CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-378
Drug Name:	Oxycodone HCl/Ibuprofen 5/400 mg
Indication(s):	Management of moderate to severe acute pain
Applicant:	Forest Laboratories, Incorporated
Date(s):	Received 05/25/04; user fee (6 months) 11/25/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Dionne L. Price, Ph.D.
Concurring Reviewers:	Thomas J. Permutt, Ph.D. S. Edward Nevius, Ph.D.
Medical Division:	Division of Critical Care, Anesthetic, and Addiction Drug Products
Clinical Team:	Rigoberto Roca, M.D.
Project Manager:	Lisa Basham-Cruz

Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Forest Laboratories proposes an oxycodone HCl/ibuprofen combination product for the short-term management of acute, moderate to severe pain. The primary claim of the applicant is that the combination product produces greater efficacy than placebo and each of the individual components as measured by magnitude of pain relief and reduction in pain intensity. My review of the statistical evidence from the previously reviewed dental pain studies and the current study in lower abdominal pain suggests that the analgesic efficacy of the combination product has been demonstrated in a single-dose setting.

1.2 Brief Overview of Clinical Studies

Oxycodone HCl/ibuprofen is a fixed-ratio combination drug product containing two approved products namely oxycodone (an opioid) and ibuprofen (a nonsteroidal anti-inflammatory agent). The combination drug product was introduced to the Division of Anesthetic, Critical Care, and Addiction Drug Products via IND 52,310. The clinical development plan was discussed during several meetings between the applicant and the division. Issues addressed included the appropriateness of the proposed indication and the need for multi-dose studies.

On 20 December 2001, the applicant submitted a New Drug Application (NDA 21-378) for oxycodone HCl/ibuprofen. Evidence of the analgesic efficacy of the product was primarily derived from two randomized, double-blind, multi-center trials (OXY-MD-05 and OXY-MD-06). Upon completion of the review, the division notified the applicant of the approvability of the product and the need to address several deficiencies. Subsequently, Forest submitted separate requests for dispute resolution to the hierarchical levels within the agency. The acting director of the Center for Drug Evaluation and Research, Dr. Steven Galson, advised the applicant of possible options to address the deficiencies and concerns of the division. Currently, the applicant has submitted multiple-dose safety data and a randomized, double-blind, multi-center trial (OXY-MD-10) in women with moderate to severe post-abdominal or pelvic surgical pain to fulfill the requirements outlined in one of the options set forth by Dr. Galson.

In OXY-MD-10, patients were randomized to a single dose of placebo, 5 mg of oxycodone HCl, 400 mg of ibuprofen, or a 5/400 mg combination of oxycodone HCl/ibuprofen. Patients assessed pain relief and pain intensity at pre-specified time increments for the 6-hour duration. An analysis of variance model was used to assess treatment group differences.

1.3 Statistical Issues and Findings

The evidence taken collectively from the current study as well as previously reviewed studies indicated statistical support favoring the combination product for the management of moderate to severe acute pain. In the dental pain studies as well as the gynecological pain study, the magnitude of pain relief through 6 hours was increased for participants receiving the oxycodone/ibuprofen combination as compared to participants receiving ibuprofen alone, oxycodone alone, and placebo. Similarly, a reduction in pain intensity through 6 hours was achieved for participants on the combination product.

Supportive evidence was additionally garnered via investigation of several secondary variables. The study protocols did not provide an explanation of the relative importance of the variables or an explanation of the role of the variables in the interpretation of the results. Thus, I viewed the secondary variables as providing potentially supportive evidence of the primary claim.

During the course of my review of OXY-MD-10, one methodological issue arose. The applicant performed an analysis on transformed data in order to meet the normality assumption accompanying the use of an analysis of variance model. In general, an analysis of variance model is robust with respect to moderate departures from the basic assumptions. Specifically, the normality assumption can be relaxed provided the sample size is large and/or the departure from normality is not extreme. I, therefore, favored the analysis on the raw data. The overall conclusions remained unchanged when analyzing the raw data.

2. INTRODUCTION

2.1 Overview

Oxycodone HCl/ibuprofen is a fixed-ratio combination drug product containing two approved compounds, namely oxycodone (an opioid) and ibuprofen (a nonsteroidal anti-inflammatory agent). The combination drug product was introduced to the Division of Anesthetic, Critical Care, and Addiction Drug Products via IND 52,310. The clinical development plan was discussed during several meetings (16 March 1999, 16 June 1999, and 26 July 2001) between the applicant, Forest Laboratories, and the division. Issues addressed included the appropriateness of the proposed indication and the need for multi-dose studies. In particular, concern existed regarding the ability of data originating from single dose dental pain studies to support a general acute pain indication. Moreover due to evidence (from IMS data) suggesting long-term use of the product, multi-dose studies to access the safety profile of the drug were strongly recommended. On 20 December 2001, the applicant submitted a New Drug Application (NDA 21-378) for oxycodone HCl/ibuprofen. The submission investigated the safety and efficacy of oxycodone HCl/ibuprofen for the management of moderate to severe acute pain. Evidence was primarily derived from two randomized, double blind, multi-center trials conducted in the United States. Based on my review of the original NDA submission, I concluded that the combination drug product produced greater pain relief and a greater pain intensity difference (from baseline) as compared to ibuprofen alone, oxycodone alone, and placebo. However, earlier time points more strongly favored the combination over the ibuprofen alone.

Upon completion of the review of NDA 21-378, the division notified the applicant of the approvability of the product and the need to address several deficiencies. The division advised Forest of the need for several elements including carcinogenicity studies, additional clinical safety data, and a multiple-dose study. Forest subsequently submitted separate requests for formal dispute resolution on 14 February 2003, 25 March 2003, and 18 September 2003 to the Office of Drug Evaluation II, Office of New Drugs, and the Center of Drug Evaluation and Research, respectively. In a letter dated 12 December 2003, Dr. Galson outlined the following paths forward:

> 1. Conduct a multiple-dose study of the oxycodone/ibuprofen (5 mg/400 mg) combination versus ibuprofen alone to satisfy the combination drug policy standard. Resubmit your NDA with the results of this study as well as full responses to the other deficiencies noted in the Division's October 12, 2002 approvable letter.
> **OR**
> 2. Resubmit your NDA to include adequate multiple-dose safety data for the oxycodone/ibuprofen (5 mg/400 mg) combination along with the data from the new gynecologic pain study, as well as full responses to the other deficiencies noted in the Division's October 18, 2002 approvable letter. DACCADP will consider this resubmission for possible approval of the combination drug product with a limited indication and labeling that describes the lack of efficacy data at multiple doses.

Forest chose to pursue the second path forward. The company submitted multiple-dose safety data and study OXY-MD-10. The study investigated the safety and efficacy of oxycodone HCl/ibuprofen in female patients with moderate to severe post-abdominal or pelvic surgical pain.

2.2 Data Sources

The applicant provided a single study in a gynecologic pain model as further support of the claims in the original NDA submission. The currently reviewed documents included volumes 1-11 dated 25 May 2004. The data from the study was archived in the Food and Drug Administration internal electronic document room under the network path location \\CDESESUB1\N21378\N_000\2004-05-25.

3. STATISTICAL EVALUATION

The main body of my evaluation of efficacy pertains to study OXY-MD-10.

3.1 Evaluation of Efficacy

Study Design and Endpoints

The study included women who had undergone lower abdominal surgery (with a standard low transverse incision or low midline incision of at least 8 cm). Eligible women had experienced moderate to severe baseline pain intensity as assessed via a questionnaire and had attained a score of 50 mm or greater on a 100 mm visual analog scale at least 14 hours following surgery. Additionally, eligible women had discontinued all analgesics prior to randomization. Patients were randomized to placebo, 5 mg of oxycodone HCl, 400 mg of ibuprofen, or a 5/400 mg combination of oxycodone HCl/ibuprofen in a 1:1:3:3 ratio, respectively. The difference between the combination product and ibuprofen alone was expected to be smaller and more difficult to distinguish than other pairwise differences; therefore, the group sizes were unequal to improve the ability to detect this difference.

Patients received a single dose of study medication and remained at the study site for 6 hours post-dosing. The study medication was dispensed in a set of one tablet and two capsules (constituting a single dose). Specifically, the combination drug product was provided as a single tablet while the oxycodone alone and ibuprofen alone were dispensed as 5 mg and 200 mg capsules, respectively. Placebo capsules and tablets identical to the active treatments were included to maintain the blind. Self-assessments of pain relief and pain intensity were made at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours post-dosing and recorded in patient diaries. Patients requiring rescue medication discontinued the recording of pain assessments.

The primary measures of efficacy were the sum of pain intensity through 6 hours (SPID6) and the total pain relief through 6 hours (TOTPAR6). The measures were defined as the area under the pain relief and pain intensity curves from 0 to 6 hours, respectively and were computed as

time-weighted averages of consecutive assessments of pain relief and pain intensity. Pain relief was represented as a categorical outcome ranging from 0 (no relief) to 4 (complete relief). Similarly, pain intensity was represented as a categorical outcome ranging from 0 (no pain) to 3 (severe pain).

Several secondary endpoints of interest were identified and included: total pain relief through 3 hours, sum of pain intensity difference through 3 hours, pain relief at each time point, pain intensity difference (from baseline) at each time point, sum of pain relief and pain intensity difference scores at each time point, peak pain relief, peak pain intensity difference, patient's global evaluation score, proportion of patients reporting pain half gone at each time point, time to onset of pain relief, and time to re-medication. Onset of pain relief was defined as the elapsed time from dosing to the patient's first recognition of pain relief (via a stopwatch). Similarly, the time to re-medication was defined as the elapsed time from dosing to administration of rescue medication. The patient's global evaluation of the medication was represented as a categorical outcome ranging from 0 (poor) to 4 (excellent).

Patient Disposition, Demographic, and Baseline Characteristics

Descriptive demographic and baseline characteristics were summarized using the 456 randomized females and did not differ between treatment arms. The ages of patients were between 20 and 75 with a mean age of 42. Approximately 71% of the study participants were Caucasian, and 16% were African American. Baseline measurements included weight, height, and pain intensity as measured on categorical and visual analog scales. A table outlining the composition of the study population is presented in the appendix.

Of the 456 women, 169 were randomized to the combination product, 175 were in the ibuprofen group, 52 were in the oxycodone group, and 60 were randomized to placebo. Thirty percent of the patients completed the study. As in previous studies, the oxycodone/ibuprofen group had the highest percentage (44%) of patients completing the study while the placebo group had the lowest percentage (8%). Twenty-nine percent of patients randomized to ibuprofen alone completed the study. Most participants discontinued due to insufficient therapeutic response. Overall, six patients discontinued due to an adverse event, and four of these six patients were randomized to the combination product.

