	39.59, 191.72	48.92, 136.49
AUC0-8 (hr*ng/mL)	n	39	38
	Mean	122.571	103.391
	SD	35.5228	27.8442
	SEM	5.6882	4.5169
	%CV	29.0	26.9
	Median(Q1,Q3)	119.900 (93.512,145.177)	101.222 (80.898,128.747)
	Min, Max	43.06, 208.15	54.82, 152.52
AUC0-12 (hr*ng/mL)	n	38	38
	Mean	136.268	115.415
	SD	35.7618	30.1436
	SEM	5.8013	4.8899
	%CV	26.2	26.1
	Median(Q1,Q3)	133.562 (103.413,155.086)	113.043 (90.598,143.021)
	Min, Max	81.45, 224.49	63.72, 168.55

Reference ID: 3983722

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUC0-6 (hr*ng/mL)	n	38	12
	Mean	68.188	84.880
	SD	23.1454	19.8660
	SEM	3.7547	5.7348
	%CV	33.9	23.4
	Median(Q1,Q3)	63.201 (51.005,87.262)	79.842 (72.943,101.033)
	Min, Max	35.01, 118.61	53.68, 122.42
AUC0-8 (hr*ng/mL)	n	38	12
	Mean	85.678	96.358
	SD	28.0185	20.6683
	SEM	4.5452	5.9664
	%CV	32.7	21.4
	Median(Q1,Q3)	80.972 (63.152,102.020)	93.285 (85.177,112.840)
	Min, Max	46.51, 148.84	61.29, 133.55
AUC0-12 (hr*ng/mL)	n	38	12
	Mean	104.011	108.519
	SD	32.5081	22.6103
	SEM	5.2735	6.5270
	%CV	31.3	20.8
	Median(Q1,Q3)	97.815 (79.224,116.917)	107.447 (95.105,124.521)
	Min, Max	56.03, 175.52	69.53, 147.15

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	MS CONTIN 60 mg tablet (manipulated)	Egalet PR Morphine 60 mg oral (manipulated)
AUC0-24 (hr*ng/mL)	n	39	38
	Mean	159.061	140.557
	SD	43.4120	36.4473
	SEM	6.9515	5.9125
	%CV	27.3	25.9
	Median(Q1,Q3)	161.698 (123.310,187.665)	131.061 (113.205,174.547)
	Min, Max	56.62, 253.35	81.60, 244.96

Table 14.2.7.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=39)

PK Parameter	Statistic	Egalet PR Morphine 60 mg oral (intact)	Egalet PR Morphine 60 mg oral (manipulated in juice)
AUC0-24 (hr*ng/mL)	n	38	12
	Mean	135.574	131.505
	SD	40.2579	28.0070
	SEM	6.5307	8.0849
	%CV	29.7	21.3
	Median(Q1,Q3)	124.976 (106.659,161.362)	134.136 (107.534,149.775)
	Min, Max	70.49, 227.41	89.83, 175.70

Reference ID: 3983722

4.1.5 Intranasal abuse liability Study 067-EG-009

2. SYNOPSIS

Name of Company: Egalet Ltd	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Egalet PR Morphine	**Volume:**	
Name of Active Ingredient: Morphine Sulfate	**Page:**	

Title of Study: A Randomized, Double-Blind, Double-Dummy, Active and Placebo-Controlled, Crossover Study Comparing the Abuse Potential of Manipulated and Manipulated/Sieved Egalet® PR Morphine Tablets versus Manipulated MS CONTIN following Intranasal Administration in Nondependent Recreational Opioid Users

Investigator and Study Center: This study was conducted at a single site in the United States of America (USA): Lynn R. Webster, MD, PRA Health Sciences, Salt Lake City, Utah.

Publication (reference): None

Study Start Date: 19 DEC 2014 **Study Completion Date**: 25 MAR 2015	**Phase of Development:** 1

Objectives: The primary objective was to compare the relative abuse potential of manipulated and manipulated/sieved Egalet Prolonged-Release (PR) morphine vs. manipulated MS CONTIN when administered intranasally.

The secondary objectives were:

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of manipulated and manipulated/sieved Egalet PR morphine and manipulated MS CONTIN following intranasal administration.
- To assess the pharmacokinetics of manipulated and manipulated/sieved Egalet PR morphine following intranasal administration.
- To assess the safety of manipulated and manipulated/sieved Egalet PR morphine following intranasal administration.

Methodology: This was a single-center, randomized, double-blind, double-dummy, crossover study assessing the abuse potential of manipulated and manipulated/sieved Egalet PR morphine vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users. Attempts to manipulate Egalet PR morphine in order to reduce particle size result in a high volume output of large particles (> 500 microns) not amenable to snorting; therefore, all subjects received a high volume manipulated Egalet PR intranasal treatment during the first treatment period and then received the remaining 4 treatments in randomized order during the second through fifth treatment periods. The study included a Screening Visit, a Qualification Phase, a Treatment Phase (comprising 5 treatment periods, each of which included a 3-day/2-night in-clinic visit), and a Follow-Up Visit. Subjects initially satisfying the inclusion and exclusion criteria during the Screening Visit were eligible for the Qualification Phase. Within 28 days after the Screening Visit, subjects reported to the study center for the Qualification Phase. During the Qualification Phase subjects underwent a Naloxone Challenge Test to ensure that they were not physically dependent on opioids and a Drug Discrimination Test to ensure that they could differentiate between the effects of 30 mg manipulated immediate-release morphine given

Reference ID: 3983722

intranasally and placebo. Subjects who successfully completed the Screening Visit, Naloxone Challenge Test, and Drug Discrimination Test remained in the clinic and began Treatment Period 1 following a minimum 48-hour washout period. To facilitate subject schedules and clinic availability, eligible subjects may have been discharged following the Qualification Phase 24 hours following last dose administered and returned for Treatment Period 1 within 30 days. During Treatment Period 1, subjects remained in the clinic through the 24-hour assessments for Treatment Day 2. For the remaining Treatment Periods (i.e., Treatment Periods 2 through 5) subjects checked in to the clinic on Day 0, at least 12 hours prior to study drug administration on Day 1, and fasted for at least 8 hours prior to receiving their study treatments. Subjects were discharged from the inpatient facility on Treatment Day 2 following the 24-hour study assessments. Following a washout period of at least 5 days between dosing, subjects reported to the study center to complete subsequent Treatment Periods. All subjects received the manipulated Egalet PR intranasal treatment (high volume) in Treatment Period 1. For the remaining 4 periods (low volume treatments), subjects were randomized to 1 of 4 treatment sequences using a computer-generated randomization scheme based on a Williams design. During the 5 Treatment Periods, subjects received each of the 5 treatments. Approximately 3 to 7 days after their final treatment doses in Treatment Period 5, subjects reported to the inpatient facility for a Follow-Up Visit. Subjects who were prematurely discontinued from the study completed an Early Termination evaluation upon discharge.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 50 recreational opioid users from a single study site in the United States were to be randomized to the Treatment Phase to ensure at least 40 subjects completed the 5-period crossover.

Analyzed: A total of 83 subjects entered the study and underwent the Naloxone Challenge Test; 80 subjects passed the test and proceeded to the Drug Discrimination Test. Fifty subjects met Drug Discrimination Test criteria, were randomized into the Treatment Phase and received at least 1 study treatment, thereby comprising the Safety population. In total, 46 subjects completed all 5 treatment periods and were included in the Completers population.

Test Product, Dose and Mode of Administration:

Naloxone Challenge Test: An initial dose of naloxone hydrochloride (HCl) of 0.2 mg was administered by intravenous (IV) bolus followed by an additional 0.6 mg of IV naloxone if no evidence of withdrawal occurred within 30 seconds.

- Naloxone HCl Injection, USP, 0.4 mg/1 mL multidose vial (Hospira, Lake Forrest, Il): NDC # 00409-1219-01, Lot # 0-080-EV, 35-511-EV, Expiry date: 01 JUN 2015, 01 NOV 2015.

