CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.	208603
DATE RECEIVED BY THE CENTER	07/11/2016
DRUG NAME	ARYMO^{TM}ER (Morphine Sulfate)
DOSAGE FORM	Oral tablets
STRENGTH	15 mg; 30 mg; 60 mg.
INDICATION	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
SPONSOR	Egalet Corporation
REVIEW FINISHED	08/15/2016
STATISTICAL REVIEWER	Tianhua Wang, Ph.D.
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/s/

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA 208-603/0001
Supplement Number:	NA
Drug Name:	Arymo ER (morphine sulfate extended-release tablets, EG-001)
Indication(s):	Management of Pain
Applicant:	Egalet
Date(s):	Date of Document: 12/14/2015 Consult received date: 1/28/2016 Completion date: 7/12/2016
Review Priority:	Normal
Biometrics Division:	Division of Biometrics VI
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Keywords: NDA review, clinical studies, Crossover design; Clinical abuse potential study; Self-reported endpoint; Multiple endpoints	

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1. EXECUTIVE SUMMARY

Egalet (the sponsor) submitted this New Drug Application, NDA 208603 on 12/14/2015 for FDA approval of an abuse deterrent Arymo ER (morphine sulfate extended-release tablets, EG-001). Under this NDA, there are two randomized, double-blind, active and placebo-controlled clinical studies in non-dependent recreational opioid users comparing the abuse potential of ARYMO ER to morphine sulfate extended-release tablets following administration via the intranasal and oral routes.

Confirmation of abuse-deterrance:
This reviewer analyzed the data of the two studies, including the analysis recommended in *FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling* published in April, 2015.

Study 067-EG-008

The abuse deterrent properties of orally administrated Egalet (60 mg) compared to MS CONTIN (60 mg) and placebo were evaluated in Study 067-EG-008 which was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of manipulated and manipulated/sieved EG-001 vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users.

The numbers of completers were 38 (97%). One dropped out and was withdrawal by subject during the Treatment phase.

This reviewer conclude that the data of Study 067-EG-008 failed to provide acceptable evidence to support that the oral manipulated Egalet (60 mg) is abuse deterrent as compared to oral manipulated MS CONTIN, 60 mg. This conclusion is based on the following evidences:

1. The value of δ*, as defined in FDA 2015 Guidance, is less than 0.05 which is not acceptable for claiming abuse deterrent of oral manipulated Egalet relative to oral manipulated MS CONTIN
2. The test of the pair-wise comparison between oral manipulated Egalet and MS CONTIN is on boundary significance with the lower limit of the 95% confidence interval less than 1 point only in drug liking VAS Emax
3. Both the tests of key secondary analyses and the responder analysis showed a weak or no difference between oral manipulated Egalet and MS CONTIN. Particularly, the abuse deterrent properties were not supported by the two critical endpoints (Take Drug Again and Overall Drug Liking) as seen in Table 1.

Table 1 Summary of Pair-wise Comparisons in Study 067-EG--008 (n=38)

Pairwise	Mean diff (se)	95% CI	p-value	Median diff	95% CI	p-value
Drug Liking						
C - P	20.1 (1.8)	16.5, 23.8	<.0001	21	18, 24	<.0001
C-T	5.0 (2.3)	0.3, 9.7	0.0385	3	2, 6	0.0069
High						

C - P	47.0 (4.1)	38.8, 55.2	<.0001	43.5	35, 51	<.0001
C-T	13.3 (5.4)	2.4, 24.2	0.0175	13.5	2, 19	0.0035
Take Drug Again						
C - P	19.0 (3.4)	12.3, 25.8	<.0001	16.5	9, 29	<.0001
C-T	7.2 (4.3)	-1.3, 15.7	0.0967	2.5	0, 11	0.0537
Overall Drug Liking						
C - P	17.6 (2.8)	12.0, 23.2	<.0001	16.5	9, 23	<.0001
C-T	4.7 (3.9)	-3.0, 12.5	0.226	2	-1, 8	0.1276

C = MS CONTIN, 60 mg oral manipulated
T = Egalet PR morphine, 60 mg oral manipulated
P = Placebo

Study 067-EG-009

The abuse deterrent properties of intranasally administrated Egalet (60 mg) compared to MS CONTIN (60 mg) and placebo were evaluated in Study 067-EG-009 which was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of manipulated and manipulated/sieved EG-001 vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users.

The numbers of completers were 46 (92%). Four subjects dropped out during the Treatment period. Three were withdrawal by subjects during the Treatment phase and one dropout due to positive breath alcohol test.

This reviewer confirmed that the data of Study 067-EG-009 support that both manipulated intranasal Egalet (high volume, 60 mg) with $\delta^* \leq 0.30$ and manipulated/Sieved intranasal Egalet (low volume, 60 mg) with $\delta^* \leq 0.50$ are abuse deterrent as compared to manipulated intranasal MS CONTIN, 60 mg.

The results of the primary endpoint were supported by the analysis of the key secondary endpoints as seen in Table 2.

Table 2 Summary of Pair-wise Comparisons in Study 067-EG--009 (n=46)

Pairwise	Mean diff (se)	95% CI	p-value	Median diff	95% CI	p-value
Drug Liking						
C - P	23.0 (2.1)	18.9, 27.2	<.0001	23	21, 27	<.0001
C-Ta	12.2 (2.1)	7.9, 16.5	<.0001	12.5	9, 17	<.0001
C-Tb	18.1 (1.9)	14.3, 21.9	<.0001	20	14, 23	<.0001
High						
C - P	50.5 (4.1)	42.3, 58.6	<.0001	50.5	42, 66	<.0001
C-Ta	33.5 (4.5)	24.4, 42.6	<.0001	33	23, 40	<.0001
C-Tb	45.4 (3.8)	37.8, 52.9	<.0001	46	35, 63	<.0001
Take drug again						
C - P	17.4 (4.0)	8.2, 26.5	<.0001	21.5	12, 35	<.0001
C-Ta	26.7 (5.4)	14.4, 39.0	<.0001	24	10, 50	<.0001

C-Tb	17.3 (4.3)	7.3, 27.2	0.0002	18	10, 27	<.0001
Overall drug liking						
C - P	20.6 (2.9)	14.8, 26.3	<.0001	20.5	14, 33	<.0001
C-Ta	18.8 (3.7)	11.3, 26.3	<.0001	15	8, 25	<.0001
C-Tb	18.2 (2.9)	12.4, 24.1	<.0001	17	11, 26	<.0001

Ta = Treatment A: Egalet PR morphine, 60 mg manipulated intranasal (high volume)
Tb = Treatment B: Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume)
C = Treatment C: MS CONTIN, 60 mg manipulated intranasal (low volume)
P = Placebo

Considerations that may limit the efficacy:

- The statistical analysis performed by the sponsor did not follow the FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling published in April, 2015. For instance, the primary hypothesis should be written as:

  $$H_o: \mu_C - \mu_T \leq (\mu_C - 50)\delta^* \text{ versus } H_a: \mu_C - \mu_T > (\mu_C - 50)\delta^*$$

  with $0< \delta^*< 1$. Pre-specify δ^*. The sponsor's analysis was eventually an analysis by setting $\delta^*=0$ which is not acceptable.

- In the study design of 067-EG-009, all subjects received manipulated intranasal Egalet PR morphine (high volume) during Treatment Period 1 while for the remaining 4 Treatment Periods, subjects were randomized based on a Williams design to 1 of 4 sequences where each subject received the remaining 4 treatments. Such a design may cause possible carryover effect from the Treatment Period 1 to Period 2, leading to a possible biased estimate on the abuse deterrent effect of manipulated/Sieved intranasal Egalet (low volume).

- Only one positive control dose was used in both studies. The FDA's draft guidance of drug abuse-deterrent recommended at least two doses of positive control in the treatment phase.

- One (2.6%) subject was excluded from the randomized population in the Study 067-EG-008, withdrawal by the subject during the Treatment phase.

- Four (8%) subjects were excluded from the randomized population in the Study 067-EG-009. Three were withdrawal by subjects during the Treatment phase and one dropout due to positive breath alcohol test.

Recommendations:
Recommendations for the proposed label are included in part 5.4.

2. INTRODUCTION

2.1 Overview

On 1/28/2016, CSS sent a consult request for statistical review of NDA 208603 in support of an abuse deterrent Arymo ER (morphine sulfate extended-release tablets, EG-001) from Egalet (the

sponsor) submitted on 12/14/2015. The corresponding study protocol and Statistical Analysis Plan are submitted under IND117317.

There were two ADF studies submitted under this NDA.

- Study 067-EG-008, entitled "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
- Study 067-EG-009, entitled 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 following Intranasal Administration in Nondependent Recreational Opioid Users.

The two ADF studies were received full statistical consult review. The design features of the two studies are shown in Table 1.1.

Table 1.1 Summaries of Clinical Pharmacology Studies

Type of Study	Study Identifier	Formulation: Development or To-Be-Marketed	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled (Analyzed)	Healthy Subjects or Patient Diagnosis	Duration of Treatment
Category 2/3 Pharmacokinetic/Clinical Abuse Potential Studies								
Clinical Abuse Deterrent (Oral)	067-EG-008	To-be-marketed	Compare the relative abuse potential of oral intact and oral manipulated EG-001 versus oral manipulated MS Contin® Determine the relationship between PK and PD parameters of oral manipulated EG-001 and manipulated MS Contin® Safety/tolerability, and PK of intact and manipulated EG-001 following oral administration Exploratory: evaluate the relative abuse potential of oral EG-001 when manipulated and administered mixed in juice	Randomized, double blind, triple-dummy, active and placebo-controlled, 4-way crossover with an exploratory 5th arm comparing the abuse potential of oral intact and oral manipulated EG-001 versus oral manipulated MS Contin®	Qualification Phase: Single oral dose of manipulated 30 mg IR morphine in solution and matching placebo Treatment Phase: EG-001 60 mg intact and manipulated (taken with juice because hard to get into solution) versus MS Contin® 60 mg manipulated and mixed into 150 mL diet cranberry juice Matching placebo Exploratory Treatment: Manipulated EG-001 60 mg mixed into 150 mL diet cranberry juice	Qualification Phase: 78 enrolled and went on to the drug discrimination test Treatment Phase: 39 enrolled (10 female and 29 male) 38 subjects completed the study Subset of 12 subjects participated in the exploratory 5th arm 39 subjects in the safety/ tolerability analysis	Healthy, non-dependent, recreational opioid users	Qualification Phase: 2 single doses separated by 24 hours Treatment Phase: 4 treatment sequences separated by a 5-day washout period Exploratory Treatment: 1 single dose after a 5-day washout period
Clinical Abuse Deterrent (Intranasal)	067-EG-009	To-be-marketed	When administered intranasally: Compare the relative abuse potential of manipulated and manipulated/sieved EG-001 versus manipulated MS Contin® Determine the relationship between PK and PD parameters of manipulated and manipulated/sieved EG-001 and manipulated MS Contin® Assess the PK of manipulated and manipulated/sieved EG-001 Safety/tolerability of manipulated and manipulated/sieved EG-001	Randomized, double blind, double-dummy, active and placebo-controlled, 5-way crossover study comparing the abuse potential of manipulated and manipulated/ sieved EG-001 versus manipulated MS Contin® following intranasal administration	Qualification Phase: Single dose of manipulated 30 mg IR morphine administered intranasally and matching placebo Treatment Phase: Manipulated for intranasal use EG-001 60 mg (high volume/large particle size) Manipulated then sieved for intranasal use EG-001 60-mg (low volume/small particle size) Manipulated for intranasal use MS Contin® 60 mg (low volume) Intact for oral administration EG-001 60 mg Matching placebo	Qualification Phase: 80 enrolled and went on to the drug discrimination test Treatment Phase: 50 treated (11 female and 39 male) 46 subjects completed the study 50 subjects in the safety/ tolerability analysis	Healthy, non-dependent, recreational opioid users	Qualification Phase: 2 single doses separated by 24 hours Treatment Phase: 5 treatment sequences separated by a 5-day washout period

Source: Sponsor's synopses-indiv-studies.pdf Table 1.

2.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown below. The data were submitted in SAS Xport transport format.

Application:	NDA208603
Company	Egalet
Drug	Arymo ER
CDER EDR link	\\Cdsesub1\evsprod\NDA208603\0001
Letter date	12/14/2015

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data. Relevant issues include:

- Whether it is possible to reproduce the primary analysis dataset from tabulation or "raw" datasets : yes
- Whether it is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form): yes.
- Whether it is possible to verify the randomized treatment assignments: yes
- Findings from the Division of Scientific Investigation or other source(s) that question the usability of the data:

  There is no problem or difficulty to process the data.

3.2 Evaluation of Efficacy: Study 067-EG-008

3.2.1 Study Design and Endpoints

This was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of EG-001 vs. MS CONTIN in nondependent recreational opioid users. The study included a Screening Visit, a Qualification Phase, a Treatment Phase, 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 underwent the Drug Discrimination Test following a minimum 12-hour washout period after the Naloxone Challenge Test. On 2 consecutive days, separated by a washout period of approximately 24 hours, subjects received the following treatments in double-blind fashion:

• Treatment X: 30 mg oral immediate-release morphine; and
• Treatment Y: placebo.

The ability to discriminate was defined as follows:

- Emax score of ≥ 65 points for Drug Liking in response to morphine, and
- ≥15-point Emax difference between morphine and placebo treatments during the first 2 hours following drug administration, and
- Placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.

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.

Following a minimum 48-hour washout period from the Drug Discrimination Test, subjects began Treatment Period 1. Subjects were randomized in a 1:1:1:1 ratio, where each subject received all study treatments separated by a minimum 5-day washout period as indicated below:

- 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

A triple-dummy design with corresponding placebo treatments relative to active drugs was used.

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. Overall study duration was approximately 11 weeks, depending on the length of time between study visits.

STUDY OBJECTIVES

Primary Objective

- To compare the relative abuse potential of oral intact and oral manipulated formulations of Egalet PR morphine vs. oral manipulated MS CONTIN.

Secondary Objectives

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of oral manipulated Egalet PR morphine; and
- To assess the safety and PK of intact and manipulated formulations of Egalet PR morphine following oral administration.

PHARMACODYNAMIC ENDPOINTS

The primary endpoint was "at the moment" Drug Liking VAS E_{max}. The secondary PD endpoints of interest include: DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy), Overall Drug Liking, TDAA, Reaction Time and Pupillometry.

The following PD parameters were calculated:

- Emax: Peak effect over the 24 hours of collection.
- TEmax: Time to peak effect.
- AUE0-x: Area under the effect-time curve to 0 to x, where x is 0.5 hours (AUE0-0.5), 1 hour (AUE0-1), 2 hours (AUE0-2), 4 hours (AUE0-4), 8 hours (AUE0-8), 12 hours (AUE0-12), and 24 hours (AUE0-24).
- AUE0-TEmax: Area under the effect-time curve from 0 to TEmax.
- Percent reduction: The percent reduction in Emax (calculated for Drug Liking only).

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.
- Drug Effects Questionnaire (DEQ): predose (except Any, Good Drug Effects, and Bad Drug Effects) 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose using a unipolar 0-100 point VAS. (Due to the exploratory nature of the fifth arm, this assessment was not collected in Treatment Period 5.)

- Overall Drug Liking: 12 and 24 hours postdose using a bipolar 0 to 100 point VAS.
- Take Drug Again Assessment (TDAA): 12 and 24 hours postdose using a bipolar 0 to 100 point VAS.
- Psychomotor Assessment—Reaction Time: predose and 30 minutes and 1, 2, 4, and 8 hours postdose (Due to the exploratory nature of the fifth arm, this assessment was not collected in Treatment Period 5).
- Pupillometry: predose and 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours
- postdose.

Sample Size Determination

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 (Emax) 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.

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.

3.2.2 Statistical Methodologies by the Sponsor

The sponsor defined the following analysis populations

- Safety population: Subjects who received at least one dose of study medication in the original 4-arm crossover treatment phase. This set was used for the safety data summaries and baseline characteristic summaries. This population was analyzed as treated.
- Completers population: All randomized subjects who completed all 4 periods of the original 4-arm crossover treatment phase and for which post-dosing PD data were available from each period. This set was used for the PD and primary analysis. This population was analyzed as randomized.
- Per-Protocol population: All subjects in the Completers population who did not have major protocol violations. This population was analysed as randomized.
- Modified Intent-to-Treat (MITT) population: All randomized subjects who completed at least 2 of the 4 periods of the original 4-arm crossover treatment phase and for which post-dosing PD data were available. This population was analysed as randomized.

Hypothesis testing:

There was no test hypothesis for the primary analysis.

For one of the secondary analyses, the null hypothesis was that 50% or fewer subjects are responders.

Sponsor's statistical methodologies:

PD parameters are summarized by parameter and treatment using descriptive statistics (n, arithmetic mean, median, SEM, SD, CV, first and third quartile limits, minimum, and maximum) for each assessment for the completer population.

The primary comparison was manipulated MS CONTIN (Treatment C) to manipulated Egalet PR (Treatment B) for Drug Liking Emax. All other comparisons were secondary. The comparison of manipulated MS CONTIN to placebo was made to confirm study validity.

For the original 4-arm crossover treatment phase each of the six comparisons were made:

- Manipulated MS CONTIN vs. Manipulated Egalet PR morphine (Treatment C vs. Treatment B) – Primary Comparison
- Manipulated MS CONTIN vs. Placebo (Treatment C vs. Treatment D) – Validity
- Manipulated MS CONTIN vs. Intact Egalet PR morphine (Treatment C vs. Treatment A)
- Manipulated Egalet PR morphine vs Placebo (Treatment B vs. Treatment D)
- Intact Egalet PR morphine vs. Placebo (Treatment A vs. Treatment D)
- Manipulated Egalet PR morphine vs. Intact Egalet PR (Treatment B vs. Treatment A)

For the original 4-arm crossover 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. LS means along with 95% CIs are provided for each treatment. LS mean differences along with 95% CIs are provided for above pairwise treatment comparisons.

The percent reduction in Emax for the VAS for the primary endpoint (Drug Liking) was calculated for each of the Egalet treatments versus the relevant comparator treatment. These percent reductions are summarized categorically for each treatment.

The percent reduction in peak effect (Emax) was calculated as:

$$\%reduction = \begin{cases} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50}\right) 100\%, i = 1, 2, \ldots, n, \ \ if\ p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \ldots, n, \ \ if\ p_i \leq 55. \end{cases}$$

where ci, ti, and pi, were the Emax values for the control (manipulated MS CONTIN [Treatment C]), the test (manipulated Egalet PR morphine [Treatment B]), and the placebo (Treatment D), respectively; from the ith subject; and n is the sample size. Additionally, the percent reduction was calculated for the comparison between manipulated MS CONTIN and intact Egalet PR morphine (Treatment C vs. Treatment A) as control and test. The percent reduction was calculated if data for the active control, test product, and placebo were available. In cases where one of those values was not available, percent reduction was set to missing. In cases where the

control was equal to 50, the percent reduction was set to the largest percentage observed in the study (negative or positive depending on the difference of ci-ti) for that comparison. If no large percentage existed (or it was less than 101%), the percent reduction was set to 101% (and set to negative or positive depending on the difference of ci-ti). A large value was used so that the subject was still counted in the analysis and would not have markedly impacted the descriptive statistical results.

The number and percent of subjects with percent reductions falling within 10% increments is provided for the following comparisons: manipulated MS CONTIN (Treatment C) to manipulated Egalet PR morphine (Treatment B) and manipulated MS CONTIN (Treatment C) to intact Egalet PR morphine (Treatment A).

The percent reduction in Drug Liking Emax was used to define a responder at several cutoffs. A responder was defined as a subject who had at least a pre-specified level of reduction, where levels less than 0%, from 10% to 90% in 10% increments, and greater than 100% were presented in an exploratory fashion. The number and percent of subjects considered responders and non-responders is presented for each comparison, manipulated MS CONTIN (Treatment C) to manipulated Egalet PR morphine (Treatment B) and manipulated MS CONTIN (Treatment C) to intact Egalet PR morphine (Treatment A). A binomial test of proportions was utilized to test the null hypothesis that 50% or fewer subjects are responders.

The normality assumption was not met for the primary and some secondary PD parameters (Emax, AUEs, and TEmax) across all subjective and objective measures; therefore, non-parametric tests (Sign test) were applied to these data and estimated median differences were provided for the PD parameters.

Multiple Comparisons/Multiplicity

No adjustments were made for multiplicity.

Handling of Dropouts or Missing Data

For PD analyses, missing data for subjects who were administered all scheduled study treatments for all the treatment periods were considered as random non-informative missing for analysis purposes. No imputation of missing values was performed.

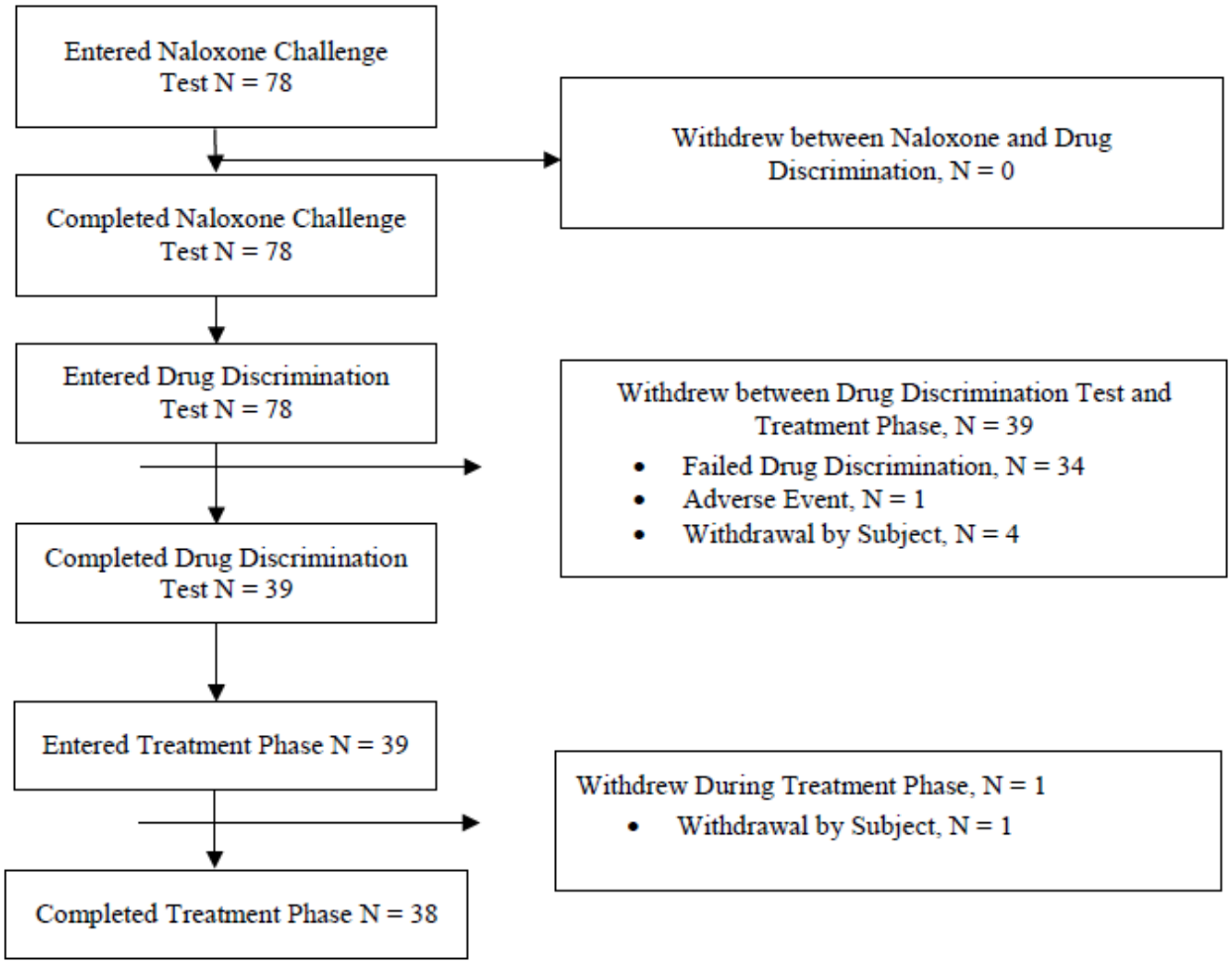
Changes in the Conduct of the Study

Changes in Planned Analyses: Analysis of TEmax for the PD parameters was not included in the SAP but was included in the final analysis tables and listings. No other changes were made to the planned analysis.

3.2.3 Sponsor's Summary and Conclusions

The subject disposition was provided by the sponsor as shown in Figure 3.2.1.

Figure 3.2.1: Subject Disposition for All Subjects



Source: sponsor's 067-eg-008-body.pdf Figure 10.1-1

Sponsor's main results are summarized in Table 3.2.1. Others are attached in Appendix 1.

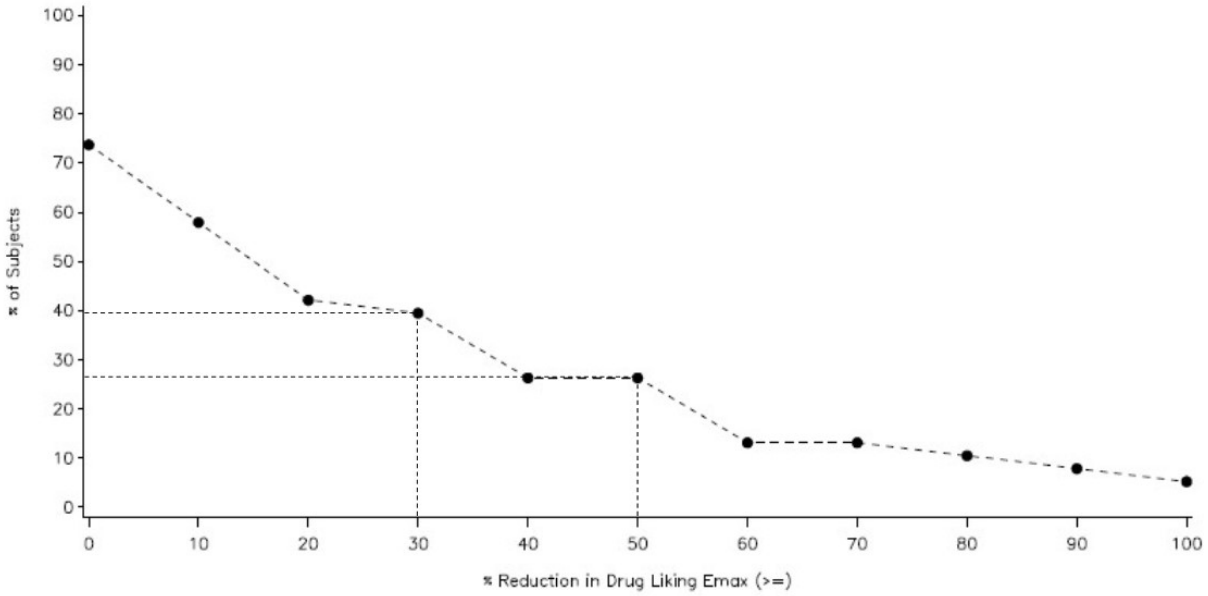
Table 3.2.1: Summary of Maximum Scores (Emax) for Drug Liking, High, Overall Drug Liking, and Take Drug Again VAS Following Oral Administration of Manipulated and Intact ARYMO ER and Manipulated Morphine Sulfate Extended-Release in Non-Dependent Recreational Opioid Users – Completers Population (N=38).