Statistical Methodologies

The efficacy endpoints, total pain relief through 6 hours and sum of pain intensity difference through 6 hours, were analyzed via analysis of variance (ANOVA) models with treatment group, center, and baseline pain intensity as effects. An examination of the consistency of the results across centers was conducted via inclusion of a treatment-by-center interaction in the ANOVA models. In addition, the Shapiro-Wilk statistic was evaluated to assess the normality of the error terms in the ANOVA models. The primary efficacy variables were to be transformed if the normality assumption was violated. Primary analyses focused on assessing treatment group differences among the combination drug product and the individual components; therefore, the applicant stated, "No multiple comparison adjustments were made for multiple endpoints and/or for multiple treatment comparisons."

The analyses of total pain relief through 3 hours (TOTPAR3) and sum of pain intensity difference through 3 hours (SPID3) were similar to those of the primary efficacy variables. Pain relief, pain intensity differences, and the global rating were additionally analyzed at each time point via an ANOVA model. Onset of pain relief and time to re-medication were analyzed utilizing a log rank test. Additional analysis pertaining to the onset of pain relief and the time to re-medication included use of the Kaplan-Meier estimator to obtain percentiles for each treatment group.

Analyses were performed on the intent-to-treat population including all randomized patients receiving the study medication and having at least one post baseline assessment of efficacy. A last observation carried forward strategy was employed to handle missing data.

Results and Conclusions

Tables 1 and 2 depict the results of the analyses on the primary efficacy variables. Table 1 varied slightly from the applicant's presentation of the results. Specifically, the applicant presented p-values resulting from an ANOVA model applied to transformed data to address the violation of the normality assumption. However, the normality assumption can be relaxed provided the sample size is large and/or departure from normality is not extreme; therefore, the transformation on the data was unnecessary. Thus, I presented Table 1 with the results from the raw, non-transformed data.

Table 1: Analysis of Total Pain Relief Scores through 6 hours (ITT Population)
(Source: Panel 9, Final Study Report OXY-MD-10, Volume 3)

Treatment Group	*N*	*Mean*	*Std Dev*	*Overall Treatment p-value*
Combination	168#	11.2	7.00	<0.0001
Ibuprofen 400 mg	174	9.5	6.87	
Oxycodone HCl 5 mg	52	7.8	6.00	
Placebo	60	5.8	5.75	
Pairwise Comparison		*Estimated Difference in Means†*	*95% CI for Difference*	*p-value**
Combination versus Ibuprofen 400 mg		1.7	0.3, 3.1	0.0157
Combination versus Oxycodone HCl 5 mg		3.2	1.2, 5.2	0.0022
Combination versus Placebo		5.3	3.4, 7.3	0.0001
Ibuprofen versus Placebo		3.6	1.7, 5.5	0.0002
Oxycodone versus Placebo		2.2	-0.3,4.6	0.0806

* P-values result from the analysis on the raw data as opposed to the transformed data
# Excludes one patient who had no post-baseline efficacy assessments but who received rescue medication within 30 minutes of study drug administration and thus was included in the ITT population
† Estimated difference in means displays the difference in means adjusted for other factors in the model

Table 2: Analysis of Pain Intensity Difference Scores through 6 hours (ITT Population)
(Source: Panel 10, Final Study Report OXY-MD-10, Volume 3)

Treatment Group	*N*	*Mean*	*Std Dev*	*Overall Treatment p-value*
Combination	168#	4.5	4.97	<0.0001
Ibuprofen 400 mg	174	3.2	4.78	
Oxycodone HCl 5 mg	52	1.6	4.81	
Placebo	60	1.0	3.87	
Pairwise Comparison		*Estimated Difference in Means†*	*95% CI for LS Difference*	*p-value*
Combination versus Ibuprofen 400 mg		1.2	0.2, 2.1	0.0147
Combination versus Oxycodone HCl 5 mg		2.7	1.4, 4.1	0.0001
Combination versus Placebo		3.3	2.1, 4.8	0.0001
Ibuprofen versus Placebo		2.3	1.0, 3.6	0.0007
Oxycodone versus Placebo		0.7	-0.9,2.4	0.3978

Excludes one patient who had no post-baseline efficacy assessments but who received rescue medication within 30 minutes of study drug administration and thus was included in the ITT population

† Estimated difference in means displays the difference in means adjusted for other factors in the model

Based on the results depicted in the tables, the applicant concluded that greater pain relief was demonstrated among the combination drug product as compared to oxycodone alone, ibuprofen alone, and placebo. In addition, the applicant concluded that a greater pain intensity difference (from baseline) was observed for the combination drug product as compared to the individual components and placebo. I am in agreement with the applicant's results.

In contrast to the previous studies conducted in a dental pain model, the analgesic efficacy (as measured by total pain relief and sum of pain intensity difference) of the oxycodone/ibuprofen combination was no different from that of ibuprofen alone through the initial three hours of the study. Graphical displays of the mean pain relief and pain intensity by time point provide a visual depiction of the differences in relief and intensity among treatments over time. The graphs as well as tabular presentations of the means and standard deviations are provided in the appendix.

The median times to onset of pain relief for the combination, ibuprofen, and oxycodone groups were 28, 31, and 42 minutes respectively. The median time could not be estimated for the placebo group due to the limited number of participants experiencing pain relief. The time to onset of pain relief did not significantly differ among treatment groups. The median times to re-medication for the combination, ibuprofen, and oxycodone groups were approximately 5, 4, and 2.5 hours respectively. The estimated time to re-medication in the combination group was significantly longer than the times to re-medication in all other groups. The applicant

additionally found that the global evaluation scores were higher in the combination group as compared to the other groups.

3.2 Evaluation of Safety

The evaluation of the multiple-dose safety data is deferred to the review of Dr. Rigoberto Roca.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Since the patient population only included females, a subgroup analysis by gender was not applicable. Moreover, the medical officer did not identify any special subgroups of interest; therefore, my subgroup analyses focused on age and race.

4.1 Gender, Race and Age

I evaluated the impact of age and race on the total pain relief and pain intensity difference through 6 hours using analysis of variance models including factors for subgroup, treatment, center, and baseline. For exploratory purposes, I categorized both the age and race variables. The first age category included all females younger than the median age of 42, and the second category included all patients 42 years of age and older. Sub-populations defined by race were categorized as Caucasian or non-Caucasian.

Among younger patients, the mean total pain relief through 6 hours was approximately 10, 8, 8, and 6 for the combination, ibuprofen alone, oxycodone alone, and placebo treatments, respectively. Additionally, the sum of pain intensity difference was 4, 2, 2, and 0.4 for the four respective treatments. Among older patients, the mean total pain relief through 6 hours was 12, 12, 8, and 6 for the combination, ibuprofen alone, oxycodone alone, and placebo treatments, respectively. Additionally, the sum of pain intensity difference was 5, 4, 2, and 1 for the four respective treatments. Overall the analgesic effect, as measured by total pain relief and sum of pain intensity difference, increased with age. Moreover, the analysis adjusted for age supported the efficacy of the combination product.

Seventy-one percent of patients were Caucasian. Among Caucasian females, the mean total pain relief through 6 hours was 10, 8, 7, and 5 for the combination, ibuprofen alone, oxycodone alone, and placebo treatments, respectively. Additionally, the sum of pain intensity difference was 4, 3, 2, and 0.4 for the four respective treatments. Among non-Caucasians, the mean total pain relief through 6 hours was 14, 10, 9, and 8 for the combination, ibuprofen alone, oxycodone alone, and placebo treatments, respectively. Additionally, the sum of pain intensity difference was 6, 4, 2, and 2 for the four respective treatments. The analgesic effect appeared somewhat larger among non-Caucasians as compared to Caucasians. The analysis adjusted for race supported the efficacy of the combination product.

The applicant did not propose any efficacy claims for any subgroups of patients and did not conduct any subgroup analyses. Overall, the results were consistent and lend support to the findings presented in preceding sections.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The collective evidence garnered from the analysis of the primary efficacy variables indicated statistical support favoring the combination product for the proposed indication. In OXY-MD-10, further investigation via several secondary variables suggested a significant longer time to re-medication among patients receiving the combination product as compared to patients in all other groups. A difference in the time to onset of pain relief among groups was not evident. In addition, a difference in the analgesic effect (as measured by total pain relief and sum of pain intensity difference) was not demonstrated through the initial 3 hours of observation. Findings regarding the time to re-medication and the time to onset of pain relief were similar in the current study and the previously reviewed dental pain studies. However, in the dental pain studies, a greater analgesic effect was demonstrated at earlier time points as evidenced by the significant differences in pain relief and pain intensity difference through the initial 3 hours.

During the course of this review, I noted the applicant performed an analysis on transformed data in order to meet the normality assumption accompanying the use of an analysis of variance model. In general, an analysis of variance model is robust with respect to moderate departures from the basic assumptions. Specifically, the normality assumption can be relaxed provided the sample size is large and/or the departure from normality is not extreme. I, therefore, considered the analysis on the raw data. The overall conclusions remained unchanged.

5.2 Conclusions and Recommendations

The applicant proposed oxycodone HCl/ibuprofen combination product for the short term management of acute, moderate to severe pain. The primary claim of the applicant was that the combination product produced greater analgesic efficacy (as measured by total pain relief through 6 hours and sum of pain intensity difference through 6 hours) than placebo and each of the individual components. My statistical review of the evidence from the previously reviewed dental pain studies and the current study in lower abdominal pain suggested that the analgesic efficacy of the combination product was demonstrated in a single-dose setting. Supportive evidence was additionally garnered via investigation of several secondary variables. The study protocols did not provide an explanation of the relative importance of the variables or an explanation of the role of the variables in the interpretation of the results. In my opinion, the secondary variables served to provide potentially supportive evidence of the primary claim only.

Of note, no multiple-dose efficacy studies have been performed for the combination product. The division's concern regarding multiple-dose efficacy studies was addressed in Dr. Galson's response to the applicant's request for dispute resolution dated 12 December 2003. According to the response, a feasible path forward for the applicant included submission of the currently reviewed study and submission of multiple dose safety data. I defer assessment of the multiple-dose data as well as the clinical meaningfulness of the detected differences to the review of Dr. Rigoberta Roca.

5.2.1 Labeling

The proposed draft label reads as follows:

> BRANDNAME was investigated in three clinical studies. Two studies involving a total of 949 patients following dental surgery (removal of ipsilateral molars) and a third study of 456 patients following abdominal/pelvic surgery was conducted. In the three studies, patients were administered a single dose of the BRANDNAME, ibuprofen alone, oxycodone alone, or placebo for acute, moderate to severe pain.
>
> In these single dose studies, BRANDNAME produced greater efficacy than placebo and each of its individual components. — No multiple dose efficacy studies have been performed with BRANDNAME.

