CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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/BLA #:	NDA 204-031
Drug Name:	Oxycodone hydrochloride and acetaminophen controlled release tablets
Indication(s):	Management of (b) (4) acute pain where the use of an opioid analgesic is appropriate
Applicant:	Mallinckrodt, Inc.
Date(s):	Letter date: May 24, 2013, PDUFA date: November 28, 2013
Review Priority:	Priority
Biometrics Division:	II
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Keywords:	NDA review, Clinical Studies

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1. EXECUTIVE SUMMARY

Mallinckrodt, Inc. submitted a New Drug Application for COV795, which is a fixed dose combination of oxycodone (OC) and acetaminophen (APAP) with potential opioid abuse-deterrent features, seeking an indication for management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. A Phase 3 efficacy study in subjects with postoperative bunionectomy pain was submitted to support the efficacy of COV795 administered twice daily in comparison to placebo. Based on my review, the study provided evidence that COV795 have an analgesic effect in comparison to placebo.

The clinical development program of COV795 was discussed at several meetings. Usually, a factorial design is required to demonstrate that each active component makes a contribution to the claimed effects of a combination product. However, based on the clinical knowledge of the combination products of OC and APAP, the division decided that a single, placebo-controlled study could be sufficient to support efficacy of this specific combination product with the abuse-deterrent features. At the End-of-Phase 1 meeting in December 2011, the applicant was informed that a single efficacy study and an open-label safety study could provide the necessary support for the safety and efficacy for the proposed indication. The design and analyses of the Phase 3 efficacy study, Study COV15000182us (Study 0182), was also discussed at the meeting.

Study 0182 was a multicenter, randomized, double-blind, placebo-controlled, and parallel-group study to evaluate the efficacy and safety of multiple doses of COV795 in subjects who were undergoing a unilateral bunionectomy procedure. The study included a 48-hour blinded dosing phase. A total of 329 subjects were randomized equally to either COV795 or placebo. Rescue medication, consisting of 400 mg ibuprofen, was provided and could be taken as needed up to 6 times per day. There were 26 subjects who were enrolled prior to protocol Amendment 2. For these subjects, the second dose of the study drug was administered as soon as needed. Subjects enrolled after Amendment 2 took the study drug every 12 hours daily.

The primary efficacy variable was the summed pain intensity difference from baseline over 48 hours after the first dose. The primary analysis was based on an analysis of covariance model (ANCOVA) with terms including treatment, baseline pain score, site, and treatment-by-site interaction. The primary efficacy population included only the 303 subjects who were enrolled after protocol Amendment 2. The applicant applied a multiple imputation procedure to impute the pain assessments that occurred within 6 hours after taking rescue medication and the missing assessments after early discontinuation of the study. As part of my review, I identified several potential statistical issues with the primary analysis. The issues were mainly about the imputation methods. However, I found that none of these issues affected the statistical conclusion from the study.

The study demonstrated the superiority of COV795 over placebo in acute pain intensity reduction. There was a statistically significant difference in the primary endpoint between the two treatment groups. The results were not sensitive to the imputation methods employed to

handle the pain scores after rescue use or the missing pain assessments after dropout. However, a high percentage of subjects in each treatment group took rescue medication for pain management during the study. Approximately 85% of the subjects in the COV795 group and 99% of the subjects in the placebo group used rescue medication at least once. The review team will need to consider the totality of evidence including findings from abuse studies to decide whether the benefit-risk profile justify the approval of the product. I think the usage of the rescue medication should be noted in the clinical study section of the label if the division decides to approve the product.

2. INTRODUCTION

2.1 Overview

Mallinckrodt, Inc. is developing COV795 as a low-dose combination opioid product (7.5 mg OC/325 mg APAP) with potential abuse-deterrent features for the management of (b) (4) (b) (4) acute pain where the use of an opioid analgesic is appropriate. The COV795 bilayer tablets contain 7.5 mg OC and 325 mg APAP per tablet, and are intended for administration as two tablets every 12 hours. The COV795 tablets contain (b) (4)% of the total OC dose and (b) (4)% of the total APAP dose in the immediate release (IR) layer. The extended release (ER) layer contains (b) (4)% of the OC and (b) (4)% of the APAP. According to the applicant, COV795 has physiochemical properties expected to make abuse difficult. The applicant purported that the combination product provides rapid and controlled absorption of OC and APAP at different rates, potentially lowering the overall dose of each active pharmaceutical ingredient and minimizing side effects. There are other approved OC/APAP combination products available. In particular, the generic drug, Percocet, is an immediate-release formulation of the combination of 7.5 mg OC and 325 mg APAP.

Usually, a factorial design is required to demonstrate that each active component makes a contribution to the claimed effects of a combination product. However, based on the clinical knowledge of the combination products of OC and APAP, the division decided that a single, placebo-controlled study could be sufficient to support efficacy of this specific combination product with the abuse-deterrent features of the IR and ER layers.

The development program of COV795 has been discussed with the agency under IND 104,702. Issues relevant to this statistical review are summarized as below:

- At the End-of-Phase 1 meeting in December 2011, the division stated that a single efficacy study and an open-label safety study could provide the necessary support for the safety and efficacy for the proposed indication. The design and analyses of the Phase 3 efficacy study, Study 0182, was also discussed at the meeting. The division advised the applicant that it might be acceptable to administer the second dose as soon as one hour after the first dose if the applicant plans to label the product to have a loading dose. Regarding the efficacy analyses, the division recommended the applicant to consult the

report on missing value from National Academy of Science (NAS) and propose a method assuming a missing not at random mechanism. In addition, the division stated that it is not appropriate to treat data from subjects who took rescue as missing at random.