Parameter	ARYMO ER		Manipulated Morphine Sulfate Extended-Release (n = 38)	Placebo (n = 38)
	Manipulated (n = 38)	Intact (n = 38)		
Maximum Drug Liking[1] (E_{max})				
Mean (SD)	68.3 (12.3)	63.2 (10.1)	73.3 (9.8)	53.3 (7.8)
Median (Q1, Q3)	67.0 (61.0, 75.0)	62.0 (56.0, 68.0)	74.0 (68.0, 79.0)	50.0 (50.0, 52.0)
Overall Drug Liking[1] (E_{max})				
Mean (SD)	65.1 (18.6)	55.7 (19.8)	69.8 (15.4)	52.2 (8.1)
Median (Q1, Q3)	63.5 (51.0, 75.0)	57.0 (50.0, 66.0)	67.5 (57.0, 81.0)	50.0 (50.0, 50.0)
Take Drug Again[1] (E_{max})				
Mean (SD)	62.9 (19.6)	54.8 (20.8)	70.1 (17.5)	51.0 (10.2)
Median (Q1, Q3)	61.5 (51.0, 71.0)	56.0 (50.0, 65.0)	68.0 (56.0, 80.0)	50.0 (50.0, 50.0)
High[2] (E_{max})				
Mean (SD)	38.8 (25.6)	26.8 (24.5)	51.9 (23.6)	5.3 (11.5)
Median (Q1, Q3)	38 (18, 58)	18.5 (7, 47)	49 (34, 72)	0 (0, 1)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)
[2] 100 point unipolar VAS (0="not at all", 100="extremely")
Sources: sponsor's clinical-overview.pdf Table 4 and 067-eg-008-body.pdf Table 14.2.4.2

The statistical tests for the pair-wise comparisons are in Appendix 1 Tables 3, 8, and 10. The percent reduction plot for drug liking VAS Emax for manipulated EG-001 versus the positive control was also provided by the sponsor as seen in Figure 3.2.2.

Figure 3.2.2: Percent Reduction Profile Plot for Drug Liking VAS Emax for Manipulated EG-001 versus Manipulated MS Contin – Completers Population (N=38)



Source: Sponsor's clinical-overview.pdf Figure 6.

Sponsor's conclusion:

Egalet PR morphine, when administered by the oral route as intact or manipulated tablets, demonstrated significantly lower subjective and physiologic effects compared to manipulated MS CONTIN. This resulted in a statistically significant decrease in the primary outcome of drug liking (Emax). Egalet PR was associated with a delay in onset of effects and lower peak exposure compared to manipulated MS CONTIN.

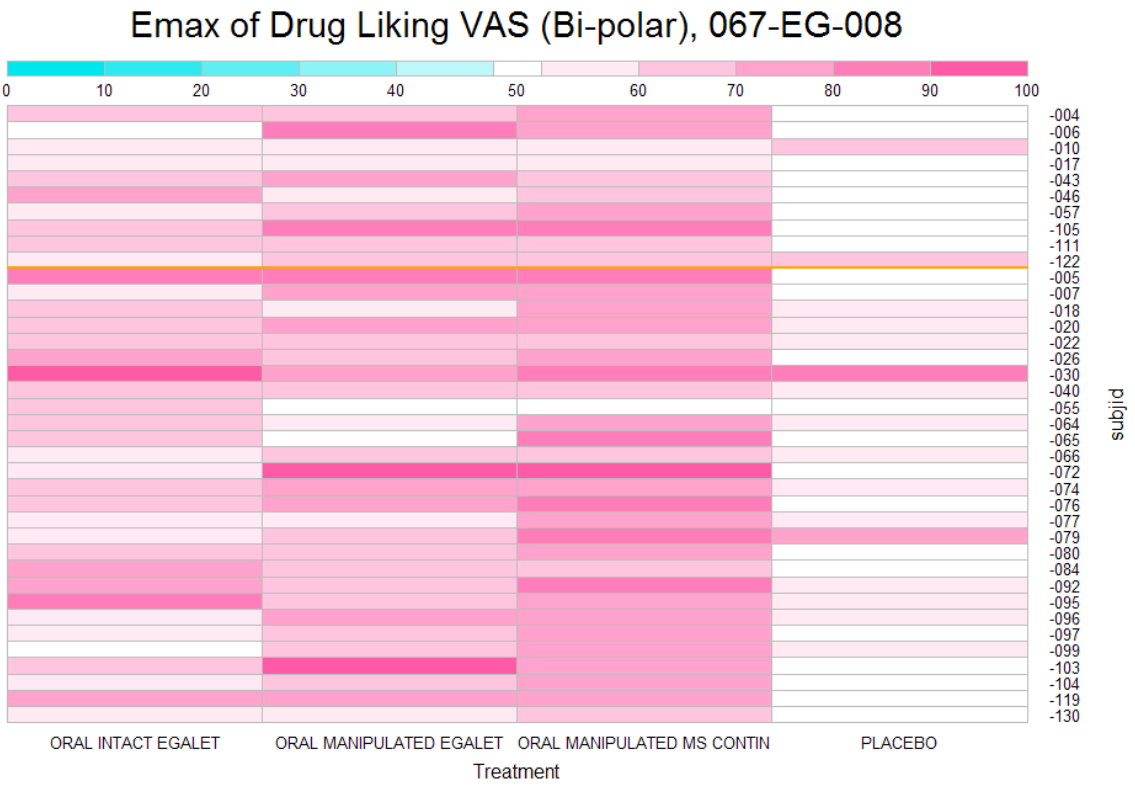
3.2.4 Reviewer's Assessment

3.2.4.1 Descriptive Analysis

This reviewer verified the sponsor's descriptive primary and key secondary results shown in Table 3.2.1. In this table, one can see similar variances among treatment arms.

Figure 3.2.3 is a heat map display, which shows individual Emax responses to each treatment as measured by Drug Liking VAS. In the figure, drug disliking is shown in blue, neutral response is shown in white and drug liking is shown in pink. The subjects (n = 38) represented above the thin orange line are females (n = 10), and the subjects below the orange line are males (n = 28).

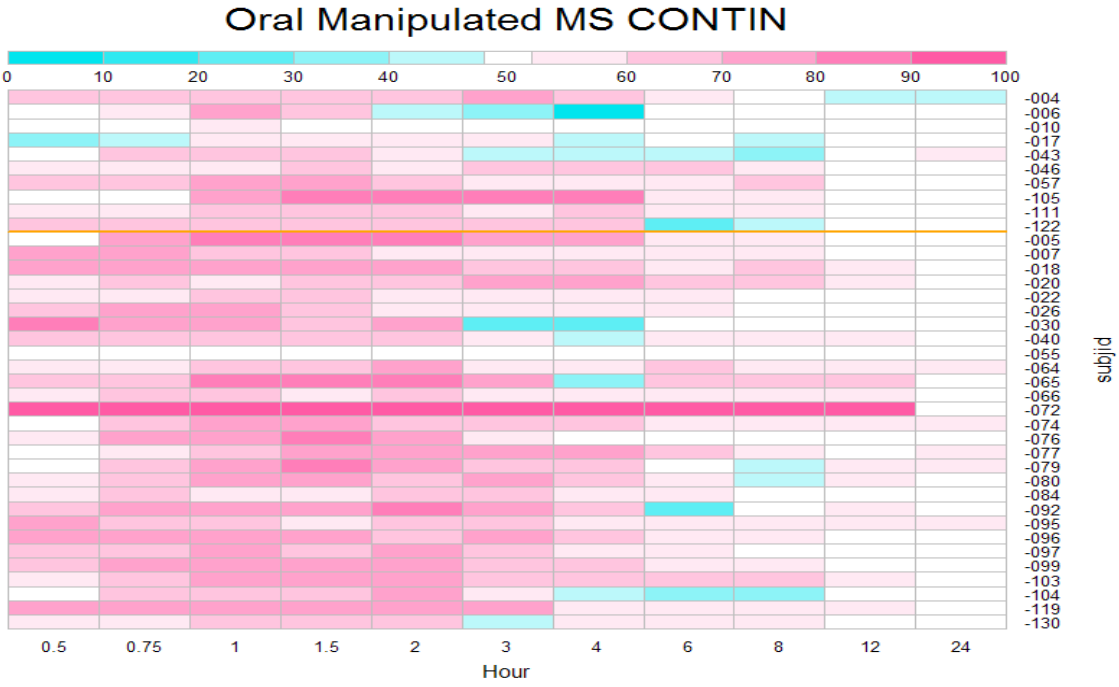
Figure 3.2.3. Heat Map for the Peak Effect (Emax) of Drug Liking VAS by Treatment.



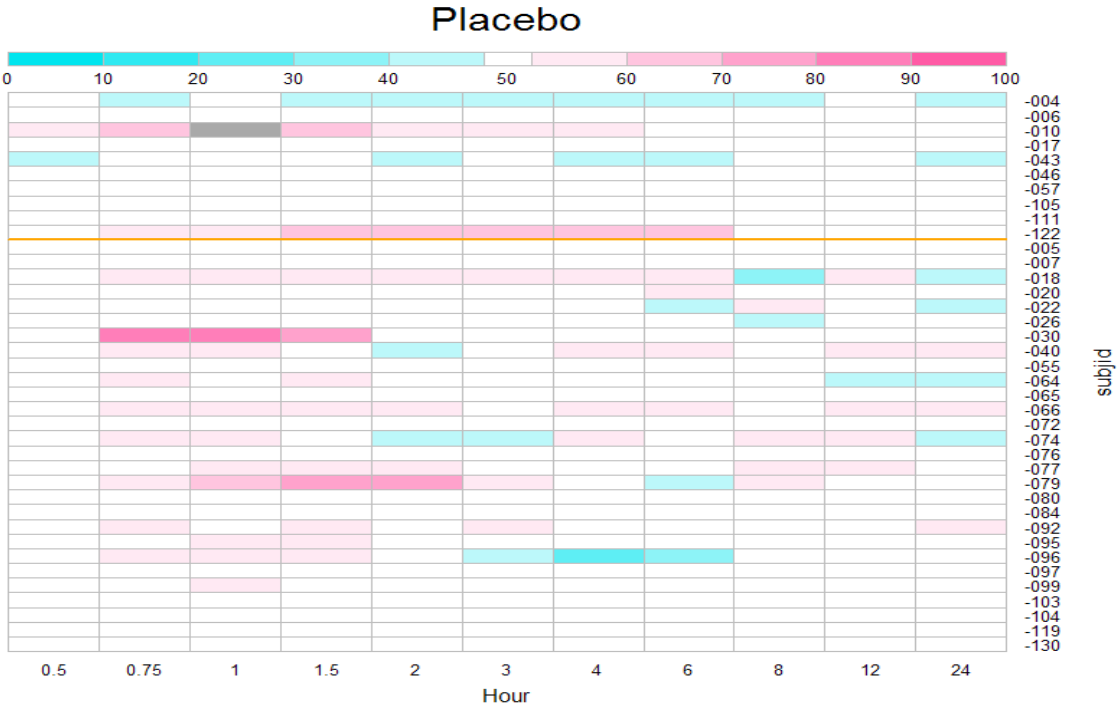
Figures 3.2.4 A-D are the individual time course response profiles for the positive control oral manipulated MS CONTIN (A), placebo (B), oral manipulated Egalet (C), and oral intact Egalet (D), respectively.

Figure 3.2.4. Heat Map for the Peak Effect (Emax) of Drug Liking VAS by Treatment.

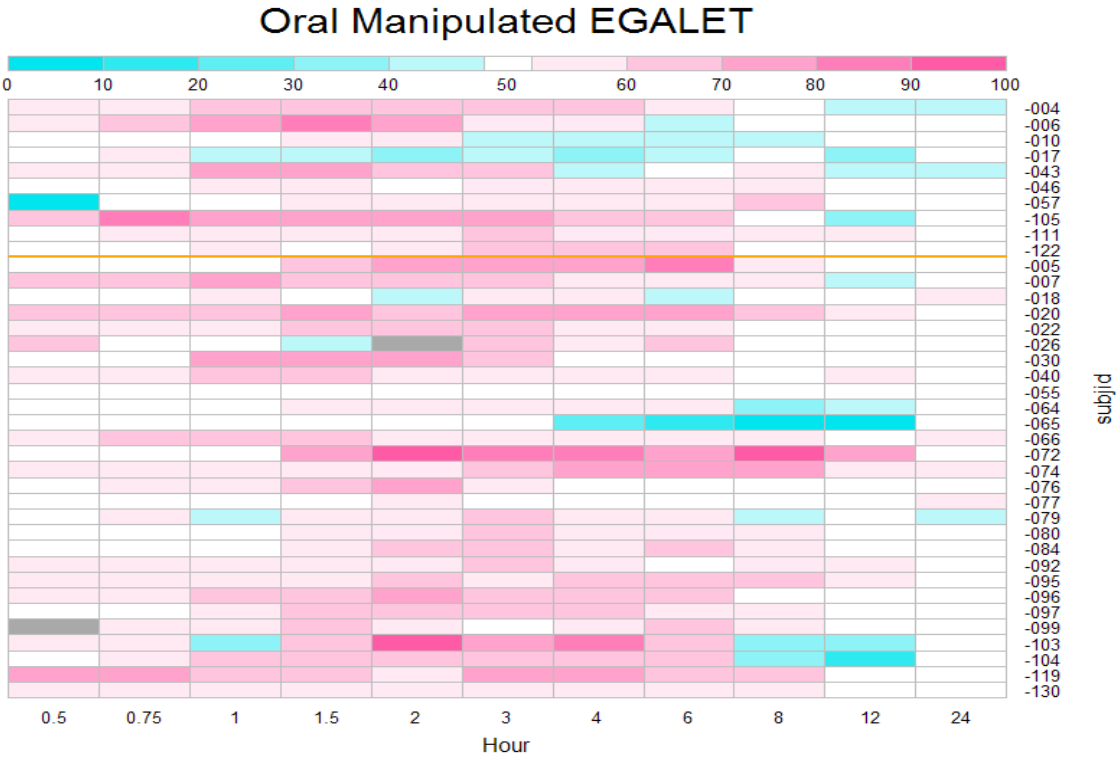
A: oral manipulated MS CONTIN



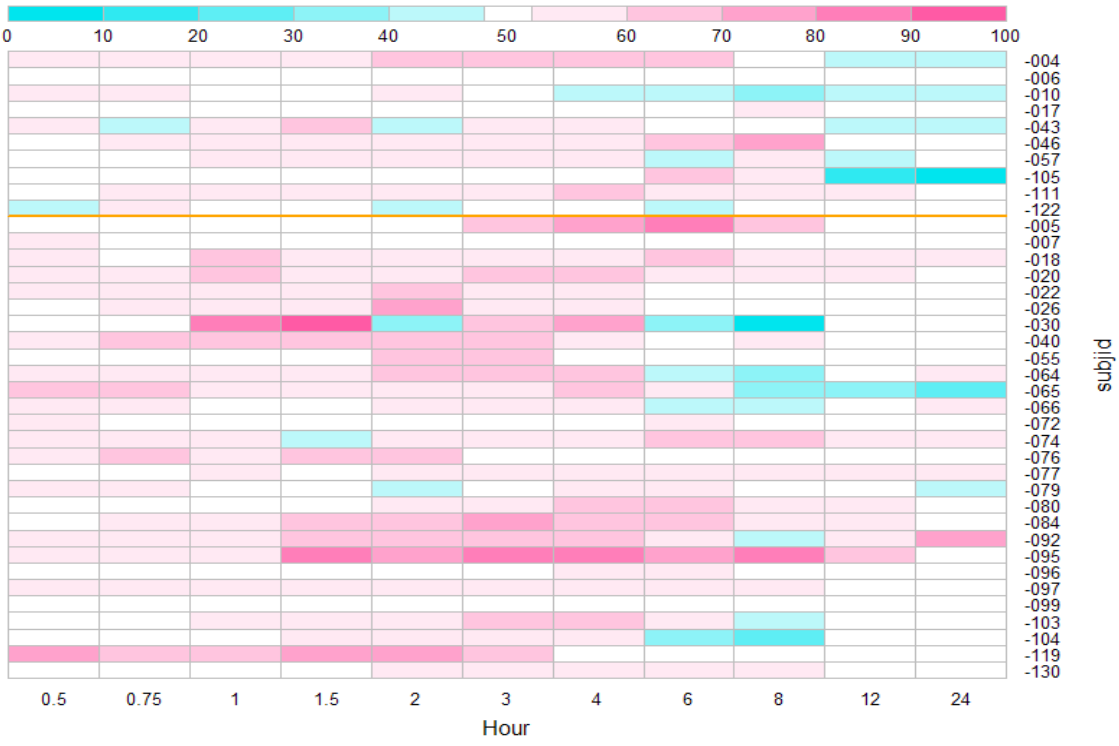
B: Placebo



C: oral manipulated Egalet



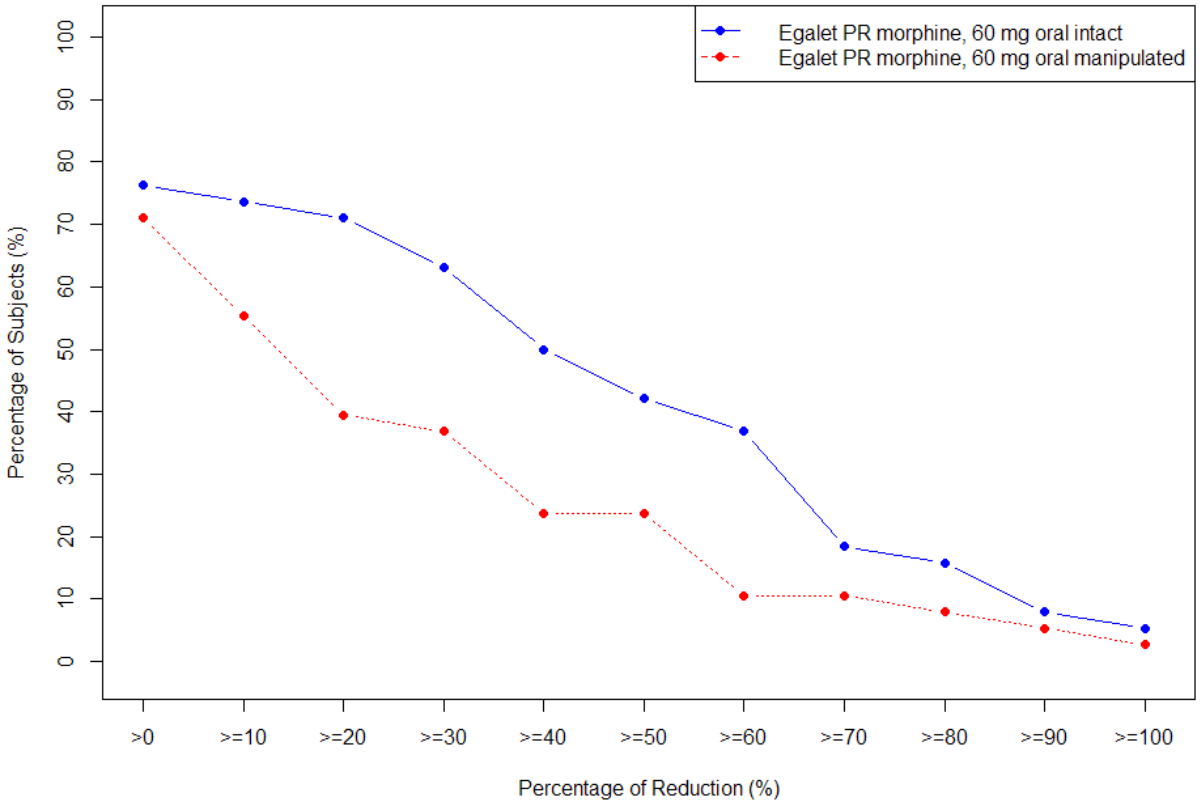
D: oral intact Egalet



3.2.4.2 Responder Analysis – Drug Liking VAS

The relationship of percent reduction and percent subjects by this reviewer is shown in Figure 3.2.5, suggesting more drug-deterrent in oral intact Egalet than in oral manipulated Egalet.

Figure 3.2.5: Percent Reduction Profile for Emax of Drug Liking VAS for Study 067-EG-008



Responder test

Responders were categorized if they demonstrated at least 30%, 40%, or 50% reduction in Emax of Drug Liking. Table 3.2.2 presents the results of the proportion test in Drug Liking VAS Emax following oral administration of Egalet. In consistence with the results in Figure 3.2.5, the oral intact Egalet had relatively more favorable abuse deterrent property than the oral manipulated Egalet does, however, no statistical significance at level of 0.05 being achieved for above categories for neither administration routes.

Table 3.2.2 "At This Moment" Drug Liking VAS Emax Responder Analysis, Completer Population (n=38)

	Percent Reduction		
	≥30%	≥40%	≥50%
Oral Manipulated Egalet			
Responder rate	0.37	0.24	0.24
Z-score	-1.62	-3.24	-3.24
P value	0.948	0.999	0.999
Oral Intact Egalet			
Responder rate	0.63	0.50	0.42
Z-score	1.62	0	-1.30
P value	0.052	0.5	0.903

3.2.4.2 Statistical Testing

This reviewer performed statistical tests on the primary and key secondary endpoints (n=38) using the mixed effect model for pairwise treatment comparisons and Wilcoxon signed-rank test on the within-subject differences as shown in Table 3.2.3.

Table 3.2.3. Summary of Pair-wise Comparison Between Treatments (n=38)

Pairwise	Mean diff (se)	95% CI	p-value	Median diff	95% CI	p-value
Drug Liking						
C - P	20.1 (1.8)	16.5, 23.8	<.0001	21	18, 24	<.0001
C-Ta	10.3 (2.1)	6.1, 14.5	<.0001	9	5, 14	<.0001
C-Tb	5.0 (2.3)	0.3, 9.7	0.0385	3	2, 6	0.0069
Ta – P	9.8 (2.0)	5.9, 13.8	<.0001	11	6, 16	<.0001
Tb – P	15.1 (2.2)	10.6, 19.6	<.0001	13.5	10, 19	<.0001
High						
C - P	47.0 (4.1)	38.8, 55.2	<.0001	43.5	35, 51	<.0001
C-Ta	25.5 (5.4)	14.7, 36.3	<.0001	28	8, 42	<.0001
C-Tb	13.3 (5.4)	2.4, 24.2	0.0175	13.5	2, 19	0.0035
Ta – P	21.5 (4.4)	12.6, 30.4	<.0001	17.5	7, 30	<.0001
Tb – P	33.7 (4.5)	24.7, 42.7	<.0001	29	21, 42	<.0001
Take Drug Again						
C - P	19.0 (3.4)	12.3, 25.8	<.0001	16.5	9, 29	<.0001
C-Ta	15.1 (4.5)	6.1, 24.2	0.0013	9	3, 21	0.0005
C-Tb	7.2 (4.3)	-1.3, 15.7	0.0967	2.5	0, 11	0.0537
Ta – P	3.9 (3.9)	-3.9, 11.7	0.3187	8	0, 13	0.1983

Tb – P	11.8 (3.6)	4.7, 19.0	0.0017	10	4, 17	0.0004
Overall Drug Liking						
C - P	17.6 (2.8)	12.0, 23.2	<.0001	16.5	9, 23	<.0001
C-Ta	14.1 (4.1)	5.9, 22.3	0.0011	11.5	2, 17	0.0004
C-Tb	4.7 (3.9)	-3.0, 12.5	0.226	2	-1, 8	0.1276
Ta – P	3.5 (3.5)	-3.6, 10.7	0.3232	7	0, 13	0.1805
Tb – P	12.9 (3.3)	6.3, 19.5	0.0003	12.5	4, 18	<.0001

C = Treatment C: MS CONTIN, 60 mg oral manipulated
P = Treatment D: Placebo
Ta = Treatment A: Egalet PR morphine, 60 mg oral intact
Tb = Treatment B: Egalet PR morphine, 60 mg oral manipulated

The primary comparison between oral manipulated MS CONTIN, 60 mg, and oral manipulated Egalet PR morphine is at boundary significance with a difference lower limit of the 95% confidence interval less than 1 point only in drug liking VSA Emax. This result is supported by a key secondary analysis of high VAS Emax, but not supported by the key secondary endpoints, take drug again and overall drug liking of which the tests are not significant at level of 0.05 (two-sided). Above results (testing median differences) are numerically different from the sponsor's (Tables 11.4.1.2-2, 11.4.1.5-2, and 11.4.1.6.1-2 shown in sponsor's 067-eg-008-body.pdf Table).

The FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling published in April, 2015 requests that the primary hypothesis should be:

$$H_o: \mu_C - \mu_T \leq (\mu_C - 50)\delta^* \text{ versus } H_a: \mu_C - \mu_T > (\mu_C - 50)\delta^*$$

with $0< \delta^*< 1$ and the δ^* should be pre-specified. The null hypothesis can be equivalently written as:

$$H_o: \mu_{C\delta} - \mu_T \leq 0 \text{ where } \mu_{C\delta} = (1- \delta^*)\, \mu_C + 50\delta^*$$

Since this study was planned at or before the FDA guidance published, such a primary analysis was not in sponsor's Statistical Analysis Plan (SAP). This reviewer did a post-hoc analysis using δ^* starting from 0.03 and increase δ^* with selected increment until the test is no longer significant at α=0.05 (two-sided). The results are summarized in Table 3.2.4.