Based on my review, I caution against any claims —

I propose the following changes to the draft label:

> BRANDNAME was investigated in three clinical studies. Two studies involving a total of 949 patients following dental surgery (removal of ipsilateral molars) and a third study of 456 patients following abdominal/pelvic surgery was conducted. In the three studies, patients were administered a single dose of the BRANDNAME, ibuprofen alone, oxycodone alone, or placebo for acute, moderate to severe pain. In these single dose studies, BRANDNAME produced greater efficacy than placebo and each of its individual component — as measured by magnitude of pain relief and the reduction in pain intensity through 6 hours. No multiple dose efficacy studies have been performed with BRANDNAME.

6. APPENDIX

Patient Demographics and Baseline Characteristics (Safety Population)
(Source: Panel 7, Final Study Report OXY-MD-10, Volume 3)

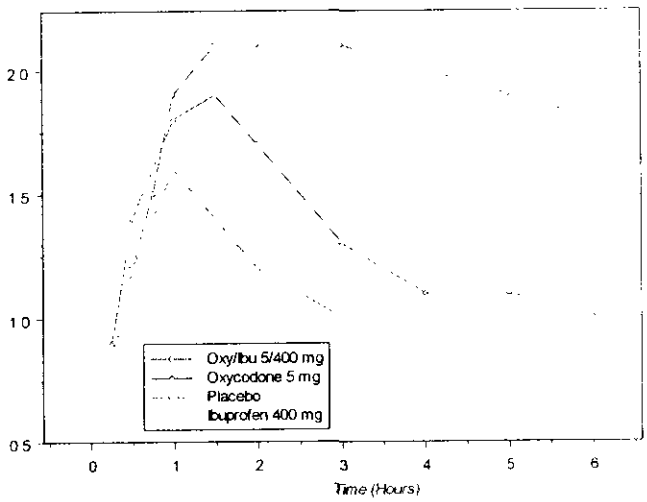
	Oxy/Ibu 5/400 N=169	*Ibuprofen 400 mg N=175*	*Oxycodone HCl 5 mg N=52*	*Placebo N=60*	*Total N=456*	*p-value[a]*
Age (years)						
Mean	42.3	41.2	40.0	42.4	41.6	0.328
Std Dev	9.78	8.30	8.42	9.19	9.01	
Median	43.0	42.0	40.5	43.0	42.0	
Range	21,75	20,66	23,59	20,70	20,75	
Race, N(%)						
White	122 (72.2%)	128 (73.1%)	33 (63.5%)	41 (68.3%)	324 (71.1%)	0.611
Black	31 (18.3%)	24 (13.7%)	11 (21.2%)	8 (13.3%)	74 (16.2%)	
Asian	4 (2.4%)	10 (5.7%)	3 (5.8%)	4 (6.7%)	21 (4.6%)	
Other	12 (7.1%)	13 (7.4%)	5 (9.6%)	7(11.7%)	37 (8.1%)	
Weight (lbs)						
Mean	170.1	172.4	179.0	166.5	171.5	0.422
Std Dev	41.56	39.53	45.27	43.73	41.52	
Median	164.0	168.0	174.0	156.0	166.0	
Range	99.0,301.9	101.0,341.7	113.0,329.0	104.0,299.4	99.0,341.7	
Height (in)						
Mean	64.6	64.6	64.3	64.3	64.5	0.808
Std Dev	2.58	3.00	2.61	2.94	2.79	
Median	65.0	65.0	64.0	64.2	65.0	
Range	58.5,74.0	53.0,72.0	59.0,74.0	56.0,72.0	53.0,74.0	
Baseline Pain Intensity, N(%)						
Moderate	130 (76.9%)	144 (82.3%)	40 (76.9%)	47 (78.3%)	361 (79.2%)	0.631
Severe	39 (23.1%)	31 (17.7%)	12 (23.1%)	13 (21.7%)	95 (20.8%)	
Baseline Pain VAS (mm)						
Mean	66.5	66.4	66.3	65.7	66.3	0.979
Std Dev	12.70	11.27	13.29	10.76	11.96	
Median	64.0	64.0	62.5	64.0	64.0	
Range	50,100	49,100	51,99	50,92	49,100	

Oxy=Oxycodone HCl; Ibu=Ibuprofen

[a] p-values for between treatment comparison from ANOVA model with treatment as factors for continuous variables and CMH test for categorical variables.

Weight and height were missing for four patients (two in the ibuprofen 400 mg group and one each in the oxycodone HCl/ibuprofen 5/400 mg and placebo groups)

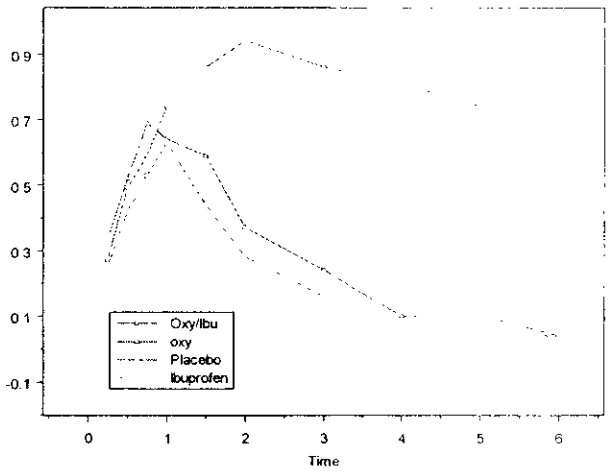
Figure 1: Mean Pain Relief Over Time



	Time (Hours)									
	0.25	**0.50**	**0.75**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**5.0**	**6.0**
Pain Relief (Mean and Std. Dev)										
Oxy/Ibu	0.78(.92)	1.19(1.04)	1.52(1.17)	1.85(1.25)	2.06(1.34)	2.15(1.43)	2.07(1.44)	2.03(1.45)	1.93(1.46)	1.82(1.45)
Ibu	0.83(.93)	1.31(1.04)	1.64(1.24)	1.74(1.30)	1.91(1.39)	1.86(1.40)	1.83(1.46)	1.65(1.41)	1.46(1.38)	1.29(1.33)
Oxy	0.88(1.0)	1.38(1.19)	1.61(1.18)	1.83(1.29)	1.87(1.25)	1.66(1.28)	1.30(1.27)	1.11(1.22)	1.08(1.22)	1.02(1.20)
Placebo	0.78(.94)	1.17(1.16)	1.43(1.33)	1.63(1.40)	1.39(1.38)	1.18(1.31)	1.03(1.24)	0.78(1.14)	0.68(1.00)	0.68(1.00)

Oxy/Ibu=Oxycodone/Ibuprofen combination, Ibu=Ibuprofen alone, Oxy=Oxycodone alone

Figure 2: Mean Pain Intensity Difference Scores Over Time



	0.25	0.50	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0
Pain Intensity Difference (Mean and Std. Dev)										
Oxy/Ibu	0.27(.60)	0.49(.69)	0.59(.77)	0.74(.83)	0.86(.95)	0.94(1.01)	0.86(1.02)	0.81(1.05)	0.74(1.04)	0.62(1.00)
Ibu	0.25(.54)	0.38(.70)	0.57(.80)	0.66(.89)	0.73(.93)	0.67(0.99)	0.66(1.03)	0.54(1.01)	0.40(.95)	0.28(.92)
Oxy	0.34(.71)	0.52(.78)	0.69(.85)	0.64(1.04)	0.59(1.01)	0.37(1.00)	0.24(.98)	0.10(.91)	0.10(.93)	0.04(.86)
Placebo	0.25(.47)	0.42(.63)	0.53(.75)	0.63(.92)	0.44(.93)	0.28(.86)	0.16(.85)	0.00(.84)	-0.08(.72)	-0.08(.72)

Oxy/Ibu=Oxycodone/Ibuprofen combination, Ibu=Ibuprofen alone, Oxy=Oxycodone alone

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

AN AMENDMENT

NDA:	21-378
Name of drug:	Oxycodone HCl / Ibuprofen 5/400 mg
Applicant:	Forest Laboratories, Inc.
Indication:	Management of moderate to severe acute pain
Documents reviewed:	Vol 78-110 dates 12/20/01; \\CDSESUB1\N21378\N_000\2002-02-08
Project manager:	Lisa Basham-Cruz
Clinical reviewer:	Shaun Comfort, M.D.
Dates:	Received 12/20/01; user fee (10 months) 10/20/02
Statistical reviewer:	Dionne Price, Ph.D.
Statistics team leader:	Tom Permutt, Ph.D.
Biometrics division director:	S. Ed Nevius, Ph.D.

Keywords: NDA review, clinical studies

A statistical review of an oxycodone HCl/ibuprofen combination product was conducted and submitted into the Division Filing System on 12 September 2002. The current document is an amendment to the review and provides further clarification regarding the secondary variable, time to onset of pain relief.

The evidence does indeed suggest that the combination product reduces the time to onset of pain relief as compared to the individual components and placebo. However, the statistical significance of this reduction in time to onset is a point that warrants clarification.

In OXY-MD-05, the median times to onset of pain relief for the 5/400 mg combination of oxycodone HCl/ibuprofen and ibuprofen 400 mg groups were 21.4 and 29.7 minutes, respectively. Moreover, a statistically significant difference in time to onset of relief was found to exist between the combination product and ibuprofen alone. In OXY-MD-06, the median times to onset of pain relief for the 5/400 mg combination of oxycodone HCl/ibuprofen, the 10/400 mg combination of oxycodone HCl/ibuprofen, and ibuprofen 400 mg groups were 25.4, 22.3, and 28.0 minutes, respectively. A statistically significant difference was found to exist between the 10/400 mg combination of oxycodone HCl/ibuprofen and ibuprofen alone; however, a statistically significant difference did not exist between the 5/400 mg combination of oxycodone HCl/ibuprofen and ibuprofen 400 mg groups. Respective median times could not be estimated for the oxycodone and placebo groups due to the limited number of participants experiencing onset of pain relief.

For clarity, I note that a statistically significant difference in the time to onset between the combination product and ibuprofen alone is reported in separate studies. However, the favored dose of the combination product varies among studies. The clinical meaningfulness of a claim that

is deferred to the review of Dr. Shaun Comfort. However,

since consistent results for the 5/400 mg combination of oxycodone HCl/ibuprofen are not obtained across studies.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-378
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Keywords: NDA review, clinical studies

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has proposed an oxycodone HCl/ibuprofen combination product for the short-term management of acute, moderate to severe pain. A primary claim of the sponsor is that the combination product produces greater efficacy than placebo and each of the individual components as measured by magnitude of pain relief and reduction in pain intensity. The evidence taken collectively from studies reviewed indicates some statistical support favoring the combination drug product for pain relief and reduction in pain intensity at later times; however, a greater treatment effect is shown at earlier times. Although statistical differences in total pain relief and pain intensity between the combination drug product and each of the individual components (as well as placebo) are noted, I suggest the clinical meaningfulness of the differences is a germane issue for consideration and defer discussion to the medical review of Dr. Shaun Comfort.