Drug Discrimination Test:

A single dose of 30 mg immediate-release morphine (pulverized with a mortar and pestle) and matching placebo with doses separated by 24 hours in a double-blind fashion.

- Treatment X: Immediate-release morphine, 30 mg, pulverized, administered intranasally (Roxane Laboratories, Columbus OH): NDC #00054-0236-25, Lot #461225A, Expiry date: 31 MAR 2016.
- Treatment Y: Placebo (Microcrystalline Cellulose Powder, FMC Biopolymer, Philadelphia PA) administered intranasally: Lot #P213825558, Expiry date: 02 APR 2017.

Treatment Phase:

One Egalet PR morphine 60 mg tablet was prepared in a standardized fashion (as detailed in the Pharmacy Manual) by a clinical pharmacist involved in the study. A two-step process was implemented to manipulate Egalet PR morphine which included: 1) a mechanical maneuver using a standard household tool; and 2) an electrical instrument to reduce its particle size. The full

output, which included all particle sizes, was identified as Treatment A, which was of high volume (Lot #SB69300301). The same process was used for Treatment B, except that the full output was then sieved through a 1000 micron filter to yield particle sizes more amenable to snorting. Treatment B, the manipulated/sieved Egalet PR morphine preparation, was a low volume treatment (Lot #SB69300301). The low-volume intranasal treatments (active drug or placebo) used in Treatments D (oral Egalet PR morphine; Lot #SB69300301) and E (placebo) matched the volume of Treatment B and Treatment C (manipulated MS CONTIN). The dose of intact oral Egalet PR morphine used was one 60 mg tablet swallowed intact. During Treatment Period 1, subjects insufflated Treatment A, an active manipulated tablet of Egalet PR morphine (high volume) plus an oral intact tablet (placebo). For the remaining 4 Treatment Periods (i.e., low volume treatments), a double-dummy design with corresponding placebo treatments relative to active drugs was used. Subjects received both an oral intact tablet (active or placebo) and an intranasal treatment (active or placebo).

Duration of Treatment: Subjects completed an initial Screening Visit to determine eligibility for the study. Eligible subjects completed a 3-day Qualification Phase and 5 Treatment Periods (each of which included a 3-day/2-night in-clinic visit) with each treatment separated by a washout period of at least 5 days. Overall study duration was approximately 11 weeks, depending on the length of time between study visits.

Reference Therapy, Dose and Mode of Administration:

Treatment Period:

- MS CONTIN, USP, 60 mg (Purdue Pharma, Stamford, CT) is an extended-release oral formulation of morphine. MS CONTIN was provided at a tablet dose of 60 mg; the dose of MS CONTIN was pulverized using a mortar and pestle and administered intranasally (NDC #9011-0262-10, Lot # WTB11, Expiry date: 31 DEC 2016).
- Matching placebo to the Egalet PR morphine or MS CONTIN treatments was provided but contained no morphine; the dose of placebo tablet was 1 tablet swallowed intact or 1 tablet ground and administered intranasally (Lot# P213825558).

Criteria for Evaluation:

Pharmacokinetic Assessments: On dosing days during each Treatment Period, blood samples were collected at predose, 15, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dose for morphine and morphine-6-glucuronide (M6G) determinations. The plasma pharmacokinetic parameters calculated included, but were not limited to, the following:

- T_{max}: The time to maximum observed plasma concentration for each subject.
- C_{max}: The maximum observed plasma concentration for each subject.
- AUC_{0-t}: Area under the plasma concentration vs. time curve from 0 to last measurable concentration.
- AUC_{0-x}: Area under the plasma concentration-time curve from 0 to x, where x was 0.25 hours ($AUC_{0-0.25h}$), 0.5 hours ($AUC_{0-0.5h}$), 1 hour (AUC_{0-1h}), 2 hours (AUC_{0-2h}), 4 hours (AUC_{0-4h}), 8 hours (AUC_{0-8h}), 12 hours (AUC_{0-12h}), and 24 hours (AUC_{0-24h}).

Pharmacodynamic Assessments:

- Drug Liking: 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose using a bipolar 0-100 point VAS.

Reference ID: 3983722

Statistical Methods:

Sample Size Determination: The proposed sample size of 40 completed subjects was expected to provide at least 90% power to detect treatment differences of ≥ 10.6 points in peak effect (E_{max}) for the bipolar Drug Liking VAS, at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming a standard deviation of differences of 20 points.

Analysis Populations:

- *Qualification Safety population* included all subjects who received at least 1 dose of any medication in the study. This population was analyzed as treated.
- *Safety population* included all subjects who received at least 1 dose of one of the 5 treatments in the Treatment Phase. This population was analyzed as treated.
- *PK population* included all randomized subjects who completed all 5 periods of the Treatment Phase and for which post-dosing PK and PD data were available from each period. This population was analyzed as treated.
- *Completers population* included all randomized subjects who completed all 5 periods of the Treatment Phase and for which post-dosing PD data were available from each period. This population was analyzed as randomized.
- *Per-Protocol (PP) population* included all subjects in the Completers population who did not have major protocol violations. This population was analyzed as randomized.
- *Modified Intent-to-Treat (MITT) population* included all randomized subjects who completed at least 2 of the 5 periods of the Treatment Phase and for which post-dosing PD data were available. This population was analyzed as randomized.

Pharmacodynamic Evaluation

The primary PD measure of interest was the Drug Liking VAS. The primary endpoint was E_{max}. PD parameters were estimated for each subject in each Treatment Period. Calculation of E_{max} used values through 24 hours post dose (observations for bipolar scale data were taken directly from the data with no adjustment). For calculations of area under the effect time curve (AUE) parameters for bipolar scales, a value of 50 was subtracted from each timepoint value prior to calculation of the AUE endpoints. For all endpoints of interest collected predose except pupillometry, the predose value was subtracted from each post-dose value prior to calculation of the PD parameters. For the Treatment Phase, each of the following ten comparisons were made:

- Manipulated Intranasal MS CONTIN vs Egalet PR morphine, 60 mg manipulated intranasal (high volume) (Treatment C vs Treatment A) – Primary Comparison
- Manipulated Intranasal MS CONTIN vs Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) (Treatment C vs Treatment B) – Primary Comparison
- Manipulated Intranasal MS CONTIN vs Placebo (Treatment C vs Treatment E) – Validity
- Manipulated Intranasal MS CONTIN vs Egalet PR morphine, 60 mg intact oral (Treatment C vs Treatment D)
- Egalet PR morphine, 60 mg manipulated intranasal (high volume) vs Placebo (Treatment A vs Treatment E)
- Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) vs Placebo (Treatment B vs Treatment E)
- Egalet PR morphine, 60 mg intact oral vs Placebo (Treatment D vs Treatment E)
- Egalet PR morphine, 60 mg manipulated intranasal (high volume) vs Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) (Treatment A vs Treatment B)

Reference ID: 3983722

- Egalet PR morphine, 60 mg manipulated intranasal (high volume) vs Egalet PR morphine, 60 mg intact oral (Treatment A vs Treatment D)
- Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) vs Egalet PR morphine, 60 mg intact oral (Treatment B vs Treatment D)

For the Treatment Phase the PD parameters were analyzed using a mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least squares (LS) means along with 95% confidence intervals (CIs) are provided for each treatment. LS mean differences along with 95% CIs are provided for the pairwise treatment comparisons defined above.

The distribution of the residuals from each parametric model were examined to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at α=0.01). If the residuals were not normally distributed, a non-parametric analysis (Wilcoxon signed-rank test) was applied for each comparison. In addition, the Hodges-Lehman estimate for the differences in two paired medians was provided and the 95% CI of the median difference.

