CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	November 26, 2004
DRUG:	Combunox (oxycodone HCl/Ibuprofen, 5 mg/400 mg tablets)
NDA:	21-378
NDA Code:	Type 4S NDA
SPONSOR:	Forest Laboratories, Inc.
INDICATION:	For the short-term (no more than 7 days) management of acute, moderate to severe pain

NDA 21-378 was originally submitted by Forest Laboratories, Inc. on December 20, 2001. At the pre-NDA meeting the Division expressed concern regarding the applicant's drug development program which consisted of single-dose efficacy studies in post-dental surgery patients. The Division clearly stated that this product would potentially be used chronically and in various acute pain settings that would require multiple-dose regimens.

Review of the application resulted in an Approvable action letter issued on October 18, 2002. Several deficiencies in various disciplines were identified in the letter, including concerns related to Chemistry, Manufacturing, and Controls (CMC), Pharmacology/toxicology, Clinical and Regulatory.

A Post-action Meeting was held on December 17, 2002, during which several deficiencies were either considered resolved or considered to have a clear path forward for resolution. However, there were four issues that were considered to be unresolved:

- assessment of the carcinogenicity potential of the combination product,

- submission of data from adequate and well-controlled multiple-dose studies, and
- submission of sufficient data to evaluate the safety of the combination product in the population and setting in which it was thought to be likely to be used.

Following the post-action meeting, the applicant requested a formal dispute resolution meeting with Dr. Robert Meyer, the Director of the Office of Drug Evaluation II, to address the following issues:

- the need for carcinogenicity studies;
- the need for clinical safety data for a minimum of three months; and
- the need for efficacy data of the combination product in multiple-dose studies up to three weeks in duration.

Dr. Meyer reaffirmed the need for the carcinogenicity and efficacy data in a letter dated March 17, 2003. However, in that letter Dr. Meyer noted that he would be willing to accept shorter-term safety data (one month) if the Sponsor was able to provide a justification for why this product was unlikely to result in increased risk compared to the individual, previously approved components, in the setting of chronic use.

The applicant then requested a formal dispute resolution with Dr. John Jenkins, Director of the Office of New Drugs. Based on the fact that the Sponsor strongly asserted their plans to market this product for acute use only, Dr. Jenkins formulated the following conclusions regarding the requirements for the approval of the application (letter dated May 29, 2003):

- Carcinogenicity studies for oxycodone would not be required prior to approval, and it would not be necessary for the applicant to conduct them as post-marketing commitments.
- A multiple-dose clinical efficacy study would still be required, in addition to the studies already submitted, to support approval and document that the product fulfilled the requirements outlined in the CFR for combination drug products.
- Collection of appropriate safety data in the multiple-dose efficacy study would be sufficient to support approval.

The applicant chose to appeal Dr. Jenkin's decision by requesting a formal dispute resolution meeting with the Acting Director of the Center for Drug Evaluation and Research, Dr. Steven Galson. That meeting was held on November 12, 2003. At the conclusion of the meeting, Dr. Galson offered the Sponsor the following options:

- Resubmission of the NDA to include the results of a new multiple-dose study of the oxycodone/ibuprofen combination tablet designed to address the standards of

the combination drug policy, as well as full responses to all of the other deficiencies identified in the Division's October 18, 2002 approvable letter.

or

- Resubmission that would include the results of an already performed post-operative pain study in patients undergoing abdominal or gynecological surgery, in addition to adequate multiple-dose safety data for the oxycodone/ibuprofen safety combination tablet, and complete responses to the other deficiencies identified in the Division's October 18, 2002 approvable letter. It was noted that the labeling would probably need to reflect a limited indication and duration of treatment and a lack of efficacy data for multiple dose regimens.

The applicant's current submission, dated May 25, 2004, is a complete response to the approvable letter. The applicant chose to follow the second option offered by Dr. Galson.

***Efficacy*:**

The single study submitted with the response to the approvable letter was reviewed by Rigoberto Roca, M.D. Dr. Roca's review provides a thorough and complete discussion of that study. Dionne L. Price, Ph.D. provided a detailed and comprehensive statistical review. Therefore, I will briefly summarize their findings.

Study OXY-MD-10 was a randomized, placebo-controlled, single-dose, parallel trial of Combunox in women who had undergone abdominal or pelvic surgery. Fourteen hours after the completion of surgery, subjects were randomized to Combunox or placebo if they had developed moderate to severe pain and a VAS pain score of greater than or equal to 50 mm on a 100-mm scale. Each patient received a single dose of study medication or placebo.

The primary outcome variables were $TOTPAR_6$ (defined as the area under the pain relief vs. time curve during the first six hours after dosing) and $SPID_6$ (defined as the area under the pain intensity vs. time curve during the first six hours after dosing). Both metrics used a categorical scale ranging from 0 (no pain) to 3 (severe pain). Both the Sponsor's and the Agency's analyses documented statistically significant treatment effects for Combunox compared to placebo and to the individual components of this fixed-dose combination drug product on both primary endpoints. The secondary endpoints were generally supportive.

***Clinical Safety*:**

Based on the agreement reached between Forest and Dr. Galson, the sponsor has provided a separate analysis of the safety data from the extension study to OXY-MD-10 and three other "lead-in" studies, OXY-MD-08, in order to allow a comparison of multi-dose

exposure to the combined data from the earlier, single-dose studies. The multiple-dose study called for a dosing regimen of one tablet of either Combunox 5 mg/400 mg or Combunox 10 mg/400 mg no more often than every six hours for up to seven days. The table on page 35 of Dr. Roca's review summarizes the number of subjects treated with from 1 to 28 doses of Combunox in these studies. Over 200 subjects received between 2 and 24 doses and an additional 32 subjects received between 25 and 28 doses. The table on page 27 of Dr. Roca's review compares the incidence of adverse events in subjects treated with the lower and higher oxycodone doses. As expected, the subjects in the 10 mg/400 mg group had a higher incidence of significant adverse events than those in the 5 mg/400 mg group.

Dr. Roca has carefully evaluated the new data and compared it to the earlier data. He has concluded, on page vii of his Executive Summary, that:

> The adverse events observed in the single dose OXY-MD-10 study were similar to what had been previously observed and submitted in the original NDA. The adverse events reported in the updated safety database in this submission were reflective of the previously observed safety profiles of opioids and NSAIDs. There were no new safety signals apparent in the current safety database.

Biopharmaceutics:

The approvable letter stated that the Sponsor had used an unapproved product as a comparator in their clinical studies, the 5-mg Roxicodone (oxycodone) tablet. However, after the letter had been issued, the Division determined that this drug product would be adequate as a comparator based on the following pharmacokinetic linkage:

- Oxycodone in Combunox was found to be biocquivalent to the 5-mg Roxicodone tablet in this application.
- Three 5-mg Roxicodone tablets were found to be biocquivalent to the 15-mg Roxicodone tablet in one of the studies submitted to NDA 21-011.
- The 15-mg Roxicodone tablet was found to be bioequivalent to the oxycodone in three 5-mg Percodan tablets in another of the studies in NDA 21-011.
- Percodan is an approved product.

Nonclinical Safety:

The approvable letter for Combunox identified three deficiencies in the adequacy of the non-clinical safety data submitted with the original application:

- Segment I and Segment III reproductive toxicology studies were absent from the submission. The letter noted that these studies could be submitted in Phase 4 with adequate justification, depending on the timing of the resubmission.

- Carcinogenicity studies were absent from the submission. These studies would be required unless the Sponsor was able to provide post-marketing data from similar combination drug products that demonstrated that Combunox would not be used chronically.

- Adequate patent certification had not been submitted for referenced products used to support the non-clinical safety of Combunox in this 505(b)(2) application.

Mamata De, Ph.D. has reviewed the response to these deficiencies. The Sponsor has agreed to submit the Segment I and Segment III studies in Phase 4. Carcinogenicity studies will no longer be required for Combunox based on the fact that the product will be limited to use in the acute pain setting and will be labeled for a treatment duration of no more than seven days. Finally, the Sponsor has provided adequate patent certification for all reference listed drugs.

An additional unresolved toxicology issue that arose after the approvable letter had been issued is the finding of a structural alert for mutagenicity for an impurity —

— The sponsor has provided two genetic toxicology studies of — which were negative. Nevertheless, as with all manufacturers and distributors of — containing opioid drugs, the Division and the Sponsor have reached an agreement for an acceptable interim specification for the impurity. Additionally, the Sponsor has agreed to a reasonable timeline for achieving the Division's defined final specification for this impurity.