The evidence suggests that the combination product reduces the time to onset of pain relief as compared to the ibuprofen alone, oxycodone alone, or placebo.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Background

Oxycodone HCl/ibuprofen is a fixed-ratio combination drug product containing two approved compounds, namely oxycodone (an opioid) and ibuprofen (a nonsteroidal anti-inflammatory agent). The combination drug product was introduced to the Division of Anesthetic, Critical Care, and Addiction Drug Products via IND 52,310. The clinical development plan was discussed during several meetings (16 March 1999, 16 June 1999, and 26 July 2001) between the sponsor, Forest Laboratories, and the division. Issues addressed included the appropriateness of the proposed indication and the need for multi-dose studies to access the safety profile of the drug. On 20 December 2001, the sponsor submitted a New Drug Application (NDA 20-973) for oxycodone HCl/ibuprofen. The present submission investigates the safety and efficacy of oxycodone HCl/ibuprofen for the management of moderate to severe acute pain. Evidence is primarily derived from two randomized, double blind, multi-center trials conducted in the United States.

Study Design

The designs of studies OXY-MD-05 and OXY-MD-06 were similar with differences arising in the sample sizes and the treatment arms. The overall sample size in the former study was 498, and patients were randomized to placebo, 5 mg of oxycodone HCl, 400 mg of

ibuprofen, or a 5/400 mg combination of oxycodone HCl/ibuprofen. Patients were distributed to treatment in a 1:1:3:3 ratio, respectively. In OXY-MD-06, the overall sample size was 682, and patients were randomized to placebo, 5 mg of oxycodone HCl, 10 mg of oxycodone HCl, 400 mg of ibuprofen, a 5/400 mg combination of oycodone HCl/ibuprofen, or a 10/400 mg combination of oxycodone HCl/ibuprofen. Patients were distributed to treatment in a 1:1:1:3:3:3 ratio, respectively.

The studies were comprised of individuals requiring the surgical removal of at least two ipsilateral, bony impacted third molars. Following baseline pain intensity assessments, patients meeting the criteria of moderate to severe pain were randomly assigned to a treatment group. Patients received a single dose of study medication (one tablet and two capsules) and remained at the study site for 6 hours post-dosing. Self-assessments of pain relief and pain intensity were made at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours post-dosing and recorded in patient diaries.

Statistical Analyses

In both studies, the primary measures of efficacy were the sum of pain intensity through 6 hours (SPID6) and the total pain relief through 6 hours (TOTPAR6). The measures were defined as the area under the pain relief and pain intensity curves from 0 to 6 hours, respectively and were computed as time-weighted averages of consecutive assessments of pain relief and pain intensity. TOTPAR6 was analyzed via an analysis of variance model with treatment group and center as main effects. SPID6 was analyzed via an analysis of variance model with treatment group, center, and baseline pain intensity as effects. No adjustments for multiplicity were conducted.

The sponsor also formulated numerous secondary variables. The variables of focus in this review included the total pain relief through 3 hours, sum of pain intensity through 3 hours, time to onset of pain relief, and time to re-medication. The former two variables were analyzed similar to the primary variables. The latter variables were analyzed via a log rank test.

Sponsor's Results and Conclusions

In both studies, a greater analgesic effect (as measured by total pain relief and the sum of pain intensity difference scores through 6 hours) was achieved by the 5/400 mg combination of oycodone HCl/ibuprofen as compared to the individual components and placebo. Evaluation of the analgesic effect through 3 hours (as measured by total pain relief and the sum of pain intensity difference scores) yielded similar conclusions.

Results from analyses indicated a significant treatment difference in favor of the combination product for the secondary variable, onset of pain relief. In both studies, the time to onset of pain relief was significantly shorter for study participants on the combination drug product as compared to participants receiving ibuprofen 400 mg. A longer duration of analgesic effect (as measured by time to re-medication) was achieved by the

combination drug product and ibuprofen alone as compared to oxycodone alone and placebo.

Study OXY-MD-06 included two additional treatment arms, namely oxycodone/ibuprofen 10/400 mg and oxycodone 10 mg. Conclusions regarding oxycodone/ibuprofen 10/400 mg and the individual components are essentially identical to those regarding the lower dose combination product and components. Based on analyses, the sponsor concludes that a greater analgesic effect was achieved by participants in the oxycodone/ibuprofen 10/400 mg group as compared to the individual components and placebo. Moreover, no statistically significant difference was found to exist between the two doses of combination product.

1.3 PRINCIPAL FINDINGS

Following my evaluation of the studies, I conclude that the combination drug product produces greater pain relief and a greater pain intensity difference (from baseline) as compared to ibuprofen alone, oxycodone alone, and placebo. However, the difference in pain relief and pain intensity among the two groups of primary interest (combination versus ibuprofen alone) is nominally significant only through 6 hours. Early time points more strongly favor the combination over the ibuprofen alone. In addition, the combination product significantly shortens the time to onset of pain relief in comparison to the individual components.

My conclusions are formulated after modifications to the analysis conducted by the sponsor. In study OXY-MD-05, the sponsor performs a post-hoc analysis in order to meet the normality assumption accompanying the use of an analysis of variance model. In general, an ANOVA model is robust with respect to moderate departures from the basic assumptions. Specifically, the normality assumption can be relaxed provided the sample size is large and/or the departure from normality is not extreme. Appealing to the aforementioned, the need to perform a transformation on the data does not seem justified. Furthermore, no such analysis was applied in OXY-MD-06 where the same lack of normality phenomena existed.

Since primary analyses focus on assessing treatment group differences among the combination drug products and the individual components, the sponsor suggests that no adjustments for multiplicity are needed in OXY-MD-06. I believe that without an adjustment, there is an increased probability of falsely declaring some dose of the combination product to be effective. In order to maintain an overall type I error rate of 0.05, I applied the Holm's stepdown method which entails ordering the p-values and comparing the values to an adjusted significance level. My analysis is post-hoc; however, the purpose is solely to validate conclusions.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Oxycodone HCl/ibuprofen is a fixed-ratio combination drug product containing two approved compounds, namely oxycodone (an opioid) and ibuprofen (a nonsteroidal anti-inflammatory agent). The combination drug product was introduced to the Division of Anesthetic, Critical Care, and Addiction Drug Products via IND 52,310. The clinical development plan was discussed during several meetings (16 March 1999, 16 June 1999, and 26 July 2001) between the sponsor, Forest Laboratories, and the division. Issues addressed included the appropriateness of the proposed indication and the need for multi-dose studies. In particular, concern existed regarding the ability of data originating from single dose dental pain studies to support a general acute pain indication. Moreover due to evidence (from IMS data) suggesting long-term use of the product, multi-dose studies to access the safety profile of the drug were strongly recommended. On 20 December 2001, the sponsor submitted a New Drug Application (NDA 20-973) for oxycodone HCl/ibuprofen. The present submission investigates the safety and efficacy of oxycodone HCl/ibuprofen for the management of moderate to severe acute pain. Evidence is primarily derived from two randomized, double blind, multi-center trials conducted in the United States. Of note, the submission does not contain the previously recommended multi-dose studies.

2.2 DATA ANALYZED AND SOURCES

The sponsor provided two studies (OXY-MD-05 and OXY-MD-06) to demonstrate the safety and efficacy of oxycodone HCl/ibuprofen for the management of moderate to severe acute pain. Additionally, four studies (604-001-01, 604-002-01, OXY-MD3-96-02, and OXY-MD3-96-1) were submitted to provide further support of the proposed efficacy claims. The studies varied from OXY-MD-05 and OXY-MD-06 in that they were conducted earlier in the trial process, used different dosage strengths, and/or defined the primary efficacy variable differently. Due to the variations, I primarily focused my review on OXY-MD-05 and OXY-MD-06. The reviewed documents included volumes 78-110 dated December 20, 2001. The data from these studies were archived in the Food and Drug Administration internal electronic document room under the network path location \\CDESESUB1\N21378\N_000\2002-02-08. (A summary of the studies is provided in Table 1.)

Table 1: Table of Studies

Study Number Number of centers (n)	Study design	Treatment arms	Primary measure of efficacy
OXY-MD-05 Multi-center (3)	Phase III, double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl/ Ibuprofen 5/400 mg combination (187) · Ibuprofen 400 mg (186) · Oxycodone HCl 5 mg (63) · Placebo (62)	Total pain relief through 6 hours and sum of pain intensity difference through 6 hours
OXY-MD-06 Multi-center (2)	Phase III, double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl /Ibuprofen 5/400 mg combination (171) · Oxycodone HCl/ Ibuprofen 10/400 mg combination (169) · Ibuprofen 400 mg (171) · Oxycodone HCl 5 mg (57) · Oxycodone HCl 10 mg (57) · Placebo (57)	Total pain relief through 6 hours and sum of pain intensity difference through 6 hours
604-001-01 Single center	Pilot study, double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl 5 mg and Ibuprofen 400 mg given together (50) · Ibuprofen 400 mg (43) · Placebo (24)	Total pain relief through 6 hours and sum of pain intensity difference through 6 hours
604-002-01 Multi-center (10)	Pilot study, double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl 5 mg and Ibuprofen 200 mg given together (39) · Ibuprofen 200 mg (38) · Placebo (20)	Total pain relief through 6 hours and sum of pain intensity difference through 6 hours
OXY-MD3-96-01 Multi-center (2)	Double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl/Ibuprofen 5/400 mg combination (171) · Ibuprofen 400 mg (168) · Oxycodone HCl 5 mg (56) · Placebo (58)	Total pain relief through 8 hours and sum of pain intensity difference through 8 hours
OXY-MD3-96-02 Multi-center (2)	Double-blind, parallel group, single dose, placebo and active controlled	· Oxycodone HCl/Ibuprofen 5/200 mg combination (41) · Oxycodone HCl/Ibuprofen 10/200 mg combination (41) · Ibuprofen 200 mg (40)	Total pain relief through 8 hours and sum of pain intensity difference through 8 hours

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

The designs of studies OXY-MD-05 and OXY-MD-06 were similar with differences arising in the sample sizes and the treatment arms. The overall sample size in the former study was 498, and patients were randomized to placebo, 5 mg of oxycodone HCl, 400 mg of ibuprofen, or a 5/400 mg combination of oycodone HCl/ibuprofen. Patients were distributed to treatment in a 1:1:3:3 ratio, respectively. In OXY-MD-06, the overall sample size was 682, and patients were randomized to placebo, 5 mg of oxycodone HCl, 10 mg of oxycodone HCl, 400 mg of ibuprofen, a 5/400 mg combination of oycodone HCl/ibuprofen, or a 10/400 mg combination of oxycodone HCl/ibuprofen. Patients were distributed to treatment in a 1:1:1:3:3:3 ratio, respectively.