The percent reduction calculation was provided if data for the active controls, test products, and placebo were available. A binomial test of proportions was utilized to test the null hypothesis that 50% or fewer subjects were responders.

Pharmacokinetic Evaluation

The plasma PK parameters were estimated from the concentration-time profiles for all PK population subjects. In estimating the PK parameters, below the quantifiable limit (BQL) values at the beginning of the profile were set to zero. BQL values that occurred after the first quantifiable point were considered missing. Values that were embedded between BQLs, or quantifiable values that occurred after two or more BQLs, were set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, were used in all computations involving sampling times. If the actual time or dose time was missing, the scheduled time may have been substituted in order to calculate the PK parameter.

Descriptive statistics (n, mean, geometric mean, SD, CV, median, minimum, and maximum) were used to summarize the calculated PK parameters by treatment.

Relative bioavailability of morphine and M6G was calculated using the ratio and 95% CI of geometric means for AUC_{inf}, AUC_{last}, and C_{max}. Analyses of C_{max} and AUCs used the natural log-transformed C_{max} and AUCs. The SAS mixed effect linear model procedure (PROC MIXED) was used to construct the analysis of variance (ANOVA) model for the PK population. The model included terms for sequence, period, and treatment as fixed effects and subject nested within sequences as a random effect. Least-squares (LS) geometric means for C_{max} and AUCs along with 95% CIs were provided for each treatment. The geometric mean ratios for C_{max} and AUCs along with 95% CI are provided. Ninety-five (95) percent CIs for the difference (test minus reference) in the mean between treatments were constructed for the natural log transformed values of each parameter. CIs are based on the least squares means estimation using the mean square error from the ANOVA models. The endpoints of the CIs were back transformed to obtain CIs for the test-to-reference ratio of geometric means of each parameter on the original scale. Least-squares geometric means for C_{max} and AUCs are provided for each treatment and each treatment comparison along with 95% CIs for the treatment comparisons. The comparisons will include Egalet PR morphine, 60 mg manipulated intranasal (high volume) versus MS CONTIN, 60 mg manipulated intranasal (low volume) (Treatment A to Treatment C), Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) versus MS CONTIN, 60 mg manipulated intranasal (low volume) (Treatment B to Treatment C), and Egalet PR morphine, 60 mg intact oral versus MS CONTIN, 60 mg manipulated intranasal (low volume) (Treatment D to Treatment C).

See summary of clinical pharmacology findings for conclusions. Also see tables with key PK and PD analyses below.

Table 14.2.10.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=46)

PK Parameter	Statistic	MS CONTIN 60 mg manipulated intranasal (low volume)	Egalet PR Morphine 60 mg manipulated sieved intranasal (low volume)	Egalet PR Morphine 60 mg manipulated intranasal (high volume)	Egalet PR Morphine 60 mg intact oral
AUC0-inf (hr*ng/mL)	n	32	30	43	28
	Mean	181.56	29.74	125.23	149.03
	SD	49.700	11.133	63.649	25.491
	SEM	8.786	2.033	9.706	4.817
	%CV	27.4	37.4	50.8	17.1
	Median(Q1,Q3)	177.61 (157.13,209.69)	29.15 (19.75,33.65)	137.70 (66.66,171.01)	153.40 (138.88,164.40)
	Min, Max	29.8, 286.0	13.0, 55.6	20.8, 244.2	85.6, 188.6
Abuse Quotient	n	37	46	45	39
	Mean	37.17	2.26	9.18	5.52
	SD	23.314	2.363	6.149	2.610
	SEM	3.833	0.348	0.917	0.418
	%CV	62.7	104.8	66.9	47.2
	Median(Q1,Q3)	35.85 (15.94,51.95)	1.49 (1.03,2.34)	7.26 (4.46,13.76)	5.01 (3.54,6.96)
	Min, Max	6.9, 88.9	0.2, 13.3	1.7, 26.7	1.9, 14.9
AUC0-tmax ((hr*ng/mL))	n	37	46	45	39
	Mean	25.985	6.627	25.130	33.380
	SD	13.4614	3.5326	16.9668	13.7308
	SEM	2.2130	0.5208	2.5293	2.1587
	%CV	51.8	53.3	67.5	41.1
	Median(Q1,Q3)	22.440 (15.740,32.720)	6.585 (3.690,9.090)	20.760 (13.870,31.360)	33.880 (23.050,43.690)
	Min, Max	1.37, 61.54	0.85, 16.31	5.29, 97.59	5.62, 75.04

Table 14.2.10.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=46)

PK Parameter	Statistic	MS CONTIN 60 mg manipulated intranasal (low volume)	Egalet PR Morphine 60 mg manipulated sieved intranasal (low volume)	Egalet PR Morphine 60 mg manipulated intranasal (high volume)	Egalet PR Morphine 60 mg intact oral
AUC(0-0.25) (hr*ng/mL)	n	37	46	45	39
	Mean	1.574	0.071	0.244	0.183
	SD	0.6290	0.0631	0.1418	0.0994
	SEM	0.1034	0.0093	0.0211	0.0159
	%CV	40.0	88.5	58.1	54.3
	Median(Q1,Q3)	1.460 (1.090,1.960)	0.060 (0.040,0.090)	0.230 (0.130,0.310)	0.170 (0.120,0.230)
	Min, Max	0.48, 3.07	0.00, 0.35	0.04, 0.68	0.00, 0.56
AUC(0-0.5) (hr*ng/mL)	n	37	46	45	39
	Mean	6.181	0.290	1.031	0.754
	SD	2.4179	0.2492	0.6186	0.4005
	SEM	0.3975	0.0367	0.0922	0.0641
	%CV	39.1	85.8	60.0	53.1
	Median(Q1,Q3)	5.820 (4.510,7.850)	0.255 (0.180,0.350)	0.920 (0.570,1.290)	0.690 (0.480,0.970)
	Min, Max	1.88, 12.00	0.00, 1.36	0.16, 2.94	0.07, 2.23
AUC(0-1) (hr*ng/mL)	n	37	46	45	39
	Mean	20.749	1.339	5.206	3.472
	SD	7.7566	0.9811	3.3693	1.6622
	SEM	1.2752	0.1447	0.5023	0.2662
	%CV	37.4	73.3	64.7	47.9
	Median(Q1,Q3)	22.070 (15.360,26.830)	1.040 (0.750,1.780)	4.270 (2.680,7.550)	3.450 (2.080,4.550)
	Min, Max	4.66, 36.24	0.00, 4.52	0.93, 13.47	0.86, 8.26

Reference ID: 3983722

Table 14.2.10.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=46)

PK Parameter	Statistic	MS CONTIN 60 mg manipulated intranasal (low volume)	Egalet PR Morphine 60 mg manipulated sieved intranasal (low volume)	Egalet PR Morphine 60 mg manipulated intranasal (high volume)	Egalet PR Morphine 60 mg intact oral
AUC(0-2) (hr*ng/mL)	n	37	46	45	39
	Mean	49.149	4.753	20.026	13.872
	SD	16.3470	2.9829	11.7978	4.7534
	SEM	2.6874	0.4398	1.7587	0.7612
	%CV	33.3	62.8	58.9	34.3
	Median(Q1,Q3)	47.530 (39.270,59.280)	3.875 (2.780,5.930)	16.350 (10.910,29.150)	13.560 (10.460,17.800)
	Min, Max	10.27, 80.73	0.48, 14.59	4.58, 46.44	4.91, 27.10
AUC(0-4) (hr*ng/mL)	n	37	46	45	39
	Mean	88.581	11.655	50.534	41.155
	SD	23.7592	5.3827	26.5739	11.7311
	SEM	3.9060	0.7936	3.9614	1.8785
	%CV	26.8	46.2	52.6	28.5
	Median(Q1,Q3)	89.570 (76.050,102.350)	11.270 (7.370,15.170)	45.320 (29.440,69.450)	42.320 (29.720,48.220)
	Min, Max	10.57, 150.96	2.71, 28.36	11.59, 100.98	18.40, 65.33
AUC(0-8) (hr*ng/mL)	n	37	46	45	39
	Mean	124.863	19.862	82.962	82.170
	SD	31.0206	7.7580	42.4829	19.8978
	SEM	5.0998	1.1439	6.3330	3.1862
	%CV	24.8	39.1	51.2	24.2
	Median(Q1,Q3)	126.070 (106.180,146.120)	19.940 (13.580,25.530)	84.670 (45.120,118.640)	86.980 (61.870,96.750)
	Min, Max	26.00, 202.02	5.08, 39.09	17.90, 170.73	41.79, 125.56