Table 3.2.4: Results of Test Required by FDA 2015 Guidance (N=38)

T	δ*	Mean diff	SE	p-value	C-T, 95% CI
Ta	0	10.3	2.1	<.0001	6.1, 14.5
Ta	0.25	4.4	1.9	0.0211	0.7, 8.2
Ta	0.30	3.2	1.8	0.0819	-0.4, 6.9
Tb	0	4.9	2.1	0.0221	0.7, 9.2
Tb	0.03	4.2	2.1	0.0457	0.1, 8.4
Tb	0.05	3.8	2.1	0.0722	-0.3, 7.9

T = test drug in the Treatment Phase
Ta = Treatment A: Egalet PR morphine, 60 mg oral intact
Tb = Treatment B: Egalet PR morphine, 60 mg oral manipulated

C = Treatment C: MS CONTIN, 60 mg oral manipulated

The test in Table 3.2.5 clearly showed that the deterrent property of oral manipulated Egalet relative to oral manipulated MS CONTIN (the primary comparison) is not acceptable because of $\delta^* < 0.05$.

In addition, this reviewer verified the sponsor's analysis of the Exploratory arm. However, the analysis was exploratory and should not count for neither supporting claims shown in the label, nor that of the oral study.

3.2.4.3 Reviewer's Summary and Conclusion

The data of Study 067-EG-008 did not provide acceptable evidence to support the abuse deterrent property of the oral manipulated Egalet when compared to oral manipulated MS CONTIN at the same dose, 60 mg. This is based on the following collective evidence:

1. The value of δ^*, as defined in FDA 2015 Guidance, is less than 0.05 which is not acceptable for claiming abuse deterrent of oral manipulated Egalet relative to oral manipulated MS CONTIN
2. The test of the pair-wise comparison between oral manipulated Egalet and MS CONTIN is on boundary significance with the lower limit of the 95% confidence interval less than 1 point only in drug liking VAS Emax
3. The tests of key secondary analyses showed a weak or no difference between oral manipulated Egalet and MS CONTIN.
4. The responder analysis does not support the abuse deterrent property of oral manipulated Egalet.

3.3 Evaluation of Efficacy: Study 067-EG-009

3.3.1 Study Design and Endpoints

This was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of manipulated and manipulated/sieved EG-001 vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users. The study included a Screening Visit, a Qualification Phase, a Treatment Phase, 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 given intranasally from placebo. Subjects underwent the Drug Discrimination Test following a minimum 12-hour washout period after the Naloxone Challenge Test. On 2 consecutive days, separated by a washout period of approximately 24 hours, subjects received the following treatments in double-blind fashion:

• Treatment X: 30 mg mmediate-release morphine, pulverized, administered intranasally

• Treatment Y: placebo administered intranasally.

Treatment order was randomly assigned using a computer-generated randomization scheme. Subjects were instructed to insufflate treatments within 5 minutes; an additional 5 minutes was allowed, if needed. If administration was not fully completed within 10 minutes, dosing was stopped and the amount of study drug not insufflated was weighed and recorded. Subjects were not allowed to blow their noses for 2 hours, and any episodes of sneezing within 1 hour were documented. Commercially available immediate-release morphine was used for the Drug Discrimination Test. The ability to discriminate was defined for Drug Liking on a bipolar 0-100 point VAS only, and was as follows:

- Emax score of ≥ 65 points for Drug Liking in response to morphine, and
- ≥15-point Emax difference between morphine and placebo treatments during the first 2 hours following drug administration, and
- Placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.

Following a minimum 48-hour washout period from the Drug Discrimination Test, subjects began Treatment Period 1. During Treatment Period 1, all subjects received Treatment A (Egalet PR morphine manipulated intranasal). For the remaining 4 Treatment Periods, subjects were randomized based on a Williams design to 1 of 4 sequences where each subject received the remaining 4 treatments. Each of the 5 study treatments were separated by a minimum 5-day washout period as indicated below:

• Treatment A: Egalet PR morphine, 60 mg manipulated intranasal (high volume)
• Treatment B: Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume)
• Treatment C: MS CONTIN, 60 mg manipulated intranasal (low volume)
• Treatment D: Egalet PR morphine, 60 mg intact oral
• Treatment E: PLACEBO

In order to control for potential sequence effects associated with administration of a high volume intranasal product (Schoedel, 2012), all subjects received the 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 volume of the investigational products during these treatment periods was standardized and matched to the volume of Treatment B and Treatment C.

Subjects were instructed to insufflate treatments within 5 minutes; an additional 10 minutes was allowed, if needed. If administration was not fully completed within 15 minutes, dosing was stopped and the amount of study drug not insufflated was weighed and recorded. Subjects were not allowed to blow their noses for 2 hours, and any episodes of sneezing within 1 hour were documented.

For all dosing periods, subjects received one of the treatments following a minimum 8-hour fast and fasted 3 hours post-dose. Water was restricted for 1 hour before and 1 hour after each drug administration, except as required for dose administration. Subjects were not allowed to blow their noses for 2 hours following intranasal dosing, and any episodes of sneezing within 1 hour of intranasal dosing were documented.

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. Overall study duration was approximately 11 weeks, depending on the length of time between study visits.

STUDY OBJECTIVES

Primary Objective

- To compare the relative abuse potential of manipulated and manipulated/sieved Egalet® PR morphine vs. manipulated MS CONTIN when administered intranasally.

Secondary Objectives

- 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 PK of manipulated and manipulated/sieved Egalet PR morphine following intranasal administration; and
- To assess the safety of manipulated and manipulated/sieved Egalet PR morphine following intranasal administration.

PHARMACODYNAMIC ENDPOINTS

The primary measures were “at the moment” Drug Liking VAS, Overall Drug Liking VAS, and Take Drug Again VAS. The secondary PD endpoints of interest include: DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy), Overall Drug Liking, TDAA, Psychomotor Assessment-Reaction Time, Pupillometry, Ease of Snorting, Pleasantness of Snorting, and Nasal Effects Assessment.

The following PD parameters were calculated:

- Emax: Peak effect over the 24 hours of collection.
- TEmax: Time to peak effect.
- AUE0-x: Area under the effect-time curve to 0 to x, where x is 0.5 hours (AUE0-0.5), 1 hour (AUE0-1), 2 hours (AUE0-2), 4 hours (AUE0-4), 8 hours (AUE0-8), 12 hours (AUE0-12), and 24 hours (AUE0-24).
- AUE0-TEmax: Area under the effect-time curve from 0 to TEmax.
- Percent reduction: The percent reduction in Emax (calculated for Drug Liking only).

Pharmacodynamic Assessments:

- Drug Liking: 15, 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.

- Drug Effects Questionnaire (DEQ): predose (except Any, Good Drug Effects, and Bad Drug Effects), 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose using a unipolar 0-100 point VAS.
- Overall Drug Liking: 12 and 24 hours postdose using a bipolar 0 to 100 point VAS.
- Take Drug Again Assessment (TDAA): 12 and 24 hours postdose using a bipolar 0 to 100 point VAS.
- Psychomotor Assessment—Reaction Time: predose and 15 and 30 minutes and 1, 2, 4, and 8 hours postdose.
- Ease of Snorting: within 5 minutes of completing intranasal administration using a bipolar 0-100 point VAS.
- Pleasantness of Snorting: within 5 minutes of completing intranasal administration using a bipolar 0-100 point VAS.
- Pupillometry: predose and 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
- Nasal Effects Assessment: predose and at 5, 15, 30, 45 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose

Sample Size Determination

A sample size of 40 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥10.6 points in peak effect (Emax) 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.

A total of 83 subjects entered the Qualification Phase and underwent the Naloxone Challenge Test; 80 subjects passed the test and proceeded to the Drug Discrimination Test. Fifty subjects met Drug Discrimination Test, 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.

3.3.2 Statistical Methodologies

The sponsor defined the following analysis populations

- 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.
- 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.

Hypothesis testing:

There was no test hypothesis for the primary analysis. For one of the secondary analyses, the null hypothesis was that 50% or fewer subjects are responders.

Sponsor's statistical methodologies:

PD parameters are summarized by parameter and treatment using descriptive statistics (n, arithmetic mean, median, SEM, SD, CV, first and third quartile limits, minimum, and maximum) for each assessment for the completer population.

The primary comparisons were Treatment C (Manipulated Intranasal MS CONTIN) vs. Treatment A (Egalet PR morphine, 60 mg manipulated intranasal [high volume]) and Treatment C (Manipulated Intranasal MS CONTIN) vs. Treatment B (Egalet PR morphine, 60 mg manipulated/sieved intranasal [low volume]). All other comparisons were secondary. The comparator, Treatment C (Manipulated Intranasal MS CONTIN), was compared with Treatment E (Placebo) to assess study validity.

For the Treatment Phase, each of the following ten comparisons was 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)
- 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.

The percent reduction in Emax for the VAS for the primary endpoint (Drug Liking) was calculated for each of the Egalet treatments versus the relevant comparator treatment. These percent reductions are summarized categorically for each treatment.

The percent reduction in peak effect (Emax) was calculated as:

$$\%reduction = \begin{cases} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50}\right) 100\%, i = 1, 2, \dots, n, \ \ if\ p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n, \ \ if\ p_i \leq 55. \end{cases}$$

where ci, ti, and pi, were the Emax values for the control (manipulated MS CONTIN [Treatment C]), the test (manipulated Egalet PR morphine [Treatments A or B]), and the placebo (Treatment E), respectively; from the ith subject; and n is the sample size. Additionally, the percent reduction was calculated for each Egalet treatment, resulting in three percent reduction calculations. The percent reduction was calculated and provided if data for the active control, test product, and placebo were available. The number and percent of subjects with percent reductions falling within 10% increments are provided for each comparison:

- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg manipulated intranasal (high volume) (Treatment A),
- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) (Treatment B),
- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg intact oral (Treatment D).

The percent reduction in Drug Liking Emax was used to define a responder at several cutoffs. A responder was defined as a subject who had at least a prespecified level of reduction, where levels from 10% to 90% in 10% increments are presented in an exploratory fashion. The number and percent of subjects considered as responders and non-responders are presented for each comparison:

- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg manipulated intranasal (high volume) (Treatment A),

- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume) (Treatment B),
- Manipulated Intranasal MS CONTIN (Treatment C) to Egalet PR morphine, 60 mg intact oral (Treatment D).

A binomial test of proportions was utilized to test the null hypothesis that 50% or fewer subjects are responders.

The normality assumption was not met for the primary and some secondary PD parameters (Emax, AUEs, and TEmax) across all subjective and objective measures; therefore, non-parametric tests (Wilcoxon Rank Sign Test) were applied to these data and estimated median differences were provided for the PD parameters.

Multiple Comparisons/Multiplicity

No adjustments were made for multiplicity.

Handling of Dropouts or Missing Data

For PD analyses, missing data for subjects who were administered all scheduled study treatments for all the treatment periods were considered as random non-informative missing for analysis purposes. No imputation of missing values was performed.

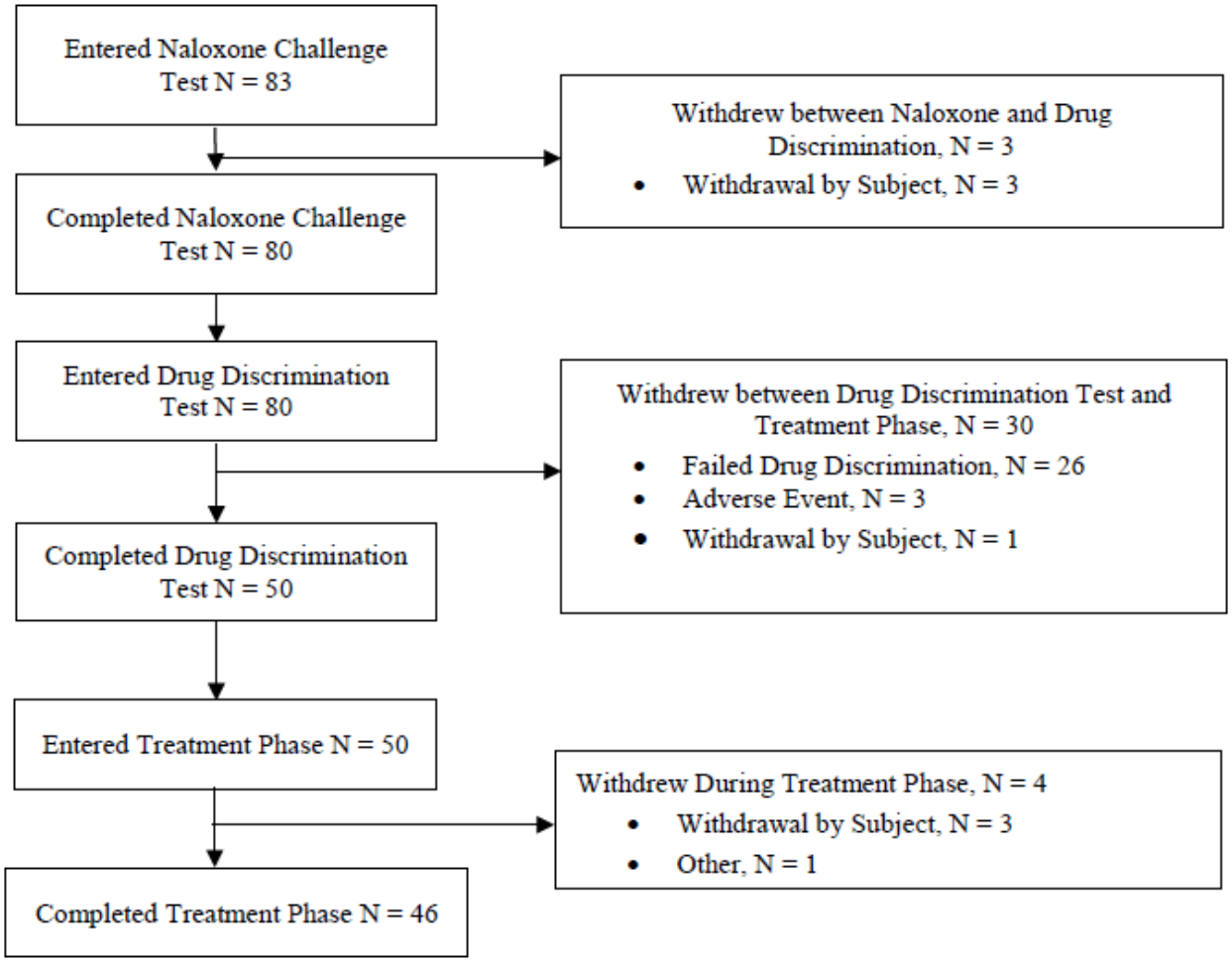
Changes in the Conduct of the Study

There were no changes to the planned analysis.

3.3.3 Sponsor's Summary and Conclusions

The subject disposition was provided by the sponsor as shown in Figure 3.3.1

Figure 3.3.1: Subject Disposition for All Subjects



Source: sponsor's 067-eg-009-body.pdf Figure 10.1-1

Sponsor's main results are summarized in Table 3.3.1. Others are attached in Appendix 2.

Table 3.3.1: Summary of Drug Liking and Take Drug Again Results (100 Point Bipolar VAS1) from Intranasal Abuse Potential Study of ARYMO ER and Morphine Sulfate Extended-Release Tablets in Non-Dependent Recreational Opioid Users

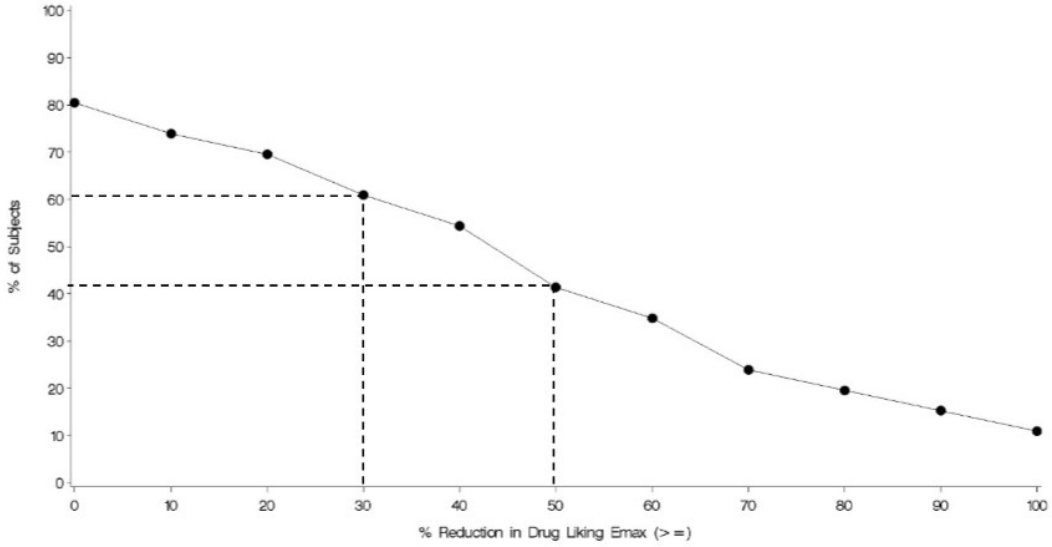
Parameter	ARYMO ER (High Volume) (n = 46)	ARYMO ER (Low Volume) (n = 46)	Morphine Sulfate Extended-Release (Low Volume) (n = 46)	Placebo (n = 46)
Maximum Drug Liking (E_{max})				
Mean (SD)	65.5 (14.3)	59.6 (12.5)	77.7 (11.7)	54.7 (10.6)
Median (Q1, Q3)	62.0 (52.0, 76.0)	52.5 (51.0, 65.0)	77.5 (70.0, 85.0)	51.0 (50.0, 58.0)
Overall Drug Liking (E_{max})				
Mean (SD)	53.9 (21.7)	54.4 (13.6)	72.7 (18.1)	52.1 (11.2)
Median (Q1, Q3)	51.0 (50.0, 67.0)	50.5 (50.0, 55.0)	71.0 (61.0, 87.0)	50.0 (50.0, 51.0)
Take Drug Again (E_{max})				
Mean (SD)	43.1 (29.6)	52.6 (17.2)	69.9 (27.4)	52.5 (12.7)
Median (Q1, Q3)	50.0 (19.0, 66.0)	50.0 (50.0, 58.0)	73.0 (57.0, 90.0)	50.0 (50.0, 51.0)
High[2]				
Mean (SD)	27.7 (4.2)	16.0 (3.5)	61.2 (3.5)	10.73 (3.0)
Median (Q1, Q3)	20 (2, 50)	5 (0, 20)	65.5 (42, 79)	0 (0, 9)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)
[2] 100 point unipolar VAS (0="not at all", 100="extremely")
Source: sponsor's clinical-overview.pdf Table 2 and 067-eg-009-body.pdf Table 14.2.4.2

The statistical tests for the pair-wise comparisons are in Appendix 2 Tables 3, 8, and 10. The percent reduction plot for drug liking VAS Emax for manipulated intranasal EG-001 versus the positive control, manipulated intranasal MS Contin, was also provided by the sponsor as seen in Figure 3.3.2 A.

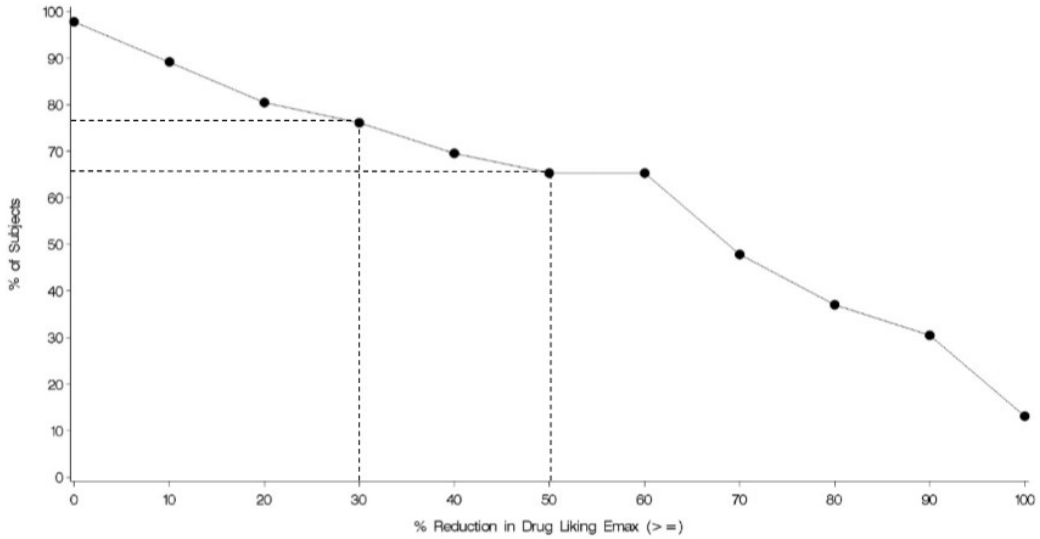
Figure 3.3.2: Percent Reduction Profile Plot for Drug Liking VAS Emax for Intranasal EG-001 versus Manipulated Intranasal MS Contin – Completers Population (N = 46)

A: Manipulated Intranasal EG-001 versus Manipulated Intranasal MS Contin



sponsor's clinical-overview.pdf Figure 3,

B: Manipulated/Sieved Intranasal EG-001 versus Manipulated Intranasal MS Contin



sponsor's clinical-overview.pdf Figure 4.

Sponsor's conclusion:

Intranasal administration of manipulated Egalet PR morphine, both a high volume version which included all particle sizes and a manipulated/sieved low volume version consisting of small

particles amenable to snorting, demonstrated significantly lower subjective drug liking, and physiologic effects compared to manipulated intranasal MS CONTIN. This is supported by a statistically significant decrease in the primary outcome of peak score on drug liking (Emax). Therefore, the results of this study indicate that Egalet PR morphine, with its abuse-deterrent properties, has lower potential for abuse via the intranasal route compared to MS CONTIN.

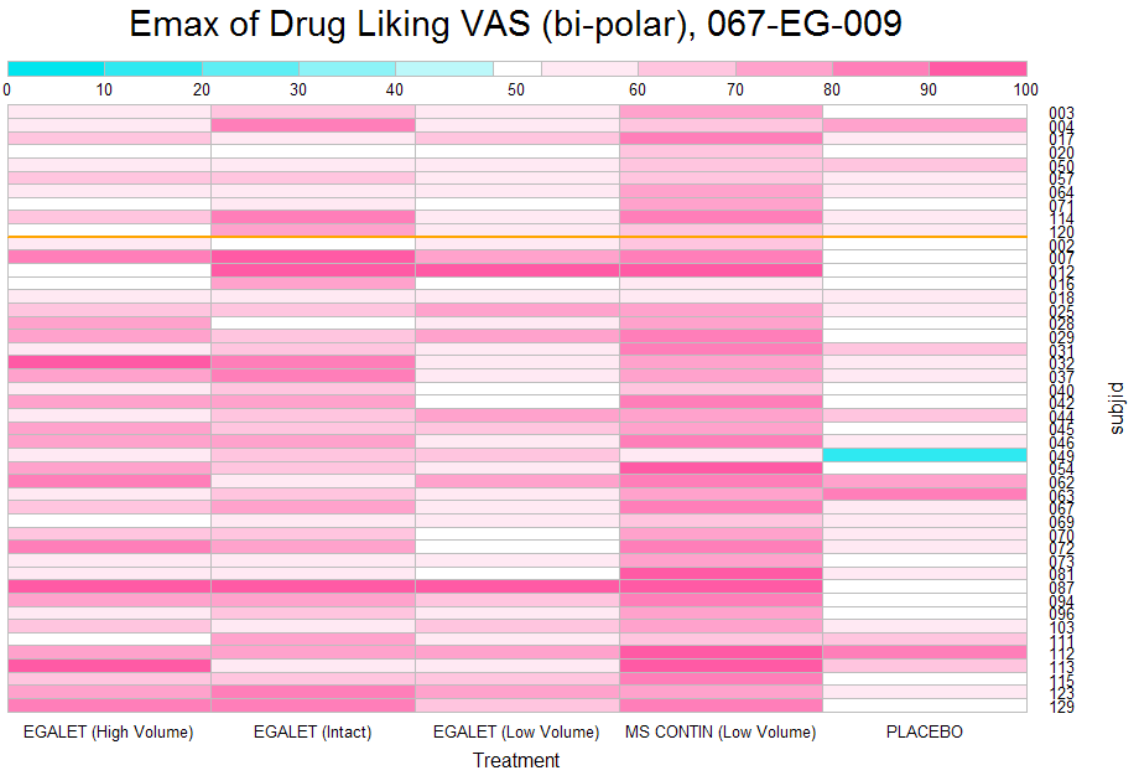
3.3.4 Reviewer's Assessment

3.3.4.1 Descriptive Analysis

This reviewer verified the sponsor's descriptive primary and key secondary results shown in Table 3.3.1. In this table, one can see similar variances among treatment arms.

Figure 3.3.3 is a heat map display, which shows individual Emax responses to each treatment as measured by Drug Liking VAS. In the figure, drug disliking is shown in blue, neutral response is shown in white and drug liking is shown in pink. The subjects (n = 46) represented above the thin orange line are females (n = 10), and the subjects below the orange line are males (n = 39).