- In the advice letter dated August 14, 2012, the division informed the applicant that it is acceptable to replace any scheduled pain assessments that occur within 6 hours of receiving rescue medication with the pre-rescue pain score. In addition, the division requested the applicant to provide additional information about how the proposed multiple imputation approach will attribute bad outcomes to patients discontinuing for adverse events.
- At the pre-NDA meeting in December 2012, the applicant stated that a method to assign bad outcomes to subjects who discontinued due to adverse events would be conducted as a post-hoc analysis as the study had been unblinded.

In this statistical evaluation, I looked how the statistical comparisons were affected by the approach to the post-rescue pain scores and the multiple imputation approach.

2.2 Data Sources

The efficacy data submitted for Study 0182 can be found at \\Cdsesub1\evsprod\NDA204031\0000\m5\datasets\cov15000182us\tabulations\sdtm.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted study tabulation datasets SDTM and analysis datasets AdaM in CDISC format. The submitted datasets and define documents are of acceptable quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 0182 was a multicenter, randomized, double-blind, placebo-controlled and parallel-group Phase 3 study to evaluate the efficacy and safety of multiple doses of COV795 in subjects who were undergoing a unilateral bunionectomy procedure. The study included a 48-hour blinded dosing phase followed by an optional open-label extension up to 14 days.

Eligible subjects had a postoperative pain intensity score of at least 4 on an 11-point numerical pain rating scale (NRS) after discontinuing the nerve block. Subjects were randomized equally to either COV795 or placebo. Rescue medication, consisting of 400 mg ibuprofen, was provided and could be taken as needed up to 6 times per day. Pain intensity was recorded at 2, 4, 8, and 12

hours after each dose, with additional recordings at 15, 30, 45, 60, and 90 minutes after the first dose.

The primary efficacy endpoint was the summed pain intensity difference from baseline during the 48 hours (SPID48) after the first dose. The pain intensity difference (PID) was defined as the baseline pain intensity score minus the pain intensity score at the time point of interest. The secondary efficacy endpoints included time to onset of confirmed perceptible pain relief, rescue medication usage, and subject's global assessment of satisfaction of the study drug.

The original protocol was amended four times. The important amendments relevant to the statistical analyses are summarized as below:

- Amendment 2: the timing of the second dose was changed. Subjects who were enrolled prior to Amendment 2 were initially given a single dose and then continued with dosing at the time a second dose was requested. These subjects were defined as Cohort 1. Subjects who were enrolled after the implementation of Amendment 2 started the trial with a fixed 12-hour dosing regimen and were defined as Cohort 2.

- Amendment 4: the sample size and primary analysis were changed. The sample size was increased to account for the increased variability due to large number of subjects that took rescue medication. The primary analysis was updated to set the pain assessments that occurred within 6 hours of rescue use as missing instead of setting all pain assessments after the first rescue as missing. In addition, the updated protocol proposed to implement the multiple imputation procedure for the intermittent missing values separately for subjects who took rescue medications and subjects who did not.

Amendment 2 affected the timing of the pain assessments. Subjects in Cohort 1 had varied number of pain assessments depending on the time of the second dose, which made it awkward to align the pain assessments to the same scheduled time points as those in Cohort 2. In Amendment 4, the sample size was increased based on a pre-specified rule in the original protocol. The primary efficacy analysis proposed in Amendment 4 will be discussed further in the section below.

3.2.2 Statistical Methodologies

The primary analysis was based on an analysis of covariance model (ANCOVA) with terms including treatment, baseline pain score, site, and treatment-by-site interaction. The applicant defined the primary efficacy population as the modified intent-to-treat (mITT) population, which included all randomized subjects from Cohort 2. As for the rationale to exclude those subjects in Cohort 1, the applicant stated that it was difficult to align the pain assessments between the two cohorts.

Any pain intensity score that was not collected because a subject withdrew before the 48-hour blinded dosing period was considered as missing. The pre-rescue pain score was used to replace the next scheduled pain assessment within 6 hours of receiving rescue. Any other scheduled pain assessments that occurred within 6 hours following rescue were considered as censored (missing) in the analyses.

To impute missing values, the applicant applied a multiple imputation procedure as follows. For each single imputation, the intermittent missing values were imputed first using a Markov Chain Monte Carlo (MCMC) method. The MCMC method was implemented separately for subjects who received rescue medication and those who did not. After the intermittent missing values were imputed, a parametric regression method was used to impute the missing values due to early discontinuation. The regression model contained terms including the indicator variables for each reason of study discontinuation, study site, baseline pain intensity score, and PID at each of the protocol specified time points. The applicant classified the reason of discontinuation into three categories: due to adverse events, due to lack of efficacy, and due to other reasons. A total of 50 imputed data sets were created.

To incorporate the division's recommendation on not assigning good pain scores to bad outcomes, the applicant conducted a post-hoc analysis by reducing the imputed PID values by the corresponding last observed PID values for subjects discontinuing for adverse events.