The studies were comprised of individuals requiring the surgical removal of at least two ipsilateral, bony impacted third molars. Following baseline pain intensity assessments, patients meeting the criteria of moderate to severe pain were randomly assigned to a treatment group. Patients received a single dose of study medication and remained at the study site for 6 hours post-dosing. The study medication was dispensed in a set of one tablet

and two capsules (constituting a single dose). Specifically, the combination drug product was provided as a single tablet while the oxycodone alone and ibuprofen alone were dispensed as 5 mg and 20 mg capsules, respectively. Placebo capsules and tablets identical to the active treatments were included to maintain the blind. Self-assessments of pain relief and pain intensity were made at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours post-dosing and recorded in patient diaries.

The proposed objective of OXY-MD-05 was to assess the efficacy of a single dose of the combination product relative to its individual components and placebo. In OXY-MD-06, the objective was to assess single doses of oxycodone/ibuprofen 5/400mg and oxycodone/ibuprofen 10/400 mg relative to the individual components and placebo.

2.3.1 STATISTICAL METHODOLOGIES

In both studies, the primary measures of efficacy were the sum of pain intensity through 6 hours (SPID6) and the total pain relief through 6 hours (TOTPAR6). The measures were defined as the area under the pain relief and pain intensity curves from 0 to 6 hours, respectively and were computed as time-weighted averages of consecutive assessments of pain relief and pain intensity. Pain relief was self-assessed by patients and was represented as a categorical outcome ranging from 0 (no relief) to 4 (complete relief). Similarly, pain intensity was represented as a categorical outcome ranging from 0 (no pain) to 3 (severe pain).

Several secondary endpoints of interest were identified and included: total pain relief through 3 hours, sum of pain intensity difference through 3 hours, pain relief at each time point, pain intensity difference (from baseline) at each time point, sum of pain relief and pain intensity difference scores at each time point, peak pain relief, peak pain intensity difference, patient's global evaluation score, proportion of patients reporting pain half gone at each time point, time to onset of pain relief, and time to re-medication. Interest focused on the sum of pain intensity through 3 hours, the total pain relief through 3 hours, time to onset of pain relief and time to re-medication. Onset of pain relief was defined as the elapsed time from dosing to the patient's first recognition of pain relief (via a stopwatch). Similarly, the time to re-medication was defined as the elapsed time from dosing to administration of rescue medication.

The efficacy endpoint, total pain relief through 6 hours, was analyzed via an analysis of variance (ANOVA) model with treatment group and center as main effects. Similarly the efficacy endpoint, sum of pain intensity difference, was analyzed via an ANOVA model with treatment, center, and baseline pain intensity as effects. An examination of the consistency of the results across centers was conducted via inclusion of a treatment-by-center interaction in the ANOVA model. Primary analyses focused on assessing treatment group differences among the combination drug product and the individual components; therefore, the sponsor states, "No adjustment for multiple comparisons was needed for multiple endpoints and/or for multiple treatment comparisons." Moreover the sponsor states, "Supportive hypothesis

testing was also performed to assess the sensitivity of the study assays by comparing the effects of the active treatment groups versus the placebo treatment group."

The aforementioned analysis plan was also followed for the secondary variables, total pain relief through 3 hours (TOTPAR3) and sum of pain intensity difference through 3 hours (SPID3). Onset of pain relief and time to re-medication were analyzed utilizing a log rank test. Further analysis pertaining to onset of pain relief and time to re-medication included use of the Kaplan-Meier estimator to obtain percentiles for each treatment group.

Analyses were performed on the intent-to-treat population consisting of all randomized patients receiving the study medication and having at least one post baseline assessment of efficacy. A last observation carried forward strategy was utilized to handle missing data.

2.3.2 SPONSOR'S RESULTS AND CONCLUSIONS

In both studies, a greater analgesic effect (as measured by total pain relief and the sum of pain intensity difference scores through 6 hours) was achieved by the 5/400 mg combination of oycodone HCl/ibuprofen as compared to the individual components and placebo. As anticipated, statistically significantly greater pain relief and pain intensity difference scores were demonstrated for the ibuprofen 400 mg arm compared to the placebo arm. In contrast, no difference was found to exist between the oxycodone 5 mg and placebo groups. Evaluation of the analgesic effect through 3 hours (as measured by total pain relief and the sum of pain intensity difference scores) yielded similar conclusions.

Results from analyses indicated a significant treatment difference in favor of the combination product for the secondary variable onset of pain relief. In both studies, the time to onset of pain relief was significantly shorter for study participants on the combination drug product as compared to participants receiving ibuprofen 400 mg. A longer duration of analgesic effect (as measured by time to re-medication) was achieved between the combination drug product and ibuprofen alone as compared to oxycodone alone and placebo.

Study OXY-MD-06 included two additional treatment arms, namely oxycodone/ibuprofen 10/400 mg and oxycodone 10 mg. Conclusions regarding oxycodone/ibuprofen 10/400 mg and the individual components are essentially identical to those regarding the lower dose combination product and components. Based on analyses, the sponsor concludes that a greater analgesic effect was achieved by participants in the oxycodone/ibuprofen 10/400 mg group as compared to the individual components and placebo. Moreover, no statistically significant difference was found to exist between the two doses of combination product.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Sample size calculations were performed for variables, TOTPAR6 and SPID6. Since the study objectives were to detect differences in both outcomes, sample size requirements were based on SPID6, the variable warranting a larger sample size. Based on data from OXY-MD3-96-01, a total of 448 patients were required for OXY-MD-05. Specifically, a group sample of size 168 was required to detect a difference of 1.35 in SPID6 between the

combination drug product and ibuprofen 400 mg assuming a standard deviation of 4.2 with 83 % power. The aforementioned difference of primary interest was expected to be smaller than differences between the combination product and oxycodone alone and between ibuprofen alone and placebo group. Therefore, group sample sizes were unequal to improve the power to detect the difference of primary interest. The sample size calculation for OXY-MD-06 mimicked the aforementioned, and a total of 672 patients were required. The number of patients randomized to OXY-MD-05 was 498, and 682 patients were randomized to OXY-MD-06.

In study OXY-MD-05, 56% of study participants were female, and the majority of study participants were Caucasian. The ages of subjects were primarily between 16 and 48 with a mean age of 24.5 years. In study OXY-MD-06, 49% of study participants were female, and 95% were Caucasian. Additionally in OXY-MD-06, the mean age was 18.5 years (range of 13 to 43 years). Baseline characteristics of interest in both studies included weight, height, baseline pain intensity, and visual analog score measuring pain at baseline. A statistically significant difference between treatment groups was noted for race and sex in the former study. The sponsor performed a post-hoc analysis adjusting the primary analysis for sex and race. Results indicated that sex and race had no impact on treatment efficacy. I attributed the imbalance to the 5% risk of committing a type I error (falsely concluding that groups differ when in reality, they do not). Since the imbalance did not exist across both studies, I did not investigate further. Detailed tables outlining the composition of the samples with respect to the demographic and baseline characteristics are presented in the appendix.

In OXY-MD-05, 51% of randomized patients completed the study. The oxycodone HCl/ibuprofen group had the highest percentage (63%) of patients completing the study while the placebo group had the lowest percentage (16%). Sixty-two percent of patients randomized to ibuprofen alone completed the study. Most participants discontinued due to insufficient therapeutic response. In OXY-MD-06, 76% of randomized patients completed the study. Similar to the previous study, the highest percentage (87%) of patients completing the study were randomized to the combination drug product followed by patients randomized to ibuprofen alone (85%).

Tables 2-5 depict the results of the sponsor's detailed analysis performed on the primary efficacy variables, total pain relief through 6 hours (TOTPAR6) and sum of pain intensity difference through 6 hours (SPID6). The tables were generated via ANOVA models previously outlined (see Section 2.3.1). Based on results illustrated in the tables, the sponsor concluded that greater pain relief was demonstrated among the combination drug product as compared to oxycodone alone, ibuprofen alone, and placebo in both studies. In addition, the sponsor concluded that a greater pain intensity difference (from baseline scores) was observed for the combination drug product as compared to the individual components and placebo.

In OXY-MD-05, conclusions were formulated based on a normalized data set. Based on the pre-specified analysis, little to no significant difference in total pain relief was found to exist between the combination drug product and ibuprofen 400 mg. This was evidenced by the

estimate of the mean difference (1.2), the confidence interval (-0.1, 2.4), and the p-value (0.07). However, the sponsor noted a violation of the normality assumption of the ANOVA model and applied a transformation to the variable TOTPAR6. The sponsor reported the p-value resulting from the analysis of the transformed variable in Table 2. A similar transformation was applied to the variable, sum of pain intensity difference through 6 hours; however, the conclusions regarding the relationship were unchanged due to the transformation. No such transformation was applied in OXY-MD-06. I will defer further discussion of the post-hoc analysis to Section 2.3.4 of this review. To further examine treatment differences, the sponsor provided graphical displays depicting the mean pain relief scores and mean pain intensity difference scores over time (see Figures 1 and 2).

Since primary analyses focus on assessing treatment group differences among the combination drug products and the individual components, the sponsor suggests that no adjustments for multiplicity are needed in OXY-MD-06. The inclusion of both doses in the study result in testing of multiple hypotheses by which either (or both) dose of the combination product may be found effective. I believe that without an adjustment, there is an increased probability of falsely declaring some dose of the combination product to be effective. Therefore, a multiplicity adjustment is warranted. In order to maintain an overall type I error rate of 0.05, I applied the Holm's stepdown method which entails ordering the p-values and comparing the values to an adjusted significance level. While the adjustment is post-hoc, it is performed solely to validate conclusions.

With regards to the primary efficacy variables in OXY-MD-05, I reanalyzed the data provided applying the pre-specified methodology and am in agreement with the sponsor's statistical results. Based on the results, I conclude that the 5/400 mg combination of oycodone HCl/ibuprofen does provide some analgesic effect (as measured by TOTPAR6 and SPID6) through 6 hours. In addition, a nominal difference between the combination product and the ibuprofen alone through 6 hours exists. A re-evaluation of the data originating from study OXY-MD-06 (with an adjustment for multiplicity) yields similar findings as the aforementioned. Although both studies yield nominally significant results, the clinical significance of the difference between the combination product and ibuprofen should also be evaluated. I will defer further comments to Section 2.3.4 of this review.

Numerous secondary variables were formulated and analyzed by the sponsor. My review focuses on the following variables: total pain relief through 3 hours (TOTPAR3), sum of the pain intensity through 3 hours (SPID3), time to onset of pain, and time to re-medication. Analysis of the variables TOTPAR3 and SPID3 demonstrated further support of a statistically significant difference between the combination product and the individual components as well as placebo. Moreover, the graphical displays depict larger differences in mean pain relief and mean pain intensity difference scores through 3 hours as compared to 6 hours between the combination product and the ibuprofen alone (see Figures 1-4).