Finally, the sponsor proposed language for the genotoxicology section of the package insert that referenced the package insert of another approved oxycodone product. However, they failed to submit adequate patent certification and a relative bioavailability study in order to allow for that product to be considered a Reference Listed Drug for their 505(b)2 application. However, the Division has determined that this reference is not necessary based on the fact that the specific genotoxicology information in the referenced label is important, but not essential for practitioners and patients, especially in light of the fact that administration of the product will be limited to no more than seven days. Therefore, the genotoxicology section of the PI will note that no genotoxicology studies have been performed for Combunox, and the Sponsor has agreed to perform those studies in Phase 4.

Chemistry, Manufacturing and Controls:

There were thirty-one individual CMC deficiencies categorized into four separate groups in the approvable letter. Danae D. Christodoulou, Ph.D. has reviewed the Sponsor's responses to these deficiencies and determined that they are sufficient to allow assurance of adequate product quality.

Discussion

Based on the complete response to the approvable letter and the agreements reached between Forest Laboratories, Inc. and the Agency during the dispute resolution process, I have determined that Combunox is safe and effective when used according to the approved package insert.

Action recommended by the Division: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
11/26/04 01:39:36 PM
MEDICAL OFFICER

Clinical Review

Application Type	NDA
Submission Number	21-378
Submission Code	N-000-AZ
Letter Date	May 5, 2004
Stamp Date	May 27, 2004
PDUFA Goal Date	November 27, 2004
Reviewer	Rigoberto Roca, M.D.
Review Completion Date	November 24, 2004
Established Name	Oxycodone HCl/Ibuprofen
Proposed Trade Name	Combunox
Therapeutic Class	Analgesic
Applicant	Forest Laboratories, Inc.
Review Clock Designation	Resubmission (Response to AE letter)
Formulation	Oxycodone 5 mg/ Ibuprofen – mg Tablets
Dosing Regimen	Not to exceed 4 tablets in a 24 hour period

Table of Contents

List of abbreviations used in this review

CMC	Chemistry, Manufacturing, and Controls
CNS	Central nervous system
DMF	Drug Master File
µg	micrograms
mg	milligrams
ng	nanograms
NDA	New Drug Application
NSAIDs	Non-steroidal anti-inflammatory drugs
PID	Pain intensity difference
PR	Pain relief
PREA	Pediatric Research Equity Act
PRID	Sum of pain relief and pain intensity difference at each timepoint
SAE	Serious adverse event
SPID	Sum of pain intensity difference
TEAE	Treatment emergent adverse event
TOTPAR	Total pain relief

1 Executive summary

1.1 Recommendations on Regulatory Action

This submission was a complete response to the approvable letter dated October 18, 2002. It also incorporated the applicant's responses to the decisional outcomes from the post-action meeting with the Division (December 17, 2002), from formal dispute resolution meetings with the Office on New Drugs (April 29, 2003), and the Center for Drug for Drug Evaluation and Research (November 12, 2003).

The applicant has submitted sufficient data to demonstrate the efficacy of a single dose of the oxycodone 5 mg/ibuprofen 400 mg combination tablet. Sufficient multiple-dose safety data has also been submitted to consider the requirements stipulated by Dr. Galson fulfilled.

It is recommended that the application be approved, with appropriate wording incorporated into the labeling to reflect the lack of efficacy data with a multiple-dose regimen.

1.2 Recommendation on Postmarketing Actions

The results from Segment I and Segment II reproductive toxicology studies with the combination tablet are pending. The applicant has indicated their plan to submit them as part of any postmarketing commitment they may be asked to perform.

It is not believed that a formal risk management program that expands on education, surveillance and intervention, is necessary at this time.

As part of the applicant's obligation to fulfill the requirements of PREA, the applicant will need to complete a clinical study that evaluates the efficacy and safety of the combination product in pediatric patients between the ages of 12 and 17 years. Clinical studies in pediatric patients between the ages of 2 and 12 years will be deferred until the applicant evaluates the feasibility of developing an age-appropriate formulation of their combination product. The requirement for clinical studies for pediatric patients younger than 2 years of age may be waived since a combination fixed dose formulation for this age group would be inappropriate.

1.3 Summary of Clinical Findings

The applicant has conducted several studies to evaluate the efficacy and safety of the oxycodone 5 mg/ ibuprofen 400 mg combination tablet. Utilizing post-surgery pain models in patients undergoing dental procedures and in patients undergoing abdominal/gynecological procedures, the applicant has demonstrated efficacy of the combination tablet compared to placebo in a 6-hour time period immediately after dosing.

The safety profile of the combination tablet was comparable to the safety profile of the individual components, i.e., oxycodone and ibuprofen.

1.4 Brief Overview of Clinical Program

This NDA was originally submitted in December 2001, at which time the clinical development program consisted of six Phase I clinical pharmacology studies and eight randomized clinical studies. The following table, adapted from Dr. Shaun Comfort's review of the original submission, summarizes the clinical program at the time of the original submission.

Phase	Exposure	Study Type/Populations	Protocol #	N (# Treated)
I	Single Dose	Clinical Pharmacology – Crossover Trial	604-003-01	24
		Clinical Pharmacology – Crossover Trial	604-003-02	24
		Clinical Pharmacology – 3 Way Crossover Trial	Oxy-PK1-96-01	24
		Clinical Pharmacology – 2 Way Crossover Trial	Oxy-PK1-96-02	25
		Clinical Pharmacology – 2 Way Crossover Trial	Oxy-PK-04	24
	Single/Multi-Dose	Clinical Pharmacology – 2 Dose Crossover Trial	Oxy-PK-03	24
		Total Clin/Pharm Subjects	**Subtotal**	**145**
II	Single-Dose	Pilot Study: Dental Surgical Pain	604-001-01	117
		Pilot Study: Dental Surgical Pain	604-002-01	97
		Clinical Study: Dental Surgical Pain	Oxy-MD3-96-02	453
III	Single-Dose	Clinical Study: Dental Surgical Pain	Oxy-MD3-96-01	122
		Clinical Study: Dental Surgical Pain	Oxy-MD-05	498
		Clinical Study: Dental Surgical Pain	Oxy-MD-06	682
		Clinical Study: Post-Surgical Orthopedic Pain	Oxy-MD-07	682
	Multi-Dose	Clinical Study: Post-Surgical Ortho/Dental Pain Extended Double-Blind Study	Oxy-MD-08	488
		Total Clinical Subjects:	**Subtotal**	**3139[++]**
I, II, III		**TOTAL SUBJECTS**	**TOTAL**	**3284[++] (2796)**

[++]It was noted in Dr. Comfort's review that clinical subjects could be counted more than once due to crossover treatments from participation in the multi-dose OXY-MD-08 study; therefore, the total number of unique subjects/patients was 2796.

In the interim, the applicant has finalized the study report on Study OXY-MD-10, a double blind, placebo controlled study in female patients with moderate to severe pain after abdominal or pelvic surgery. This study, plus an update of the safety database, constitutes the clinical information of the current submission. Since the majority of the clinical studies of the development program have already been reviewed by Dr. Shaun Comfort during the previous review cycle, only the new study submitted with this application was reviewed.

1.4.1 Efficacy

Study OXY-MD-10, entitled "A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg in

Female Patients with Moderate to Severe Post-Abdominal or Pelvic Surgical Pain," evaluated the efficacy and safety of a single dose of the combination tablet of oxycodone HCl/ibuprofen (5 mg/400 mg) compared to 400 mg of ibuprofen alone, 5 mg of oxycodone alone, and placebo, in post-operative surgical pain model.

The primary efficacy variables were the total of the pain relief scores through 6 hours ($TOTPAR_6$) and the sum of pain intensity difference through 6 hours ($SPID_6$). The $TOTPAR_6$ is an estimate of the area under the pain relief vs. time curve during the first 6 hours of dosing. The $SPID_6$ is an estimate of the area under the pain intensity difference vs. time curve during the first 6 hours of dosing. The primary analysis was a statistical comparison of the effect that the combination of oxycodone HCl/ibuprofen (5 mg/400 mg) had on $TOTPAR_6$ and $SPID_6$ compared to individual components. An analysis comparing the combination against placebo allowed for an assessment of assay sensitivity of the study.