In my opinion, there were several potential issues in the applicant's primary efficacy analysis. First, the primary efficacy population did not include all randomized subjects. This concern was alleviated after I found only 26 subjects (8%) were excluded and including these subjects did not change the conclusion (see Section 3.2.3).

Second, the method to handle the pain scores after receiving rescue was not desirable. The applicant replaced the next pain assessment with the pre-rescue score and set the other pain assessments within 6 hours as missing, which created a large number of intermittent missing values. These intermittent missing values were imputed using a MCMC multiple imputation method. It appears that the MCMC model assumed all subjects who took rescue were alike and the other subjects were alike, regardless of treatment assignment or disposition. This imputation model seems ignoring the treatment difference and assumed missing at random. In addition, it does not necessarily impute bad pain scores to those who took rescue. The impact of the imputation method on the treatment comparison can only be evaluated through sensitivity analyses.

Third, the proposed parametric regression method for imputation seems theoretically unfeasible in general. According to the applicant, the purpose to include the indictor variables for dropout reason was to let the data from like subjects (same dropout pattern) help determine the imputation of the missing values due to early discontinuation. However, I do not think this purpose was fully achievable in general by using the model proposed, as there would be no more observations to utilize when it comes to the time points that all subjects alike were discontinued.

For example, if those dropouts all discontinued at 24 hours, then there will no more observations from these dropouts to estimate the model for imputing the scores after 24 hours.

Finally, the protocol did not specify the estimand as recommend by the NAS report. It appears that the proposed methods were to estimate what would have been observed if the subjects had continued the study drug. Whether it is clinically meaningful to do so in an analgesic trial seems questionable to me and beyond the scope of this statistical review.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 329 subjects were randomized from five sites, 164 to COV795 and 165 to placebo. There were 26 subjects in Cohort 1 and 303 subjects in Cohort 2. The 303 subjects in Cohort 2 constituted the mITT population, the primary efficacy population. Overall, approximately 11% of the subjects discontinued early (Table 1). The dropout rates of the COV795 and placebo groups were 10% and 12% respectively. The most common reasons for early discontinuation were lack of efficacy and adverse events. Of the 22 subjects in the mITT population that discontinued because of lack of efficacy, seven subjects (5%) were taking COV795 and 15 subjects (10%) were taking placebo. There were seven subjects (5%) from the COV795 group and two subjects (1%) from the placebo group who discontinued because of adverse events. The disposition including subjects from both Cohort 1 and Cohort 2 was similar.

The demographic and baseline characteristics were similar between the two treatment groups (Table 2). The majority of subjects were female (85%) and mean subject age was 43 years. Overall, 59% of subjects were white.

Table 1: Subject Disposition − Number (%) of Patients

	COV795	Placebo	Total
Modified Intention-to-treat (mITT)	**150**	**153**	**303**
Discontinuation during blinded dosing period	15 (10%)	19 (12%)	34 (11%)
Lack of efficacy	7 (5%)	15 (10%)	22 (7%)
Adverse event	7 (5%)	2 (1%)	9 (3%)
Withdrawal by subject	1 (1%)	2 (1%)	3 (1%)

Source: Clinical study report, Table 14.1-1 and Table 14.1-3

Table 2: Summary of Demographics and Baseline Characteristics

	COV795 (N=150)	Placebo (N=153)	All Subjects (N=303)
Mean age (SD)	42 (13)	44 (14)	43 (14)
Gender, n (%)			
Male	19 (13%)	26 (17%)	45 (15%)
Female	131 (87%)	127 (83%)	258 (85%)
Ethnicity, n (%)			
Hispanic or Latino	37 (25%)	40 (26%)	77 (25%)
Not Hispanic or Latino	113 (75%)	113 (74%)	226 (75%)
Race, n(%)			
American Indian or Alaska Native	3 (2%)	0	3 (1%)
Asian	13 (9%)	11 (7%)	24 (8%)
Black or African American	48 (32%)	45 (29%)	93 (30%)
Native Hawaiian or Other pacific Islander	0	1 (1%)	2 (1%)
White or Caucasian	85 (57%)	95 (62%)	180 (59%)
Other	1 (1%)	1 (1%)	2 (1%)
Baseline pain intensity			
Mean (SD)	6 (2)	6 (2)	6 (2)
(Min, Max)	(4, 10)	(1, 10)	(1, 10)

Source: Clinical study report, Table 14.1-4.1; SD: standard deviation

3.2.4 Results and Conclusions

I replicated the applicant's results for the primary efficacy analysis (Table 3). COV795 was superior to placebo in terms of SPID48 with statistical significance. If divided by 48 (duration in hours), the treatment difference 48 translates to a treatment effect of 1 in terms of average pain reduction from baseline over 48 hours on a scale of 0 to 10.