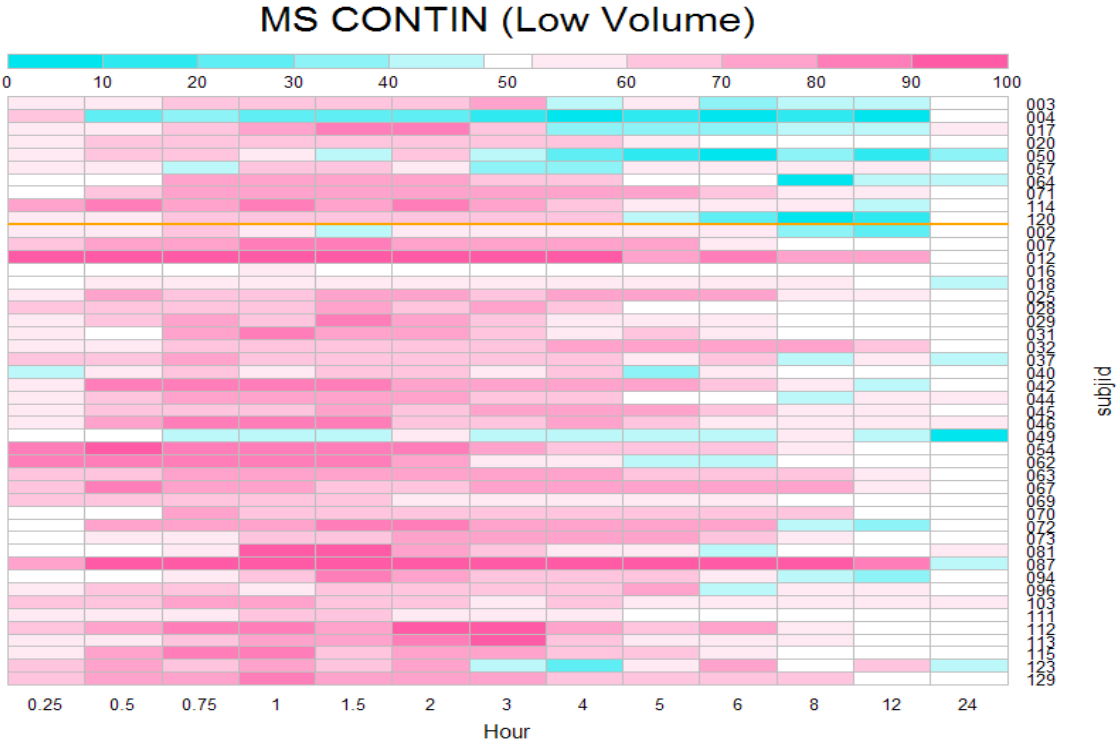
Figure 3.3.3 Heat Map for the Peak Effect (Emax) of Drug Liking VAS by Treatment.



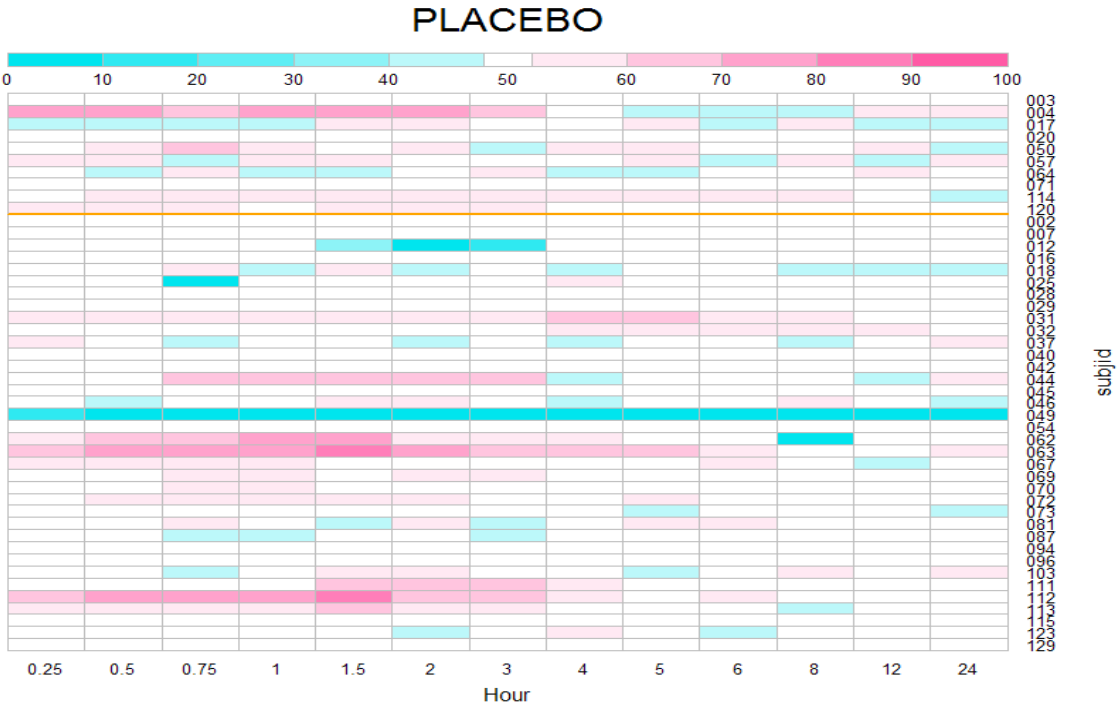
Figures 3.3.4 are the individual time course response profiles for the positive control manipulated intranasal MS CONTIN (A), placebo (B), manipulated intranasal Egalet (high volume) (C), manipulated/sieved intranasal Egalet (low volume) (D), and oral intact Egalet (E), respectively.

Figure 3.3.4. Heat Map for the Peak Effect (Emax) of Drug Liking VAS by Treatment.

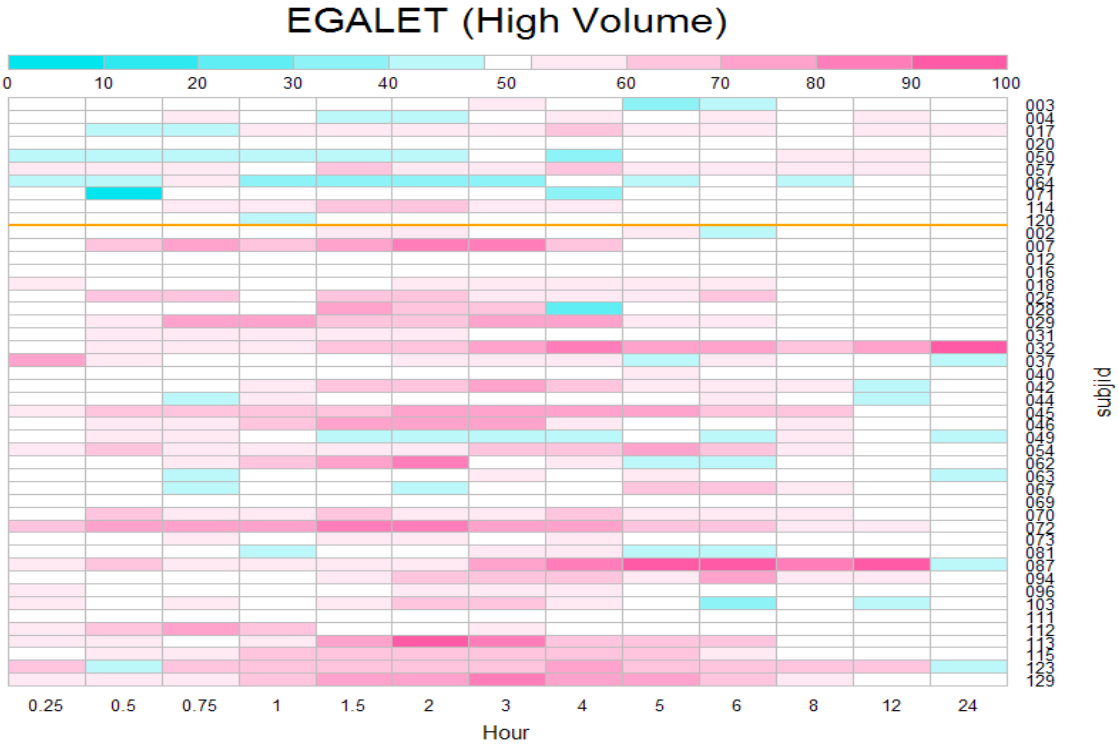
A: manipulated intranasal MS CONTIN



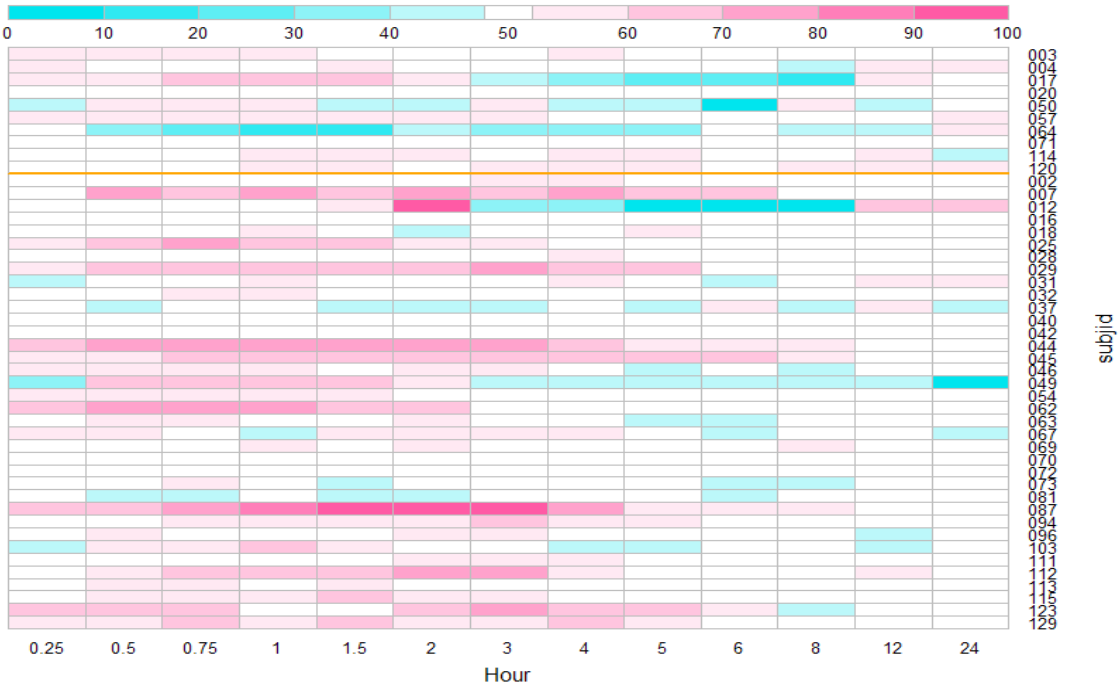
B: Placebo



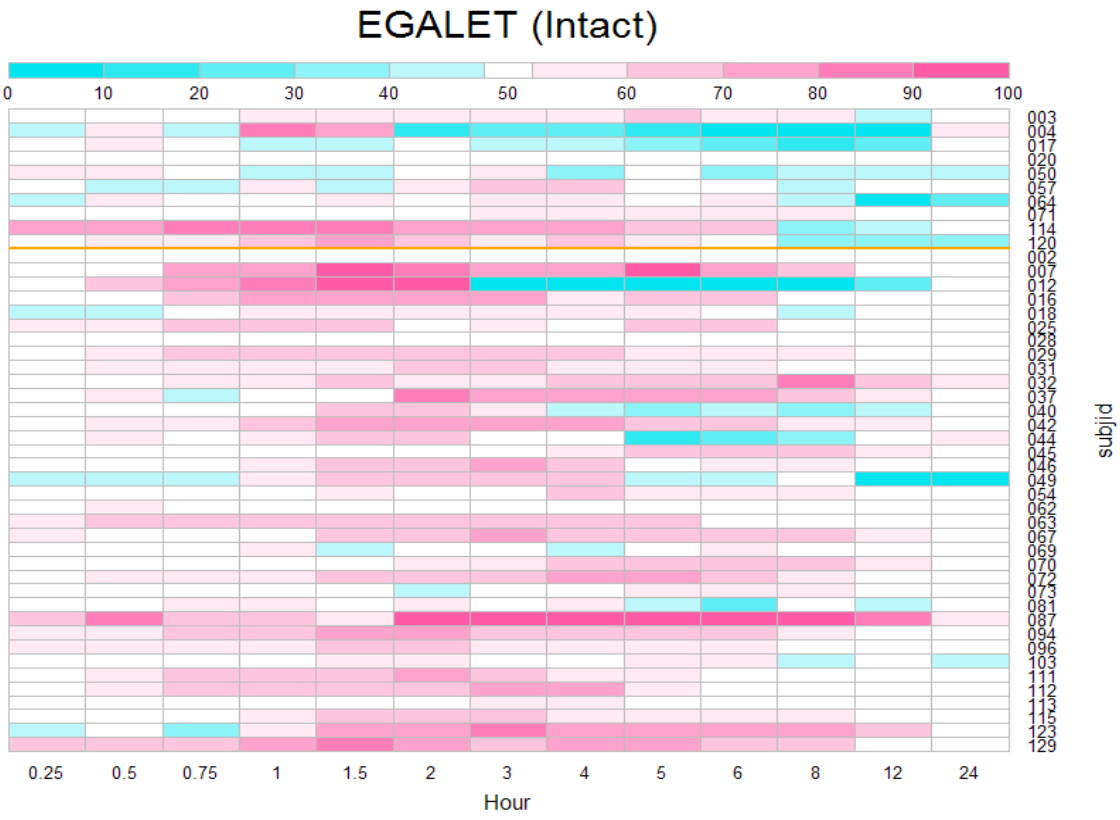
C: manipulated intranasal Egalet (high volume)



D: manipulated/Sieved intranasal Egalet (low volume)



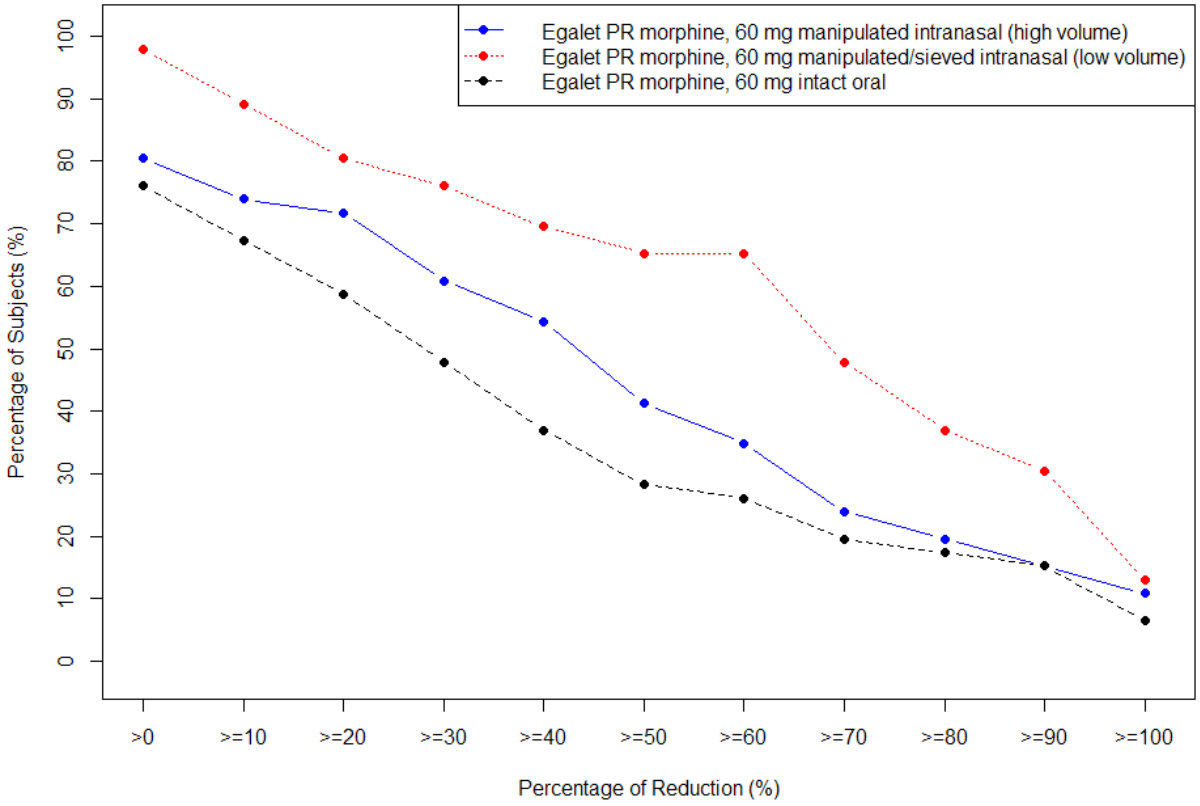
E: Oral Intact Egalet



3.3.4.2 Responder Analysis – Drug Liking VAS

The relationship of percent reduction and percent subjects by this reviewer is shown in Figure 3.3.5, suggesting an order of relative drug liking from high to low: manipulated/Sieved intranasal Egalt, oral intact Egalet, and manipulated intranasal Egalet.

Figure 3.3.5: Percent Reduction Profile for Emax of Drug Liking VAS for Study 067-EG-009



Responder proportion test

Responders were categorized into those who demonstrated at least 30%, 40%, or 50% reduction in Emax of Drug Liking. Table 3.3.2 presents the results of the proportion test in Drug Liking VAS Emax score following administration of Egalet. In consistence with the results in Figure 3.3.5, the Manipulated/Sieved intranasal Egalet had more favorable abuse deterrent property than the manipulated intranasal Egalet, at significance level of 0.025 (1-sided).

Table 3.3.2 "At This Moment" Drug Liking VAS Emax Responder Analysis, Completers Population (n=46)

	Percent Reduction		
	≥30%	≥40%	≥50%
Manipulated intranasal Egalet			
Responder rate	0.61	0.54	0.41
Z-score	1.47	0.59	-1.18
P value	0.07	0.278	0.881
Manipulated/Sieved intranasal Egalet			
Responder rate	0.76	0.70	0.65
Z-score	3.54	2.65	2.06
P value	0.0002	0.004	0.019
Oral intact Egalet			
Responder rate	0.48	0.37	0.28
Z-score	-0.29	-1.77	-2.95
P value	0.616	0.962	0.998

Above responder analyses support 1) the abuse-deterrent property of intranasal IN; and 2) no difference between the oral tablete and the positive control.

3.3.4.3 Statistical Testing

This reviewer performed statistical tests on the primary and key secondary endpoints (n=38) using the mixed effect model for pairwise treatment comparisons and Wilcoxon signed-rank test on the within-subject differences as shown in Table 3.3.3. The design that all subjects received the same treatment drug in the first treatment period prohibited the presence of "treatment period" as a fixed factor in the mixed effect model. Therefore, the model contains only the treatment and sequence as fixed factors.

Table 3.2.3. Summary of Pair-wise Comparison Between Treatments (n=46)

Pairwise	Mean diff (se)	95% CI	p-value	Median diff	95% CI	p-value
Drug Liking						
C - P	23.0 (2.1)	18.9, 27.2	<.0001	23	21, 27	<.0001
C-Ta	12.2 (2.1)	7.9, 16.5	<.0001	12.5	9, 17	<.0001
C-Tb	18.1 (1.9)	14.3, 21.9	<.0001	20	14, 23	<.0001
C-Tc	9.2 (2.1)	5.0, 13.3	<.0001	10	4, 16	0.0001
Ta – P	10.8 (2.4)	6.0, 15.6	<.0001	8	3, 21	<.0001
Tb – P	4.9 (2.2)	0.6, 9.3	0.0276	0.5	0, 8	0.0787
Tc - P	13.9 (2.3)	9.2, 18.6	<.0001	13	4, 19	<.0001
High						
C - P	50.5 (4.1)	42.3, 58.6	<.0001	50.5	42, 66	<.0001
C-Ta	33.5 (4.5)	24.4, 42.6	<.0001	33	23, 40	<.0001
C-Tb	45.4 (3.8)	37.8, 52.9	<.0001	46	35, 63	<.0001
C-Tc	24.5 (4.4)	15.8, 33.2	<.0001	28.5	9, 36	<.0001
Ta – P	17.0 (4.8)	7.5, 26.5	0.0007	16	3, 38	0.0017
Tb – P	5.1 (4.0)	-3.0, 13.2	0.2119	0	0, 7	0.1802
Tc - P	26.0 (4.6)	16.8, 35.2	<.0001	23	11, 37	<.0001
Take drug again						
C - P	17.4 (4.0)	8.2, 26.5	<.0001	21.5	12, 35	<.0001
C-Ta	26.7 (5.4)	14.4, 39.0	<.0001	24	10, 50	<.0001
C-Tb	17.3 (4.3)	7.3, 27.2	0.0002	18	10, 27	<.0001
C-Tc	10.9 (4.7)	0.2, 21.7	0.0229	7.5	0, 21	0.0003
Ta – P	-9.4 (4.4)	-19.5, 0.8	0.038	-1.5	-24, 8	0.0466
Tb – P	0.1 (3.0)	-6.8, 7.1	0.9715	0	0, 1	0.6880
Tc - P	6.4 (3.5)	-1.7, 14.6	0.0732	4	0, 14	0.0620
Overall drug liking						
C - P	20.6 (2.9)	14.8, 26.3	<.0001	20.5	14, 33	<.0001
C-Ta	18.8 (3.7)	11.3, 26.3	<.0001	15	8, 25	<.0001
C-Tb	18.2 (2.9)	12.4, 24.1	<.0001	17	11, 26	<.0001
C-Tc	13.3 (4.0)	5.4, 21.2	0.0013	13.5	4, 20	<.0001
Ta – P	1.8 (3.3)	-4.9, 8.4	0.5941	0	0, 14	0.5219
Tb – P	2.3 (2.4)	-2.4, 7.1	0.3303	0	0, 2	0.3963
Tc - P	7.3 (3.6)	0.2, 14.4	0.0451	4.5	0, 16	0.0149

T = test drug in the Treatment Phase
Ta = Treatment A: Egalet PR morphine, 60 mg manipulated intranasal (high volume)
Tb = Treatment B: Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume)
C = Treatment C: MS CONTIN, 60 mg manipulated intranasal (low volume)
Tc = Treatment D: Egalet PR morphine, 60 mg intact oral
P = Placebo

The primary comparison between the positive control, manipulated intranasal MS CONTIN, 60 mg, and each of other treatments are significant at level of 0.05 (two-sided). Above results are supported by the secondary analyses on three key secondary endpoints, VAS Emax of high, take drug again, and overall drug liking. These results (testing median differences) are numerically different from the sponsor's (Appendix 2: Tables 11.4.1.2-2, 11.4.1.4-2, and 11.4.1.5-2 shown in sponsor's 067-eg-009-body.pdf Table).

This reviewer further performed a hypothesis test based on the FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling published in April, 2015 that the primary hypothesis should be:

$$H_o: \mu_C - \mu_T \leq (\mu_C - 50)\delta^* \text{ versus } H_a: \mu_C - \mu_T > (\mu_C - 50)\delta^*$$

with $0< \delta^*< 1$ and the δ^* should be pre-specified. The null hypothesis can be equivalently written as:

$$H_o: \mu_{C\delta} - \mu_T \leq 0 \text{ where } \mu_{C\delta} = (1- \delta^*)\mu_C + 50\delta^*$$

As for the study 067_eg-008, this study was planned at or before the FDA guidance published, such a primary analysis was not done. This reviewer did the post-hoc analysis using δ^* starting from 0.05 and increase δ^* with an increment of 0.05 until the test is no longer significant. The results are summarized in Table 3.3.4.

Table 3.3.4: Test of Primary Hypothesis Required by FDA Guidance (N=46)

T	δ*	Mean diff	SE	p-value	C-T, 95% CI
Ta[1]	0	12.2	2.0	<.0001	8.2, 16.2
Ta[1]	0.25	5.3	2.0	0.0080	1.4, 9.2
Ta[1]	0.30	3.9	1.9	0.0447	0.1, 7.8
Tb	0	18.1	2.0	<.0001	14.1, 22.1
Tb	0.50	4.3	1.8	0.0169	0.8, 7.9
Tb	0.55	2.9	1.8	0.0992	-0.6, 6.4
Tc	0	9.2	2.0	<.0001	5.1, 13.2
Tc	0.15	5.2	2.0	0.0114	1.2, 9.2
Tc	0.20	3.8	2.0	0.0561	-0.1, 7.7

Ta = Treatment A: Egalet PR morphine, 60 mg manipulated intranasal (high volume)
Tb = Treatment B: Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume)
C = Treatment C: MS CONTIN, 60 mg manipulated intranasal (low volume)
Tc = Treatment D: Egalet PR morphine, 60 mg intact oral
[1] Treatment period was not included in the mixed effect model

The results in Table 3.3.4 clearly showed that drug abuse deterrent property is observed in both manipulated intranasal Egalet (high volume) and manipulated/sieved intranasal Egalet (low volume) related to manipulated intranasal MS CONTIN, while the manipulated/sieved intranasal Egalet (low volume) being more potent ($\delta^* = 0.5 > 0.30$) as an abuse deterrent product.