Utilizing these two efficacy variables, the applicant has adequately demonstrated that greater pain relief was reported by patients on the Oxycodone HCl/Ibuprofen (5 mg/400 mg) treatment group compared to ibuprofen alone, oxycodone alone, or placebo. Similarly, the applicant has adequately demonstrated that a greater pain intensity difference from baseline was observed for patients on the Oxycodone HCl/Ibuprofen (5 mg/400 mg) treatment group compared to ibuprofen alone, oxycodone alone, or placebo.

1.4.2 Safety

For purposes of the response to the AE letter, this submission's safety summary contains the safety data from Study OXY-MD-10 (the gynecologic pain study), and the resubmission of the safety data from five single-dose studies that used the to-be-marketed formulation of Oxycodone HCl/Ibuprofen (5 mg/400 mg) and one multiple-dose study. Therefore, a significant portion of the safety data in this submission has already been reviewed during the first review cycle.

The adverse events observed in the single dose OXY-MD-10 study were similar to what had been previously observed and submitted in the original NDA. The adverse events reported in the updated safety database in this submission were reflective of the previously observed safety profiles of opioids and NSAIDs. There were no new safety signals apparent in the current safety database.

1.4.3 Dosing Regimen and Administration

In order to be reflect the clinical data submitted by the applicant in support of this application, the **Dosage and Administration** section of the label should state that the dosing regimen of the product should not exceed four tablets in a 24-hour time period. It should also state that the duration of treatment is not to exceed 7 days.

1.4.4 Drug-Drug Interactions

Formal drug-drug interaction studies were not performed by the applicant with their combination product. However a significant amount of information is known about oxycodone and ibuprofen. The label will reflect such information as appropriate, including information from the referenced listed drugs. Specifically, the label will identify the drugs that might interact and potentiate the known adverse effects of opioids and/or nonsteroidal anti-inflammatory drugs.

1.4.5 Special Populations

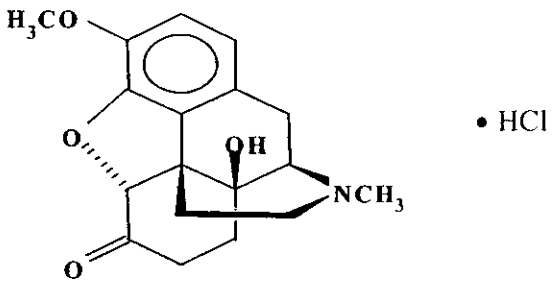
The applicant did not perform studies with their combination product to specifically address special populations. As with drug-drug interactions information, the product's package insert and labeling will reflect information identified in the referenced listed drug products.

2 Introduction and Background

2.1 Product Information

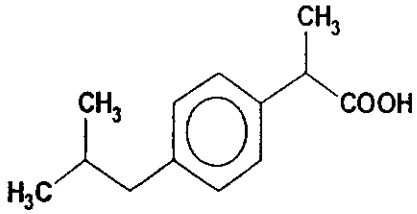
The applicant's product, Combunox, is a fixed-dose combination tablet containing 5 mg of oxycodone HCl and 400 mg of ibuprofen. It is intended for oral administration. The applicant is seeking the indication of short term management of acute moderate to severe pain, and defines short term as no longer than seven days.

Oxycodone is a centrally acting semi-synthetic μ-receptor agonist. Its chemical name is 4-5a-Epoxy-14-hydroxy-3-methoxy-methylmorphinan-6-one-hydrochloride, its chemical formula is $C_{18}H_{21}NO_4$?HCl and its molecular weight is 351 daltons. Its structural formula is



• HCl

Ibuprofen is a non-steroidal anti-inflammatory analgesic with antipyretic properties. The mechanism of action is thought to be related to its inhibition of cyclooxygenase activity and prostaglandin synthesis. Its chemical name is (±)-2-(p-isobutylphenyl) propionic acid, its chemical formula is $C_{13}H_{18}O_2$ and its molecular weight is 206 daltons. Its structural formula is



The fixed combination tablet also contains the following inactive ingredients: sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, calcium stearate, carboxymethylcellulose, povidone, Opadry® II White, and Y-22719 coloring agent (which contains titanium dioxide, polydextrose, hypormellose, triacetin and polyethylene glycol 8000).

2.2 Currently Available Treatment for Indications

There are several treatments available for this indication, i.e., the management of moderate to severe pain. Appendix A contains a partial list of currently approve products, however it is incomplete in that there are several generic products available, as well as opioid products that are being marketed but which do not have approved NDAs. Products that also contain a combination of an opioid and a non-steroidal anti-inflammatory agent include Percocet ®, and Percodan ® which are a combination of oxycodone and acetaminophen, and oxycodone and aspirin, respectively.

2.3 Availability of Proposed Active Ingredients in the United States

Oxycodone and ibuprofen have been commercially available for decades, with ibuprofen having switched to over-the-counter status. The adverse event profile of oxycodone is well-known, particularly for its ability to cause CNS and respiratory depression, as with other opioids. The adverse event profile of ibuprofen is also well-known, particularly its gastrointestinal and renal toxicities.

2.4 Important Issues with Pharmacologically Related Products

The primary issues are the known adverse event profiles of the two components of the combination. Opioids are known to cause CNS and respiratory depression, as well as nausea and vomiting. Since it contains oxycodone, the combination product is expected to have the same abuse liability, potential for physical dependence and subsequently, withdrawal symptoms as any other oxycodone product.

Since the combination product also contains ibuprofen, it will be expected to have similar effects attributed to NSAIDs, specifically risk for gastrointestinal bleeding, hepatic enzyme elevations, and renal toxicity.

2.5 Presubmission Regulatory Activity

NDA 21-378 was originally received by the Division on December 20, 2001. It is noted that during the pre-NDA meeting of July 26, 2001, the Division had expressed concerns that the applicant's drug development program, which consisted of single-dose studies, would provide adequate data to assess a product that would potentially be used in chronic indications, and in multiple-dose regimens.

Review of the application resulted in an Approvable action letter to be sent to the applicant October 18, 2002. Several deficiencies in the following disciplines were identified in the letter: Chemistry, Manufacturing, and Controls (CMC); Pharmacology/toxicology; Clinical; and Regulatory.

A Post-action meeting was held with the applicant on December 17, 2002, during which several deficiencies were either considered resolved or considered to have a clear path forward for resolution identified. However, there were four issues that were considered

unresolved: submission of Segment I (fertility) and Segment III (peri- and post-natal development) studies, the need for assessment of the carcinogenicity potential of the combination product, the need to submit data from adequate and well-controlled multiple-dose studies, the need to submit sufficient data to evaluate the safety of the combination product in the population and setting in which it was likely to be used.

The applicant requested a formal dispute resolution meeting with Dr. Robert Meyer, the Director of the Office of Drug Evaluation II on February 14. 2003 to address the following three issues:

1. the need for carcinogenicity studies;
2. the need for clinical safety data for a minimum of three months; and
3. the efficacy of the combination product in multiple-dose studies up to three weeks in duration.

Dr. Meyer reaffirmed the need for the submission of these data in a letter dated March 17, 2003. Dr. Meyer also noted a willingness to accept shorter term data (1 month) if the applicant was able to provide a justification why the combination product, in the setting of increased use, was unlikely to result in increased risk compared to the individual, previously approved components.

The applicant then requested a formal dispute resolution with Dr. John Jenkins, the Director of the Office of the New Drugs. This meeting was held on April 29, 2003.

Based on the applicant's strong assertion that the intention is to only market their combination product for acute use, Dr. Jenkins identified the following conclusions regarding the requirements for the approval of the applicant's application (letter dated May 29, 2003):

- Carcinogenicity studies for oxycodone would not be required prior to approval, and it would not be necessary for the applicant to conduct them as post-marketing commitments.
- A multiple-dose clinical efficacy study would be required, in addition to the studies already submitted, to support approval
- Collection of appropriate safety data in the multiple-dose efficacy study would be sufficient to support approval

The applicant chose to appeal the decision by requesting a formal dispute resolution meeting with the director of the Center for Drug Evaluation and Research. The meeting was held on November 12, 2003. At the conclusion of the meeting, the following options were offered to the applicant:

1. Resubmission of the NDA to include the results of a multiple-dose study of the oxycodone/ibuprofen combination tablet design to address the standards of the combination drug policy, as well as full responses to all the deficiencies identified in the Division's October 18, 2002 approvable letter.

or

2. Resubmission of the NDA to include the results of the post-operative pain study in patients undergoing abdominal or gynecological surgery, adequate multiple-dose safety data for the oxycodone/ibuprofen safety combination tablet, and complete responses to the other deficiencies identified in the Division's October 18, 2002 approvable letter. It was noted that the labeling would probably need to reflect a limited indication and the lack of efficacy data with multiple dose regimens.