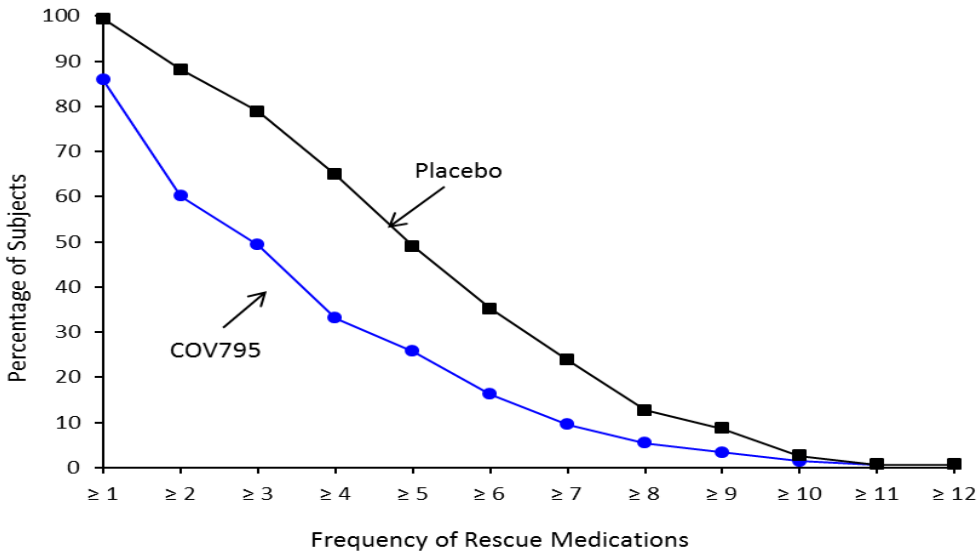
Table 3: Primary Efficacy Analysis Results (SPID48)

Method	Statistics	COV795 (N=150)	Placebo (N=153)	95% CI	P-value
Multiple imputation (50 imputations)	Mean (SE)	115 (7)	67 (7)		
(pain scores 6 hours after rescue censored)	Difference (SE)	48 (11)		(27, 69)	<0.001

Source: Clinical Study Report, Table 14.2-2.1; SE: standard error; CI: confidence interval

A high percentage of subjects took rescue medication for pain management during the 48 hours after the first dose (Figure 1). Approximately 85% of the subjects in the COV795 group and 99% of the subjects in the placebo group took rescue medication at least once. Subjects in the placebo group took rescue more often than subjects in the COV795 group. There was consistently higher percentage of subjects in the placebo group than in the COV795 group for each category of frequency. For example, approximately 89% of the subjects in the placebo group took rescue at least twice. In contrast, about 60% of the subjects in the COV795 group took rescue at least twice.

Figure 1: **Percentage of Subjects with Different Frequency of Rescue Use**



Since I have concerns on the primary analysis methods as stated in Section 3.2.2, I relied on sensitivity analyses to investigate the robustness of conclusion of the primary analysis.

The applicant conducted several sensitivity analyses based on different analysis populations or methods for handling missing values. The results from these sensitivity analyses (Table 4) were similar to those from the primary analysis:

> *Sensitivity analysis 1* applied the primary analysis method to all the randomized subjects from both Cohort 1 and Cohort 2. The results indicated that including the 26 subjects from Cohort 1 did not change the conclusion. The other sensitivity analyses were all applied to the mITT population.
>
> *Sensitivity analysis 2* set the pain scores within 8 hours after taking rescue medication as missing and imputed them using the multiple imputation approach as in the primary analysis.
>
> *Sensitivity analysis 3* utilized the pain scores collected after rescue in the analysis and applied the multiple imputation approach to the missing values due to dropout.
>
> *Sensitivity analysis 4* used a hybrid last observation carried forward (LOCF) and baseline observation carried forward approach (BOCF), in which the baseline observations were carried forward for missing values due to discontinuation for adverse events and the last observations were carried forward for other missing values including those set to missing after rescue use.

Sensitivity analysis 5 was the applicant's post-hoc analysis, in which the imputed PID values were further reduced by the corresponding last observed values for subjects discontinuing for adverse events.

I conducted additional sensitivity analyses (Sensitivity analyses 6 and 7) to further investigate the variation of the estimations. Sensitivity analysis 6 replaced the pain scores within 6 hours after rescue with the pre-rescue score. Sensitivity analysis 7 utilized the pain scores after rescue in the analysis. Both analyses applied a BOCF approach for dropouts. I viewed these sensitivity analyses as utility based analyses in which I assumed subjects went back to baseline condition once they discontinued the study drug. Both sensitivity analyses yielded results in favor of COV795 with statistical significance. The sensitivity analysis using the pre-rescue score carried forward approach provided evidence that subjects in the COV795 group had better pre-rescue scores than subjects in the placebo group (Table 4, sensitivity analysis 6). The sensitivity analysis utilizing the pain scores after rescue assured me that subjects randomized to COV795 experienced better pain reduction even more subjects in the placebo group sought rescue medication for pain management (Table 4, sensitivity analysis 7).

Table 4: Sensitivity Analyses for SPID48

Method	Statistics	COV795 (N=150)	Placebo (N=153)	95% CI	P-value
Analyses reported by the applicant					
Sensitivity analysis 1					
Multiple imputation	Mean (SE)	114 (7)	64 (7)		
combining Cohort 1 and cohort 2	Difference (SE)	49 (10)		(29, 70)	<0.001
Sensitivity analysis 2					
Multiple imputation	Mean (SE)	111 (8)	60 (8)		
8-hour window for rescue	Difference (SE)	51 (10)		(30, 71)	<0.001
Sensitivity analysis 3					
Multiple imputation	Mean (SE)	119 (7)	76 (7)		
utilizing post-rescue pain scores	Difference (SE)	43 (10)		(23, 64)	<0.001
Sensitivity analysis 4					
BOCF/LOCF	Mean (SE)	102 (8)	49 (8)		
6-hour window for rescue	Difference (SE)	53 (11)		(31, 75)	<0.001
Sensitivity analysis 5					
Multiple imputation	Mean (SE)	113 (8)	66 (8)		
forced reduction for adverse events	Difference (SE)	47 (11)		(26, 67)	<0.001
Additional analyses conducted by this reviewer					
Sensitivity analysis 6					
Pre-rescue carried forward 6 hours	Mean (SE)	105 (7)	55 (7)		
BOCF for other missing values	Difference (SE)	50 (10)		(30, 70)	<0.001
Sensitivity analysis 7					
utilizing post-rescue pain scores	Mean (SE)	114 (7)	71 (7)		
BOCF for other missing values	Difference (SE)	44 (10)		(24, 64)	<0.001