Results from analyses indicated a significant treatment difference in favor of the combination product for the onset of pain relief. In both studies, the time to onset of pain relief was significantly shorter for study participants on the combination drug product as compared to participants receiving ibuprofen 400 mg. In OXY-MD-05, the median times to

onset of pain relief for the combination and ibuprofen 400 mg groups were 21.4 and 29.7 minutes, respectively. In OXY-MD-06, the median times to onset of pain relief for the 5/400 mg combination of oycodone HCl/ibuprofen and ibuprofen 400 mg groups were 25.4 and 28.0 minutes, respectively. Respective median times could not be estimated for the oxycodone 5 mg and placebo groups due to the limited number of participants experiencing onset of pain relief. Moreover, the time to re-medication could not be estimated for the combination product or ibuprofen alone as less that 50 % of patients in those groups requested rescue medication.

The sponsor submitted study OXY-MD-07 as part of the 120-day safety update. Although the study was not submitted in support of efficacy claims, I conducted a brief review of the sponsor's results. The design of OXY-MD-07 mimicked that of OXY-MD-06; however, the patient population included patients demonstrating moderate to severe post-orthopedic surgical pain. Six hundred and eighty-four patients were randomized to treatments. Of particular interest, results from the sponsor's analysis indicated that no statistically significant treatment differences in total pain relief or total pain intensity reduction, or time to onset existed between either dose of the combination product and ibuprofen alone. Moreover, the lack of significant differences was evident in evaluations through 3 hours (TOTPAR3 and SPID3) as well as through 6 hours (TOTPAR6 and SPID6).

Table 2: Analysis of Total Pain Relief Scores through 6 hours (TOTPAR6) for OXY-MD-05 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Combination *	186	13.3	0.52	12.3, 14.4	
Ibuprofen 400 mg	186	12.2	0.52	11.3, 13.2	
Oxycodone 5 mg	63	4.3	0.82	2.7, 5.9	<0.001
Placebo	62	4.2	0.83	2.5, 5.8	

Pairwise Comparison	*Difference in LS Mean*		*95% CI for LS Difference*	*p-value*
Combination vs. Ibuprofen 400 mg	1.2	0.65	-0.1, 2.4	0.012†
Combination vs. Oxycodone 5 mg	9.1	0.91	7.3, 10.8	<0.001
Combination vs. Placebo	9.2	0.91	7.4, 11.0	<0.001
Ibuprofen 400 mg vs. Placebo	8.0	0.91	6.2, 9.8	<0.001
Oxycodone 5 mg vs. Placebo	0.1	1.11	-2.1, 2.3	0.911

* Combination = oxycodone HCl/ibuprofen 5/400 mg combination treatment group.
† Analysis of normalized data; p= 0.070 for analysis of raw dataset

Table 3: Analysis of Pain Intensity Difference Scores through 6 hours (SPID6) for OXY-MD-05 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Combination *	186	6.54	0.42	5.71, 7.37	
Ibuprofen 400 mg	186	5.41	0.44	4.56, 6.27	
Oxycodone 5 mg	63	0.14	0.60	-1.03, 1.31	<0.001
Placebo	62	0.32	0.59	-0.85, 1.48	
Pairwise Comparison		***Difference in LS Mean***		***95% CI for LS Difference***	***p-value***
Combination vs. Ibuprofen 400 mg		1.13	0.41	0.31, 1.94	0.002†
Combination vs. Oxycodone 5 mg		6.40	0.58	5.26, 7.54	<0.001
Combination vs. Placebo		6.22	0.58	5.08, 7.37	<0.001
Ibuprofen 400 mg vs. Placebo		5.10	0.58	3.95, 6.25	<0.001
Oxycodone 5 mg vs. Placebo		-0.18	0.71	-1.58, 1.22	0.805

* Combination = oxycodone HCl/ibuprofen 5/400 mg combination treatment group.
† Analysis of normalized data; p= 0.007 for analysis of raw dataset.

Table 4: Analysis of Total Pain Relief Scores through 6 hours (TOTPAR6) for OXY-MD-06 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Oxy/Ibu 5/400 mg	170	15.76	0.42	14.93, 16.59	
Oxy/Ibu 10/400 mg	168	15.68	0.43	14.85, 16.52	
Ibuprofen 400 mg	169	14.46	0.43	13.63, 15.30	<0.001
Oxycodone 5 mg	57	8.62	0.73	7.19, 10.05	
Oxycodone 10 mg	56	8.91	0.74	7.47, 10.36	
Placebo	56	6.27	0.74	4.82, 7.71	
Pairwise Comparison		***Difference in LS Mean***	***SE***	***95% CI for Difference***	***p-value***
Oxy/Ibu 5/400 mg vs Ibu 400 mg		1.30	0.60	0.13, 2.47	0.030
Oxy/Ibu 10/400 mg vs Oxy 5 mg		7.14	0.84	5.49, 8.79	<0.001
Oxy/Ibu 10/400 mg vs Ibu 400mg		1.22	0.60	0.05, 2.40	0.0412
Oxy/Ibu 10/400 mg vs Oxy 10 mg		6.77	0.85	5.11, 8.44	<0.001
Oxy/Ibu 5/400 mg vs Oxy/Ibu 10/400 mg		0.07	0.60	-1.10, 1.25	0.9004
Oxycodone 5 mg vs. Oxycodone 10 mg		-0.29	1.03	-2.32, 1.74	0.7762
Versus Placebo					
Oxy/Ibu 5/400 mg		9.49	0.85	7.83, 11.15	<0.001
Oxy/Ibu 10/400 mg		9.42	0.85	7.75, 11.08	<0.001
Ibuprofen 400 mg		8.19	0.85	6.53, 9.85	<0.001
Oxycodone 5 mg		2.35	1.03	0.32, 4.38	0.0234
Oxycodone 10 mg		2.64	1.04	0.60, 4.68	0.0111

Oxy = Oxycodone; Ibu = Ibuprofen

Table 5: Analysis of Pain Intensity Difference Scores through 6 hours (SPID6) for OXY-MD-06 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Oxy/Ibu 5/400 mg	170	8.28	0.31	7.68, 8.89	
Oxy/Ibu 10/400 mg	168	8.27	0.31	7.66, 8.88	
Ibuprofen 400 mg	169	7.39	0.31	6.78, 8.00	<0.001
Oxycodone 5 mg	57	3.30	0.53	2.26, 4.34	
Oxycodone 10 mg	56	3.37	0.53	2.32, 4.42	
Placebo	56	1.74	0.54	0.69, 2.79	
Pairwise Comparison		***Difference in LS Mean***	***SE***	***95% CI for Difference***	***p-value***
Oxy/Ibu 5/400 mg vs Ibu 400 mg		0.89	0.43	0.05, 1.74	0.0389
Oxy/Ibu 10/400 mg vs Oxy 5 mg		4.98	0.61	3.79, 6.18	<0.001
Oxy/Ibu 10/400 mg vs Ibu 400mg		0.88	0.43	0.03, 1.73	0.0430
Oxy/Ibu 10/400 mg vs Oxy 10 mg		4.90	0.61	3.70, 6.11	<0.001
Oxy/Ibu 5/400 mg vs Oxy/Ibu 10/400 mg		0.02	0.43	-0.83, 0.87	0.9720
Oxycodone 5 mg vs. Oxycodone 10 mg		-0.07	0.75	-1.54, 1.40	0.9278
Versus Placebo					
Oxy/Ibu 5/400 mg		6.54	0.61	5.34, 7.75	<0.001
Oxy/Ibu 10/400 mg		6.53	0.61	5.32, 7.73	<0.001
Ibuprofen 400 mg		5.65	0.61	4.44, 6.85	<0.001
Oxycodone 5 mg		1.56	0.75	0.09, 3.03	0.0381
Oxycodone 10 mg		1.62	0.75	0.15, 3.10	0.0312

Oxy = Oxycodone; Ibu = Ibuprofen

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Figure 1:Mean Pain Relief Scores over Time OXY-MD-05
(as presented by the sponsor)

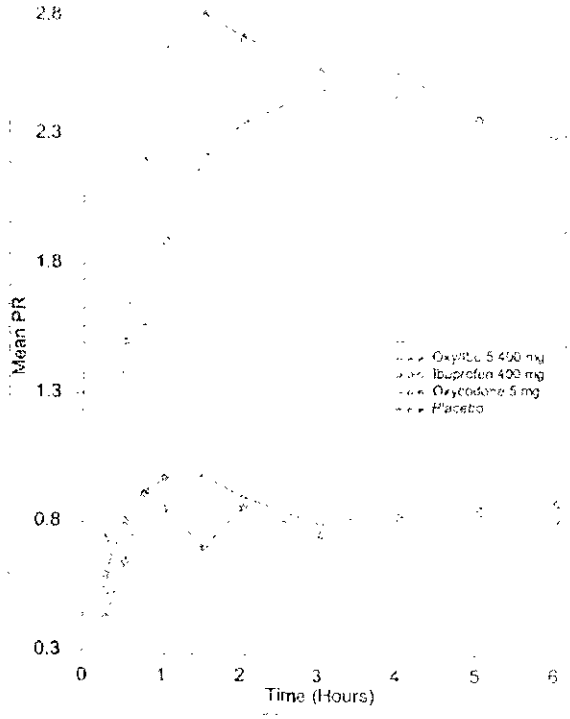

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Figure 2: Mean Pain Intensity Difference Scores over Time OXY-MD-05 (as presented by the sponsor)

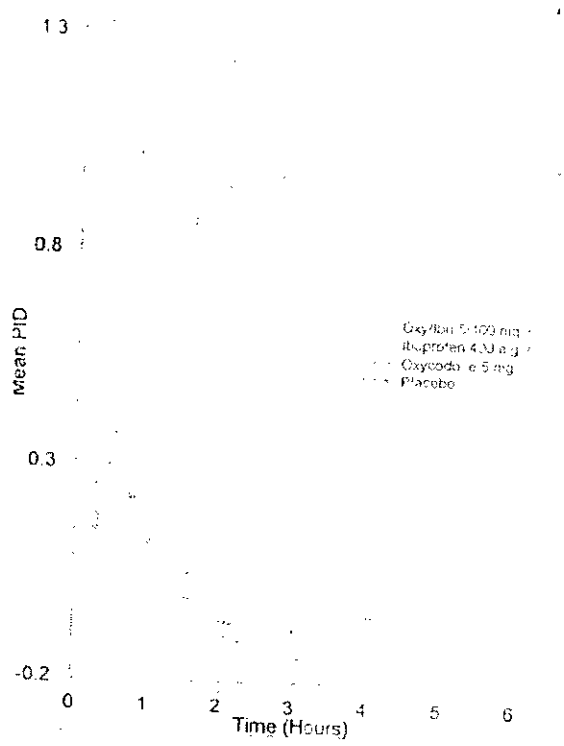


Figure 3: Mean Pain Relief Scores over Time OXY-MD-06 (as presented by the sponsor)