The applicant's current submission dated May 25, 2004, received May 27, 2004 is the applicant's Complete Response to the October 18, 2002 approvable letter. The applicant chose to follow the second option stipulated by Dr. Galson. The current submission contains the results of Study OXY-MD-10, a study that evaluated the safety and efficacy of a single dose of the combination tablet in comparison to oxycodone alone, ibuprofen alone, and placebo; a safety update; and the results of two mutagenicity assays on 14-hydroxycodinone.

2.6 Other Relevant Background Information

This type of fixed combination oral formulation is not approved in any foreign market. There is no other relevant background information at this time.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if applicable)

There were several issues identified in the approvable letter that related to chemistry, manufacturing, and controls. These deficiencies related to:

- Acceptance specifications for oxycodone HCl
- Acceptance specifications for —
- Excipients used in the manufacture of the drug product
- The drug product manufacturing and drug product specifications
- Packaging, stability, environmental assessment, labeling and referenced DMFs.

These deficiencies have been adequately addressed in this submission. For complete details, please refer to the reviews by Drs. Christodoulou and Harapanhalli.

3.2 Animal Pharmacology/Toxicology

During the Formal Dispute Resolution process, the need for carcinogenicity studies was addressed. Although the applicant was encouraged by Dr. John Jenkins to consider doing the studies, it was determined that it would not be necessary for the applicant to conduct carcinogenicity studies prior to approval, nor would it be necessary for carcinogenicity studies to be performed as part of any Phase 4 commitments.

The following two issues were also identified as deficiencies in the approvable action letter: the need to submit the results from Segment I and Segment III reproductive toxicology studies, and the need to assess the genetic toxicology potential of an impurity that contains a structural alert for mutagenicity. — Ongoing discussions with the applicant identified potential strategies to address these two deficiencies. The applicant's Complete Response contains an agreement by the applicant to perform Segment I and III studies as Phase 4 commitments and the results of an *in* vivo cytogenetic assay (mouse micronucleus) and *in vitro* reverse mutation assay with —

For complete details, the reader is referred to Drs. Mamata De and Dan Mellon's reviews. In summary, the results of the two genetic toxicology studies for — were negative; however, — has tested positive in the *in vitro* chromosome aberration assay. Therefore, the Division does not consider the — to be adequately qualified and has requested the applicant to either submit data to support the position that the *in vitro* data are not biologically relevant, or reduce the levels to NMT — Simultaneously, the applicant is to submit interim specifications and an aggressive clear plan to reduce the levels pending review of such data.

4 Data sources, Review Strategy and Data Integrity

4.1 Sources of Clinical Data

The primary sources of clinical data reviewed during this review cycle consisted of the study report from Study OXY-MD-10, and a safety update which integrated the safety databases of one multiple-dose study, five single-dose studies with the to-be-marketed formulation. All the studies, except for Study OXY-MD-10, had been previously submitted to the Division.

4.2 Table of Clinical Studies

Section **1.4 Brief Overview of Clinical Program** of this review contains a table that summarizes the studies that constituted the applicant's development program at the time of the original submission. The only addition to that table is Study OXY-MD-10. The majority of the clinical studies submitted by the applicant have already been reviewed during the first review cycle by Dr. Shaun Comfort.

The current submission consists of the study report of study OXY-MD-10, as well as resubmission of the safety data from five single-dose studies conducted with the to-be-marketed formulation and the one multiple-dose study conducted as an extension study. The table below summarizes the studies reviewed for this submission.

Study No	Study Name	Study Objective
604-001-01	*A Double-Blind, Single Dose Clinical Evaluation of Ibuprofen (400 mg) and Oxycodone Given Together, Ibuprofen (400 mg) Alone and Placebo in Patients with Moderate to Severe Pain Secondary to Surgical Removal of Partial or Complete Bony Impacted Third Molars*	Assess the comparative safety and efficacy of concomitantly administered oxycodone and ibuprofen. Patients were randomized in a 2:2:1 ratio (combination:ibuprofen:placebo).
OXY-MD3-96-01	*A Double-Blind, Single Dose Clinical Evaluation of the Analgesic Efficacy, Safety and Pharmacokinetics of Oxycodone HCl 5 mg/Ibuprofen 400 mg versus Ibuprofen 400 mg Alone, Oxycodone HCl 5 mg Alone and Placebo in Patients with Moderate to Severe Pain Following Dental Surgery*	The combination formulation was compared to ibuprofen alone, oxycodone alone, and placebo in a 3:3:1:1 ratio, respectively. Pharmacokinetic data was obtained in a subset of patients.
OXY-MD-05	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg//Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone and Oxycodone HCl 5 mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery*	Similar to OXY-MD3-96-01.
OXY-MD-06	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy, Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone, Oxycodone 10 mg Alone, and Oxycodone 5 mg in Patients with Moderate to Severe Pain Following Dental Surgery*	Comparative study which added a treatment arm of Oxycodone HCl 10 mg/Ibuprofen 400 mg.

Study No	Study Name	Study Objective
OXY-MD-07	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and, Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg compared to Ibuprofen 400 mg Alone, Oxycodone 5 mg Alone, and Oxycodone 10 mg in Patients with Moderate to Severe Post-Orthopedic Surgical Pain*	To be marketed combination formulation was compared to a combination containing 10 mg of oxycodone, to ibuprofen alone, oxycodone alone (both 10 mg and 5 mg), and placebo in a post-orthopedic surgery pain model. Patients were randomized in a 3:3:3:1:1:1 ratio.
OXY-MD-08	*A Randomized, Double-Blind, Multiple-Dose Evaluation of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/ibuprofen 400 mg and Oxycodone HCl 10 mg/ibuprofen 400 mg in Patients with Moderate to Severe Pain Following Dental or Orthopedic Surgery*	Multiple-dose extension study which compared the to-be-marketed formulation to a combination formulation containing 10 mg of oxycodone. Patients were randomized in a 1:1 ratio after completing the 6-hour post-dosing period in Studies OXY-MD-05, OXY-MD-06, or OXY-MD-07.
OXY-MD-10	*A Double-Blind, Placebo and Comparator Controlled, Single Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5mg, Ibuprofen 400 mg in Female Patients with Moderate to Severe Post-Abdominal or Pelvic Surgical Pain*	The combination formulation was compared to ibuprofen alone, oxycodone alone, and placebo in a 3:3:1:1 ratio, respectively in a post-operative surgical pain model.

4.3 Review Strategy

There was only one new clinical trial, OXY-MD-10, reported in this submission. This trial was reviewed for confirmation of the efficacy and safety of one dose of the applicant's combination drug product. The submission's of eleven volumes and SAS® Software transport files containing the data from the safety update were used during the conduct of this review.

The reviews from the team from the first review cycle were also reviewed, as well as documentation from the multiple communications with the company in the post-action period including, but not limited to, the minutes from the Formal Dispute Resolution minutes.

4.4 Data Quality and Integrity

The Division of Scientific Investigations was not asked to inspect clinical sites during this review cycle. In the course of the review, the clinical source data was compared to the data listings. No significant findings were noted that would bring into question the data quality or the integrity of the submission.

4.5 Compliance with Good Clinical Practices

Study OXY-MD-10 appeared to be conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

In compliance with 21 CFR Part 54, the applicant submitted a completed Form FDA 3454, in which it was certified that no financial arrangement existed between the applicant and the clinical investigators that would, by the value of the compensation, affect the outcome of the study. The applicant also certified that none of the investigators had a proprietary interest in the product, nor in the company, and that none of the investigators were the recipients of significant payments as defined in 21 CFR 54.2(f).

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5 Clinical Pharmacology

No additional clinical pharmacology data was submitted with the current submission. Dr. David Lee's review of the original submission noted the following with respect to pharmacokinetics, pharmacodynamics, and exposure response relationships.

5.1 Pharmacokinetics

From Dr. Lee's review of the original application, the following information is available regarding the components.

Oxycodone

After a single administration of the 5 mg/400 mg tablet under fasted conditions to healthy volunteers, the C_{max} and AUC_8 values ranged from 9.8 to 11.7 ng/ml and 51.4 to 60.6 ng•hr/ml respectively. Peak concentrations were reached around 1.3 to 2.1 hours, and the terminal half-life ranged from 3.1 to 3.7 hours; oxycodone is 45% protein bound. Dose proportionality was observed between single doses of 5 mg/400 mg tablets and 10 mg/400 mg tablets. Less than 4% of the administered dose was excreted unchanged in the urine.