SD: standard deviation; CI: confidence interval
Source: Clinical Study Report, Table 14.2-2.3 and Table 14.2-2.7

The results from the sensitivity analyses alleviated my concerns on the primary analysis. Overall, the similarities among the estimated treatment differences and the standard errors from these analyses led me to conclude that there was statistically significant difference between groups due to treatments. Specifically, the sensitivity analyses utilizing the pain scores collected after rescue and the one carrying the pre-rescue score forward for 6 hours decreased my concern on the impact of the MCMC imputation method on the treatment comparison. The sensitivity analyses using BOCF for missing values due to discontinuations in combination with the overall low dropout rate made me less concerned about the parametric imputation method for the dropouts.

To compare the pain reduction effect over time, the average pain intensity over time of each treatment group was depicted through 48 hours after the first dose in Figure 2. The average pain intensity was calculated utilizing the pain scores after rescue and a BOCF approach for pain scores after discontinuation. Similar patterns were observed using the pre-rescue score carried forward for 6 hours after rescue (Figure 3). There were apparent repeated u-shape curvatures in the pain curve of the COV795 group, matching the dosing interval of the drug. Pain intensity was reduced faster for subjects taking COV795. It appears that the drug effect was maximized at approximately 4 hours after each dose and became diminished at the end of the dosing intervals. The patterns observed from the pain curves clearly indicated a drug effect. The diminished treatment effect at the end of each doing interval suggests that a shorter dosing interval might be needed to maximize the treatment effect.

Approximately 50% of the subjects taking COV795 and 30% of the subjects taking placebo experienced confirmed perceptible pain relief within one hour after the first dose (Figure 4). Analyses of other secondary efficacy endpoints including the time to first rescue and patient's global impression were supportive to the primary analysis.

Figure 2: **Average Pain Intensity Over Time – Including Pain Intensities After Rescue**