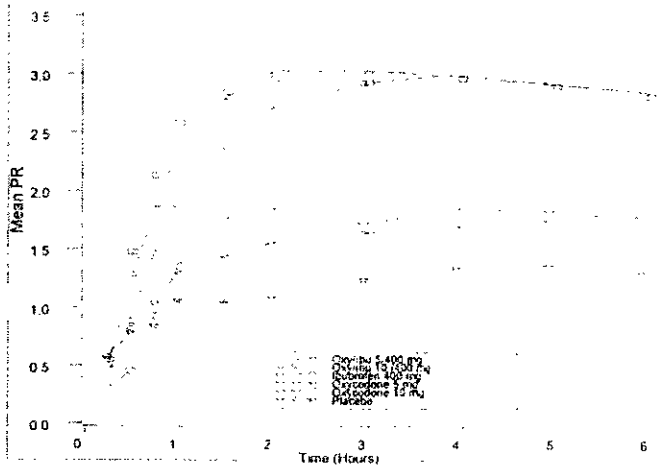
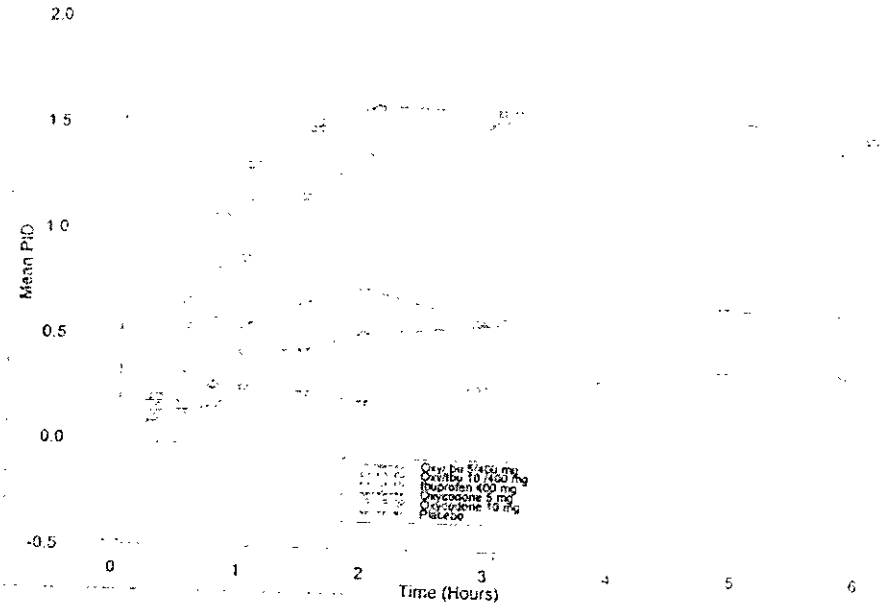


Figure 4: Mean Pain Intensity Difference Scores over Time OXY-MD-06 (as presented by the sponsor)



2.3.4 STATISTICAL REVIEWER'S FINDINGS

Two methodological issues warranting discussion were identified during the course of my review. In study OXY-MD-05, the sponsor performs a post-hoc analysis in order to meet the normality assumption accompanying the use of an analysis of variance model. In general, an ANOVA model is robust with respect to moderate departures from the basic assumptions. Specifically, the normality assumption can be relaxed provided the sample size is large and/or the departure from normality is not extreme. Appealing to the aforementioned, the need to perform a transformation on the data does not seem justified. Furthermore, no such analysis was applied in OXY-MD-06 where the same lack of normality phenomena existed. As such, the results (from the raw data) in OXY-MD-05 may have been acceptable had they been significant thus adding to the probability of error.

In OXY-MD-06, the sponsor's analyses are conducted with no adjustments for multiplicity. The inclusion of both doses in the study result in testing of multiple hypotheses by which either (or both) dose of the combination product may be found effective. I believe that without an adjustment, there is an increased probability of falsely declaring some dose of the combination product to be effective. In order to maintain an overall type I error rate of

0.05, I applied the Holm's stepdown method which entails ordering the p-values and comparing the values to an adjusted alpha level. My analysis is post-hoc; however, the purpose is solely to validate conclusions.

Following my evaluation of the studies, I conclude that the combination drug product produces greater pain relief and a greater pain intensity difference (from baseline) as compared to the individual components and placebo. However, the difference in pain relief and pain intensity among the combination product and ibuprofen alone groups is nominally significant only through 6 hours. Early time points more strongly favor the combination over the ibuprofen alone. I refer to Dr. Shaun Comfort's clinical review to address the clinical significance of the results.

Additionally, the sponsor investigates the time to onset of pain relief and the duration of pain relief. I conclude that the combination product promotes more rapid onset of relief as compared to each of the individual components. In addition, fewer patients receiving the combination drug product or ibuprofen alone required rescue medication. The sponsor uses the outcome, time to re-medication (the time between dosing and rescue medication use), as a measure of duration of pain relief. I disagree as duration of relief implies that relief has been achieved and should therefore be calculated from beginning of pain relief to the end of relief.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analyses were performed with respect to gender, race and age for studies OXY-MD-05 and OXY-MD-06 combined. The measures of efficacy were total pain relief through 6 hours and sum of pain intensity difference through 6 hours. Initial analyses were conducted via analysis of variance models including factors for the subgroup, treatment, protocol, study site within protocol, and subgroup by treatment interaction. An additional effect for baseline pain intensity was included for analyses of the sum of pain intensity difference. Subsequent analyses were conducted in each subgroup.

Among males and females receiving oxycodone HCl/ibuprofen, an analgesic effect (as measured by total pain relief and the sum of pain intensity difference scores through 6 hours) was evident. The effect appeared somewhat greater for the combination drug product as compared to the ibuprofen alone with the difference among treatments being more apparent among females. Due to the limited number of minority study participants, sub-populations defined by race were categorized as Caucasians or non-Caucasians. Among racial groups, the combination drug product produced greater pain relief and a greater pain intensity difference (from baseline) as compared to the individual components and placebo. The effect appeared somewhat larger among non-Caucasians as compared to Caucasians. Lastly, further support favoring the combination product is provided from examination of the sub-population categorized by age.

Overall, there did not exist any age, race, or gender effects as evidenced by the lack of statistical significance achieved with the varying subgroup factors in the model. The sponsor does not propose any efficacy claims for any subgroups of patients. Overall, the results were consistent and lend support to the findings presented in preceding sections.

2.5 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

A primary claim of the sponsor is that the combination product produces greater efficacy than placebo and each of the individual components as measured by magnitude of pain relief and reduction in pain intensity. The evidence taken collectively from both studies reviewed indicates some statistical support favoring the combination drug product for pain relief and reduction in pain intensity at later times; however, a greater treatment effect is shown at earlier times. Although differences in total pain relief and pain intensity from baseline between the combination drug product and ibuprofen alone are noted, the clinical meaningfulness of the difference is a germane issue for consideration.

The evidence suggests that the combination product reduces the time to onset of pain relief as compared to the ibuprofen alone, oxycodone alone, or placebo. With regards to

Duration of relief implies that relief has been achieved and should therefore be calculated from beginning of pain relief to the end of relief. However, the sponsor measures duration from the time of dosing until re-medication. This latter measurement provides information on time to re-medication only.

2.6 CONCLUSIONS AND RECOMMENDATIONS

As a result of the clinical studies conducted, the sponsor claims that the combination produces "greater efficacy than placebo and each of its individual components given at the same dose as measured by magnitude of pain relief, the reduction in pain intensity

In addition, the sponsor proposes the use of an oxycodone/ibuprofen combination product for the short-term management of acute, moderate to severe pain.

The combination product produces greater relief of pain and greater reduction in pain intensity as compared to each component; however, the effect is more strongly favored at earlier timepoints and is only nominal at later timepoints. Moreover, the product significantly shortens the time to onset of pain relief in comparison to ibuprofen alone and oxycodone alone.

Issues pertaining to the clinical meaningfulness of the detected differences in addition to the necessary evidence required for an acute indication are beyond the scope of my review. Attention to these germane issues is deferred to the medical review of Dr. Shaun Comfort.

2.7 LABELLING

The proposed draft labeling reads as follows:

> BRANDNAME was investigated in — clinical studies involving a total of 949 patients post dental surgery (removal of ipsilateral molars) who were administered a single dose of the BRANDNAME, ibuprofen alone, oxycodone HCl alone or placebo for acute, moderate to severe pain. BRANDNAME produced greater efficacy than placebo and each of its individual components — as measu red by the magnitude of pain relief, the reduction in pain intensity a —

Of note, the patient total refers to the pooled patient population and excludes the oxycodone HCl 10 mg/ ibuprofen 400 mg and oxycodone HCl 10 mg groups. The statement regarding — presents a somewhat misleading representation of the effect of the drug throughout the investigated time course.

Therefore, I recommend a slightly more descriptive statement drafted as follows:

> BRANDNAME was investigated in — clinical studies involving a total of 949 patients post dental surgery (removal of ipsilateral molars) who were administered a single dose of the BRANDNAME, ibuprofen alone, oxycodone HCl alone or placebo for acute, moderate to severe pain. BRANDNAME produced greater efficacy than placebo and each of its individual components — as measu red by the magnitude of pain relief and the reduction in pain intensity. — e strongly favored at earlier

I caution against a — for reasons detailed in my review. The aforementioned recommendations are based on my statistical review, and I defer further recommendations regarding the appropriateness of the indication to my medical colleagues.

2.8 APPENDIX

This appendix contains detailed tables of the subject demographics and baseline characteristics. Moreover, detailed tables regarding total pain relief through 3 hours and sum of pain intensity difference scores through 3 hours are also included.