Table 14.2.10.2.1
Summary of Plasma Morphine Pharmacokinetic Parameters by Treatment
Population: PK (N=46)

PK Parameter	Statistic	MS CONTIN 60 mg manipulated intranasal (low volume)	Egalet PR Morphine 60 mg manipulated sieved intranasal (low volume)	Egalet PR Morphine 60 mg manipulated intranasal (high volume)	Egalet PR Morphine 60 mg intact oral
AUC(0-12) (hr*ng/mL)	n	37	44	45	39
	Mean	139.747	24.196	96.423	97.595
	SD	34.3998	9.2717	49.3258	22.9206
	SEM	5.6553	1.3978	7.3530	3.6702
	%CV	24.6	38.3	51.2	23.5
	Median(Q1,Q3)	136.970 (123.350,159.410)	24.335 (17.305,30.250)	95.770 (54.180,134.860)	102.040 (77.530,113.490)
	Min, Max	20.51, 214.77	5.49, 43.11	19.89, 192.89	49.75, 146.56
AUC(0-24) (hr*ng/mL)	n	37	43	45	39
	Mean	165.437	27.296	113.375	124.594
	SD	41.6579	11.6608	58.7699	26.6538
	SEM	6.8485	1.7783	8.7609	4.2680
	%CV	25.2	42.7	51.8	21.4
	Median(Q1,Q3)	163.540 (148.000,186.280)	27.260 (18.370,33.650)	102.380 (63.090,157.980)	127.460 (102.460,141.030)
	Min, Max	29.72, 245.87	5.63, 50.60	20.78, 232.44	67.76, 187.75

Table 14.2.10.3.1
Relative Bioavailability Analyses for Plasma Morphine
Population: PK (N=46)

Parameter	Effect Comparison	F-value	P-value	Estimate	90% CI
Cmax (ng/mL)	Sequence	0.17	0.9164		
	Treatment	238.0	<.0001		
	Least Square Geometric Means (Back-transformed)				
	Manip. Intranasal high vol. Egalet PR (A)			16.48	(14.58, 18.62)
	Manip./Sieved Intranasal low vol. Egalet PR (B)			3.93	(3.48, 4.43)
	Manip. Intranasal low vol. MS CONTIN (C)			33.47	(29.34, 38.18)
	Egalet PR morphine, 60 mg intact oral (D)			16.30	(14.33, 18.55)
	Ratio of Comparisons				
	Manip. Intranasal high vol. Egalet PR vs Manip. Intranasal low vol. MS CONTIN (A vs C)			0.4922	(0.4279, 0.5662)
	Manip./Sieved Intranasal low vol. Egalet PR vs Manip. Intranasal low vol. MS CONTIN (B vs C)			0.1173	(0.1020, 0.1349)
	Intact Oral Egalet PR vs Manip. Intranasal low vol. MS CONTIN (D vs C)			0.4871	(0.4218, 0.5624)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
Emax	Manip. Intranasal high vol. Egalet PR (A)	62.00			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	52.50			
	Manip. Intranasal low vol. MS CONTIN (C)	77.50			
	Egalet PR morphine, 60 mg intact oral (D)	68.00			
	Placebo (E)	51.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	12.00	(8.00, 15.50)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	18.50	(14.00, 22.00)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	23.50	(19.50, 27.50)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		0.0001	9.00	(4.50, 13.50)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		<.0001	11.00	(5.00, 16.50)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.0787	3.00	(0.00, 7.50)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		<.0001	13.00	(7.50, 18.50)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0008	5.00	(2.00, 8.50)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.1798	-2.50	(-6.50, 1.00)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		<.0001	-9.00	(-13.00, -4.50)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-0.25	Manip. Intranasal high vol. Egalet PR (A)	0.00			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	0.00			
	Manip. Intranasal low vol. MS CONTIN (C)	0.76			
	Egalet PR morphine, 60 mg intact oral (D)	0.00			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	0.71	(0.39, 1.12)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	0.79	(0.43, 1.23)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	0.81	(0.46, 1.30)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	0.82	(0.47, 1.17)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.3731	0.00	(0.00, 0.13)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.3569	0.00	(0.00, 0.12)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.5075	0.00	(-0.07, 0.00)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.8346	0.00	(-0.06, 0.06)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.2514	0.00	(0.00, 0.12)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.2906	0.00	(0.00, 0.13)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-0.5	Manip. Intranasal high vol. Egalet PR (A)	0.00			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	0.01			
	Manip. Intranasal low vol. MS CONTIN (C)	2.73			
	Egalet PR morphine, 60 mg intact oral (D)	0.00			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	2.95	(1.73, 4.15)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	2.88	(1.88, 3.82)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	3.49	(2.22, 4.64)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	3.05	(1.95, 4.06)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.1395	0.19	(0.00, 0.88)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1233	0.18	(-0.01, 1.11)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.4355	0.01	(0.00, 0.26)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.7866	0.00	(-0.32, 0.25)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.3806	0.13	(-0.19, 0.63)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.5579	0.11	(-0.25, 0.53)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-0.75	Manip. Intranasal high vol. Egalet PR (A)	0.50			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	0.31			
	Manip. Intranasal low vol. MS CONTIN (C)	6.54			
	Egalet PR morphine, 60 mg intact oral (D)	0.25			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	6.02	(4.06, 8.43)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	5.94	(4.18, 7.69)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	7.55	(5.31, 9.47)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	6.38	(4.33, 8.27)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.1376	0.43	(0.00, 2.38)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1544	0.44	(-0.14, 2.46)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.2775	0.29	(-0.31, 1.36)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.7002	0.00	(-0.82, 0.40)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.5042	0.21	(-0.61, 1.38)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.5279	0.25	(-0.54, 1.39)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-1	Manip. Intranasal high vol. Egalet PR (A)	0.51			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	0.51			
	Manip. Intranasal low vol. MS CONTIN (C)	12.39			
	Egalet PR morphine, 60 mg intact oral (D)	0.57			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	9.84	(7.30, 12.77)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	10.05	(7.43, 12.61)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	12.12	(9.18, 14.92)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	9.80	(7.48, 12.63)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.1394	0.69	(-0.17, 3.63)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.2067	0.56	(-0.43, 3.59)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.1352	0.76	(-0.10, 3.16)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.9059	0.00	(-1.38, 1.02)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.7917	0.13	(-1.72, 1.36)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.8431	0.12	(-1.76, 1.90)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-1.5	Manip. Intranasal high vol. Egalet PR (A)	3.26			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	1.00			
	Manip. Intranasal low vol. MS CONTIN (C)	24.17			
	Egalet PR morphine, 60 mg intact oral (D)	4.23			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	17.62	(13.88, 21.77)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	18.37	(14.22, 22.48)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	21.66	(17.49, 26.36)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	16.96	(12.38, 20.65)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0530	2.86	(0.00, 7.09)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1857	1.31	(-0.82, 5.70)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0101	3.38	(0.55, 8.78)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.5576	0.55	(-1.22, 3.06)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.4193	-1.37	(-5.04, 1.84)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.2906	-1.51	(-5.70, 1.48)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-2	Manip. Intranasal high vol. Egalet PR (A)	7.63			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	1.37			
	Manip. Intranasal low vol. MS CONTIN (C)	35.29			
	Egalet PR morphine, 60 mg intact oral (D)	10.72			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	23.69	(18.31, 29.36)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	26.85	(20.73, 31.81)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	31.26	(25.50, 37.81)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	22.18	(16.50, 27.73)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0078	7.09	(1.53, 12.65)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1746	1.69	(-0.50, 9.22)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0015	6.95	(2.40, 15.62)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.2769	1.70	(-1.07, 5.88)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.2517	-3.09	(-8.18, 1.74)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0663	-4.78	(-10.55, 0.26)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-3	Manip. Intranasal high vol. Egalet PR (A)	15.51			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	2.45			
	Manip. Intranasal low vol. MS CONTIN (C)	54.60			
	Egalet PR morphine, 60 mg intact oral (D)	20.85			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	32.90	(23.23, 41.81)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	41.37	(31.49, 49.98)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	50.19	(41.08, 58.96)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	29.92	(21.18, 39.32)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0017	16.08	(5.12, 26.34)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1236	3.47	(-0.68, 14.60)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0001	17.49	(7.50, 29.02)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0308	6.22	(0.31, 12.57)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.2759	-4.96	(-14.45, 3.67)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0093	-10.82	(-18.63, -2.13)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-4	Manip. Intranasal high vol. Egalet PR (A)	19.77			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	3.43			
	Manip. Intranasal low vol. MS CONTIN (C)	71.91			
	Egalet PR morphine, 60 mg intact oral (D)	24.80			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	39.53	(26.14, 52.86)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	53.44	(39.28, 66.27)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	64.62	(52.36, 76.38)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	35.93	(21.32, 48.36)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0015	23.59	(7.75, 37.29)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.1228	4.10	(-0.60, 19.35)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		<.0001	26.92	(12.52, 40.26)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0080	10.21	(2.52, 18.48)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.2759	-5.95	(-18.63, 5.58)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0017	-16.28	(-27.47, -5.78)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-5	Manip. Intranasal high vol. Egalet PR (A)	15.96			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	3.19			
	Manip. Intranasal low vol. MS CONTIN (C)	80.77			
	Egalet PR morphine, 60 mg intact oral (D)	32.86			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	43.92	(28.66, 60.86)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	63.88	(45.33, 79.54)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	75.35	(59.13, 89.82)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	38.36	(19.42, 54.40)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0011	28.85	(7.75, 44.79)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.2301	3.30	(-1.65, 21.96)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		<.0001	31.95	(16.12, 49.88)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0034	12.35	(3.94, 25.40)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.4258	-6.70	(-23.51, 6.95)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0003	-23.22	(-36.28, -10.45)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-6	Manip. Intranasal high vol. Egalet PR (A)	20.58			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	2.93			
	Manip. Intranasal low vol. MS CONTIN (C)	85.99			
	Egalet PR morphine, 60 mg intact oral (D)	45.66			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	46.08	(29.02, 64.10)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	70.86	(49.97, 89.75)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	81.99	(62.90, 99.46)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		0.0001	39.78	(18.04, 58.76)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0014	33.36	(10.16, 52.07)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.3438	2.27	(-2.84, 14.31)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		<.0001	36.45	(16.73, 57.28)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0006	17.08	(5.75, 34.34)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.5594	-7.45	(-26.46, 10.68)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0001	-30.32	(-44.96, -16.00)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-8	Manip. Intranasal high vol. Egalet PR (A)	19.91			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	2.94			
	Manip. Intranasal low vol. MS CONTIN (C)	87.39			
	Egalet PR morphine, 60 mg intact oral (D)	51.18			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		<.0001	45.89	(26.00, 67.80)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	77.76	(54.41, 103.07)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	88.27	(66.23, 112.15)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		0.0015	40.44	(13.68, 62.24)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0010	39.35	(13.96, 61.46)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.5196	1.51	(-6.35, 15.81)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0009	42.88	(16.52, 69.90)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0001	29.45	(11.37, 45.29)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.5444	-6.42	(-29.15, 14.89)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0001	-40.82	(-59.51, -20.14)