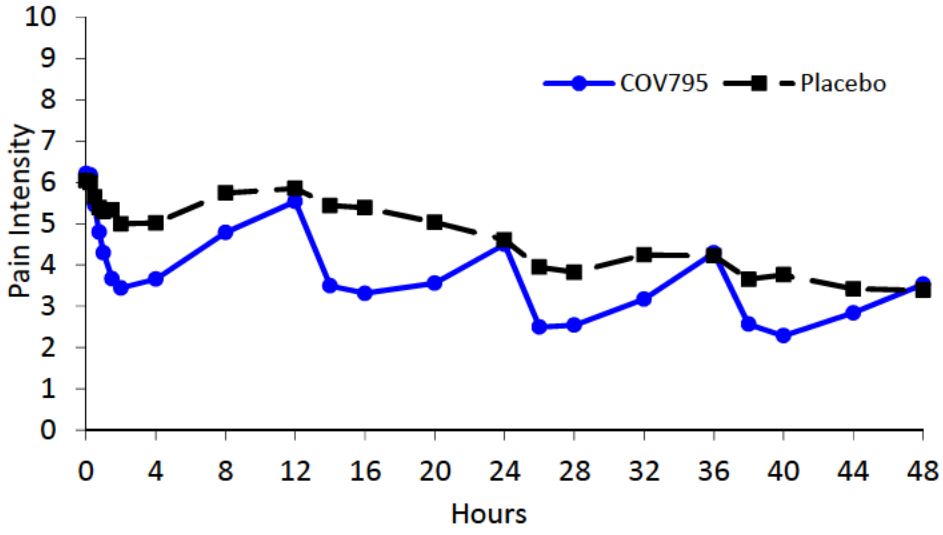


Figure 3: Average Pain Intensity Over Time –Pre-rescue Score Carried 6 Hours

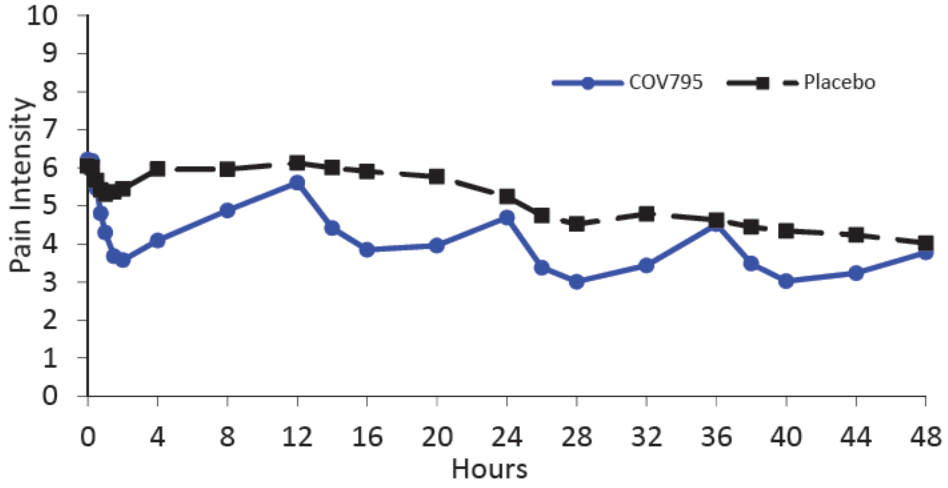
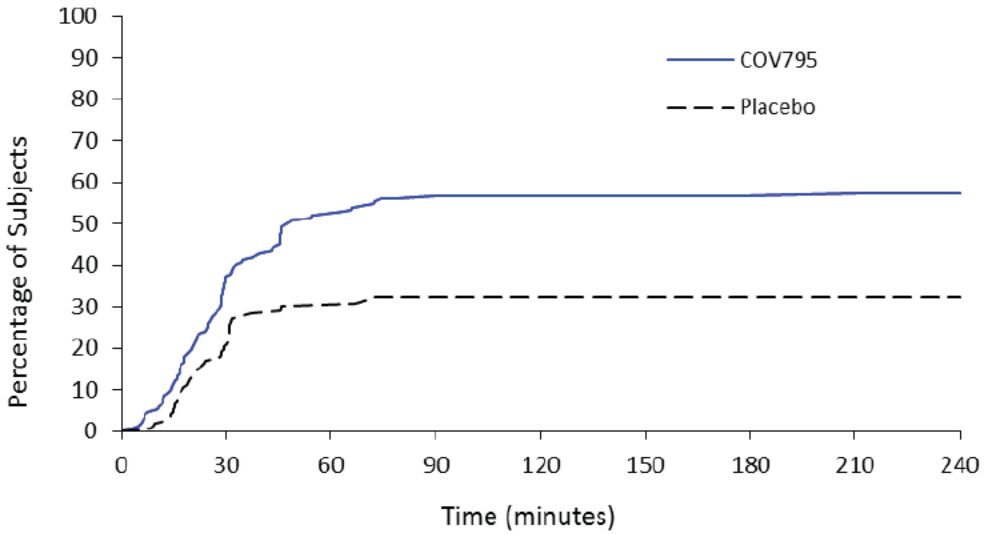


Figure 4: Time to Confirmed Perceptible Pain Relief



3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Elizabeth Kilgore. The reader is referred to Dr. Kilgore's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant did not include the subgroup analyses by age, gender, or race in the original submission. Subgroup analyses were subsequently submitted in response to the division's request. I also conducted separate subgroup summaries. Findings from the subgroup analyses of the primary efficacy endpoints were consistent with those observed in the overall population. The SPID48 scores were greater in the COV795 group than in the placebo group for all conducted analyses.

4.1 Gender, Age and Race

The applicant provided subgroup analyses for gender, age and race (Table 5). Subgroup analyses of gender used the same method as in the primary analysis. Subgroup analyses for race were conducted by classifying the subjects into white, black, or other races. Sites 204 and 205 were excluded by the applicant because of zero subjects in the black placebo group. As there were few subjects older than 65, the applicant only included results for subjects younger than 65 for the age subgroup analysis.

Table 5: Applicant's Subgroup Analyses of SPID48

Subgroup	COV795	Placebo	Difference	p-value
Overall (n=303)	114.9 (7.64)	66.9 (7.60)	48.0 (10.54)	<0.001
By Gender				
Female (n=258)	113 (8.22)	71.4 (8.39)	41.5	0.0003
Male (n=45)	121 (20.6)	44.7 (15.7)	76.8	0.0035
By Race				
White (n=114)	110 (10.4)	51.7 (10.6)	58.7	<0.0001
Black (n=87)	98.8 (14.9)	56.2 (16.9)	42.6	0.0586
Other (n=23)	130 (24.8)	106 (40.4)	23.9	0.6151
By Age				
Age<65 (n=291)	115 (7.68)	63.8 (8.18)	51.5	<0.001

Source: Table 14.2.2.9, Table 14.2.2.10, and Table 14.2.2.11

I conducted separate subgroup summaries by gender, age, and race for all the randomized subjects (Table 6). For age, subjects were classified as ≤ 45 or >45 years old. I used the post-rescue scores and a BOCF approach for dropouts in the calculation of SPID48. The findings from the subgroups summaries were consistent with those observed in the overall population. COV795 were numerically better placebo in all the subpopulations.

Table 6: Reviewer's Subgroup Summaries of SPID48

Subgroups	Statistics	COV795 (N=150)	Placebo (N=153)
Sex			
Female	n (%)	131 (87%)	127 (83%)
	Mean (SD)	111 (96)	64 (88)
Male	n (%)	19 (13%)	26 (17%)
	Mean (SD)	130 (86)	43 (106)
Race			
Black	n (%)	48 (32%)	45 (29%)
	Mean (SD)	110 (88)	66 (95)
Other	n (%)	17 (11%)	13 (8%)
	Mean (SD)	140 (88)	90 (76)
White	n (%)	85 (57%)	95 (62%)
	Mean (SD)	109 (100)	54 (91)
Age			
>45	n (%)	65 (43%)	77 (50%)
	Mean (SD)	117 (97)	64 (89)
<=45	n (%)	85 (57%)	76 (50%)
	Mean (SD)	110 (93)	57 (94)

SD: Standard deviation

4.2 Other Special/Subgroup Populations

No other subgroup summaries were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Several statistical issues in the applicant's efficacy analyses were identified. However, none of the issues affected the statistical conclusions from the study.