A standardized high-fat breakfast increased the C_{max} and AUC_8 values by 16.2% and 19.7% respectively, which was felt to not be clinically significant. After oral administration of the 5 mg/400 mg tablet four times a day for 3.5 days, C_{max} increased by 50-65%; trough concentrations did not change.

No gender differences were observed.

Ibuprofen

After a single administration of the 5 mg/400 mg tablet under fasted conditions to healthy volunteers, the C_{max} and AUC_8 values ranged from 18.5 to 34.3 µg/ml and 86.5 to 134.3 µg•hr/ml respectively. Peak concentrations were reached around 1.6 to 3.1 hours, and the terminal half-life ranged from 1.8 to 2.6 hours; ibuprofen is ~90% protein bound. Less than 0.2% of the administered dose was excreted unchanged in the urine. Dose linearity was not assessed because the dose of the ibuprofen in the combination product is unchanged.

A standardized high-fat breakfast increased the C_{max} and AUC_8 values by 16% and 5.2% respectively, which was felt to not be clinically significant. After oral administration of the 5 mg/400 mg tablet four times a day for 3.5 days, no accumulation was observed.

No gender differences were observed.

5.2 Pharmacodynamics

Formal pharmacodynamic assessments were performed in two studies, OXY-MD-05 and OXY-MD3-96-01, where an attempt was made by the applicant to determine if there was an exposure-response relationship (see next section).

5.3 Exposure-Response Relationships

Two studies, OXY-MD-05 and OXY-MD3-96-01 evaluated pharmacokinetic parameters and pharmacodynamic endpoints related to the pain relief (e.g., $TOTPAR_6$, $TOTPAR_8$, $SPID_6$, $SPID_8$). Dr. Lee's review indicates that there does no appear to be any exposure-response relationship between the oxycodone and ibuprofen plasma concentrations and primary efficacy results (i.e., response).

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6 Integrated Review of Efficacy

6.1 Indication

The indication sought by the applicant is management of moderate to severe pain. The language in the proposed package insert stipulates that the product is indicated for the short term management of acute moderate to severe pain, identified by the applicant as up to 7 days.

As noted in *Section 2.5: Presubmission Regulatory Activity* of this review, the applicant opted for the second option proposed by Dr. Galson after the formal dispute resolution meeting of November 12, 2003. Specifically, instead of conducting a multiple-dose study evaluating the oxycodone HCl/ibuprofen (5 mg/400 mg) combination versus ibuprofen alone and oxycodone alone to satisfy the combination drug policy standard, they chose to submit the results of a post-operative gynecologic pain study along with multiple-dose safety data.

6.1.1 Methods

Study OXY-MD-10, entitled "A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg in Female Patients with Moderate to Severe Post-Abdominal or Pelvic Surgical Pain," is the only clinical study submitted in this Complete Response, and is the only study reviewed for evidence of efficacy in this review cycle.

Additional materials reviewed included the reviews by Drs. Shaun Comfort, Cynthia McCormick, members of the clinical review team for the earlier NDA submission by the applicant. Dr. David Lee's clinical pharmacology review was also reviewed.

6.1.2 General Discussion of Endpoints

The applicant's intention was to evaluate the efficacy and safety of a single dose of the combination tablet of oxycodone HCl/ibuprofen (5 mg/400 mg) compared to 400 mg of ibuprofen alone, 5 mg of oxycodone alone, and placebo, in post-operative surgical pain model.

The primary efficacy variables were the total of the pain relief scores through 6 hours ($TOTPAR_6$) and the sum of pain intensity difference through 6 hours ($SPID_6$). The $TOTPAR_6$ is an estimate of the area under the pain relief vs. time curve during the first 6 hours of dosing. The $SPID_6$ is an estimate of the area under the pain intensity difference vs. time curve during the first 6 hours of dosing. The primary analysis was a statistical comparison of the effect that the combination of oxycodone HCl/ibuprofen (5 mg/400 mg) had on $TOTPAR_6$ and $SPID_6$ compared to individual components. An analysis comparing the combination against placebo allowed for an assessment of assay sensitivity of the study.

Although TOTPAR scores are currently not a preferred variable for evaluation of analgesics in a clinical trial, SPID scores are and their inclusion as one of the efficacy variables in this study makes the primary variables acceptable.

The applicant also evaluated seven secondary efficacy variables: total of the pain relief scores through 3 hours ($TOTPAR_3$), the sum of pain intensity difference through 3 hours ($SPID_3$), pain relief (PR), pain intensity difference (PID), the sum of pain relief and pain intensity difference at each timepoint (PRID), onset of PR, and time to remedication.

6.1.3 Study Design

The criteria for an adequate and well-controlled clinical trial (21 CFR 314.126) were met by Study Oxy-MD-10. It was a multicenter, double-blind, double-dummy, randomized, parallel-group, placebo- and active-controlled study. Patients were randomized to one of the following treatment groups:

1. oxycodone HCl/ibuprofen (5 mg/400 mg)
2. ibuprofen 400 mg alone
3. oxycodone HCl 5 mg alone
4. placebo

A single dose of study medication was administered post-operatively to female patients with moderate to severe surgical pain following lower abdominal surgery with a low midline incision of at least 8 cm, or a standard low transverse incision. The following gynecological procedures were acceptable for the study:

Abdominal hysterectomy	*Oophorectomy*	*Infertility surgery*	*Pelvic pain surgery*
Myomectomy	*Residual ovary surgery*	*Adhesion surgery*	*Nodal resection*
Unilateral or bilateral salpingectomy	*Endometriosis surgery*	*Marshall-Marchetti-Krantz procedure*	*Anterior/posterior colporrhaphy*

Secondary procedures that were permitted were minor bladder repairs, omentectomy or tummy tuck, as well as incidental appendectomy or abdominal lipectomy, as long as the original incision was not extended. Patients undergoing a Caesarian section were permitted provided that they were not breast-feeding.

Additional inclusion criteria for participation in the study included:

- at least 18 years of age and in good general health
- a negative pregnancy test prior to dosing if of child-bearing potential
- able to abstain from drinking any alcohol, caffeine, or smoking for 8 hours prior to surgery and until completion of the post-dosing study period
- able to ingest and absorb oral medication
- expected to remain at the surgical facility for a minimum of 6 hours after surgery medication dosing, to allow for completion of pain and safety assessments
- need for dosing with study medication at least 14 hours post-operatively, but not more than 48 hours post-operatively

- alert and able to communicate with study personnel and able to complete the study as instructed
- able to understand the study procedures and the use of pain scales, and operate a PCA device
- Physical status classification of PS1 to PS3 (based on classification scheme from the American Society of Anesthesiologists)
    - PS-1: a normal healthy patient
    - PS-2: a patient with mild systemic disease that results in no functional limitation
    - PS-3: a patient with mild systemic disease that results in functional limitation
    - PS-4: a patient with severe systemic disease that is a constant threat to life
    - PS-5: a moribund patient who is not expected to survive without the operation
    - PS-6: a declared brain-dead patient whose organs are being removed for donor purposes
- Able to understand and sign an informed consent form

The following would disqualify a patient from participation in the study:

- pregnant or breastfeeding at the time of study drug administration
- recently started on tricyclic antidepressants (less than three months), or a dose change within the previous two months
- on monoamine oxidase inhibitor or antipsychotic medications, or dosed within 14 days prior to surgery; on systemic corticosteroids or terminated treatment within 7 days prior to surgery
- on sedatives, hypnotics, tranqilizers, or anxiolytics at greater than approved doses
- significant coexisting illnesses
- recent participation in a clinical trial (within 30 days or 5 half-lives, whichever is longer)
- employees or relatives of employees at the clinical site
- known history of allergy or serious adverse event with ibuprofen, oxycodone, codeine, acetaminophen, and/or any other nonsteroidal anti-inflammatory drug (NSAID) or opioid drug(s) or analgesic combination
- recent ingestion of the following
    - short acting analgesics within 8 hours of study drug administration
    - long-acting NSAIDs within 24 of study drug administration
    - systemic steroids within 72 hours of study drug administration
- epidural or intrathecal opioids or local anesthetics following surgery
- infiltration of long-acting anesthetics, opioids, or corticosteroids into the operative field at the time of surgery

Randomization was to be in a 3:3:1:1 ratio (combination: ibuprofen alone: oxycodone alone: placebo). Randomization would occur 14 hours after surgery, after all other analgesics had been discontinued, if the patient's baseline pain intensity had become moderate to severe and if they reported a score of = 50 mm on a visual analog scale (100

mm VAS). Since it was a double-dummy design, each patient received one tablet and two capsules.