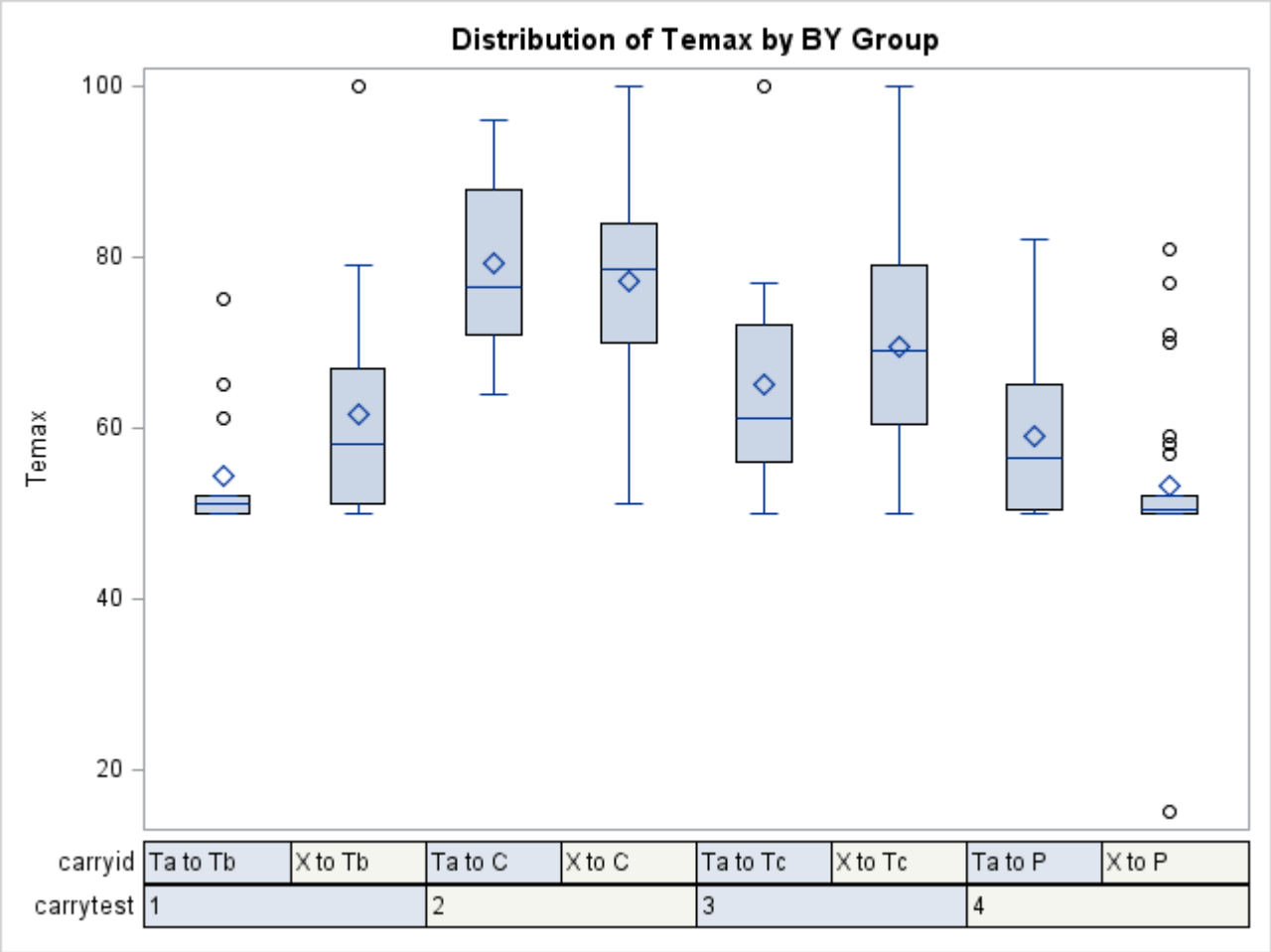
Since, all subjects received manipulated intranasal Egalet PR morphine (high volume) during Treatment Period 1 while for the remaining 4 Treatment Periods, subjects were randomized

based on a Williams design to 1 of 4 sequences where each subject received the remaining 4 treatments, this reviewer evaluated the possible carryover effect. Figure 3.3.6 compared the levels of drug liking VAS Emax between each of the following pairs:

- **Ta to Tb versus X to Tb**: Emax of manipulated/Sieved intranasal Egalet (low volume) treatment in Treatment Period 2 verses that in all other Treatment Periods
- **Ta to C versus X to C**: Emax of manipulated intranasal MS CONTIN treatment in Treatment Period 2 verses that in all other Treatment Periods
- **Ta to Tc versus X to Tc**: Emax of oral intact Egalet treatment in Treatment Period 2 verses that in all other Treatment Periods
- **Ta to P versus X to P**: Emax of placebo treatment in Treatment Period 2 verses that in all other Treatment Periods

All above descriptive comparisons, except for the last one (the placebo treatment), suggest possible carryover effect. As seen in Figure 3.3.6, the carryover effect for manipulated intranasal MS CONTIN appears small, suggesting no difference between the prior treatments of C, being Ta and others; however, obvious carryover effects exist for other treatments. The mean Emax of placebo is larger when the prior treatment is Ta than that when the prior treatments are others; on the opposite, the mean Emaxes of manipulated/Sieved intranasal Egalet (low volume) and oral intact Egalet are obviouslt smaller when the prior treatment is Ta than that when the prior treatments are others. In other words, such a study design could lead to a larger mean Emax of placebo, but smaller mean Emaxes of manipulated/Sieved intranasal Egalet (low volume) and oral intact Egalet, leading to smaller mean differences between placebo and the manipulated/Sieved intranasal Egalet (low volume) or the oral intact Egalet, but larger mean differences between manipulated intranasal MS CONTIN and the manipulated/Sieved intranasal Egalet (low volume) or the oral intact Egalet. Thus, it would be likely favorable to claim Egalet (Tb and Tc) abuse deterrent. However, the quantitative comparisons by statistical tests are not available due to the limit of the small sample sizes.

Figure 3.3.6: Comparison of Mean Emax of Drug Liking VAS in Treatment Period 2 to the Thereafter Treatment Periods in Study 067-EG-009



Ta = Treatment A: Egalet PR morphine, 60 mg manipulated intranasal (high volume)
Tb = Treatment B: Egalet PR morphine, 60 mg manipulated/sieved intranasal (low volume)
C = Treatment C: MS CONTIN, 60 mg manipulated intranasal (low volume)
Tc = Treatment D: Egalet PR morphine, 60 mg intact oral
P = Treatment E: Placebo

3.3.4.4 Reviewer's Summary and Conclusion

The data of Study 067-EG-009 provides statistical evidence to support the abuse deterrent property of both the manipulated intranasal Egalet (high volume) and manipulated/Sieved intranasal Egalet (low volume) when compared to manipulated intranasal MS CONTIN at the same dose, 60 mg. Thisconclusion is based on the following collective evidence:

1. The value of $\delta^{*}>0.2$ as defined in FDA 2015 Guidance for the primary analysis
2. The lower limits of the 95% confidence interval are 5 or more points in drug liking VAS Emax from the tests of the pair-wise comparisons between each of the intranasal treatments of Egalet and the intranasal MS CONTIN
3. The tests of key secondary analyses support the results of the primary endpoint analysis

4. The responder analysis supports abuse deterrent property of both the manipulated intranasal Egalet (high volume) and manipulated/Sieved intranasal Egalet (low volume) when compared to manipulated intranasal MS CONTIN.

However, there are possible carryover effects due to the study design.

3.4 Evaluation of Safety

An evaluation of the safety of Egalet in both Studies 067-EG-008 and 067-EG-009 is included in the clinical review by Dr. James Tolliver.

3.5 Benefit:Risk Assessment (Optional)

I did not conduct a benefi-risk analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No subgroups were analyzed due to small samples sizes in each subgroup.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The statistical analysis performed by the sponsor did not follow the FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling published in April, 2015. For instance, the primary hypothesis should be written as:

$$H_o: \mu_C - \mu_T \leq (\mu_C - 50)\delta^* \text{ versus } H_a: \mu_C - \mu_T > (\mu_C - 50)\delta^*$$

with $0 < \delta^* < 1$. Pre-specify δ^*. The sponsor's analysis was eventually an analysis by setting $\delta^*=0$ which is not acceptable.

- In the study design of 067-EG-009, all subjects received manipulated intranasal Egalet PR morphine (high volume) during Treatment Period 1 while for the remaining 4 Treatment Periods, subjects were randomized based on a Williams design to 1 of 4 sequences where each subject received the remaining 4 treatments. Such a design may cause possible carryover effect from the Treatment Period 1 to Period 2, leading to a possible biased estimate about the abuse deterrent effect of manipulated/Sieved intranasal Egalet (low volume).
- Only one positive control dose was used in either study. The FDA's draft guidance of drug abuse-deterrent recommended at least two doses of positive control in the treatment phase.
- One (2.6%) subject was excluded from the randomized population in the Study 067-EG-008, withdrawal by the subject during the Treatment phase.

  Four (8%) subjects were excluded from the randomized population in the Study 067-EG-009. Three were withdrawal by subjects during the Treatment phase and one dropout due to positive breath alcohol test.

5.2 Collective Evidence

The conclusions of this reviewer are based on the following collective evidence for the two studies:

1. The results of descriptive analyses are the same between the sponsor and this reviewer
2. The results of hypothesis tests (testing median differences) of this reviewer are numerically different from those of the sponsor
3. The fixed factors of sequence and period in the mixed effect model are not significant at level of 0.10 for both studies
4. The rates of missing data of the two studies (<10%) are in the range as seen from the data by other sponsors for similar studies
5. There are no missing data for selecting the primary and key secondary endpoints (Emax) from the completers population
6. The primary analysis recommended by FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling published in April, 2015 provided insight information quantitatively about if and how the test drug, EGALET, is abuse deterrent relative to the positive control, MS CONTIN when administrated in different routes. The relative order

of abuse deterrent potent by treatments are consistent with the results of the traditional tests (delta*=0) and descriptive analysis.

5.3 Conclusions and Recommendations

Two randomized, double-blind, active and placebo-controlled clinical studies in non-dependent recreational opioid users were conducted to characterize the abuse potential of ARYMO ER following administration via the intranasal and oral routes compared to morphine sulfate extended-release tablets. This reviewer conclude the following about the data.

Study 067-EG-008

The abuse deterrent properties of orally administrated Egalet (60 mg) compared to MS CONTIN (60 mg) and placebo were evaluated in Study 067-EG-008 which was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of manipulated and manipulated/sieved EG-001 vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users.

The numbers of completers were 38 (97%). One dropped out and was withdrawal by subject during the Treatment phase.

This reviewer conclude that the data of Study 067-EG-008 failed to provide acceptable evidence to support that the oral manipulated Egalet (60 mg) is abuse deterrent as compared to oral manipulated MS CONTIN, 60 mg. This conclusion is based on the following evidences:

1. The value of δ*, as defined in FDA 2015 Guidance, is less than 0.05 which is not acceptable for claiming abuse deterrent of oral manipulated Egalet relative to oral manipulated MS CONTIN
2. The test of the pair-wise comparison between oral manipulated Egalet and MS CONTIN is on boundary significance with the lower limit of the 95% confidence interval less than 1 point only in drug liking VAS Emax
3. Both the tests of key secondary analyses and the responder analysis showed a weak or no difference between oral manipulated Egalet and MS CONTIN. Particularly, the abuse deterrent properties were not supported by the two critical endpoints (Take Drug Again and Overall Drug Liking).

Study 067-EG-009

The abuse deterrent properties of intranasally administrated Egalet (60 mg) compared to MS CONTIN (60 mg) and placebo were evaluated in Study 067-EG-009 which was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study assessing the abuse potential of manipulated and manipulated/sieved EG-001 vs. manipulated MS CONTIN when administered intranasally to nondependent recreational opioid users.

The numbers of completers were 46 (92%). Four subjects dropped out during the Treatment period. Three were withdrawal by subjects during the Treatment phase and one dropout due to positive breath alcohol test.

This reviewer confirmed that the data of Study 067-EG-009 support that both manipulated intranasal Egalet (high volume, 60 mg) with $\delta^* \leq 0.30$ and manipulated/Sieved intranasal Egalet (low volume, 60 mg) with $\delta^* \leq 0.50$ are abuse deterrent as compared to manipulated intranasal MS CONTIN, 60 mg. However, the conclusion about the abuse deterrent effect of manipulated intranasal Egalet (high volume) could be biased due to the design weakness which may cause possible carryover effect from the Treatment Period 1 to Period 2.

5.4 Labeling Recommendations

The statistical review addresses statements in the label (section 9.2: Abuse) concerning:

1. Change the last line of the first paragraph on Page 16 to:

   "……, increased tolerance, and sometimes physical withdrawal symptoms."

2. In the line 7 of the first paragraph on Page 17, delete "(b) (4),":

   (b) (4),,

3. Change the lines 1-2 of the second paragraph on Page 21 to:

   "(b) (4)

4. Make the following changes to the last paragragh on Page 22:

   (b) (4)

5. In the line 4 of the first paragraph of "Summary" on Page 23, delete the statement about (b) (4):

   "(b) (4). …."

6 Appendix

Appendix 1 Table 1

Table 11.2.1-1: Subject Demographics - All Analysis Populations

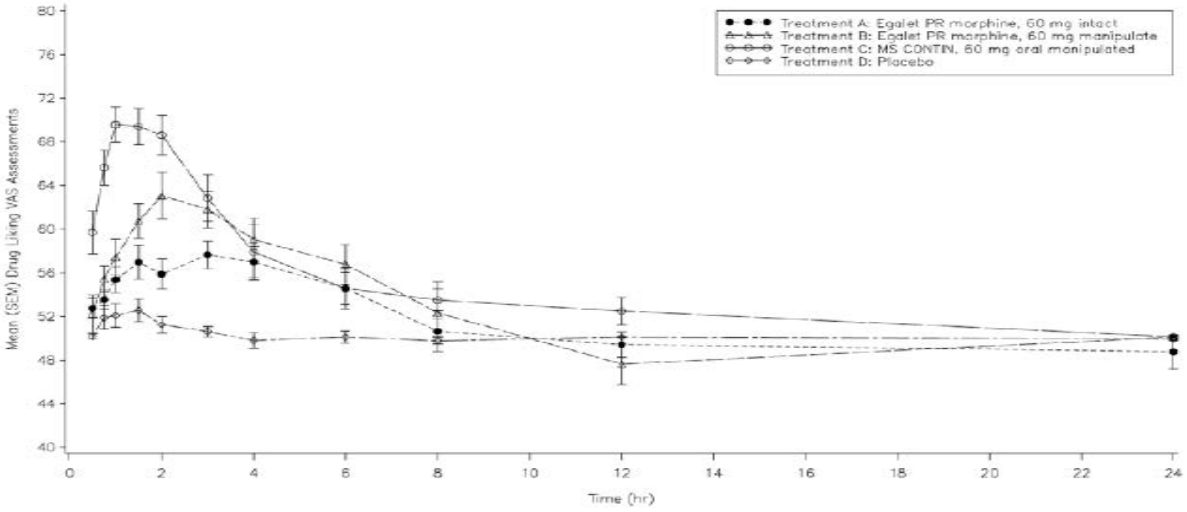
	Qualification Safety Population	Safety Population	PK Population	Completers Population	Exploratory Population
Age (yrs)					
Mean (SD)	25.7 (5.82)	24.3 (4.13)	24.3 (4.13)	24.3 (4.18)	24.1 (5.23)
Range	18 - 48	18 - 35	18 - 35	18 - 35	18 - 35
Sex					
Male	61 (78.2)	29 (74.4)	29 (74.4)	28 (73.7)	9 (75.0)
Female	17 (21.8)	10 (25.6)	10 (25.6)	10 (26.3)	3 (25.0)
Race					
White	69 (88.5)	36 (92.3)	36 (92.3)	35 (92.1)	11 (91.7)
Black or African American	6 (7.7)	1 (2.6)	1 (2.6)	1 (2.6)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (1.3)	1 (2.6)	1 (2.6)	1 (2.6)	1 (8.3)
Other	1 (1.3)	1 (2.6)	1 (2.6)	1 (2.6)	0 (0.0)
American Indian or Alaskan Native	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity					
Not Hispanic or Latino	67 (85.9)	34 (87.2)	34 (87.2)	33 (86.8)	10 (83.3)
Hispanic or Latino	11 (14.1)	5 (12.8)	5 (12.8)	5 (13.2)	2 (16.7)
BMI (kg/m^2)					
Mean (SD)	23.97 (3.443)	24.28 (3.827)	24.28 (3.827)	24.29 (3.877)	25.68 (4.274)
Range	19.0 - 32.5	19.4 - 31.9	19.4 - 31.9	19.4 - 31.9	19.4 - 31.0

BMI = body mass index; PK = pharmacokinetic; SD = standard deviation; yrs = years
Source: Table 14.1.4, Table 14.1.5, Table 14.1.7, Table 14.1.9 and Table 14.1.10

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Figure 1

Figure 11.4.1.2-1: Mean ± SEM Drug Liking Scores over Time - Completers Population (N = 38)



Source: Figure 14.2.1.7
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.

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 2

Table 11.4.1.2-1: Descriptive Statistics for PD Parameters for Drug Liking VAS - Completers Population (N = 38)

Parameter	Statistic	Manipulated MS CONTIN (N=38)	Manipulated Egalet PR Morphine (N=38)	Intact Egalet PR Morphine (N=38)	Placebo (N=38)
E_{max} (points)	Mean (SD)	73.3 (9.81)	68.3 (12.28)	63.2 (10.07)	53.3 (7.82)
	Median	74.0	67.0	62.0	50.0
AUE_{0-8}	Mean (SD)	75.938 (72.4831)	61.290 (68.4464)	39.851 (45.8591)	4.018 (19.8282)
	Median	77.930	56.723	32.293	0.000
AUE_{0-24} (h· points)	Mean (SD)	103.869 (144.9556)	47.657 (167.9159)	29.122 (139.0128)	3.963 (20.8278)
	Median	82.710	54.945	31.325	0.000
TE_{max} (h)	Median	1.02	1.99	3.00	0.52
	Range	0.5 – 4.0	0.5 – 8.0	0.5 – 24.0	0.5 – 8.0

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

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 3

Table 11.4.1.2-2: Statistical Analysis of Primary Comparisons for PD Parameters of Drug Liking VAS - Completers Population (N = 38)

	E_{max}			AUE_{0-8}		
	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value
Pairwise Comparisons						
MS CONTIN vs. Placebo						
Manipulated MS CONTIN - Placebo	20.50	16.50, 24.00	**<0.0001**	69.95	47.92, 90.97	**<0.0001**
Egalet PR Morphine vs. MS CONTIN						
Manipulated MS CONTIN - Manipulated Egalet PR Morphine	4.00	1.00, 8.00	**0.0069**	9.82	-7.90, 28.13	0.2668
Manipulated MS CONTIN - Intact Egalet PR Morphine	9.50	5.50, 14.50	**<0.0001**	30.65	13.88, 48.84	**0.0008**
Egalet PR Morphine vs. Placebo						
Manipulated Egalet PR Morphine - Placebo	14.50	10.00, 19.00	**<0.0001**	55.43	34.93, 79.29	**<0.0001**
Intact Egalet PR Morphine - Placebo	10.00	6.50, 14.00	**<0.0001**	34.64	19.11, 49.86	**<0.0001**
Manipulated vs. Intact Egalet PR Morphine						
Manipulated Egalet PR Morphine – Intact Egalet PR Morphine	4.00	-0.50, 9.00	0.0738	22.16	-1.54, 42.87	0.0752

Source: Table 14.2.1.3
AUE = area under the effect curve; CI = confidence interval; E_{max} = maximum (peak) effect; PD = pharmacodynamic; PR=prolonged-release; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 4

Table 11.4.1.3-1: Statistical Analysis for Exploratory Comparisons for PD Parameters for Drug Liking VAS – Exploratory Population (N = 12)			
	E_{max}		
	Median Difference	**95% CI**	**P-Value**
Pairwise Comparisons			
MS CONTIN vs. Egalet PR Morphine			
Manipulated MS CONTIN - Manipulated Egalet PR Morphine in Juice	0.50	-4.00, 6.00	0.8960
Egalet PR Morphine vs. Placebo			
Manipulated Egalet PR Morphine in Juice - Placebo	18.50	10.50, 26.50	**0.0015**
Egalet PR Morphine vs. Egalet PR Morphine			
Manipulated Egalet PR Morphine in Juice – Manipulated Egalet PR Morphine	6.50	-0.50,10.50	0.0669
Manipulated Egalet PR Morphine in Juice – Intact Egalet PR Morphine	13.50	6.50, 17.50	**0.0029**
CI = confidence interval; E_{max} = maximum (peak) effect; h = hour; PD = pharmacodynamic; PR=prolonged-release VAS = visual analog scale Source: Table 14.2.1.4			

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 5

Table 11.4.1.4-2: Responder Analyses of the Percentage of Subjects with a Reduction in Peak Effect (E_{max}) for Drug Liking VAS - Completers Population (N = 38)		
	Manipulated MS CONTIN vs. Manipulated Egalet PR Morphine	
	N (%)	**P-Value**
Responder at <10%	28 (73.68)	0.0025
Responder at 10%	22 (57.89)	0.2088
Responder at 20%	16 (42.11)	0.7912
Responder at 30%	15 (39.47)	0.8721
Responder at 40%	10 (26.32)	0.9975
Responder at 50%	10 (26.32)	0.9975
Responder at 60%	5 (13.16)	1.00
Responder at 70%	5 (13.16)	1.00
Responder at 80%	4 (10.53)	1.00
Responder at 90%	3 (7.89)	1.00
Responder at 100%	2 (5.26)	1.00
Source: Table 14.2.1.6 E_{max} = maximum (peak) effect; PR=prolonged-release; VAS = visual analog scale		

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 6

Table 11.4.1.5-1: Descriptive Statistics for Overall Drug Liking VAS and Take Drug Again Assessment - Completers Population (N = 38)

Time Point	Statistic	Manipulated MS CONTIN (N=38)	Manipulated Egalet PR Morphine (N=38)	Intact Egalet PR Morphine (N=38)	Placebo (N=38)	Exploratory Treatment (N=12)
Overall Drug Liking VAS						
12 Hour	Mean (SD)	67.7 (15.44)	62.1 (19.42)	54.4 (20.30)	50.3 (12.09)	65.3 (15.14)
	Median (Q1, Q3)	63.5 (57.0, 78.0)	63.0 (50.0, 72.0)	55.5 (50.0, 64.0)	50.0 (50.0, 50.0)	63.5 (53.5, 73.0)
24 Hour	Mean (SD)	67.2 (15.32)	61.9 (19.41)	53.3 (19.86)	51.4 (7.14)	52.2 (20.53)
	Median (Q1, Q3)	66.0 (57.0, 77.0)	58.5 (50.0, 71.0)	52.5 (50.0, 64.0)	50.0 (50.0, 50.0)	54.5 (45.5, 63.0)
Take Drug Again Assessment						
12 Hour	Mean (SD)	67.4 (19.22)	59.7 (20.24)	53.0 (21.56)	50.5 (11.34)	55.0 (21.97)
	Median (Q1, Q3)	67.5 (52.0, 79.0)	58.5 (50.0, 67.0)	54.0 (50.0, 63.0)	50.0 (50.0, 50.0)	54.0 (50.0, 64.5)
24 Hour	Mean (SD)	66.7 (16.26)	60.3 (20.10)	53.2 (20.72)	50.0 (11.18)	55.0 (24.74)
	Median (Q1, Q3)	64.0 (55.0, 78.0)	58.5 (50.0, 71.0)	54.5 (50.0, 62.0)	50.0 (50.0, 50.0)	59.0 (51.0, 64.5)

SD = standard deviation; VAS = visual analog scale
Source: Table 14.2.2.1 and 14.2.3.1

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 7

Table 11.4.1.5-2: Statistical Analyses for Overall Drug Liking VAS and Take Drug Again Assessment - Completers Population (N = 38)

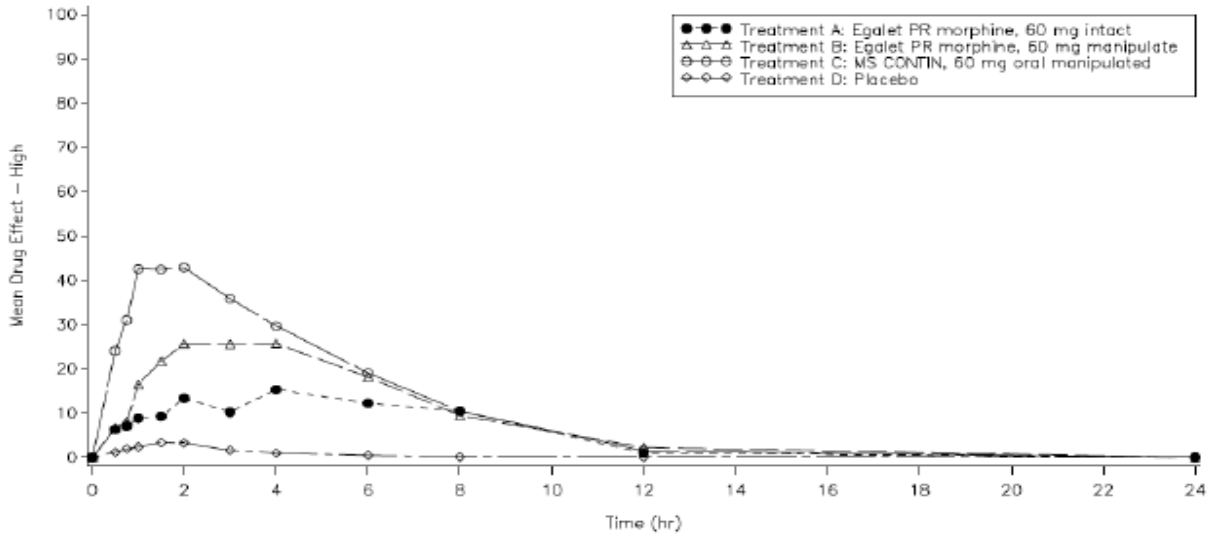
	Overall Drug Liking VAS E_{max}			Take Drug Again Assessment E_{max}		
	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value
Pairwise Comparisons						
MS CONTIN vs. Placebo						
Manipulated MS CONTIN - Placebo	17.50	11.50, 24.00	**<0.0001**	19.00	12.00, 25.50	**<0.0001**
Egalet PR Morphine vs. MS CONTIN						
Manipulated MS CONTIN - Manipulated Egalet PR Morphine	3.50	-1.00, 11.00	0.1276	5.50	0.00, 14.50	0.0537
Manipulated MS CONTIN - Intact Egalet PR Morphine	12.00	5.50, 20.50	**0.0004**	12.00	5.00, 23.00	**0.0005**
Egalet PR Morphine vs. Placebo						
Manipulated Egalet PR Morphine - Placebo	12.50	6.50, 19.00	**<0.0001**	11.50	5.50, 19.00	**0.0004**
Intact Egalet PR Morphine - Placebo	6.00	-2.00, 11.00	0.1805	6.50	-1.50, 11.50	0.1983
Manipulated vs. Intact Egalet PR Morphine						
Manipulated Egalet PR Morphine – Intact Egalet PR Morphine	6.00	1.00, 12.00	**0.0194**	4.00	0.00, 10.50	0.0543

Source: Table 14.2.2.2 and Table 14.2.3.2
CI = confidence interval; E_{max} = maximum (peak) effect; PR = prolonged-release; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Figure 2

Figure 11.4.1.6.1-1: Arithmetic Mean ± SEM High VAS over Time - Completers Population (N = 38)



Source: Figure 14.2.4.4
DEQ=drug effects questionnaire; hr=hour; PR=prolonged-release; SEM=standard error of the mean
DEQ High item: "I am feeling high…" where values are anchored on the left by "not at all" (score of 0) and on the right by "extremely" (score of 100).