First, the applicant excluded the first 26 subjects enrolled prior to protocol Amendment 2 from the primary efficacy population. I found including the 26 subjects in the primary analysis did not change the conclusion. Thus, I am not concerned about it.

Second, I think the strategy the applicant implemented to handle the pain scores following rescue use was not desirable. The applicant replaced the next scheduled assessments and set the other assessments within 6 hours as missing, which created a large number of intermittent missing values. These intermittent missing values were subsequently imputed using a MCMC approach with the assumption that subjects who took rescue were all alike and the other subjects were all alike. This assumption seems questionable to me and also inconsistent with the model assumption underlying the parametric regression imputation method. Nevertheless, sensitivity analyses utilizing the pain scores collected after rescue use and the pre-rescue score carried forward approach reduced my concerns on the applicant's approach. I think the fact that the

primary endpoint SPID48 was calculated as a summary measure using all observed and imputed pain scores instead of a single imputed value also contributed to the robustness of the results to different imputation methods.

Third, the applicant applied a parametric regression approach with indicators for different dropout patterns in the model to impute the pain scores after early discontinuation. According to the applicant, the purpose to include the indictor variables for the dropout reason was to let the data from like subjects (same dropout pattern) help determine the imputation of the missing values due to early discontinuation. However, I do not think this purpose was fully achievable in general by using the model proposed, as there would be no more observations to utilize when it comes to the time points that all subjects alike were discontinued. Furthermore, the method might assign good pain scores to subjects who discontinued early due to adverse events. Nevertheless, I am not overly concerned as the discontinuation rate was low and various sensitivity analyses did not yield different conclusion.

5.2 Collective Evidence

The collective evidence from Study 0182 was in support of the efficacy of COV795 in comparison to placebo. There was statistically significant difference in the primary endpoint between the treatment groups. This conclusion was supported by the similarity of the results from various sensitivity analyses. The secondary efficacy endpoints were also in favor of COV795. However, a high percentage of subjects in both treatment groups took rescue medication for additional pain management, which may indicate that COV795 did not provide sufficient analgesic effect to some patients. Nevertheless, it appears that subjects in the placebo group used rescue more often than those in the COV795 group.

5.3 Conclusions and Recommendations

Study 0182 demonstrated that COV795 was better than placebo in acute pain intensity reduction. Since a high percentage of subjects also took rescue medication for pain management during the study, I would recommend the applicant include the information about the rescue and the percentage of subjects who used rescue in the clinical study section of the label if the division decides to approve the product.

5.4 Labeling Recommendations

The applicant submitted the following wording to add to the clinical study section of the label for review:

(b) (4)

I have the following general recommendations to the applicant:

- Include only data from the 303 subjects who administered the study drug for a fixed every 12 hours;
- Include the percentage of subjects who used rescue;
- Include a graph to depict the average pain intensity over the first 48 hours for each treatment; pain intensities after rescue should be included;
- Re-phrase the sentence about the primary efficacy endpoint to avoid using the phrase "[redacted]";
- Remove promotional claims by deleting the last two sentences.

Specifically, I recommend the following texts: "Efficacy was demonstrated in one multicenter, randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose clinical trial comparing XARTEMIS XR and placebo in patients with acute pain following a unilateral first metatarsal bunionectomy. A total of 303 patients with a mean age of 43 (range 18 to 73) years, meeting criteria for randomization (pain intensity ≥4 on a 0 to 10 numerical pain rating scale) and receiving a fixed-dose of [redacted] (XARTEMIS XR, 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen tablets [redacted] every 12 hours over 48 hours were [redacted]