Dosing regimen (table adapted from applicant's submission, Vol. 3, page 31):

Treatment Group	Study regimen dispensed		
Oxycodone HCl/ibuprofen (5 mg/400 mg)	5 mg oxycodone HCl + 400 mg ibuprofen tablet x 1	Placebo capsule x 1	Placebo capsule x 1
Ibuprofen 400 mg	Placebo tablet x 1	200 mg ibuprofen capsule x 1	200 mg ibuprofen capsule x 1
Oxycodone HCl 5 mg	Placebo tablet x 1	5 mg oxycodone HCl capsule x 1	Placebo capsule x 1
Placebo	Placebo tablet x 1	Placebo capsule x 1	Placebo capsule x 1

There were two amendments made to the protocol, described below:
Amendment #1; February 14, 2002

1. eliminated the laboratory determinations at the screening visit
2. defined in greater detail the acceptable surgical procedures and the procedures for intraoperative anesthesia, and specified more precisely the time period during which non-study analgesics were permitted
3. raised the minimum age to 18; specified the need for the patient to understand the study procedures, operation of a PCA device, and length of hospital stay; acceptable categories from the American Society of Anesthesiologists
4. specified contraindicated medications
5. permitted physical examinations to be performed by an appropriately qualified health care provider, other than a physician
6. further defined the time period for completion of screening procedures

Amendment #2 April 26, 2002

1. allowed for pregnancy tests to be completed on urine or serum samples
2. further specified exclusionary time period for tricyclic antidepressants
3. allowed antiemetic medications during the study
4. decreased the minimal time period post-surgery after which randomization could occur
5. included changes in sponsor contacts
6. corrected the reference citation regarding criteria for patient randomization

Neither of the two amendments would be expected to result in changes in the design of the study that would cause concern.

The table on the page that follows, which is adapted from the applicant's submission (Vol. 3, p 37), summarizes the timing of the evaluations that were performed in the study. The following clarifications are noted regarding the different evaluations:

- the informed consent could be obtained either pre-surgery or pre-dosing

- concomitant medication information was collected throughout the study; only analgesic medication information was recorded during surgery
- the final assessment was to be completed at the 6th hour post-dosing, at the time of rescue medication, or at a premature discontinuation (whichever occurred sooner)
- a physical exam was completed at screening, but only vital signs were performed at other timepoints denoted as "physical exam"
- a serum or urine pregnancy test was obtained immediately prior to surgery for any female of childbearing potential, unless the patient was undergoing a hysterectomy or a caesarian section
- only the adverse events that were ongoing at the time of dosing were recorded

Summary of timing of study evaluations

	Pre-surgery		***Post-surgery dosing***										
			Pre-dosing		**Post-dosing**								
	Screening		*Baseline*		*15 min*	*30 min*	*45 min*	*1 hour*	*1.5 hours*	*2 hours*	*3 hours*	*4 hours*	*5 hours*	*6 hours (final)*
Informed consent	X	Surgery		Dosing										
Inclusion/exclusion criteria	X		X											
Randomization			X											
Medical/Surgical/ Medication history	X													
Concomitant medications	X		X		At any time									X
Physical exam	X		X		X					X				X
Pregnancy test	X													
Patient diary			X		X	X	X	X	X	X	X	X	X	X
Global rating														X
Adverse events			X		At any time									X
Patient Diary Review														X

6.1.4 Efficacy Findings

The study involved 26 study centers in the United States. A total of 633 patients were screened for the study; 456 patients were randomized to the treatment groups as follows.

Oxycodone HCl/Ibuprofen (5 mg/400 mg):	169
Ibuprofen 400 mg:	175
Oxycodone HCl 5 mg:	52
Placebo:	60

Demographics

A review of the demographic and baseline characteristics of the safety population showed relative comparability among the treatment groups. The table below was adapted from the applicant's submission (Vol. 3, p 56-57).

	Oxycodone HCl 5mg /Ibuprofen 400 mg N = 169	***Ibuprofen 400 mg N = 175***	***Oxycodone HCl 5 mg N = 52***	***Placebo N = 60***
Age				
Mean	42.3	41.2	40	42.4
Std Dev	9.78	8.3	8.42	9.19
Median	43	42	40.5	43
Range	21, 75	20, 66	23, 59	20, 70
Race, N (%)				
White	122 (72.2)	128 (73.1)	33 (63.5)	41 (68.3)
Black	31 (18.3)	24 (13.7)	11 (21.2)	8 (13.3)
Asian	4 (2.4)	10 (5.7)	3 (5.8)	4 (6.7)
Other	12 (7.1)	13 (7.4)	5 (9.6)	7 (11.7)
Weight (lbs)				
Mean	170.1	172.4	179	166.5
Std Dev	41.56	39.53	45.27	43.73
Median	164	168	174	156
Range	99, 301	101, 348	113, 329	104, 299
Baseline Pain Intensity, N (%)				
Moderate	130 (77)	144 (82)	40 (77)	47 (78)
Severe	39 (23)	31 (18)	12 (23)	13 (22)
Baseline Pain VAS (mm)				
Mean	66.5	66.4	66.3	65.7
Std Dev	12.7	11.27	13.29	10.76
Median	64	64	62.5	64
Range	50, 100	49, 100	51, 99	50, 92

Similar comparability was also noted across the treatment groups with respect to type of surgical procedure performed, duration of surgery, and hours from end of surgery till study drug dosing.

Patient Disposition
The number of patients randomized to each of the treatment arms and their final disposition is summarized in the table below.

Population	***Oxycodone HCl/Ibuprofen (5 mg/400 mg)***	***Ibuprofen 400 mg***	***Oxycodone HCl 5 mg***	***Placebo***	***Total***
Randomized	169	175	52	60	456
Safety	169	175	52	60	456
Intent-to-treat	169	174	52	60	455

The applicant defined the different patient population as follows:

- Randomized population – all patients who were randomized into the study
- Safety population – all patients who were treated and received at least one dose of study medication
- Intent-to-treat population – all randomized patients with at least one post-baseline efficacy assessment

Only one patient was excluded from the intent-to-treat population (in the ibuprofen 400 mg only group) because post-dosing assessments for pain relief and pain intensity were missing.

The disposition of the randomized population, with respect to either study completion, or the reason for discontinuation, is summarized in the table below (adapted from the applicant's submission, Vol. 3, p 55).

	Oxycodone HCl/Ibuprofen (5 mg/400 mg) N = 169	***Ibuprofen 400 mg N = 175***	***Oxycodone HCl 5 mg N = 52***	***Placebo N = 60***	***Total N = 456***
Completed study	75 (44 %)	50 (29%)	8 (15%)	5 (8%)	138 (30%)
Discontinued study	94 (56%)	125 (71%)	44 (85%)	55 (92%)	318 (70%)
Discontinuation reason					
Adverse event(s)	4 (2%)	1 (0.6%)	1 (1.9%)	0	6 (1%)
Insufficient therapeutic response	90 (53%)	123 (70%)	43 (82.7%)	55 (92%)	311 (68%)
Protocol violation	0	1 (0.6%)	0	0	1 (0.2%)

*percentages are relative to total number of patients in that treatment group in the safety population

Efficacy

The applicant evaluated two primary efficacy variables, $TOTPAR_6$ and $SPID_6$, in the intent-to-treat population; a last-observation-carried-forward imputation scheme was used to handle missing data. $TOTPAR_6$ was defined as the area under the pain relief vs. time curve during the first six hours of dosing. The measures were computed as time-weighted averages of consecutive assessments of pain relief, which were represented as a categorical outcome from 0 (no relief) to 4 (complete relief). $SPID_6$ was defined as the area under the pain intensity vs. time curve during the first six hours of dosing, and the measures were computed in a similar manner, with the categorical outcomes ranging from 0 (no pain) to 3 (severe pain).

As noted by Dr. Dionne Price, the statistical reviewer, the endpoints were analyzed by analysis of variance (ANOVA) models with treatment group, center, and baseline pain intensity as effects. An inclusion of a treatment-by-center interaction in the ANOVA models examined the consistency of the results across study centers, and the Shapiro-Wilk statistic was evaluated to assess the normality of the error terms in the ANOVA models. For additional details, the reader is referred to Dr. Price's review.