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 8

Table 11.4.1.6.1-1: Descriptive Statistics for PD Parameters for High and Good Effects VAS - Completers Population (N = 38)

Parameter	Statistic	Manipulated MS CONTIN (N=38)	Manipulated Egalet PR Morphine (N=38)	Intact Egalet PR Morphine (N=38)	Placebo (N=38)
High					
E_{max}	Mean (SD)	51.9 (23.62)	38.8 (25.59)	26.8 (24.53)	5.3 (11.54)
	Median	49.0	38.0	18.5	0.0
AUE_{0-8}	Mean (SD)	215.06 (149.230)	150.60 (137.362)	90.82 (92.684)	9.69 (29.479)
	Median	171.94	103.63	55.93	0.00
TE_{max} (h)	Median	1.50	3.00	2.51	0.51
	Range	0.5 – 6.00	0.5 – 6.00	0.5 – 8.00	0.5 – 8.00
Good Effects					
E_{max}	Mean (SD)	50.9 (24.91)	35.4 (27.17)	25.9 (24.54)	6.4 (16.01)
	Median	52.0	25.5	17.5	0.0
AUE_{0-8}	Mean (SD)	212.23 (160.123)	149.74 (149.231)	89.13 (96.146)	12.24 (35.158)
	Median	202.70	91.75	59.08	0.00
AUE_{0-24}	Mean (SD)	262.49 (227.235)	202.12 (260.446)	123.89 (156.870)	13.03 (36.134)
	Median	213.93	104.00	56.98	0.00
TE_{max} (h)	Median	1.50	3.00	2.51	0.51
	Range	0.5 – 4.00	0.5 – 8.00	0.5 – 8.00	0.5 – 4.00

AUE = area under the effect curve; E_{max} = maximum (peak) effect; h = hour; PD = pharmacodynamic; TE_{max} = time to maximum (peak) effect
Source: Table 14.2.4.2

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Table 9

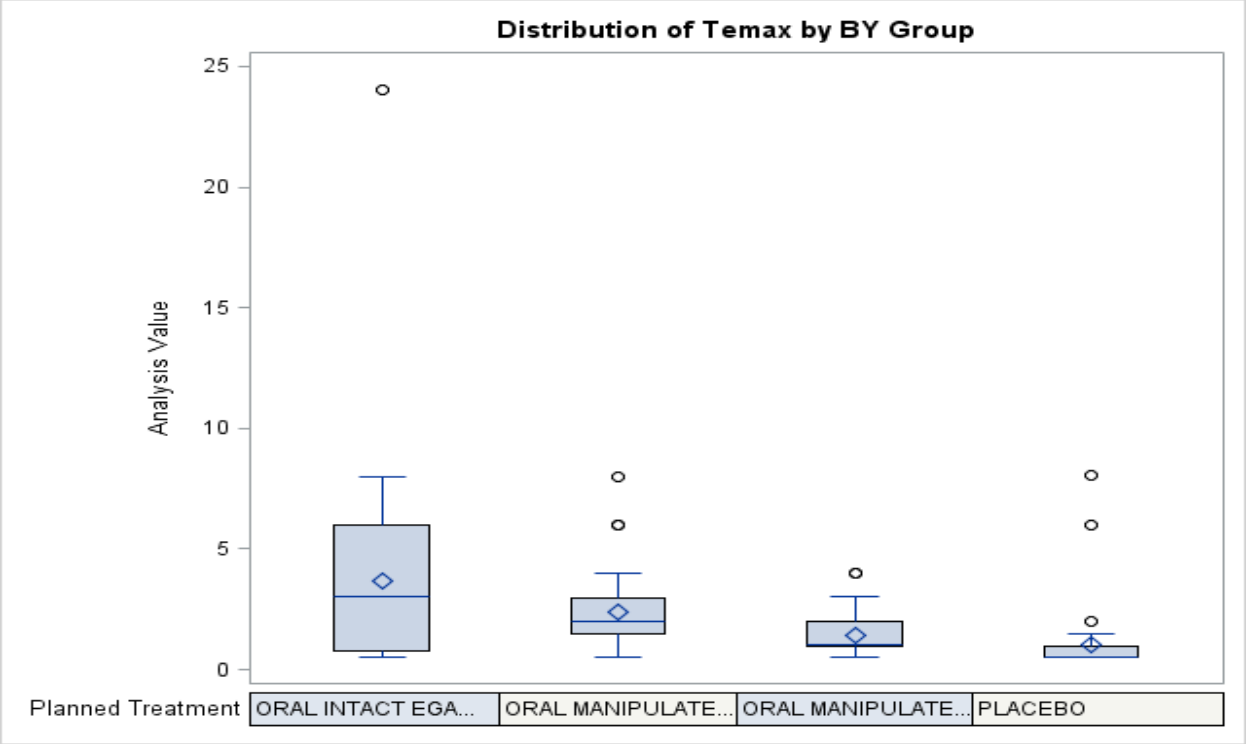
Table 11.4.1.6.1-2: Statistical Analysis for Select PD Parameters for Good Effects and High VAS– Completers Population (N = 38)

	High						Good Effects					
	E_{max}			AUE_{0-8}			E_{max}			AUE_{0-8}		
	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value
Pairwise Comparisons												
MS CONTIN vs. Placebo												
Manipulated MS CONTIN - Placebo	45.50	38.00, 54.50	**<0.0001**	192.40	148.72, 244.81	**<0.0001**	44.50	36.00, 53.50	**<0.0001**	189.15	141.77, 237.30	**<0.0001**
Egalet PR Morphine vs. MS CONTIN												
Manipulated MS CONTIN- Manipulated Egalet PR Morphine	11.50	3.50, 20.00	**0.0035**	45.62	8.37, 86.13	**0.0119**	11.50	4.50, 23.00	**0.0025**	37.17	3.99, 83.52	**0.0293**
Manipulated MS CONTIN- Intact Egalet PR Morphine	26.00	14.50, 36.50	**<0.0001**	112.78	57.26, 172.54	**<0.0001**	24.50	14.00, 36.50	**<0.0001**	109.98	60.08, 165.12	**<0.0001**
Egalet PR Morphine vs. Placebo												
Manipulated Egalet PR Morphine - Placebo	33.00	23.00, 43.50	**<0.0001**	114.74	77.85, 176.05	**<0.0001**	27.50	17.50, 38.50	**<0.0001**	107.32	71.86, 180.37	**<0.0001**
Intact Egalet PR Morphine- Placebo	20.00	11.50, 31.00	**<0.0001**	73.95	40.53, 109.06	**<0.0001**	17.50	9.50, 31.00	**<0.0001**	69.11	38.51, 105.02	**<0.0001**
Egalet PR Morphine vs. Egalet PR Morphine												
Manipulated Egalet PR Morphine – Intact Egalet PR Morphine	10.50	1.00, 21.00	**0.0304**	48.55	9.58, 98.59	**0.0202**	7.00	-1.00, 19.50	0.0946	48.05	3.87, 97.63	**0.0307**

Source: Table 14.2.4.3
AUE = area under the effect curve; CI = confidence interval; E_{max} = maximum (peak) effect; PD = pharmacodynamic; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 1 Figure 3: Check the distribution of TEmax of the drug liking VAS (Study 067-EG-008)



Appendix 1 Table 10

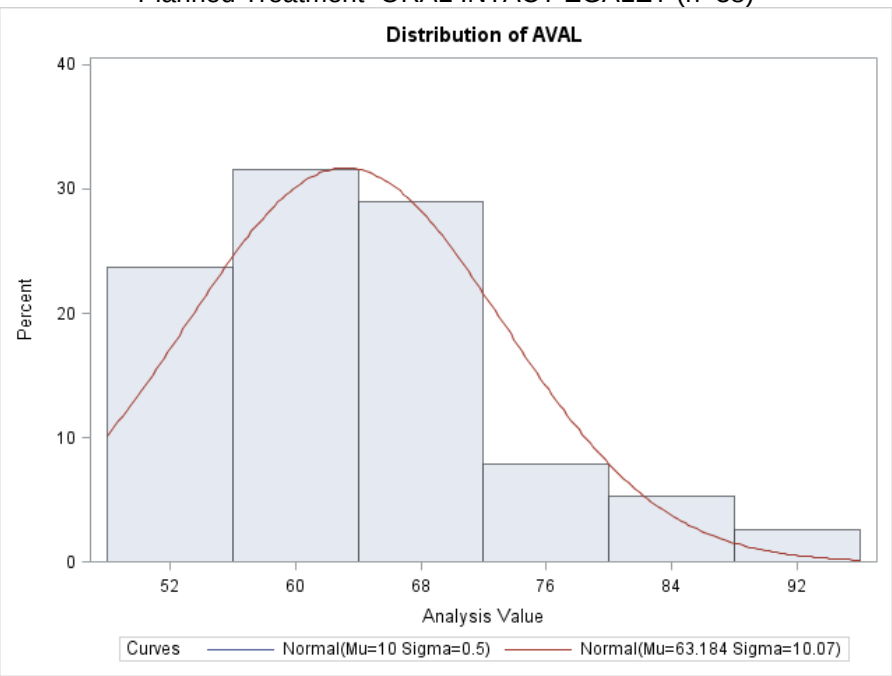
PDTEST	PARAM	T	obsN	mean	stderr	min	Q1	median	Q3	max	lclm	uclm
Drug Liking (Bipolar VAS)	AUE0-8	C	38	75.93763	11.75831	-66.13	43.50	77.93	109.68	385.75	52.11	99.76
Drug Liking (Bipolar VAS)	AUE0-8	P	38	4.017632	3.216552	-60.95	0.00	0.00	2.00	86.30	-2.50	10.53
Drug Liking (Bipolar VAS)	AUE0-8	Ta	38	39.85092	7.439331	-34.67	4.39	32.29	54.49	209.16	24.78	54.92
Drug Liking (Bipolar VAS)	AUE0-8	Tb	38	61.28961	11.10347	-148.38	28.31	56.72	86.58	244.34	38.79	83.79
Drug Liking (Bipolar VAS)	Emax	C	38	73.28947	1.59208	50.00	68.00	74.00	79.00	100.00	70.06	76.52
Drug Liking (Bipolar VAS)	Emax	P	38	53.34211	1.269108	50.00	50.00	50.00	52.00	89.00	50.77	55.91
Drug Liking (Bipolar VAS)	Emax	Ta	38	63.18421	1.633511	50.00	56.00	62.00	68.00	91.00	59.87	66.49
Drug Liking (Bipolar VAS)	Emax	Tb	38	68.34211	1.991546	50.00	61.00	67.00	75.00	100.00	64.31	72.38
Drug Liking (Bipolar VAS)	TEmax (hr)	C	38	1.450526	0.143444	0.49	1.00	1.02	2.00	4.01	1.16	1.74
Drug Liking (Bipolar VAS)	TEmax (hr)	P	38	1.052368	0.240738	0.49	0.50	0.52	0.99	8.03	0.56	1.54
Drug Liking (Bipolar VAS)	TEmax (hr)	Ta	38	3.662105	0.663648	0.50	0.75	3.00	6.00	24.01	2.32	5.01
Drug Liking (Bipolar VAS)	TEmax (hr)	Tb	38	2.389211	0.261436	0.49	1.49	1.99	2.99	8.00	1.86	2.92
I am feeling dizzy.	Emax	C	38	9.157895	2.618602	0.00	0.00	1.00	12.00	79.00	3.85	14.46
I am feeling dizzy.	Emax	P	38	0.342105	0.169831	0.00	0.00	0.00	0.00	5.00	0.00	0.69
I am feeling dizzy.	Emax	Ta	38	8.210526	2.435267	0.00	0.00	0.00	10.00	59.00	3.28	13.14
I am feeling dizzy.	Emax	Tb	38	7.342105	2.020266	0.00	0.00	0.00	12.00	50.00	3.25	11.44
I am feeling high.	AUE0-8	C	38	215.0621	24.20829	1.38	100.47	171.94	314.51	617.71	166.01	264.11
I am feeling high.	AUE0-8	P	38	9.687105	4.782094	-7.76	0.00	0.00	0.76	163.62	0.00	19.38
I am feeling high.	AUE0-8	Ta	38	90.82158	15.0354	0.00	17.72	55.93	153.28	387.62	60.36	121.29
I am feeling high.	AUE0-8	Tb	38	150.6003	22.28302	0.00	61.45	103.63	193.00	547.41	105.45	195.75
I am feeling high.	Emax	C	38	51.94737	3.831246	2.00	34.00	49.00	72.00	100.00	44.18	59.71
I am feeling high.	Emax	P	38	5.289474	1.872504	0.00	0.00	0.00	1.00	46.00	1.50	9.08
I am feeling high.	Emax	Ta	38	26.81579	3.98001	0.00	7.00	18.50	47.00	87.00	18.75	34.88
I am feeling high.	Emax	Tb	38	38.76316	4.151716	0.00	18.00	38.00	58.00	100.00	30.35	47.18
I am feeling high.	TEmax (hr)	C	38	1.846316	0.212167	0.50	1.00	1.50	2.01	6.00	1.42	2.28
I am feeling high.	TEmax (hr)	P	38	0.917632	0.204947	0.49	0.50	0.51	0.75	8.00	0.50	1.33
I am feeling high.	TEmax (hr)	Ta	38	2.946053	0.364644	0.50	0.75	2.51	4.01	8.01	2.21	3.68
I am feeling high.	TEmax (hr)	Tb	38	3.041579	0.258423	0.49	1.99	3.00	3.99	6.00	2.52	3.57
I am feeling nauseous.	Emax	C	38	14.89474	3.672742	0.00	0.00	1.50	26.00	75.00	7.45	22.34
I am feeling nauseous.	Emax	P	38	0.736842	0.633	-1.00	0.00	0.00	0.00	24.00	-0.55	2.02
I am feeling nauseous.	Emax	Ta	38	7.315789	2.429696	-1.00	0.00	0.00	9.00	68.00	2.39	12.24
I am feeling nauseous.	Emax	Tb	38	9.631579	2.319569	0.00	0.00	0.50	14.00	49.00	4.93	14.33
I am feeling sick.	Emax	C	38	12.31579	3.375947	0.00	0.00	0.00	14.00	73.00	5.48	19.16
I am feeling sick.	Emax	P	38	0.447368	0.225341	0.00	0.00	0.00	0.00	8.00	-0.01	0.90
I am feeling sick.	Emax	Ta	38	6.868421	2.617963	0.00	0.00	0.00	4.00	67.00	1.56	12.17
I am feeling sick.	Emax	Tb	38	9.631579	2.253627	0.00	0.00	1.00	19.00	52.00	5.07	14.20
I am feeling sleepy.	Emax	C	38	31.10526	4.083027	-12.00	13.00	27.00	48.00	82.00	22.83	39.38
I am feeling sleepy.	Emax	P	38	4.342105	2.103062	-3.00	0.00	0.00	0.00	60.00	0.08	8.60
I am feeling sleepy.	Emax	Ta	38	21.5	3.457268	0.00	1.00	19.00	30.00	84.00	14.49	28.51
I am feeling sleepy.	Emax	Tb	38	30.23684	4.456592	0.00	4.00	27.50	52.00	90.00	21.21	39.27
I can feel a drug effect.	Emax	C	38	52.89474	3.785461	2.00	34.00	55.50	70.00	100.00	45.22	60.56
I can feel a drug effect.	Emax	P	38	5.894737	2.104925	0.00	0.00	0.00	3.00	47.00	1.63	10.16
I can feel a drug effect.	Emax	Ta	38	26.60526	3.711222	0.00	9.00	17.50	47.00	68.00	19.09	34.12
I can feel a drug effect.	Emax	Tb	38	38.42105	4.082477	0.00	18.00	39.00	61.00	99.00	30.15	46.69
I can feel bad drug effects.	Emax	C	38	13.84211	3.205065	0.00	0.00	6.00	23.00	74.00	7.35	20.34
I can feel bad drug effects.	Emax	P	38	1.315789	1.078106	0.00	0.00	0.00	0.00	41.00	-0.87	3.50
I can feel bad drug effects.	Emax	Ta	38	9.631579	3.209698	0.00	0.00	1.00	9.00	86.00	3.13	16.14
I can feel bad drug effects.	Emax	Tb	38	16.28947	3.328165	0.00	0.00	4.00	33.00	72.00	9.55	23.03
I can feel good drug effects.	Emax	C	38	50.92105	4.04058	2.00	30.00	52.00	69.00	100.00	42.73	59.11
I can feel good drug effects.	Emax	P	38	6.421053	2.596538	0.00	0.00	0.00	1.00	80.00	1.16	11.68
I can feel good drug effects.	Emax	Ta	38	25.89474	3.981606	0.00	6.00	17.50	49.00	81.00	17.83	33.96
I can feel good drug effects.	Emax	Tb	38	35.39474	4.406697	0.00	13.00	25.50	60.00	100.00	26.47	44.32
Take Drug Again (Bipolar VA	Emax	C	38	70.10526	2.838415	35.00	56.00	68.00	80.00	100.00	64.35	75.86
Take Drug Again (Bipolar VA	Emax	P	38	51	1.658634	12.00	50.00	50.00	50.00	88.00	47.64	54.36
Take Drug Again (Bipolar VA	Emax	Ta	38	54.84211	3.3773	0.00	50.00	56.00	65.00	100.00	48.00	61.69
Take Drug Again (Bipolar VA	Emax	Tb	38	62.92105	3.180976	0.00	51.00	61.50	71.00	100.00	56.48	69.37
Overall Drug Liking VAS (Bip	Emax	C	38	69.78947	2.492709	31.00	57.00	67.50	81.00	100.00	64.74	74.84
Overall Drug Liking VAS (Bip	Emax	P	38	52.23684	1.306747	47.00	50.00	50.00	50.00	90.00	49.59	54.88
Overall Drug Liking VAS (Bip	Emax	Ta	38	55.65789	3.204122	8.00	50.00	57.00	66.00	100.00	49.17	62.15
Overall Drug Liking VAS (Bip	Emax	Tb	38	65.05263	3.020072	19.00	51.00	63.50	75.00	100.00	58.93	71.17

Appendix 1 Table 11: Correlation between treatments

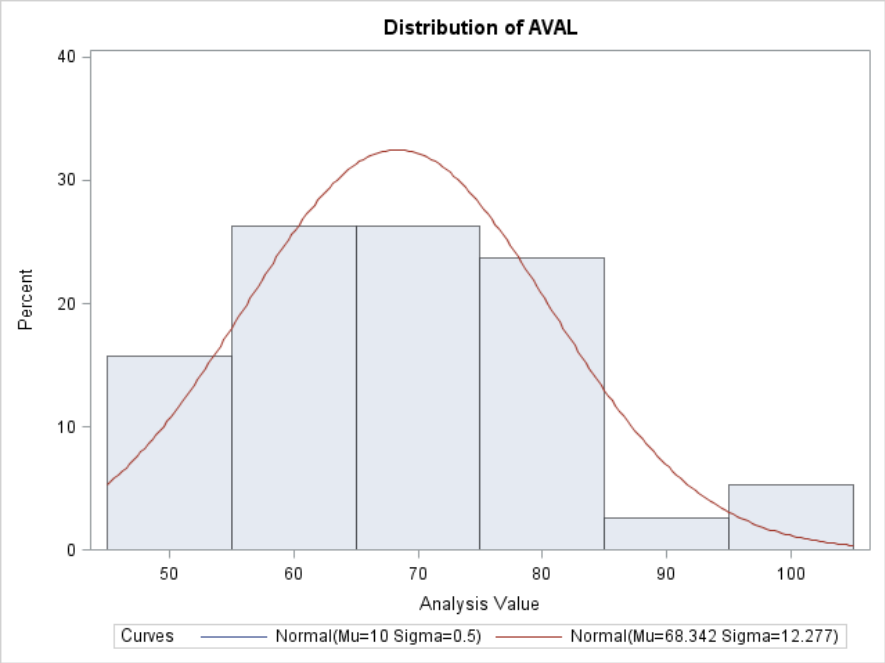
Pearson Correlation Coefficients, N = 38
Prob > |r| under H0: Rho=0

	emaxORAL MANIPULATED EGALET	emaxORAL INTACT EGALET	Emax ORAL MANIPULATED MS_CONTIN	Emax PLACEBO
emaxORAL MANIPULATED_EGALET	1.00000	0.10988 0.5114	0.46708 0.0031	-0.01504 0.9286
emaxORAL INTACT_EGALET	0.10988 0.5114	1.00000	0.05277 0.7530	0.13229 0.4285
emaxORAL MANIPULATED_MS_CONTIN	0.46708 0.0031	0.05277 0.7530	1.00000	0.10428 0.5333
emaxPLACEBO	-0.01504 0.9286	0.13229 0.4285	0.10428 0.5333	1.00000

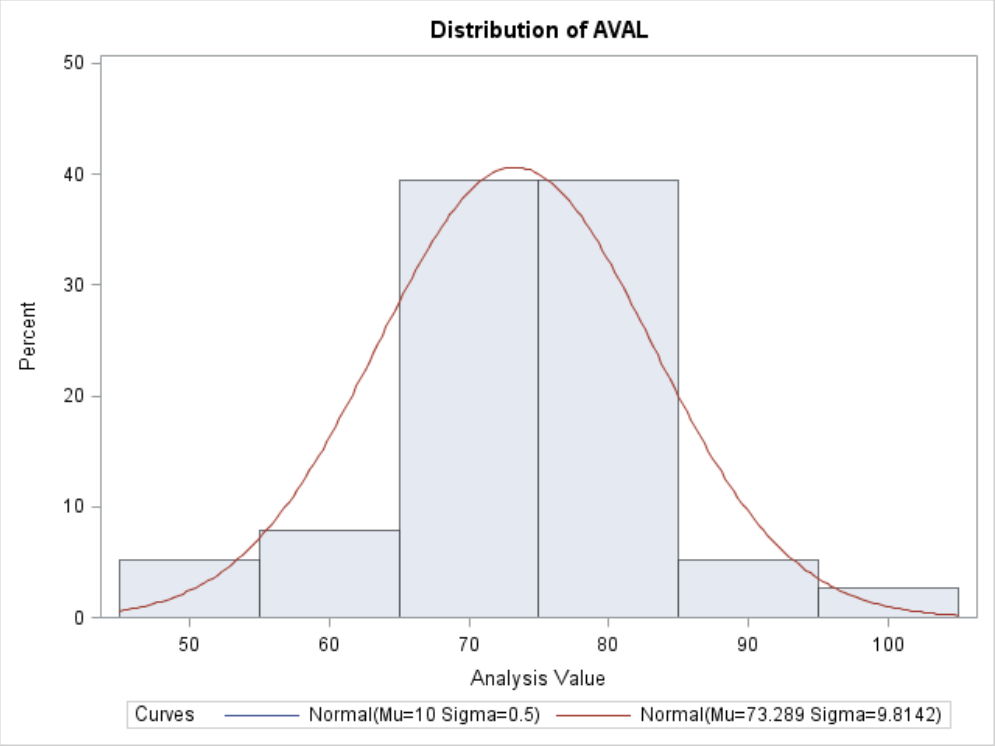
Appendix 1 Figure 4: Histograms of Drug liking Emax by Treatment



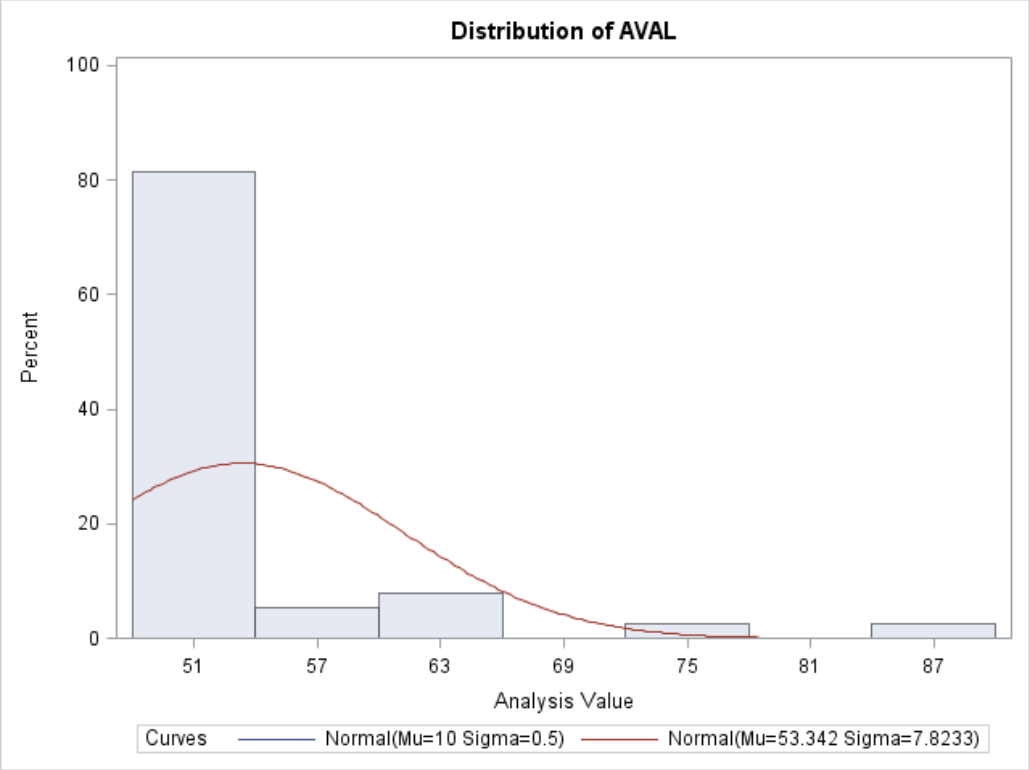
Planned Treatment=ORAL MANIPULATED EGALET (n=38)



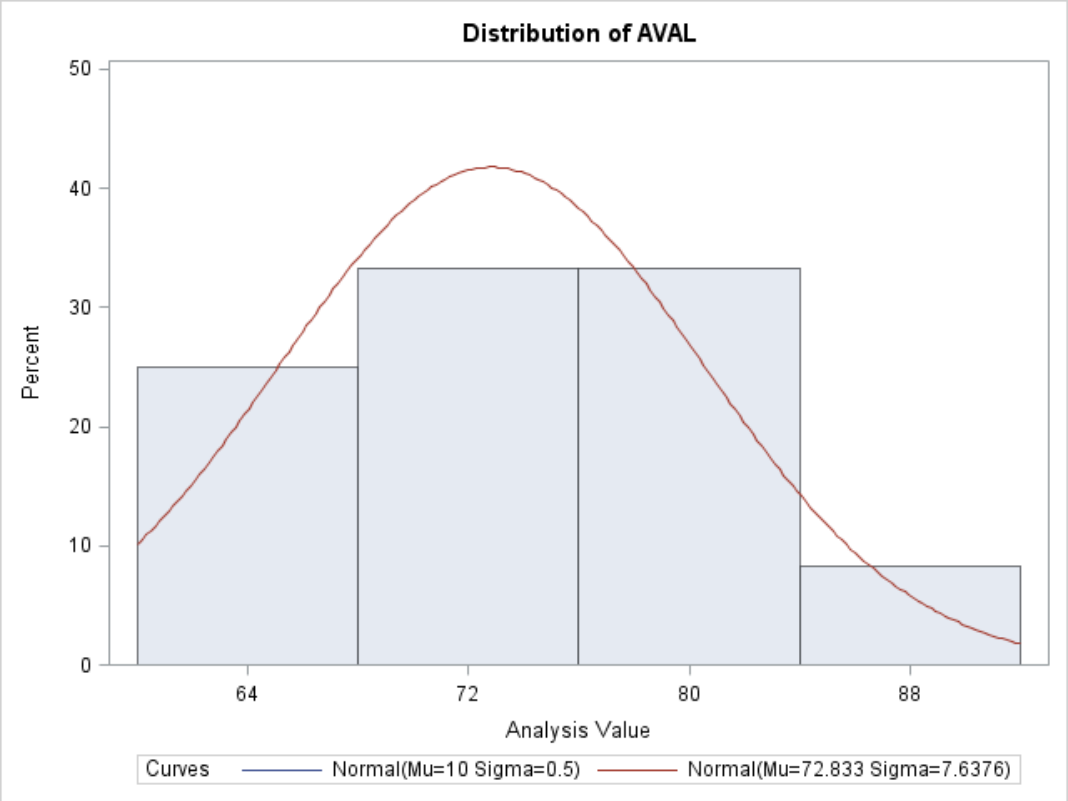
Planned Treatment=ORAL MANIPULATED MS CONTIN (n=38)