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/s/

FENG LI
10/25/2013

JANICE A DERR
10/25/2013

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

Statistical Consult Review

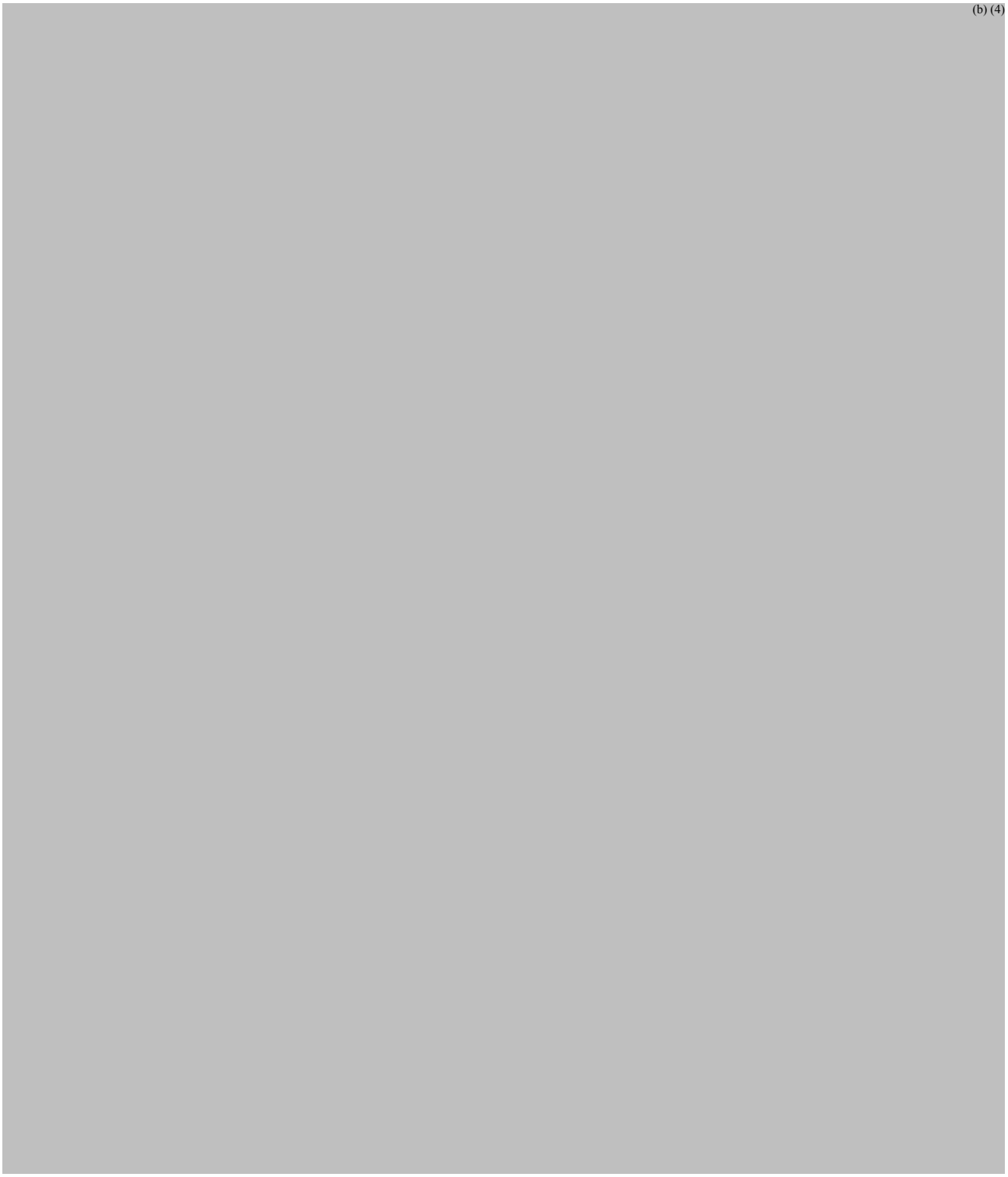
CLINICAL STUDIES

NDA Number:	204031
Drug Name:	COV795: Oxycodone hydrochloride/acetaminophen Multilayer extended-release tablets
Evaluation:	Percent Reduction
Applicant:	Mallinckrodt, Inc
Protocol Number:	12-181-05
Proposed Indication	Management of (b) (4) acute pain
Date(s):	Consult received date: 10/09/2013 Completion date: 10/09/2013
Review Priority:	S
Biometrics Division:	DB VI
Statistical Reviewer:	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
Concurring Reviewers:	Yi Tsong, Ph.D., Acting Division Director, OB/DBVI
Medical Division:	Controlled Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OCD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS
Project Manager:	Corinne P. Moody, Science Policy Analyst, OCD/CSS
Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints	

Percent reduction for NDA 204031

The NDA 204031 was originally reviewed by Dr. Vicki Lancaster. By the request of CSS reviewer Dr. James Tolliver, this reviewer did the following percent reduction analysis for NDA 204031.

(b) (4)



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/s/

ANNA SUN
10/09/2013

YI TSONG
10/09/2013

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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	204031
Drug Name:	COV795: Oxycodone hydrochloride/acetaminophen Multilayer extended-release tablets
Indication:	Management of (b) (4) acute pain
Study number:	COV15000244
Applicant:	Mallinckrodt, Inc.
Date(s):	Date of Document: March 11, 2013 PDUFA date: Completion date:
Review Priority:	
Biometrics Division:	DBVI
Statistical Reviewer:	Vicki Lancaster, Ph.D., Generics Team OTS/OB/DBVI
Concurring Reviewers:	Yi Tsong, Ph.D., Acting Division Director OTS/OB/DBVI
Medical Division:	Control Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OCD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader, OCD/CSS
Project Manager:	Corinne P. Moody, Science Policy Analyst, OCD/CSS

Keywords: *William's Latin Square, Crossover, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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/s/

VICKI A LANCASTER
08/26/2013

YI TSONG
08/26/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204031 **Applicant: Mallinckrodt Inc.** **Stamp Date: May 24, 2013**

Drug Name: Xartemis **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	See clinical review also.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		Subgroup analyses for race, gender and age were not provided.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Also refer to clinical review.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	See clinical review.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Information request to Sponsor:

We could not identify the location of the subgroup analyses for age, gender, or race for your efficacy Study COV15000182US. You should either specify the location of the subgroup analyses in the current submission or submit them if you have not done so.

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Feng Li	July 3, 2013
Reviewing Statistician	Date
Janice Derr	July 3, 2013
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

FENG LI
07/03/2013

JANICE A DERR
07/03/2013