Reference ID: 3983722

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-12	Manip. Intranasal high vol. Egalet PR (A)	19.77			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	1.87			
	Manip. Intranasal low vol. MS CONTIN (C)	94.44			
	Egalet PR morphine, 60 mg intact oral (D)	57.17			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		0.0071	39.08	(12.32, 68.63)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		<.0001	78.94	(50.73, 110.03)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		<.0001	92.94	(63.31, 125.20)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		0.0105	40.31	(10.09, 66.82)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0007	43.10	(17.42, 74.75)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.4630	2.92	(-6.43, 18.79)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0099	45.87	(12.13, 83.54)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0001	36.11	(12.30, 58.26)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.9425	1.20	(-26.46, 28.69)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0075	-35.32	(-63.98, -7.62)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
AUE0-24	Manip. Intranasal high vol. Egalet PR (A)	19.77			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	3.49			
	Manip. Intranasal low vol. MS CONTIN (C)	100.43			
	Egalet PR morphine, 60 mg intact oral (D)	44.50			
	Placebo (E)	0.00			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		0.1730	32.30	(-16.46, 66.75)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		0.0004	77.18	(42.60, 114.04)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		0.0001	94.96	(55.62, 131.91)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		0.0391	43.45	(1.22, 83.05)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		0.0009	42.93	(19.17, 76.71)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.2906	5.93	(-4.99, 24.75)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		0.0554	43.23	(0.44, 89.77)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0001	37.07	(16.13, 60.53)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.4065	11.55	(-19.52, 63.88)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.1589	-23.99	(-62.04, 14.74)

Table 14.2.1.3
Statistical Analysis of PD Parameters for Drug Liking VAS
Population: Completers (N=46)

Parameter	Treatment Comparison	Median	Signed Rank P-value	Hodges-Lehmann Estimate	Hodges-Lehmann 95% CI
TEmax	Manip. Intranasal high vol. Egalet PR (A)	1.75			
	Manip./Sieved Intranasal low vol. Egalet PR (B)	1.01			
	Manip. Intranasal low vol. MS CONTIN (C)	1.01			
	Egalet PR morphine, 60 mg intact oral (D)	2.00			
	Placebo (E)	0.63			
	Differences in Medians				
	Manip. Intranasal low vol. MS CONTIN vs Manip. Intranasal high vol. Egalet (C v A)		0.0385	-0.66	(-1.38, -0.02)
	Manip. Intranasal low vol. MS CONTIN vs Manip./Sieved Intranasal low vol. Egalet PR (C v B)		0.7219	-0.11	(-0.52, 0.38)
	Manip. Intranasal low vol. MS CONTIN vs Placebo (C v E)		0.0053	0.49	(0.13, 0.88)
	Manip. Intranasal low vol. MS CONTIN vs Egalet PR morphine, 60 mg intact oral (C v D)		<.0001	-1.00	(-1.50, -0.50)
	Manip. Intranasal high vol. Egalet PR vs Placebo (A v E)		<.0001	1.25	(0.62, 2.01)
	Manip./Sieved Intranasal low vol. Egalet PR vs Placebo (B v E)		0.0538	0.50	(-0.01, 1.12)
	Egalet PR morphine, 60 mg intact oral vs Placebo (D v E)		<.0001	1.50	(0.88, 2.12)
	Manip. Intranasal high vol. Egalet PR vs Manip./Sieved Intranasal low vol. Egalet PR (A v B)		0.0639	0.74	(-0.00, 1.49)
	Manip. Intranasal high vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (A v D)		0.5007	-0.25	(-1.00, 0.51)
	Manip./Sieved Intranasal low vol. Egalet PR vs Egalet PR morphine, 60 mg intact oral (B v D)		0.0251	-0.75	(-1.63, -0.01)

Reference ID: 3983722

4.1.6 Bioanalytical method validation across different PK studies.

Table 6: Plasma Bioanalytical Method Validation Summary (87126TEA)