Planned Treatment=PLACEBO (n=38)



Planned Treatment=ORAL MANIPULATED EGALET (EXPLORATORY, n=12)



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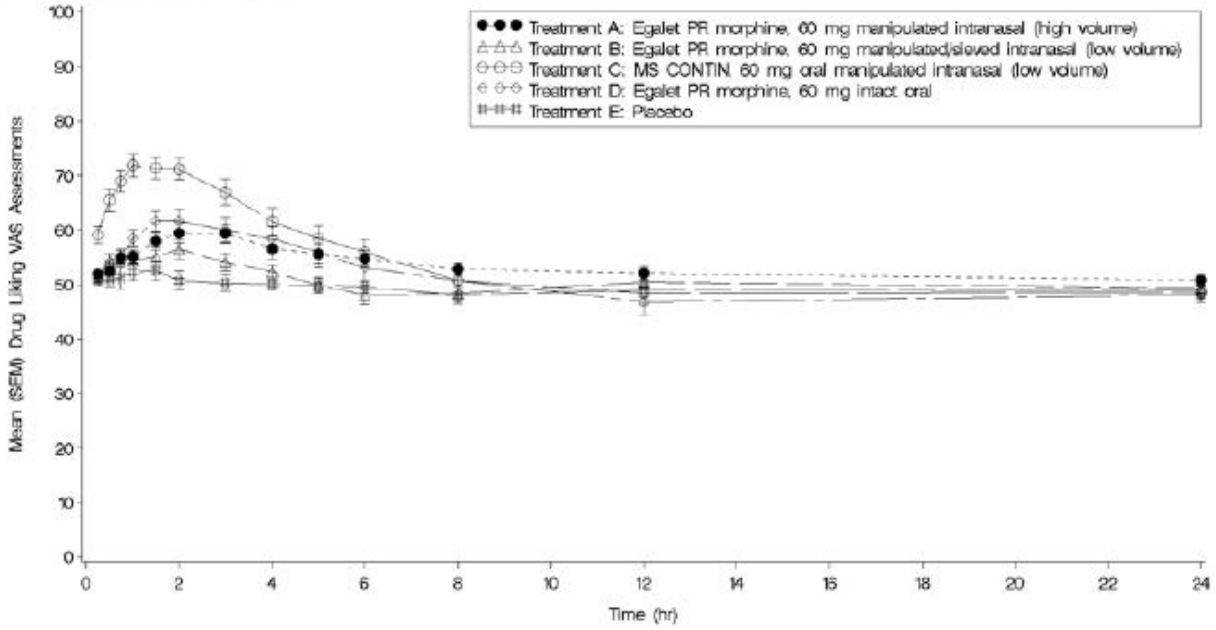
Appendix 2 Table 1

Table 11.2.1-1: Subject Demographics - All Analysis Populations				
	Qualification Safety Population (N=80)	**Safety Population (N=50)**	**PK/Completers/PP Populations (N=46)**	**MITT Population (N=49)**
Age (years)				
Mean (SD)	27.5 (8.15)	27.9 (8.01)	28.1 (8.12)	27.7 (8.03)
Range	18 – 55	19 – 55	19 – 55	19 – 55
Sex				
Male	59 (73.8)	39 (78.0)	36 (78.3)	39 (79.6)
Female	21 (26.3)	11 (22.0)	10 (21.7)	10 (20.4)
Race				
White	72 (90.0)	47 (94.0)	44 (95.7)	46 (93.9)
Black or African American	6 (7.5)	3 (6.0)	2 (4.3)	3 (6.1)
Asian	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity				
Not Hispanic or Latino	68 (85.0)	45 (90.0)	42 (91.3)	44 (89.8)
Hispanic or Latino	12 (15.0)	5 (10.0)	4 (8.7)	5 (10.2)
BMI (lb/m^2)				
Mean (SD)	24.33 (3.278)	24.17 (3.012)	24.02 (2.949)	24.12 (3.025)
Range	18.7 – 31.5	18.7 – 31.2	18.7 – 31.2	18.7 – 31.2
Source: Table 14.1.4, Table 14.1.5, Table 14.1.6, Table 14.1.7, Table 14.1.8, and Table 14.1.9 BMI = body mass index; MITT = modified intent-to-treat; N = number of subject; PK = pharmacokinetic; PP = per protocol; SD = standard deviation				

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Figure 1

Figure 11.4.1.2-1: Mean ± SEM Drug Liking Scores over Time – Completers Population (N = 46)



Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Table 2

Table 11.4.1.2-1: 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

Source: sponsor's 067-eg-009-body.pdf

Appendix 2 Table 3

Table 11.4.1.2-2: Statistical Analysis of Primary Comparisons for PD Parameters of Drug Liking VAS - Completers Population (N = 46)

	E_{max}			AUE_{0-8}		
	Median Difference	95% CI	P-Value	Median Difference	95% CI	P-Value
Pairwise Comparisons						
MS CONTIN vs. Placebo						
Manipulated Intranasal MS CONTIN - Placebo	23.50	19.50, 27.50	**<0.0001**	88.27	66.23, 112.15	**<0.0001**
Egalet PR Morphine vs. MS CONTIN						
Manipulated Intranasal MS CONTIN - Manipulated Intranasal Egalet PR Morphine	12.00	8.00, 15.50	**<0.0001**	45.89	26.00, 67.80	**<0.0001**
Manipulated Intranasal MS CONTIN – Manipulated/sieved Intranasal Egalet PR Morphine	18.50	14.00, 22.00	**<0.0001**	77.76	54.41, 103.07	**<0.0001**
Manipulated Intranasal MS CONTIN - Intact Oral Egalet PR Morphine	9.00	4.50, 13.50	**0.0001**	40.44	13.68, 62.24	**0.0015**
Egalet PR Morphine vs. Placebo						
Manipulated Intranasal Egalet PR Morphine - Placebo	11.00	5.00, 16.50	**<0.0001**	39.35	13.96, 61.46	**0.0010**
Manipulated/sieved Intranasal Egalet PR Morphine - Placebo	3.00	0.00, 7.50	0.0787	1.51	-6.35, 15.81	0.5196
Intact Oral Egalet PR Morphine - Placebo	13.00	7.50, 18.50	**<0.0001**	42.88	16.52, 69.90	**0.0009**
Egalet PR Morphine vs. Egalet PR Morphine						
Manipulated Intranasal Egalet PR Morphine – Manipulated/sieved Intranasal Egalet PR Morphine	5.00	2.00, 8.50	**0.0008**	29.45	11.37, 45.29	**0.0001**
Manipulated Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-2.50	-6.50, 1.00	0.1798	-6.42	-29.15, 14.89	0.5444
Manipulated/sieved Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-9.00	-13.00, -4.50	**<0.0001**	-40.82	-59.51, -20.14	**0.0001**

Source: Table 14.2.1.3

AUE = area under the effect curve; CI = confidence interval; E_{max} = maximum (peak) effect; PD = pharmacodynamic; PR=prolonged-release; VAS = visual analog scale

Source: sponsor's 067-eg-009-body.pdf

Appendix 2 Table 4

Table 11.4.1.3-1: Summary of the Percent Reduction in Drug Liking VAS E_{max} - Completers Population (N = 46)

	Manipulated Intranasal MS CONTIN vs. Manipulated Intranasal Egalet PR Morphine	Manipulated Intranasal MS CONTIN vs. Manipulated/Sieved Intranasal Egalet PR Morphine
Percent Reduction in E_{max}		
Mean (SD)	36.0 (49.42)	30.8 (218.13)
Median	42.2	68.5

Source: Table 14.2.1.4

E_{max} = maximum (peak) effect; N = number of subjects; PR=prolonged-release; SD = standard deviation; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Table 5

Table 11.4.1.3-2: Responder Analyses of the Percentage of Subjects with a Reduction in Drug Liking VAS E_{max} - Completers Population (N = 46)				
	Manipulated Intranasal MS CONTIN vs. Manipulated Intranasal Egalet PR Morphine		Manipulated Intranasal MS CONTIN vs. Manipulated/Sieved Intranasal Egalet PR Morphine	
	N (%)	P-Value	N (%)	P-Value
Responder ≤ 0%	9 (19.57)	1.00	1 (2.17)	1.00
Responder at <10%	37 (80.43)	**<0.0001**	45 (97.83)	**<0.0001**
Responder at 10%	34 (73.91)	**0.0008**	41 (89.13)	**<0.0001**
Responder at 20%	32 (69.57)	**0.0057**	37 (80.43)	**<0.0001**
Responder at 30%	28 (60.87)	0.0920	35 (76.09)	**0.0003**
Responder at 40%	25 (54.35)	0.3294	32 (69.57)	**0.0057**
Responder at 50%	19 (41.30)	0.8490	30 (65.22)	**0.0270**
Responder at 60%	16 (34.78)	0.9730	30 (65.22)	**0.0270**
Responder at 70%	11 (23.91)	0.9997	22 (47.83)	0.5585
Responder at 80%	9 (19.57)	1.00	17 (36.96)	0.9481
Responder at 90%	7 (15.22)	1.00	14 (30.43)	0.9943
Responder at 100%	5 (10.87)	1.00	6 (13.04)	1.00

Source: Table 14.2.1.5

E_{max} = maximum (peak) effect; N = number of subjects; PR=prolonged-release; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Table 6

Table 11.4.1.4-1: Descriptive Statistics for Overall Drug Liking and Take Drug Again VAS - Completers Population (N = 46)						
Timepoint	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)
Overall Drug Liking VAS						
12 Hour	Mean (SD)	69.4 (21.85)	52.5 (22.11)	50.2 (16.20)	57.0 (25.15)	49.5 (12.12)
	Median	70.5	51.0	50.0	57.0	50.0
24 Hour	Mean (SD)	63.5 (22.19)	44.9 (24.17)	51.7 (16.26)	53.9 (24.84)	51.8 (10.98)
	Median	64.5	50.0	50.0	55.0	50.0
Take Drug Again VAS						
12 Hour	Mean (SD)	66.8 (27.40)	39.2 (29.99)	49.7 (18.56)	54.8 (25.35)	50.3 (14.18)
	Median	71.0	50.0	50.0	53.5	50.0
24 Hour	Mean (SD)	65.9 (27.05)	39.3 (29.02)	50.7 (17.37)	57.0 (24.54)	51.3 (10.54)
	Median	72.0	50.0	50.0	55.0	50.0

Source: Table 14.2.2.1 and 14.2.3.1

N = number of subjects; PR = prolonged-release; SD = standard deviation; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Table 7

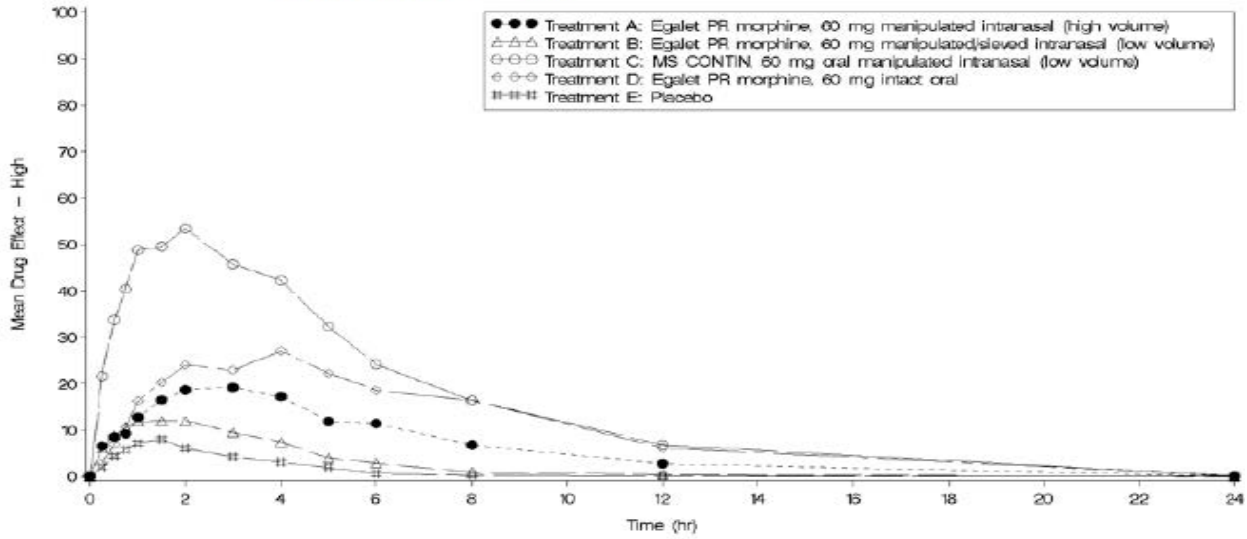
Table 11.4.1.4-2: Statistical Analyses for Overall Drug Liking VAS and Take Drug Again VAS - Completers Population (N = 46)				
	Overall Drug Liking VAS E_{max}		Take Drug Again VAS E_{max}	
	Median Difference	P-Value	Median Difference	P-Value
Pairwise Comparisons				
MS CONTIN vs. Placebo				
Manipulated Intranasal MS CONTIN - Placebo	21.00	**<0.0001**	20.00	**<0.0001**
Egalet PR Morphine vs. MS CONTIN				
Manipulated Intranasal MS CONTIN - Manipulated Intranasal Egalet PR Morphine	18.00	**<0.0001**	26.00	**<0.0001**
Manipulated Intranasal MS CONTIN – Manipulated/Sieved Intranasal Egalet PR Morphine	18.00	**<0.0001**	18.00	**<0.0001**
Manipulated MS CONTIN - Intact Oral Egalet PR Morphine	12.50	**<0.0001**	11.00	**0.0003**
Egalet PR Morphine vs. Placebo				
Manipulated Intranasal Egalet PR Morphine - Placebo	3.00	0.5219	-8.50	**0.0466**
Manipulated/Sieved Intranasal Egalet PR Morphine - Placebo	0.50	0.3963	0.50	0.6880
Intact Oral Egalet PR Morphine - Placebo	7.50	**0.0149**	5.50	0.0620
Egalet PR Morphine vs. Egalet PR Morphine				
Manipulated Egalet PR Morphine – Manipulated/Sieved Intranasal Egalet PR Morphine	1.00	0.6804	-10.50	**0.0236**
Manipulated Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-3.50	0.3097	-15.00	**0.0016**
Manipulated/Sieved Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-7.00	0.0669	-4.50	0.1375

Source: Table 14.2.2.2 and Table 14.2.3.2
E_{max} = maximum (peak) effect; PR = prolonged-release; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Figure 2

Figure 11.4.1.5.1-1: Arithmetic Mean ± SEM High VAS over Time - Completers Population (N = 46)



Source: Figure 14.2.4.7
DEQ=drug effects questionnaire; hr=hour; PR=prolonged-release; SEM=standard error of the mean
DEQ High item: "I am feeling high…" where values are anchored on the left by "not at all" (score of 0) and on the right by "extremely" (score of 100).
Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Table 8

Table 11.4.1.5-1: Descriptive Statistics for PD Parameters for High and Good Effects 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=45)	Intact Oral Egalet PR Morphine (N=46)	Placebo (N=46)
High						
E_{max}	Mean (SD)	61.2 (23.55)	27.7 (28.15)	16.0 (23.19)	36.7 (28.08)	10.7 (20.20)
	Median	65.5	20.0	5.0	34.0	0.0
AUE_{0-8}	Mean (SD)	279.70 (158.632)	104.87 (128.158)	52.93 (93.423)	155.70 (160.836)	23.81 (49.945)
	Median	241.13	57.75	5.94	118.46	0.00
TE_{max} (h)	Median	2.00	2.01	0.76	3.50	0.26
	Range	0.5 – 5.0	0.2 – 6.0	0.2 – 12.0	0.3 – 12.0	0.2 – 8.0
Good Effects						
E_{max}	Mean (SD)	57.4 (24.12)	29.2 (29.83)	17.7 (24.21)	37.0 (28.78)	10.9 (20.27)
	Median	62.0	17.0	4.5	32.5	0.0
AUE_{0-8}	Mean (SD)	271.56 (163.730)	111.30 (132.226)	54.39 (90.191)	150.92 (151.580)	25.94 (57.679)
	Median	266.43	53.66	7.71	116.41	0.00
TE_{max} (h)	Median	2.00	2.00	1.00	3.01	0.26
	Range	0.2 – 6.0	0.2 – 6.0	0.2 – 6.0	0.3 – 12.0	0.2 – 5.0

Source: Table 14.2.4.2
AUE = area under the effect curve; E_{max} = maximum (peak) effect; h = hour; N = number of subjects; PR = prolonged-release; SD = standard deviation; TE_{max} = time to maximum (peak) effect
Source: sponsor's 067-eg-008-body.pdf

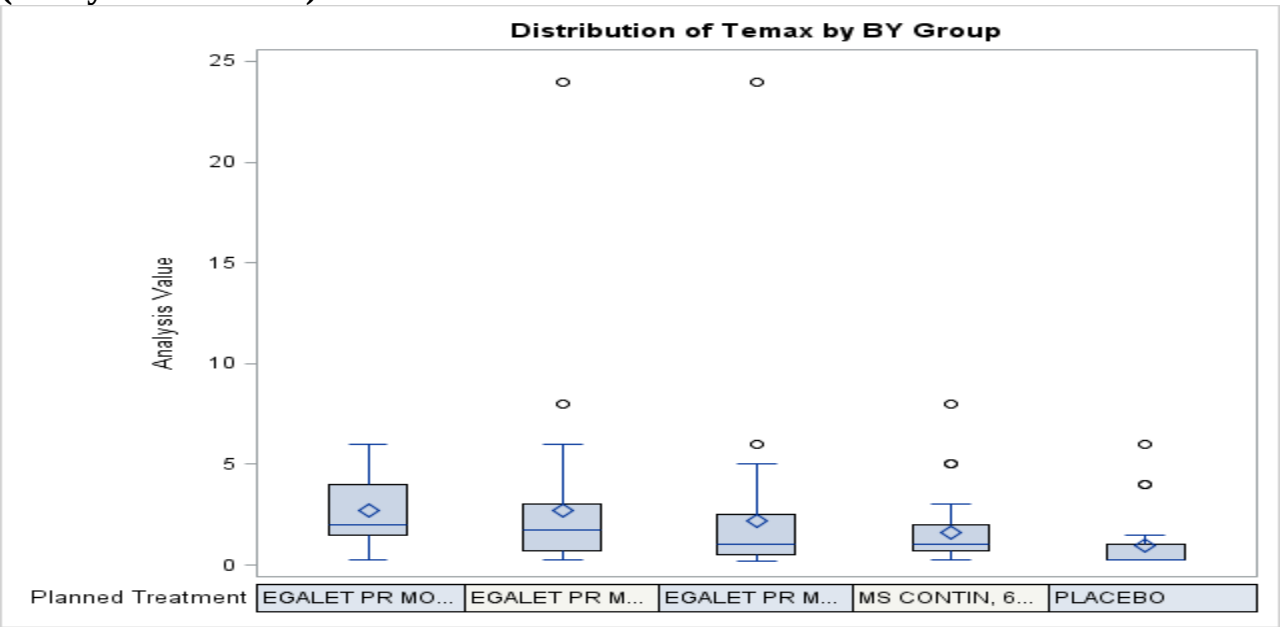
Appendix 2 Table 9

Table 11.4.1.5-2: Statistical Analysis for Select PD Parameters for High and Good Effects VAS – Completers Population (N = 46)								
	High				Good Effects			
	E_{max}		AUE_{0-8}		E_{max}		AUE_{0-8}	
	Median Difference	P-Value	Median Difference	P-Value	Median Difference	P-Value	Median Difference	P-Value
Pairwise Comparisons								
MS CONTIN vs. Placebo								
Manipulated Intranasal MS CONTIN - Placebo	53.50	**<0.0001**	246.98	**<0.0001**	47.50	**<0.0001**	239.24	**<0.0001**
Egalet PR Morphine vs. MS CONTIN								
Manipulated Intranasal MS CONTIN - Manipulated Intranasal Egalet PR Morphine	32.50	**<0.0001**	167.47	**<0.0001**	27.50	**<0.0001**	149.94	**<0.0001**
Manipulated Intranasal MS CONTIN – Manipulated/Sieved Intranasal Egalet PR Morphine	45.00	**<0.0001**	225.06	**<0.0001**	39.50	**<0.0001**	215.47	**<0.0001**
Manipulated Intranasal MS CONTIN - Intact Oral Egalet PR Morphine	24.00	**<0.0001**	127.81	**<0.0001**	20.50	**<0.0001**	123.03	**<0.0001**
Egalet PR Morphine vs. Placebo								
Manipulated Intranasal Egalet PR Morphine - Placebo	19.50	**0.0017**	72.78	**0.0003**	20.00	**0.0012**	76.56	**0.0002**
Manipulated/Sieved Intranasal Egalet PR Morphine - Placebo	3.00	0.1802	9.33	0.0518	5.00	0.1197	11.90	**0.0295**
Intact Oral Egalet PR Morphine - Placebo	25.00	**<0.0001**	113.06	**<0.0001**	24.50	**<0.0001**	109.93	**<0.0001**
Egalet PR Morphine vs. Egalet PR Morphine								
Manipulated Intranasal Egalet PR Morphine – Manipulated/Sieved Egalet PR Morphine	9.50	**0.0002**	43.73	**0.0004**	9.50	**0.0006**	41.35	**0.0002**
Manipulated Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-7.50	0.1189	-34.65	0.0852	-5.50	0.1601	-34.71	0.0917
Manipulated/Sieved Intranasal Egalet PR Morphine – Intact Oral Egalet PR Morphine	-21.00	**<0.0001**	-100.0	**<0.0001**	-19.00	**<0.0001**	-94.62	**<0.0001**

Source: Table 14.2.4.3
AUE = area under the effect curve; E_{max} = maximum (peak) effect; N = number of subjects; PD = pharmacodynamic; VAS = visual analog scale

Source: sponsor's 067-eg-008-body.pdf

Appendix 2 Figure 3: Check the distribution of TEmax of the drug liking VAS (Study 067-EG-009)