Dr. Price noted that the applicant's results in the submission for the primary efficacy variables include p-values resulting from an ANOVA model applied to transformed data to address the violation of the normality assumption. However, it is the Division's interpretation that the normality assumption can be relaxed when the sample size is large, and/or the departure from normality is not extreme, therefore Dr. Price felt that transformation of the data was not necessary. The tables that follow are from Dr. Price's review and depict the results from the raw, non-transformed data. Although the results vary slightly from what is presented by the applicant in the submission, the overall conclusions are not changed.

$TOTPAR_6$

This endpoint represents an estimate of the area under the pain relief vs. time curve during the first 6 hours of dosing.

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

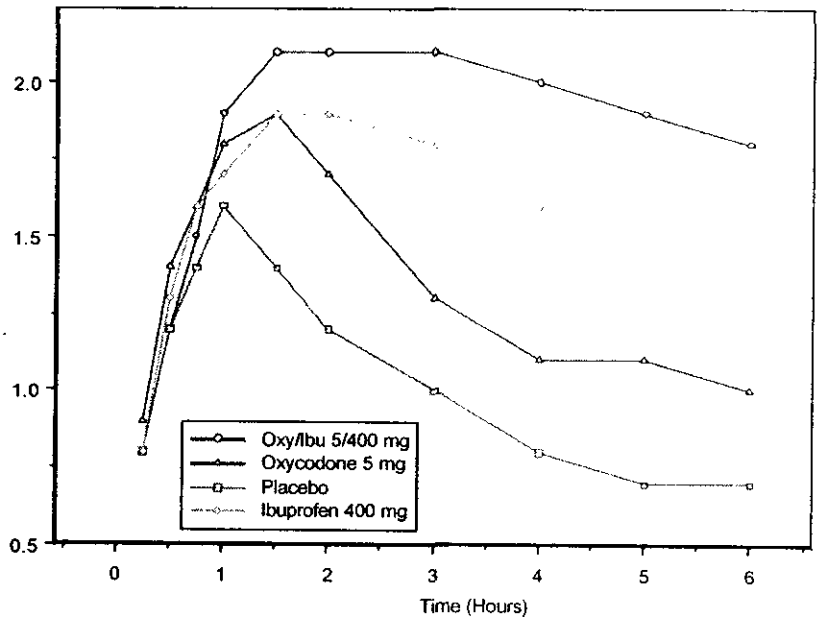
Treatment Group	*N*	*Mean*	*Std Dev*	*Overall Treatment p-value*
Combination	168#	11.2	7.00	<0.0001
Ibuprofen 400 mg	174	9.5	6.87	
Oxycodone HCl 5 mg	52	7.8	6.00	
Placebo	60	5.8	5.75	
Pairwise Comparison		*Estimated Difference in Means†*	*95% CI for Difference*	*p-value**
Combination versus Ibuprofen 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

A visual depiction of the differences in mean pain relief among treatments over time appears in the graph below, also reproduced from Dr. Price's review of this submission.

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)
Oxycodone HCl/Ibuprofen (5 mg/400 mg)	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

$SPID_6$

This endpoint represents an estimate of the area under the pain intensity difference score vs. time curve during the first 6 hours of dosing. As with the $TOTPAR_6$, it contains the results of the ANOVA from raw, non-transformed data.

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

A visual depiction of the differences in mean pain intensity difference among treatments over time appears in the graph on the next page, also reproduced from Dr. Price's review of this submission

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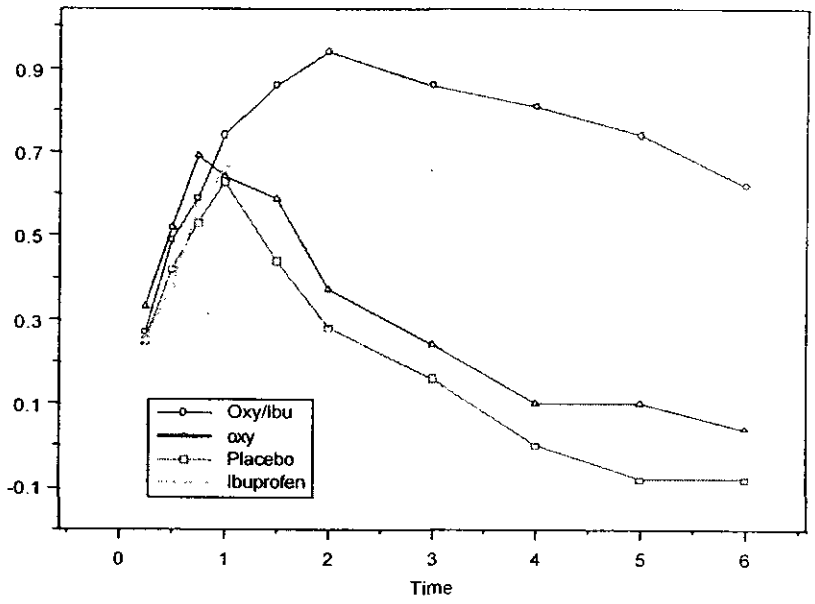
Figure 2: Mean Pain Intensity Difference Scores Over Time



	Time (Hours)									
	0.25	**0.50**	**0.75**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**	**5.0**	**6.0**
Pain 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

Based on the results depicted in the tables and graphs above, the applicant has adequately demonstrated that greater pain relief was reported by patients on the Oxycodone HCl/Ibuprofen (5 mg/400 mg) treatment group compared to oxycodone alone, ibuprofen alone, or placebo. Similarly, the applicant has adequately demonstrated that a greater pain intensity difference from baseline was observed for patients on the Oxycodone HCl/Ibuprofen (5 mg/400 mg) treatment group compared to ibuprofen alone, oxycodone alone, or placebo.

Secondary Efficacy Variables

There were seven efficacy parameters identified by the applicant as secondary endpoints. These were: total of the pain relief scores through 3 hours ($TOTPAR_3$), the sum of pain intensity difference through 3 hours ($SPID_3$), pain relief (PR), pain intensity difference (PID), the sum of pain relief and pain intensity difference at each timepoint (PRID), onset of PR, and time to remedication.

Since the relative importance of these variables in interpreting the results of the study is unclear, they can only be viewed as potentially being supportive of the primary objectives, and not able to support individual claims on their own. That noted, there were several interesting observations reported by the applicant on a few of the variables.

- *TOTPAR$_3$ and SPID$_3$* – although the combination tablet demonstrated statistically significant greater pain relief and greater difference in pain intensity (from baseline) compared to placebo, there was no statistical difference demonstrated in either variable when the combination tablet was compared to the individual components.
- *Onset of pain relief* – the median time to onset of pain relief for the combination, ibuprofen, and oxycodone groups were 28, 31, and 41 minutes respectively. This value could not be calculated for the placebo group because fewer than 50% of the patients in this treatment group experienced pain relief.
- *Time to Remedication* – the estimated time to remedication was longer for the combination tablet treatment group (5.23 hours) than for ibuprofen alone treatment group (3.95 hours), oxycodone alone treatment group (2.5 hours), or placebo treatment group (2.28 hours). However, since this variable was defined as the elapsed time from study medication dosing to the time when the patient was administered rescue medication, there are several unknown variables that could potentially impact when the rescue medication was actually administered (nursing personnel staffing, other activities going on the unit at the time that the rescue medication was requested, etc.). Therefore, this time period is at best a rough estimate.

6.1.5 Clinical Microbiology

This section is not applicable to this review because the antimicrobiological effect of the oxycodone HCl/ibuprofen (5 mg/400 mg) combination was not being evaluated.

6.1.6 Efficacy Conclusion

The applicant has adequately demonstrated, using a moderate to severe post-surgical model, that the combination tablet of Oxycodone HCl/Ibuprofen (5 mg/400 mg) has greater pain relief, and a greater difference in pain intensity (from baseline) during the first six hours post-dose, compared to ibuprofen alone (400 mg), oxycodone alone (5 mg), and placebo.

7 Integrated Review of Safety

7.1 Methods and Findings

As noted in *Section 2.5: Presubmission Regulatory Activity* of this review, the applicant was given the option of addressing the concerns in the October 18, 2002 AE letter by submitting data from the gynecologic pain study and multiple dose safety data.

The applicant noted that the 120-Day Safety Update to the original NDA (submitted April 16, 2002) contained safety data from seven single-dose, double-blind, placebo- or active-controlled efficacy and safety studies; from one multiple dose, double-blind safety study comparing the combination tablet to another combination tablet formulation containing 10 mg of oxycodone; and from six clinical pharmacology studies.