Parameter	Morphine	M3G	M6G
Standard Concentrations (ng/mL)[1]	0.25, 0.50, 2.50, 5.00, 10.0, 20.0, 40.0, 50.0	5.00, 10.00, 50.0, 100, 200, 400, 800, 1,000	1.00, 2.00, 10.0, 20.0, 40.0, 80.0, 160, 200
Linear Range (ng/mL)	0.250 to 50.0	5.00 to 1,000	1.00 to 200
Correlation Coefficient (r^2)	0.9919	0.9954	0.9927
Recovery (%)	0.75 ng/mL: 101.2% 17.50 ng/mL: 96.7% 37.5 ng/mL: 94.3%	15.00 ng/mL: 93.7% 350.00 ng/mL: 91.5% 750.00 ng/mL: 93.7%	3.00 ng/mL: 96.8% 70.0 ng/mL: 91.5% 150 ng/mL: 92.2%
LLOQ (ng/mL)	0.25	5.00	1.00
Intra-Assay Precision (%CV) at LLOQ	8.84	6.66	13.9
Intra-Assay Accuracy (% difference from theoretical) at LLOQ	-3.33	-2.10	5.50
Inter-Assay Precision (%CV) at LLOQ	9.92	5.46	13.3
Inter-Assay Accuracy (% bias) at LLOQ	3.20	-0.22	6.08
QC Concentrations (ng/mL)	QC1: 0.75 ng/mL QC2: 17.5 ng/mL QC3: 37.5 ng/mL ULQC: 50.0 ng/mL	QC1: 15.0 ng/mL QC2: 350.0 ng/mL QC3: 750 ng/mL ULQC: 1,000 ng/mL	QC1: 3.00 ng/mL QC2: 70.0 ng/mL QC3: 150 ng/mL ULQC: 200 ng/mL
Intra-Assay Precision (% CV) of Quality Control Samples	QC1: 7.34 QC2: 2.38 QC3: 2.46 ULQC: 3.18	QC1: 6.51 QC2: 5.35 QC 3: 3.83 ULQC: 5.07	QC1: 3.09 QC2: 2.66 QC3: 3.96 ULQC: 2.08
Intra-Assay Accuracy (% difference from theoretical) of Quality Control Samples	QC1: -6.67 QC2: -0.82 QC3: 0.18 ULQC: -1.06	QC1: -5.76 QC2:-4.25 QC 3: -4.69 ULQC: -6.00	QC1: 2.22 QC2: 0.11 QC3: -0.93 ULQC: -0.41
Inter-Assay Precision (% CV) of Quality Control Samples	QC1: 9.40 QC2: 5.14 QC3: 3.09	QC1: 5.05 QC2: 4.58 QC 3: 4.77	QC1: 6.67 QC2: 3.78 QC3: 4.34
Inter-Assay Accuracy (% difference from theoretical) of Quality Control Samples	QC1: -2.63 QC2: 1.29 QC3: 1.85	QC1: -0.58 QC2: -1.43 QC3: -1.97	QC1: -0.23 QC2: 0.78 QC3: -0.25

Reference ID: 3983722

Parameter	Morphine	M3G	M6G
Stability			
Short-Term Stability of Analytes in Matrix	23 h (QC1 and QC3) at Room Temperature	23 h (QC1 and QC3) at Room Temperature	23 h (QC1 and QC3) at Room Temperature
Short-Term Stability of Analytes in Solution (50/50 Water:Methanol)	24 h 18 min (QC 1) at Room Temperature	24 h 18 min (QC 1) at Room Temperature	24 h 18 min (QC 1) at Room Temperature
Freeze/Thaw Stability	4 cycles (QC1 and QC3) at -20°C and -80°C	4 cycles (QC1 and QC3) at -20°C and -80°C	4 cycles (QC1 and QC3) at -20°C and -80°C
Freeze/Thaw Stability in Fortified Matrix (Naltrexone, Naltrexone-3-glucuronide, 6-β-Naltrexol, 6-β-Naltrexol-3-Glucuronide)	4 cycles (QC1 and QC3) at -20°C and -80°C	4 cycles (QC1 and QC3) at -20°C and -80°C	4 cycles (QC1 and QC3) at -20°C and -80°C
Long-Term Stability of Analytes in matrix	9, 108, and 945 days (QC1 and QC3) at -20°C and -80°C	9, 108, and 945 days (QC1 and QC3) at -20°C and -80°C	9 and 108 days (QC1 and QC3) at -20°C and 945 days at -80°C
Long-Term Stability in Fortified Matrix (Naltrexone, Naltrexone-3-glucuronide, 6-β-Naltrexol, 6-β-Naltrexol-3-Glucuronide)	65 and 132 days (QC1 and QC3) at -20°C and -80°C	65 and 132 days (QC1 and QC3) at -20°C and -80°C	65 days (QC1 and QC3) at -20°C and -80°C
Dilution Integrity	Up to 200 ng/mL	Up to 4,000 ng/mL	Up to 800 ng/mL
Hemolysis Evaluation	No effect from hemolysis on quantitation of morphine	No effect from hemolysis on quantitation of M3G	No effect from hemolysis on quantitation of M6G
Lipemia Evaluation	No effect from lipemia on quantitation of morphine	No effect from lipemia on quantitation of M3G	No effect from lipemia on quantitation of M6G
Matrix Factor Evaluation (%CV ≤15%)	Met acceptance criteria	Met acceptance criteria	Met acceptance criteria

CV=coefficient of variation; LLOQ = lower limit of quantitation; M3G = morphine-3β-glucuronide; M6G = morphine-6β-glucuronide; QC = quality control; ULQC = upper limit of quantitation

[1] Partial validations were also conducted on modified calibration ranges.

Table 7: Plasma Bioanalytical Method Validation Summary (LCMS454)

Parameter	Morphine	M3G	M6G
Standard Concentrations (ng/mL)	0.500, 0.750, 1.25, 3.00, 7.50, 20.0, 40.0, 50.0	10.0, 15.0, 25.0, 60.0, 150, 400, 800, 1,000	2.00, 3.00, 5.00, 12.0, 30.0, 80.0, 160, 200
Linear Range (ng/mL)	0.500 to 50.0	10.0 to 1,000	2.00 to 200
Correlation Coefficient (r)	0.9993	0.9996	0.9994
Recovery (%)	1.00 ng/mL: 85.8% 5.00 ng/mL: 92.0% 37.5 ng/mL: 93.0%[1]	20.0 ng/mL: 49.5% 100 ng/mL: 53.2% 750 ng/mL: 53.6%	4.00 ng/mL: 68.3% 20.0 ng/mL: 74.7% 150 ng/mL: 74.7%[1]
LLOQ (ng/mL)	0.500	10.0	2.00
Intra-Assay Precision (%CV) at LLOQ	1.33 to 6.24	1.35 to 4.42	2.63 to 3.45
Intra-Assay Accuracy (% difference from theoretical) at LLOQ	-4.55 to 3.93	-0.21 to 7.40	-1.70 to 2.63
Inter-Assay Precision (%CV) at LLOQ	5.25	4.17	4.11
Inter-Assay Accuracy (% difference from theoretical) at LLOQ	0.58	2.17	1.04
QC Concentrations (ng/mL)	1.00, 2.00, 5.00, 12.5, 37.5	20.0, 40.0, 100, 250, 750	4.00, 8.00, 20.0, 50.0, 150
Intra-Assay Precision (% CV) of Quality Control Samples	1.00 ng/mL: 3.41 to 4.71 2.00 ng/mL: 2.37 to 4.22 5.00 ng/mL: 1.48 to 2.11 12.5 ng/mL: 0.847 to 1.91 37.5 ng/mL: 1.16 to 2.39	20.0 ng/mL: 1.01 to 3.41 40.0 ng/mL: 2.39 to 3.97 100 ng/mL: 1.91 to 3.63 250 ng/mL: 1.50 to 2.39 750 ng/mL: 1.34 to 2.80	4.00 ng/mL: 0.997 to 4.26 8.00 ng/mL: 2.06 to 2.44 20.0 ng/mL: 2.13 to 3.42 50.0 ng/mL: 2.44 to 2.58 150 ng/mL: 1.66 to 2.44