Summary of Subject Demographics and Baseline Characteristics OXY-MD-05

	Oxy/Ibu 5/400 mg N=187	*Ibuprofen 400 mg N=186*	*Oxycodone 5 mg N = 63*	*Placebo N=62*	*Total N=498*	*p-value*[a]
AGE (YEARS)						
Mean (SD)	24.7 (5.3)	24.1(5.1)	24.3 (5.2)	24.8 (5.5)	24.5 (5.2)	0.677
Median	24.0	23.0	24.0	23.0	23.0	
Range	16-40	16-48	16-40	17-42	16-48	
SEX, N(%)						
Male	69 (36.9)	85(45.7)	30(47.6)	35(56.5)	219(44.0)	0.041
Female	118(63.1)	101(54.3)	33(52.4)	27(43.5)	279(56.0)	
RACE, N (%)						
White	116(62.0)	138(74.2)	48(76.2)	48(77.4)	350(70.3)	0.023
Black	19(10.2)	16(8.6)	7(11.1)	9(14.5)	51(10.2)	
Asian	17(9.1)	14(7.5)	2(3.2)	3(4.8)	36(7.2)	
Other	35(18.7)	18(9.7)	6(9.5)	2(3.2)	61(12.2)	
WEIGHT(LBS)						
Mean (SD)	154.7(34.0)	159.6(37.0)	158.8(28.3)	163.8(36.0)	158.2(34.8)	0.291
Median	150.0	155.0	155.0	157.0	152.0	
Range	92-270	90-300	110-245	105-300	90-300	
HEIGHT (IN)						
Mean (SD)	66.5(4.4)	67.1(4.3)	67.6(3.7)	67.4(3.5)	67.0(4.2)	0.161
Median	66.0	67.0	68.0	67.3	67.0	
Range	52-76	51-80	60-76	59-75	51-80	
BASELINE PAIN INTENSITY, N (%)						
Moderate	169 (90.4)	173(93.0)	58(92.1)	56(90.3)	456(91.6)	0.804
Severe	18(9.6)	13(7.0)	5(7.9)	6(9.7)	42(8.4)	
BASELINE PAIN VAS (MM)						
Mean (SD)	59(8.8)	58(7.2)	57.8(7.2)	58.5(8.6)	58.4(8.0)	0.629
Median	57.0	57.0	56.0	56.0	56.0	
Range	49-92	49-82	50-81	49-89	49-92	

[a] P-values for between treatment comparison from ANOVA model with treatment as factors for continuous variables and CMH test for categorical variables.

Summary of Subject Demographics and Baseline Characteristics OXY-MD-06

	Oxy/Ibu 5/400 mg N=171	*Oxy/Ibu 10/400 mg N=169*	*Ibuprofen 400 mg N=171*	*Oxy 5 mg N = 57*	*Oxy 10 mg N =57*	*Placebo N=57*	*Total N=682*	*p-value* [a]
AGE								
Mean (SD)	18.9 (4.2)	18.4(2.7)	18.4(3.4)	18.1 (2.4)	18.7 (2.7)	18.2 (2.5)	18.5 (3.3)	0.436
Median	18.0	18.0	18.0	18.0	18.0	18.0	18.0	
Range	14-40	13-30	14-43	13-26	14-27	14-25	13-43	
SEX N (%)								
Male	85 (49.7)	89(52.7)	93(54.4)	24(42.1)	31(54.4)	27(47.4)	349(51.2)	0.632
Female	86(50.3)	80(47.3)	78(45.6)	33(57.9)	26(45.6)	30(52.6)	333(48.8)	
RACE N (%)								
White	159(93.0)	161(95.3)	163(95.3)	53(93.0)	55(96.5)	55(96.5)	646(94.7)	0.797
Asian	1(0.6)	1(0.6)	3(1.8)	1(1.8)	0	0	6(0.9)	
Other	11(6.4)	7(4.1)	5(2.9)	3(5.3)	2(3.5)	2(3.5)	30(4.4)	
WEIGHT (LBS)								
Mean (SD)	146.8(30.0)	151.2(33.2)	150.4(29.6)	148.3(36.6)	149.5(33.3)	151.4(32.6)	149.5(31.7)	0.831
Median	145.0	145.0	150.0	136.0	145.0	146.5	145.0	
Range	93-300	105-295	95-260	101-260	100-255	105-255	93-300	
HEIGHT (IN)								
Mean (SD)	67.6(3.8)	68.3(4.1)	67.9(3.9)	67.2(3.8)	68.0(4.3)	67.9(3.6)	67.9(3.9)	0.478
Median	68.0	68.0	68.0	67.0	67.0	68.0	68.0	
Range	58-78	60-80	57-77	58-75	60-78	61-76	57-80	
BASELINE PAIN INTENSITY								
Moderate	97(56.7)	92(54.4)	99(57.9)	36(63.2)	34(59.6)	36(59.6)	394(57.8)	0.809
Severe	74(43.3)	77(45.6)	72(42.1)	21(36.8)	23(40.4)	21(36.8)	288(42.2)	
BASELINE PAIN VAS (MM)								
Mean (SD)	74.9(10.5)	75.8(10.1)	74.4(10.9)	74.3(11.1)	74.2(10.9)	73.6(12.3)	74.8(10.7)	0.729
Median	73.0	75.0	74.0	74.0	71.0	71.0	74.0	
Range	56-98	52-98	55-100	54-98	50-98	55-99	50-100	

[a] P-values for between treatment comparison from ANOVA model with treatment as factors for continuous variables and CMH test for categorical variables.

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Analysis of Total Pain Relief Scores through 3 hours (TOTPAR3) for OXY-MD-05 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Combination *	186	6.43	0.24	5.97, 6.90	
Ibuprofen 400 mg	186	5.35	0.24	4.89, 5.81	
Oxycodone 5 mg	63	2.17	0.37	1.44, 2.90	<0.001
Placebo	62	2.03	0.38	1.29, 2.77	

Pairwise Comparison	*Difference in LS Mean*	*SE*	*95% CI for LS Difference*	*p-value*
Combination vs. Ibuprofen 400 mg	1.08	0.29	0.51, 1.66	<0.001
Combination vs. Oxycodone 5 mg	4.26	0.41	3.45, 5.07	<0.001
Combination vs. Placebo	4.40	0.41	3.59, 5.22	<0.001
Ibuprofen 400 mg vs. Placebo	3.32	0.41	2.51, 4.13	<0.001
Oxycodone 5 mg vs. Placebo	0.14	0.50	-0.85, 1.13	0.7780

* Combination = oxycodone HCl/ibuprofen 5/400 mg combination treatment group.

Analysis of Pain Intensity Difference Scores through 3hours (SPID3) for OXY-MD-05 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Combination *	186	3.19	0.19	2.83, 3.56	
Ibuprofen 400 mg	186	2.43	0.19	2.05, 2.81	
Oxycodone 5 mg	63	0.27	0.26	-0.25, 0.79	<0.001
Placebo	62	0.24	0.26	-0.27, 0.75	

Pairwise Comparison	*Difference in LS Mean*	*SE*	*95% CI for LS Difference*	*p-value*
Combination vs. Ibuprofen 400 mg	0.76	0.18	0.40, 1.12	<0.001
Combination vs. Oxycodone 5 mg	2.92	0.26	2.42, 3.43	<0.001
Combination vs. Placebo	2.95	0.26	2.45, 3.46	<0.001
Ibuprofen 400 mg vs. Placebo	2.19	0.26	1.69, 2.70	<0.001
Oxycodone 5 mg vs. Placebo	0.03	0.31	-0.59, 0.65	0.9227

* Combination = oxycodone HCl/ibuprofen 5/400 mg combination treatment group.

Analysis of Total Pain Relief Scores through 3 hours (TOTPAR3) for OXY-MD-06 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Oxy/Ibu 5/400 mg	170	6.98	0.19	6.61,7.35	
Oxy/Ibu 10/400 mg	168	7.05	0.19	6.67,7.42	
Ibuprofen 400 mg	169	5.92	0.19	5.55,6.29	<0.001
Oxycodone 5 mg	57	3.67	0.32	3.04,4.31	
Oxycodone 10 mg	56	3.83	0.33	3.19,4.47	
Placebo	56	2.67	0.33	2.03,3.31	
Pairwise Comparison		***Difference in LS Mean***	*SE*	*95% CI for Difference*	*p-value*
Oxy/Ibu 5/400 mg vs Ibu 400 mg		1.07	0.27	0.55,1.59	0.0389
Oxy/Ibu 10/400 mg vs Oxy 5 mg		3.31	0.37	2.58,4.05	<0.001
Oxy/Ibu 10/400 mg vs Ibu 400mg		1.13	0.27	0.61,1.65	0.0430
Oxy/Ibu 10/400 mg vs Oxy 10 mg		3.22	0.38	2.47,3.96	<0.001
Oxy/Ibu 5/400 mg vs Oxy/Ibu 10/400 mg		-0.06	0.27	-0.58,0.46	0.815
Oxycodone 5 mg vs. Oxycodone 10 mg		-0.16	0.46	-1.06,0.75	0.732
Versus Placebo					
Oxy/Ibu 5/400 mg		4.31	0.38	3.58,5.05	<0.001
Oxy/Ibu 10/400 mg		4.38	0.38	3.64,5.12	<0.001
Ibuprofen 400 mg		3.25	0.38	2.51, 3.99	<0.001
Oxycodone 5 mg		1.00	0.46	0.10, 1.91	0.029
Oxycodone 10 mg		1.16	0.46	0.25, 2.07	0.012

Oxy = Oxycodone; Ibu = Ibuprofen

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Analysis of Pain Intensity Difference Scores through 3 hours (SPID3) for OXY-MD-06 (as presented by sponsor)

Treatment Group	*N*	*LS Mean*	*SE*	*95% CI for LS Mean*	*Overall treatment p-value*
Oxy/Ibu 5/400 mg	170	3.57	0.14	3.31, 3.84	
Oxy/Ibu 10/400 mg	168	3.66	0.14	3.39, 3.93	
Ibuprofen 400 mg	169	2.92	0.14	2.65, 3.18	<0.001
Oxycodone 5 mg	57	1.28	0.23	0.82, 1.74	
Oxycodone 10 mg	56	1.43	0.24	0.97, 1.89	
Placebo	56	0.67	0.24	0.21, 1.14	
Pairwise Comparison		***Difference in LS Mean***	***SE***	***95% CI for Difference***	***p-value***
Oxy/Ibu 5/400 mg vs Ibu 400 mg		0.66	0.19	0.29, 1.03	<0.001
Oxy/Ibu 10/400 mg vs Oxy 5 mg		2.29	0.27	1.77, 2.82	<0.001
Oxy/Ibu 10/400 mg vs Ibu 400mg		0.74	0.19	0.37, 1.12	<0.001
Oxy/Ibu 10/400 mg vs Oxy 10 mg		2.23	0.27	1.70, 2.76	<0.001
Oxy/Ibu 5/400 mg vs Oxy/Ibu 10/400 mg		-0.08	0.19	0.46, 0.29	0.663
Oxycodone 5 mg vs. Oxycodone 10 mg		-0.15	0.33	-0.80, 0.50	0.648
Versus Placebo					
Oxy/Ibu 5/400 mg		2.90	0.27	2.37, 3.43	<0.001
Oxy/Ibu 10/400 mg		2.99	0.27	2.45, 3.52	<0.001
Ibuprofen 400 mg		2.24	0.27	1.71, 2.77	<0.001
Oxycodone 5 mg		0.61	0.33	-0.04, 1.26	0.066
Oxycodone 10 mg		0.76	0.33	0.11, 1.41	0.022

Oxy = Oxycodone; Ibu = Ibuprofen

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/s/

Dionne Price
9/11/02 12:03:28 PM
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Thomas Permutt
9/12/02 02:27:42 PM
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