Tc: oral intact Ta: high (32) Tb: low (64) C P

Appendix 2 Table 10

PDTEST	PARAM	T	obsN	mean	stderr	min	Q1	median	Q3	max	lclm	uclm
Drug Liking (Bipolar VAS)	AUE0-8	Tc	46	49.40	14.13	-225.60	1.50	51.18	99.45	339.64	20.94	77.86
Drug Liking (Bipolar VAS)	AUE0-8	Ta	46	46.73	9.44	-32.01	0.00	19.91	88.20	247.06	27.73	65.73
Drug Liking (Bipolar VAS)	AUE0-8	Tb	46	13.49	8.41	-163.18	0.00	2.94	22.75	191.63	-3.45	30.43
Drug Liking (Bipolar VAS)	AUE0-8	C	46	91.96	14.97	-264.69	27.82	87.39	145.05	387.11	61.81	122.11
Drug Liking (Bipolar VAS)	AUE0-8	P	46	0.91	9.60	-387.56	0.00	0.00	6.16	113.73	-18.43	20.24
Drug Liking (Bipolar VAS)	AUEtema>	Tc	46	23.03	4.16	0.00	3.12	13.94	32.47	145.93	14.66	31.40
Drug Liking (Bipolar VAS)	AUEtema>	Ta	46	32.58	15.16	-13.75	0.37	5.02	30.37	692.23	2.05	63.11
Drug Liking (Bipolar VAS)	AUEtema>	Tb	46	5.63	2.98	-92.73	0.01	2.04	8.58	59.94	-0.38	11.64
Drug Liking (Bipolar VAS)	AUEtema>	C	46	25.15	4.60	-2.14	6.92	15.51	27.45	161.25	15.90	34.41
Drug Liking (Bipolar VAS)	AUEtema>	P	46	3.51	1.49	-13.26	0.00	0.00	1.63	47.01	0.51	6.52
Drug Liking (Bipolar VAS)	Emax	Tc	46	68.54	2.00	50.00	59.00	68.00	77.00	100.00	64.51	72.57
Drug Liking (Bipolar VAS)	Emax	Ta	46	65.48	2.11	50.00	52.00	62.00	76.00	100.00	61.24	69.72
Drug Liking (Bipolar VAS)	Emax	Tb	46	59.61	1.85	50.00	51.00	52.50	65.00	100.00	55.89	63.33
Drug Liking (Bipolar VAS)	Emax	C	46	77.70	1.72	51.00	70.00	77.50	85.00	100.00	74.23	81.17
Drug Liking (Bipolar VAS)	Emax	P	46	54.67	1.56	15.00	50.00	51.00	58.00	82.00	51.53	57.82
Drug Liking (Bipolar VAS)	TEmax (hr	Tc	46	2.58	0.27	0.25	1.01	2.00	4.00	8.02	2.03	3.13
Drug Liking (Bipolar VAS)	TEmax (hr	Ta	46	2.70	0.55	0.23	0.74	1.75	3.05	24.00	1.59	3.80
Drug Liking (Bipolar VAS)	TEmax (hr	Tb	46	2.03	0.53	0.22	0.51	1.01	3.00	24.00	0.95	3.10
Drug Liking (Bipolar VAS)	TEmax (hr	C	46	1.55	0.21	0.24	0.75	1.01	1.52	8.01	1.12	1.98
Drug Liking (Bipolar VAS)	TEmax (hr	P	46	1.02	0.19	0.24	0.26	0.63	1.50	6.01	0.64	1.40
I am feeling dizzy.	Emax	Tc	46	8.61	2.19	0.00	0.00	0.00	17.00	74.00	4.20	13.02
I am feeling dizzy.	Emax	Ta	46	3.80	0.99	0.00	0.00	0.00	3.00	28.00	1.80	5.81
I am feeling dizzy.	Emax	Tb	45	1.96	0.73	0.00	0.00	0.00	1.00	26.00	0.49	3.42
I am feeling dizzy.	Emax	C	46	15.11	2.80	0.00	0.00	9.00	23.00	93.00	9.47	20.75
I am feeling dizzy.	Emax	P	46	1.41	0.86	-1.00	0.00	0.00	0.00	38.00	-0.32	3.15
I am feeling high.	AUE0-8	Tc	46	155.70	23.71	0.00	26.89	118.46	225.86	620.30	107.94	203.46
I am feeling high.	AUE0-8	Ta	46	104.87	18.90	-5.25	3.97	57.75	182.14	536.94	66.81	142.92
I am feeling high.	AUE0-8	Tb	45	52.93	13.93	0.00	0.00	5.94	57.41	379.01	24.86	81.00
I am feeling high.	AUE0-8	C	46	279.70	23.39	1.78	173.37	241.13	348.29	736.62	232.60	326.81
I am feeling high.	AUE0-8	P	46	23.81	7.36	-1.64	0.00	0.00	26.39	180.08	8.98	38.65
I am feeling high.	Emax	Tc	46	36.67	4.14	0.00	11.00	34.00	52.00	100.00	28.34	45.01
I am feeling high.	Emax	Ta	46	27.65	4.15	0.00	2.00	20.00	50.00	100.00	19.29	36.01
I am feeling high.	Emax	Tb	45	16.00	3.46	0.00	0.00	5.00	20.00	92.00	9.03	22.97
I am feeling high.	Emax	C	46	61.15	3.47	5.00	42.00	65.50	79.00	100.00	54.16	68.14
I am feeling high.	Emax	P	46	10.70	2.98	0.00	0.00	0.00	9.00	69.00	4.70	16.70
I am feeling high.	TEmax (hr	Tc	46	3.47	0.37	0.25	1.50	3.50	5.00	12.01	2.73	4.21
I am feeling high.	TEmax (hr	Ta	46	2.42	0.26	0.23	0.99	2.01	4.00	5.99	1.89	2.95
I am feeling high.	TEmax (hr	Tb	45	1.46	0.30	0.22	0.26	0.76	2.00	12.00	0.85	2.06
I am feeling high.	TEmax (hr	C	46	2.06	0.18	0.49	1.01	2.00	2.01	5.02	1.69	2.43
I am feeling high.	TEmax (hr	P	46	0.93	0.22	0.22	0.26	0.26	1.01	8.00	0.50	1.37
I am feeling nauseous.	Emax	Tc	46	10.65	3.06	0.00	0.00	0.00	10.00	100.00	4.49	16.82
I am feeling nauseous.	Emax	Ta	46	4.41	1.43	0.00	0.00	0.00	2.00	52.00	1.53	7.29
I am feeling nauseous.	Emax	Tb	45	3.02	1.22	0.00	0.00	0.00	1.00	42.00	0.56	5.49
I am feeling nauseous.	Emax	C	46	13.24	3.40	0.00	0.00	1.00	17.00	99.00	6.40	20.08
I am feeling nauseous.	Emax	P	46	0.87	0.39	0.00	0.00	0.00	1.00	17.00	0.08	1.66
I am feeling sick.	Emax	Tc	46	10.91	3.02	0.00	0.00	0.00	15.00	100.00	4.83	17.00
I am feeling sick.	Emax	Ta	46	5.70	1.59	0.00	0.00	0.50	6.00	52.00	2.49	8.90
I am feeling sick.	Emax	Tb	45	3.22	1.22	0.00	0.00	0.00	1.00	37.00	0.77	5.67
I am feeling sick.	Emax	C	46	12.91	3.25	0.00	0.00	1.00	17.00	97.00	6.37	19.45
I am feeling sick.	Emax	P	46	1.15	0.52	-1.00	0.00	0.00	1.00	19.00	0.10	2.21
I am feeling sleepy.	Emax	Tc	46	35.57	4.85	-1.00	7.00	26.50	63.00	100.00	25.80	45.33
I am feeling sleepy.	Emax	Ta	46	20.78	3.72	0.00	1.00	10.00	30.00	95.00	13.29	28.27
I am feeling sleepy.	Emax	Tb	45	12.40	3.69	-3.00	0.00	1.00	12.00	100.00	4.97	19.83
I am feeling sleepy.	Emax	C	46	44.41	4.71	0.00	17.00	41.00	70.00	100.00	34.93	53.90
I am feeling sleepy.	Emax	P	46	11.74	3.50	-15.00	0.00	0.00	10.00	100.00	4.68	18.80

Appendix 2 Table 10 (cont.)

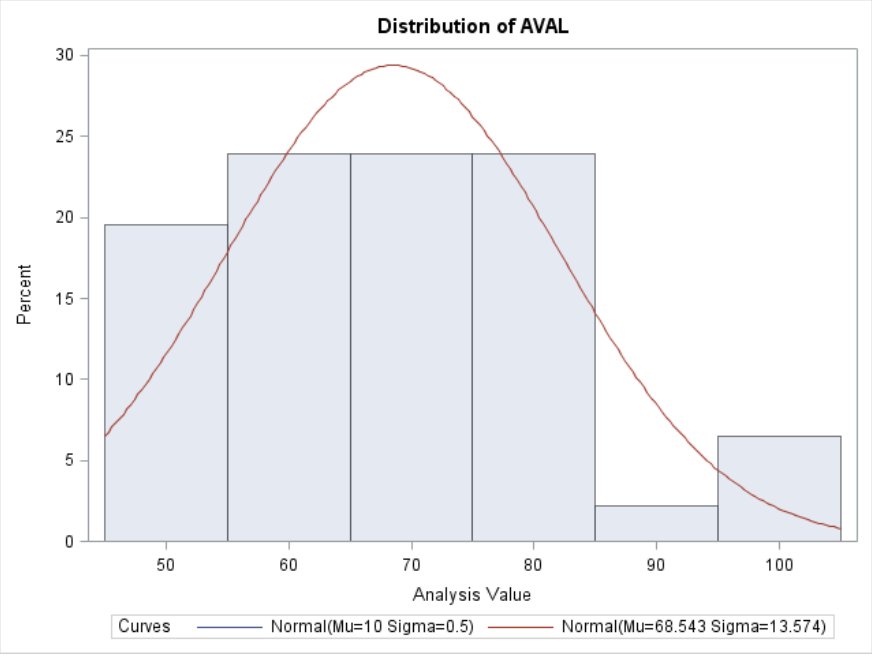
PDTEST	PARAM	T	obsN	mean	stderr	min	Q1	median	Q3	max	lclm	uclm
I can feel a drug effect.	Emax	Tc	46	39.96	4.01	0.00	19.00	38.00	60.00	100.00	31.89	48.03
I can feel a drug effect.	Emax	Ta	46	31.59	4.28	0.00	4.00	23.50	50.00	100.00	22.96	40.21
I can feel a drug effect.	Emax	Tb	46	18.02	3.46	0.00	0.00	6.50	26.00	93.00	11.05	25.00
I can feel a drug effect.	Emax	C	46	62.63	3.62	4.00	47.00	64.00	82.00	100.00	55.34	69.92
I can feel a drug effect.	Emax	P	46	11.50	3.02	0.00	0.00	1.00	8.00	69.00	5.42	17.58
I can feel bad drug effects.	Emax	Tc	46	13.74	3.24	0.00	0.00	3.00	21.00	98.00	7.22	20.26
I can feel bad drug effects.	Emax	Ta	46	9.13	2.47	0.00	0.00	1.00	14.00	85.00	4.15	14.11
I can feel bad drug effects.	Emax	Tb	46	7.02	2.53	0.00	0.00	0.00	4.00	100.00	1.92	12.12
I can feel bad drug effects.	Emax	C	46	20.00	3.77	0.00	0.00	7.50	33.00	100.00	12.41	27.59
I can feel bad drug effects.	Emax	P	46	2.00	1.32	0.00	0.00	0.00	0.00	60.00	-0.66	4.66
I can feel good drug effects.	Emax	Tc	46	37.04	4.24	0.00	16.00	32.50	54.00	100.00	28.50	45.59
I can feel good drug effects.	Emax	Ta	46	29.22	4.40	0.00	1.00	17.00	51.00	100.00	20.36	38.07
I can feel good drug effects.	Emax	Tb	46	17.67	3.57	0.00	0.00	4.50	28.00	94.00	10.48	24.86
I can feel good drug effects.	Emax	C	46	57.41	3.56	5.00	39.00	62.00	75.00	100.00	50.25	64.58
I can feel good drug effects.	Emax	P	46	10.87	2.99	0.00	0.00	0.00	10.00	72.00	4.85	16.89
Need to blow your nose at th	Emax	Tc	46	0.85	0.12	0.00	0.00	1.00	1.00	3.00	0.61	1.08
Need to blow your nose at th	Emax	Ta	46	2.13	0.12	0.00	2.00	2.00	3.00	3.00	1.88	2.38
Need to blow your nose at th	Emax	Tb	45	0.91	0.15	0.00	0.00	1.00	1.00	3.00	0.62	1.20
Need to blow your nose at th	Emax	C	46	1.00	0.14	0.00	0.00	1.00	1.00	3.00	0.73	1.27
Need to blow your nose at th	Emax	P	46	0.83	0.11	0.00	0.00	1.00	1.00	2.00	0.60	1.05
Overall Drug Liking VAS (Bipo	Emax	Tc	46	59.39	3.56	0.00	50.00	59.00	77.00	100.00	52.21	66.57
Overall Drug Liking VAS (Bipo	Emax	Ta	46	53.89	3.20	0.00	50.00	51.00	67.00	100.00	47.44	60.34
Overall Drug Liking VAS (Bipo	Emax	Tb	46	54.43	2.01	21.00	50.00	50.50	55.00	100.00	50.38	58.48
Overall Drug Liking VAS (Bipo	Emax	C	46	72.67	2.67	32.00	61.00	71.00	87.00	100.00	67.29	78.06
Overall Drug Liking VAS (Bipo	Emax	P	46	52.11	1.65	0.00	50.00	50.00	51.00	81.00	48.79	55.43
Rate any nasal congestion at	Emax	Tc	46	0.76	0.11	0.00	0.00	1.00	1.00	3.00	0.53	0.99
Rate any nasal congestion at	Emax	Ta	46	2.13	0.13	0.00	2.00	2.00	3.00	3.00	1.86	2.40
Rate any nasal congestion at	Emax	Tb	45	1.04	0.13	0.00	0.00	1.00	2.00	3.00	0.78	1.31
Rate any nasal congestion at	Emax	C	46	0.87	0.12	0.00	0.00	1.00	1.00	3.00	0.62	1.12
Rate any nasal congestion at	Emax	P	46	0.59	0.10	0.00	0.00	0.00	1.00	2.00	0.38	0.79
Rate any nasal discharge at th	Emax	Tc	46	0.70	0.12	0.00	0.00	1.00	1.00	3.00	0.45	0.94
Rate any nasal discharge at th	Emax	Ta	46	1.28	0.14	0.00	0.00	1.00	2.00	3.00	1.00	1.57
Rate any nasal discharge at th	Emax	Tb	45	0.78	0.14	0.00	0.00	0.00	1.00	3.00	0.49	1.06
Rate any nasal discharge at th	Emax	C	46	0.83	0.13	0.00	0.00	1.00	1.00	3.00	0.57	1.08
Rate any nasal discharge at th	Emax	P	46	0.54	0.10	0.00	0.00	0.00	1.00	2.00	0.34	0.75
Rate facial pain/pressure at t	Emax	Tc	46	0.52	0.12	-1.00	0.00	0.00	1.00	3.00	0.28	0.76
Rate facial pain/pressure at t	Emax	Ta	46	0.98	0.15	0.00	0.00	1.00	2.00	3.00	0.68	1.28
Rate facial pain/pressure at t	Emax	Tb	45	0.47	0.11	0.00	0.00	0.00	1.00	3.00	0.25	0.68
Rate facial pain/pressure at t	Emax	C	46	0.74	0.12	0.00	0.00	1.00	1.00	3.00	0.49	0.99
Rate facial pain/pressure at t	Emax	P	46	0.41	0.09	0.00	0.00	0.00	1.00	2.00	0.23	0.60
Rate intranasal irritation this	Emax	Tc	46	0.85	0.10	0.00	0.00	1.00	1.00	3.00	0.65	1.05
Rate intranasal irritation this	Emax	Ta	46	1.46	0.15	0.00	1.00	1.00	2.00	3.00	1.15	1.77
Rate intranasal irritation this	Emax	Tb	45	0.76	0.11	0.00	0.00	1.00	1.00	2.00	0.54	0.97
Rate intranasal irritation this	Emax	C	46	0.98	0.11	0.00	1.00	1.00	1.00	3.00	0.76	1.20
Rate intranasal irritation this	Emax	P	46	0.78	0.09	0.00	0.00	1.00	1.00	2.00	0.61	0.96
Rate nasal burning at this mo	Emax	Tc	46	0.72	0.09	0.00	0.00	1.00	1.00	3.00	0.53	0.90
Rate nasal burning at this mo	Emax	Ta	46	0.80	0.11	0.00	0.00	1.00	1.00	3.00	0.59	1.02
Rate nasal burning at this mo	Emax	Tb	45	0.71	0.10	0.00	0.00	1.00	1.00	3.00	0.50	0.92
Rate nasal burning at this mo	Emax	C	46	1.02	0.11	0.00	1.00	1.00	1.00	3.00	0.80	1.24
Rate nasal burning at this mo	Emax	P	46	0.74	0.10	0.00	0.00	1.00	1.00	2.00	0.54	0.94
Take Drug Again Assessment	Emax	Tc	46	58.93	3.67	0.00	45.00	56.00	75.00	100.00	51.55	66.32
Take Drug Again Assessment	Emax	Ta	46	43.13	4.36	0.00	19.00	50.00	66.00	100.00	34.35	51.91
Take Drug Again Assessment	Emax	Tb	46	52.61	2.54	0.00	50.00	50.00	58.00	100.00	47.49	57.73
Take Drug Again Assessment	Emax	C	46	69.87	4.04	0.00	57.00	73.00	90.00	100.00	61.73	78.01
Take Drug Again Assessment	Emax	P	46	52.50	1.87	0.00	50.00	50.00	51.00	99.00	48.74	56.26

Appendix 2 Table 11: Correlation between treatments

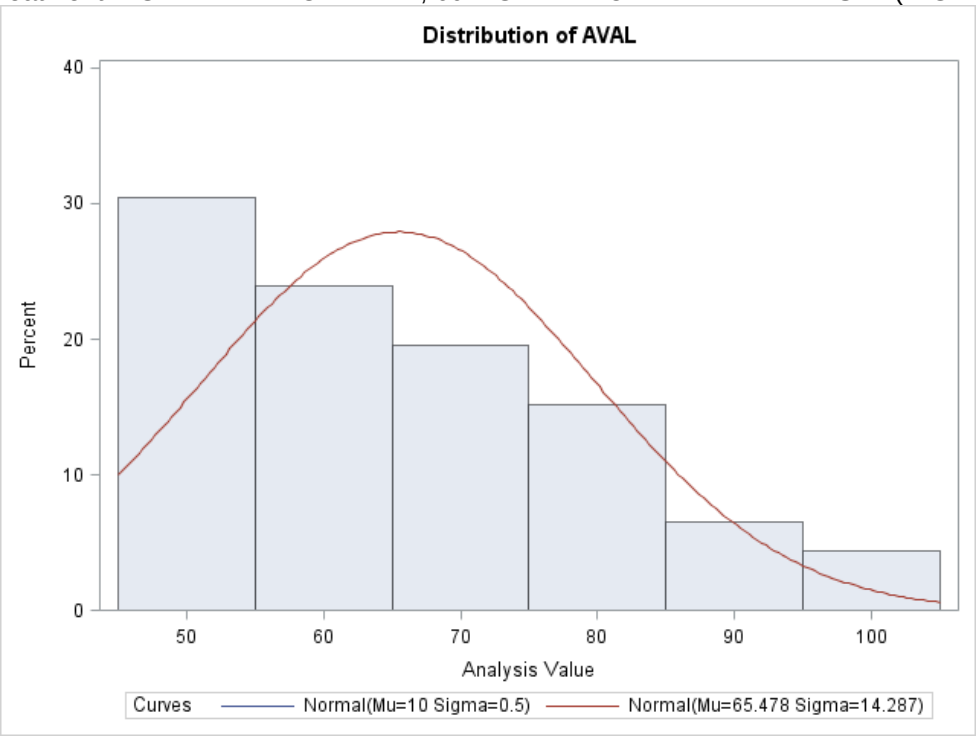
Pearson Correlation Coefficients, N = 46 Prob > |r| under H0: Rho=0					
	emaxTa	**emaxTb**	**emaxTc**	**emaxC**	**emaxP**
emaxTa	1.00000	0.34318 0.0195	0.37860 0.0095	0.52116 0.0002	0.03568 0.8139
emaxTb	0.34318 0.0195	1.00000	0.51042 0.0003	0.46510 0.0011	-0.03865 0.7987
emaxTc	0.37860 0.0095	0.51042 0.0003	1.00000	0.29805 0.0442	0.02010 0.8945
emaxC	0.52116 0.0002	0.46510 0.0011	0.29805 0.0442	1.00000	0.24849 0.0959
emaxP	0.03568 0.8139	-0.03865 0.7987	0.02010 0.8945	0.24849 0.0959	1.00000

Appendix 2 Figure 4: Histograms of Drug liking Emax by Treatment

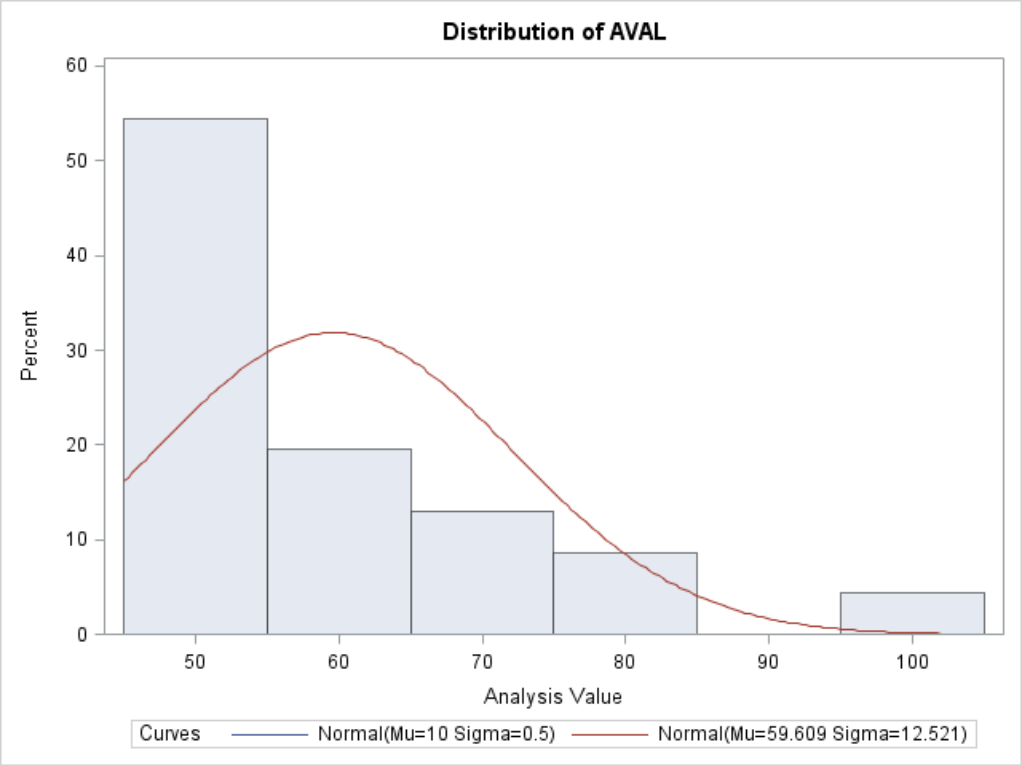
Planned Treatment=EGALET PR MORPHINE, 60 MG INTACT ORAL



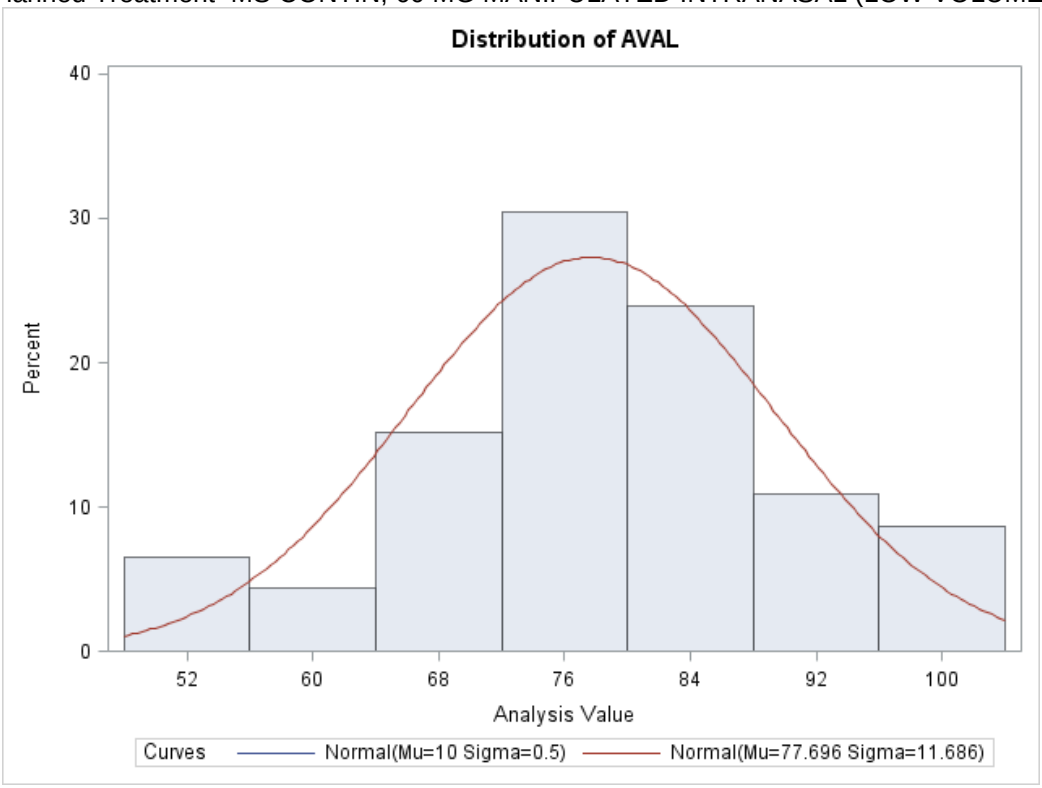
Planned Treatment=EGALET PR MORPHINE, 60 MG MANIPULATED INTRANASAL (HIGH VOLUME)



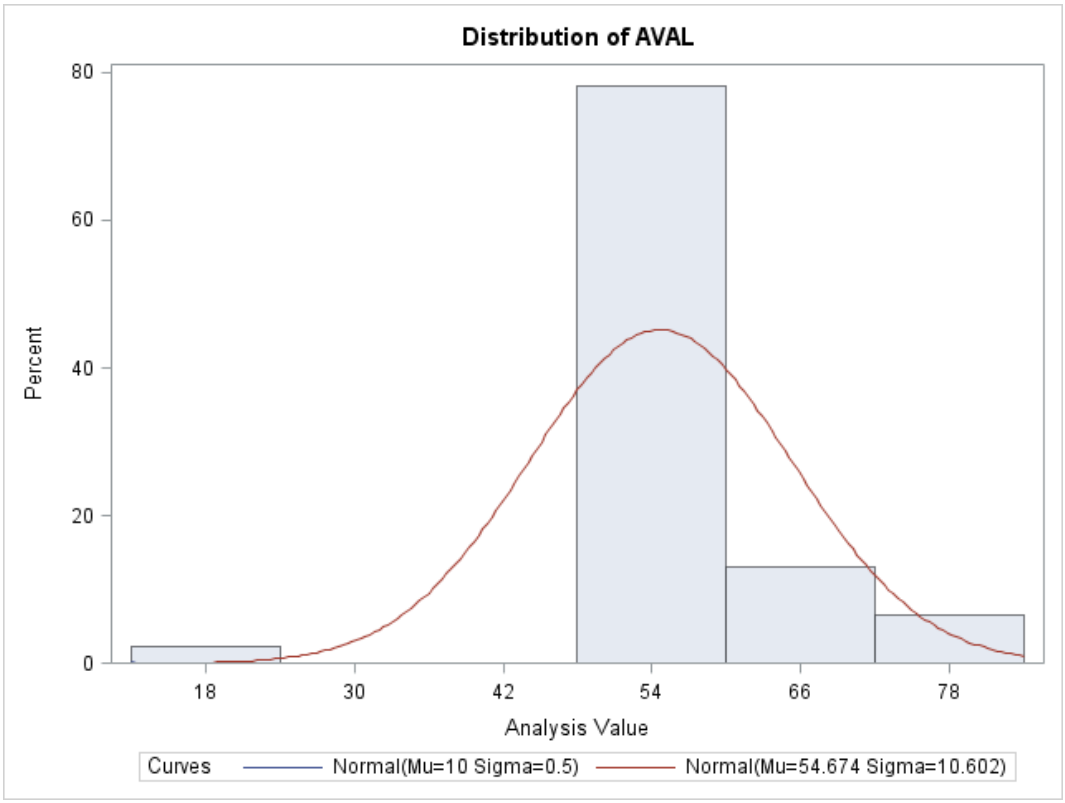
Planned Treatment=EGALET PR MORPHINE, 60 MG MANIPULATED/SIEVED INTRANASAL (LOW VOLUME)



Planned Treatment=MS CONTIN, 60 MG MANIPULATED INTRANASAL (LOW VOLUME)



Planned Treatment=PLACEBO



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