Reference ID: 3983722

Parameter	Morphine	M3G	M6G
Intra-Assay Accuracy (% difference from theoretical) of Quality Control Samples	1.00 ng/mL: -1.72 to 8.55 2.00 ng/mL: -0.568 to 3.12 5.00 ng/mL: -2.77 to 2.40 12.5 ng/mL: -1.19 to 2.54 37.5 ng/mL: -0.221 to 0.907	20.0 ng/mL: -1.89 to 2.91 40.0 ng/mL: -0.112 to 2.84 100 ng/mL: 0.272 to 2.46 250 ng/mL: -0.948 to 3.61 750 ng/mL: -0.190 to 1.73	4.00 ng/mL: 0.156 to 3.55 8.00 ng/mL: 0.297 to 1.09 20.0 ng/mL: 0.658 to 2.74 50.0 ng/mL: 1.46 to 3.22 150 ng/mL: 2.61 to 5.39
Inter-Assay Precision (% CV) of Quality Control Samples	1.00 ng/mL: 5.83 2.00 ng/mL: 3.51 5.00 ng/mL: 2.76 12.5 ng/mL: 2.47 37.5 ng/mL: 2.00	20.0 ng/mL: 2.78 40.0 ng/mL: 2.79 100 ng/mL: 2.85 250 ng/mL: 2.62 750 ng/mL: 2.63	4.00 ng/mL: 3.19 8.00 ng/mL: 3.41 20.0 ng/mL: 2.75 50.0 ng/mL: 2.32 150 ng/mL: 3.16
Inter-Assay Accuracy (% difference from theoretical) of Quality Control Samples	1.00 ng/mL: 1.61 2.00 ng/mL: 1.62 5.00 ng/mL: 0.334 12.5 ng/mL: 0.899 37.5 ng/mL: 0.442	20.0 ng/mL: 0.889 40.0 ng/mL: 1.07 100 ng/mL: 0.799 250 ng/mL: 1.62 750 ng/mL: 1.17	4.00 ng/mL: 2.15 8.00 ng/mL: 1.64 20.0 ng/mL: 2.49 50.0 ng/mL: 2.36 150 ng/mL: 4.58
Stability			
Short-Term Stability in Thawed Matrix	24 h (1.00 and 37.5 ng/mL) at Room Temperature	24 h (20.0 and 750 ng/mL) at Room Temperature	24 h (4.00 and 150 ng/mL) at Room Temperature
Freeze/Thaw Stability	3 cycles (1.00 and 37.5 ng/mL) from -20°C	5 cycles (20.0 and 750 ng/mL) from -20°C	5 cycles (4.00 and 150 ng/mL) from -20°C
Freeze/Thaw Stability in the Presence of Naltrexone	5 cycles (1.00 and 37.5 ng/mL) from -20°C and -70°C	5 cycles (20.0 and 750 ng/mL) from -20°C and -70°C	5 cycles (4.00 and 150 ng/mL) from -20°C and -70°C
Extract Stability	137 h (0.500[1], 1.00, 2.00, 5.00, 12.5, and 37.5 ng/mL) at 2-8°C	137 h (10.0, 20.0, 40.0, 100, 250, and 750 ng/mL) at 2-8°C	137 h (2.00, 4.00, 8.00, 20.0, 50.0, and 150 ng/mL) at 2-8°C
Long-Term Stability in Frozen Matrix	63, 331, and 556 days (1.00 and 37.5 ng/mL) at -20°C	63, 239, 244, 331, and 556 days (20.0 and 750 ng/mL) at -20°C	63, 239, 244, 331, and 556 days (4.00 and 150 ng/mL) at -20°C
Stability in Frozen Lithium Heparin Human Plasma	148 and 187 days (1.00 and 37.5 ng/mL) at -20°C and -70° C	148 days (20.0 and 750 ng/mL) at -20°C and -70°C	148 and 187 days (4.00 and 150 ng/mL) at -20°C and -70°C

Reference ID: 3983722

Parameter	Morphine	M3G	M6G
Stability in Frozen Sodium Heparin Human Plasma	1,970 days (1.00 and 37.5 ng/mL) at -20°C	1,970 days (20 and 750 ng/mL) at -20°C	1,970 days (4.00 and 150 ng/mL) at -20°C
Stability in Frozen Matrix in the Presence of Naltrexone	15 and 79 days at -20°C and 15 days at -70°C (1.00 and 37.5 ng/mL)	15 and 79 days at -20°C and 15 days at -70°C (20.0 and 750 ng/mL)	15 and 79 days at -20°C and 15 days at -70°C (4.00 and 150 ng/mL)
Hemolysis Evaluation	No effect from hemolysis on quantitation of morphine	No effect from hemolysis on quantitation of M3G	No effect from hemolysis on quantitation of M6G
Lipemia Evaluation	No effect from lipemia on quantitation of morphine	No effect from lipemia on quantitation of M3G	No effect from lipemia on quantitation of M6G
Matrix Factor Evaluation (IS-Normalized CV ≤15%)	Matrix effects were consistent across the lots tested	Matrix effects were consistent across the lots tested	Matrix effects were consistent across the lots tested

CV=coefficient of variation; IS = internal standard; LLOQ = lower limit of quantitation; M3G = morphine-3β-glucuronide; M6G = morphine-6β-glucuronide; QC = quality control

[1] Outlier value deleted as determined by the Dixon (rank) test.

Table 8: Plasma Bioanalytical Method Validation Summary (AHUB2)

Parameter	Morphine	M3G	M6G
Standard Concentrations (ng/mL)	0.100, 0.175, 0.300, 1.00, 2.50, 7.50, 20.0, 25.0	2.00, 3.50, 6.00, 20.0, 50.0, 150, 400, 500	0.500, 0.875, 1.50, 5.00, 12.5, 37.5, 100, 125
Correlation Coefficient (r)	0.9971	0.9988	0.9983
Average Recovery (%)	66.8%	18.2%	34.3%
LLOQ (ng/mL)	0.100	2.00	0.500
QC Concentrations (ng/mL)	0.100, 0.250[1], 0.500, 1.50, 5.00, and 19.0[1]	2.00, 5.00[1], 10.0, 30.0, 100, and 380[1]	0.500, 1.25[1], 2.50, 7.50, 25.0, and 95.0[1] ng/mL
Intra-Assay Precision (% CV) of Quality Control Samples	0.100 ng/mL: 4.95 to 10.4 0.250 ng/mL: 1.55 to 6.16[2] 0.500 ng/mL: 3.72 to 9.24 1.50 ng/mL: 2.83 to 7.25 5.00 ng/mL: 2.79 to 6.51 19.0 ng/mL: 1.44 to 5.42	2.00 ng/mL: 3.52 to 10.6 5.00 ng/mL: 0.596 to 13.6 10.0 ng/mL: 1.90 to 3.13 30.0 ng/mL: 1.40 to 3.21 100 ng/mL: 1.48 to 3.10 380 ng/mL: 1.11 to 4.93	0.500 ng/mL: 4.05 to 9.69 1.25 ng/mL: 2.75 to 13.3 2.50 ng/mL: 1.56 to 4.01 7.50 ng/mL: 1.77 to 2.53 25.0 ng/mL: 1.33 to 2.98 95.0 ng/mL: 0.968 to 2.31
Intra-Assay Precision (% CV) of Quality Control Samples Fortified with Naltrexone	0.250 ng/mL: 2.33 to 10.4 19.0 ng/mL: 2.16 to 4.57	5.00 ng/mL: 1.45 to 8.17 380 ng/mL: 1.86 to 3.31	1.25 ng/mL: 2.49 to 5.95 95.0 ng/mL: 1.77 to 2.59
Intra-Assay Accuracy (% difference from theoretical) of Quality Control Samples	0.100 ng/mL: -7.50 to 6.98 0.250 ng/mL: -2.02 to 2.77[2] 0.500 ng/mL-3.36 to 1.30 1.50 ng/mL: -6.35 to 0.763 5.00 ng/mL: -2.59 to 3.06 19.0 ng/mL: 4.86 to 11.6	2.00 ng/mL: -9.28 to 6.37 5.00 ng/mL: -2.36 to 8.04 10.0 ng/mL: 1.57 to 5.00 30.0 ng/mL: 2.30 to 5.32 100 ng/mL: 3.49 to 7.44 380 ng/mL: -7.70 to 2.53	0.500 ng/mL: -4.27 to 4.88 1.25 ng/mL: -3.18 to 6.05 2.50 ng/mL: 0.892 to 4.19 7.50 ng/mL: 1.67 to 5.34 25.0 ng/mL: -1.59 to 3.93 95.0 ng/mL: -10.1 to -0.915

Reference ID: 3983722

Parameter	Morphine	M3G	M6G
Intra-Assay Accuracy (% difference from theoretical) of Quality Control Samples Fortified with Naltrexone	0.250 ng/mL: -5.92 to 5.29 19.0 ng/mL: 3.55 to 8.98	5.00 ng/mL: -1.07 to 8.71 380 ng/mL: -6.87 to 1.71	1.25 ng/mL: -0.948 to 5.73 95.0 ng/mL: -9.53 to -0.546
Inter-Assay Precision (%CV) of Quality Control Samples	0.100 ng/mL: 8.65 0.250 ng/mL: 9.19 0.500 ng/mL: 6.27 1.50 ng/mL: 5.28 5.00 ng/mL: 5.37 19.0 ng/mL: 4.27	2.00 ng/mL: 8.95 5.00 ng/mL: 7.42 10.0 ng/mL: 2.66 30.0 ng/mL: 2.42 100 ng/mL: 2.76 380 ng/mL: 4.78	0.500 ng/mL: 7.25 1.25 ng/mL: 7.27 2.50 ng/mL: 2.96 7.50 ng/mL: 2.63 25.0 ng/mL: 3.05 95.0 ng/mL: 4.21
Inter-Assay Precision (% CV) of Quality Control Samples Fortified with Naltrexone	0.250 ng/mL: 7.70 19.0 ng/mL: 3.85	5.00 ng/mL: 6.20 380 ng/mL: 4.35	1.25 ng/mL: 4.87 95.0 ng/mL: 4.37
Inter-Assay Accuracy (% difference from theoretical) of Quality Control Samples	0.100 ng/mL: 1.70 0.250 ng/mL: -1.11 0.500 ng/mL: -1.12 1.50 ng/mL: -2.53 5.00 ng/mL: -0.104 19.0 ng/mL: 7.77	2.00 ng/mL: 1.15 5.00 ng/mL: 2.44 10.0 ng/mL: 3.85 30.0 ng/mL: 4.14 100 ng/mL: 4.67 380 ng/mL: -1.19	0.500 ng/mL: 1.49 1.25 ng/mL: 1.07 2.50 ng/mL: 2.79 7.50 ng/mL: 3.25 25.0 ng/mL: 1.83 95.0 ng/mL: -4.77
Inter-Assay Accuracy (% difference from theoretical) of Quality Control Samples Fortified with Naltrexone	0.250 ng/mL: -0.860 19.0 ng/mL: 6.70	5.00 ng/mL: 3.28 380 ng/mL: -0.779	1.25 ng/mL: 1.97 95.0 ng/mL: -4.58
Stability			
Short-Term Stability in Thawed Matrix	25 h (0.25 and 19 ng/mL)[1] at Room Temperature	25 h (5.00 and 380 ng/mL)[1] at Room Temperature	25 h (1.25 and 95.0 ng/mL)[1] at Room Temperature
Freeze/Thaw Stability	5 cycles (0.25 and 19 ng/mL)[1] from -20°C and -70°C	5 cycles (5.00 and 380 ng/mL)[1] from -20°C and -70°C	5 cycles (1.25 and 95.0 ng/mL)[1] from -20°C and -70°C
Extract Stability	136.75 h (0.25 and 19 ng/mL)[1, 2] at 2 to 8°C	136.75 h (5.00 and 380 ng/mL)[1, 2] at 2 to 8°C	136.75 h (1.25 and 95.0 ng/mL)[1, 2] at 2 to 8°C
Long-Term Stability in Frozen Matrix	7 days (0.25 and 19 ng/mL)[1] at -20°C and -70°C	7 days (5.00 and 380 ng/mL)[1] at -20°C and -70°C	7 days (1.25 and 95.0 ng/mL)[1] at -20°C and -70°C

Reference ID: 3983722

Parameter	Morphine	M3G	M6G
Dilution Linearity	1.50 ng/mL diluted 5-fold 125 ng/mL diluted 10-fold	30.0 ng/mL diluted 5-fold 2500 ng/mL diluted 10-fold	7.50 ng/mL diluted 5-fold 625 ng/mL diluted 10-fold
Selectivity	No significant interfering peaks noted in blank human plasma samples	No significant interfering peaks noted in blank human plasma samples	No significant interfering peaks noted in blank human plasma samples
Hemolysis Evaluation	No effect from hemolysis on quantitation of morphine	No effect from hemolysis on quantitation of M3G	No effect from hemolysis on quantitation of M6G
Lipemia Evaluation	No effect from lipemia on quantitation of morphine	No effect from lipemia on quantitation of M3G	No effect from lipemia on quantitation of M6G

CV=coefficient of variation; LLOQ = lower limit of quantitation; M3G = morphine-3β-glucuronide; M6G = morphine-6β-glucuronide; QC = quality control

[1] With and without naltrexone.

[2] After excluding one statistical outlier.

4.1.7 OCP Filing Form.

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208603	**SDN**	1
Applicant	Egalet USA	**Submission Date**	12/15/2015
Generic Name	Morphine Extended Release Tablets	**Brand Name**	Arymo Tablets
Drug Class	Opioid		
Indication	Chronic Pain Management		
Dosage Regimen	Twice Daily Administration		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun, Xu, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	2/12/2016	**74-Day Letter Date**	2/28/2016
Review Due Date	9/10/2016	**PDUFA Goal Date**	10/15/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: Because the NDA is based on two BE studies supporting the application, the results have to be confirmed by an OSI inspection.

Clinical Pharmacology Package

Reference ID: 3983722

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		3	067-EG-011: Fasted BE and Food-effect study 60 mg (BE established). 067-EG-012: Fasted BA/BE study 30 mg & 2X 15 mg (BE established). 067-EG-006: Fasted BE study with 15 mg.
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☑ Multiple Dose	1	**Simulations to address multiple dose PK (acceptable since single dose is BE)**
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary		1	In vitro alcohol interaction study based biowaiver of

Reference ID: 3983722

Drug		in vivo study. (Biopharm team will review)
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☑ Healthy Subjects	2	067-EG-008: Pharmacokinetic Oral Abuse Deterrence study (Category 2/3). 067-EG-009: Clinical Intranasal Abuse Potential Study (Category 2/3).
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	5
Total Number of Studies to be Reviewed				5

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
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)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm,	☑Yes ☐No ☐N/A	

Reference ID: 3983722

summary-biopharm, pharmkin-written-summary)?		
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?	☑Yes ☐No ☐N/A	
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?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
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?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and	☑Yes ☐No ☐N/A	

biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?		
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

Reference ID: 3983722

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
09/09/2016

YUN XU
09/09/2016