For purposes of the response to the AE letter, this submission's safety summary contains the safety data from Study OXY-MD-10 (the gynecologic pain study), and the resubmission of the one multiple-dose study and five single-dose studies that used the to-be-marketed formulation of Oxycodone HCl/Ibuprofen (5 mg/400 mg). Therefore, a significant portion of the safety data in this submission has already been reviewed during the first review cycle. The seven studies that comprise this safety update are identified in the table below.

Study No	Study Name	Study Objective
604-001-01	*A Double-Blind, Single Dose Clinical Evaluation of Ibuprofen (400 mg) and Oxycodone Given Together, Ibuprofen (400 mg) Alone and Placebo in Patients with Moderate to Severe Pain Secondary to Surgical Removal of Partial or Complete Bony Impacted Third Molars*	Assess the comparative safety and efficacy of concomitantly administered oxycodone and ibuprofen. Patients were randomized in a 2:2:1 ratio (combination:ibuprofen:placebo).
OXY-MD3-96-01	*A Double-Blind, Single Dose Clinical Evaluation of the Analgesic Efficacy, Safety and Pharmacokinetics of Oxycodone HCl 5 mg/Ibuprofen 400 mg versus Ibuprofen 400 mg Alone, Oxycodone HCl 5 mg Alone and Placebo in Patients with Moderate to Severe Pain Following Dental Surgery*	The combination formulation was compared to ibuprofen alone, oxycodone alone, and placebo in a 3:3:1:1 ratio, respectively. Pharmacokinetic data was obtained in a subset of patients.
OXY-MD-05	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg//Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone and Oxycodone HCl 5 mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery*	Similar to OXY-MD3-96-01.
OXY-MD-06	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy, Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone, Oxycodone 10 mg Alone, and Oxycodone 5 mg in Patients with Moderate to Severe Pain Following Dental Surgery*	Comparative study which added a treatment arm of Oxycodone HCl 10 mg/Ibuprofen 400 mg.

OXY-MD-07	*A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and, Safety of Oxycodone HCl 5 mg/Ibuprofen 400 mg and Oxycodone HCl 10 mg/Ibuprofen 400 mg compared to Ibuprofen 400 mg Alone, Oxycodone 5 mg Alone, and Oxycodone 10 mg in Patients with Moderate to Severe Post-Orthopedic Surgical Pain*	To-be-marketed combination formulation was compared to a combination containing 10 mg of oxycodone, to ibuprofen alone, oxycodone alone (both 10 mg and 5 mg), and placebo in a post-orthopedic surgery pain model. Patients were randomized in a 3:3:3:1:1:1 ratio.
OXY-MD-08	*A Randomized, Double-Blind, Multiple-Dose Evaluation of the Analgesic Efficacy and Safety of Oxycodone HCl 5 mg/ibuprofen 400 mg and Oxycodone HCl 10 mg/ibuprofen 400 mg in Patients with Moderate to Severe Pain Following Dental or Orthopedic Surgery*	Multiple-dose extension study which compared the to-be-marketed formulation to a combination formulation containing 10 mg of oxycodone. Patients were randomized in a 1:1 ratio after completing the 6-hour post-dosing period in Studies OXY-MD-05, OXY-MD-06, or OXY-MD-07.
OXY-MD-10	*A Double-Blind, Placebo and Comparator Controlled, Single Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCl 5mg, Ibuprofen 400 mg in Female Patients with Moderate to Severe Post-Abdominal or Pelvic Surgical Pain*	The combination formulation was compared to ibuprofen alone, oxycodone alone, and placebo in a 3:3:1:1 ratio, respectively in a post-operative surgical pain model.

The numbers of patients enrolled in the studies are summarized in the table below (adapted from the Applicant's submission, Vol. 2, p 25)

Study Groups	*Treatment Group*				
	Oxycodone HCl 5 mg/Ibuprofen 400 mg	*Ibuprofen 400 mg*	*Oxycodone HCl 5 mg*	*Placebo*	*Total**
CLINICAL STUDIES					
Single-dose (placebo-controlled)					
604-001-01	50	43	0	24	117
OXY-MD3-96-01	171	168	56	58	453
OXY-MD-05	187	186	63	62	498
OXY-MD-06	171	171	57	57	456
OXY-MD-07	175	170	58	54	457
OXY-MD-10	169	175	52	60	456
Multiple Dose					
OXY-MD-08	(156)†	0	0	0	(156)†
Total*	923 (156)†	913	286	315	2437 (156)†

*Patients were counted only once in each treatment group, even if they were exposed to more than one treatment.
†the number in parenthesis is the number of patient in Study OXY-MD-08 not previously administered the proposed to be marketed formulation in one of the lead-in studies (OXY-MD-05, OXY-MD-06, or OXY-MD-07).

A total of 1079 patients received the Oxycodone HCl 5mg/Ibuprofen 400 mg combination in the clinical studies.

7.1.1 Deaths

There was only one death reported in the entire NDA safety database. Patient 080071 was a 66-year old female who enrolled in the multiple-dose study after completing the single-dose orthopedic pain surgery trial. She had a total right knee replacement and was originally assigned to the ibuprofen treatment group. In the multiple dose trial she was randomized to the oxycodone HCl 5 mg/ ibuprofen 400 mg treatment group. Fourteen days after terminating the 6 days of treatment, during which time she received 7 doses of study drug, she expired at home from a pulmonary embolism.

The patient's post-operative status, with its concurrent decreased mobility, may have placed her at increased risk for a thromboembolic event, a known risk in this post-operative setting. Dr. Comfort noted that it was unclear from the patient narrative whether the patient was on any antiplatelet agent or anticoagulant after her Enoxaparin was discontinued (approximately 2 weeks before). The clinical scenario is compatible with the time course of post-operative pulmonary embolism; therefore it is difficult to ascribe the event to the study drug.

7.1.2 Other Serious Adverse Events

There were 18 patients who reported serious adverse events (SAEs) in the resubmission's safety database of single-dose clinical studies (2437 patients). The distribution according to treatment groups is summarized in the table below.

	Treatment Group				
	Oxycodone HCl 5 mg /Ibuprofen 400 mg N = 923	*Ibuprofen 400 mg N = 913*	*Oxycodone HCl 5 mg N = 286*	*Placebo N = 315*	*Total N = 2437*
Number of SAEs	8 (0.9%)	5 (0.5%)	4 (1.4%)	1 (0.3%)	18 (0.7%)

The most commonly reported SAE was ileus (6 patients), followed by abscess and fever (3 patients each), then general edema and anemia (2 patients each).

The data on SAEs for the multiple-dose population came entirely from Study OXY-MD-08, the extension study and were evenly divided between the two treatment groups. Of the 14 patients who experienced an SAE, 12 had undergone orthopedic surgery, and the SAEs experienced by these patients were consistent with post-operative complications. The remaining two patients had oral infections, and were status-post dental surgery.

7.1.3 Dropouts and Other Significant Adverse Events

Nineteen patients reported an adverse event that was associated with their discontinuation from the study in the single-dose clinical trials. The most common reason was related to the gastrointestinal system – nausea and/or vomiting. The second most common reason was headache. The overall incidence of adverse events leading to discontinuation was ~1%, summarized in the following table, adapted from the applicant's submission (Vol. 2, p 45).

	Treatment group			
Body System ***Preferred Term***	*Oxycodone HCl 5 mg /Ibuprofen 400 mg* *N = 923* *n (%)*	*Ibuprofen 400 mg* *N = 913* *n (%)*	*Oxycodone HCl 5 mg* *N = 286* *n (%)*	*Placebo* *N = 315* *n (%)*
Number of patients with at least one AE leading to discontinuation	11 (1.2)	4 (0.4)	1 (0.3)	3 (1.0)
Digestive System				
Vomiting	7 (0.8)	3 (0.3)	1 (0.3)	1 (0.3)
Nausea	2 (0.2)	0	0	0
Body as whole				
Headache	3 (0.3)	1 (0.1)	0	1 (0.3)
Pain	1 (0.1)	0	0	0
Pain back	1 (0.1)	0	0	0
Nervous system				
Somnolence	0	0	0	1 (0.3)
Skin and appendages				
Sweat	1 (0.1)	0	0	0

The incidence of adverse events that were associated with discontinuation was higher in the multiple dose study, OXY-MD-08. In this extension study, patients were randomized to either oxycodone HCl 5 mg/Ibuprofen 400 mg or oxycodone HCl 10 mg/Ibuprofen 400 mg. The types of adverse events were comparable with what was observed in the single dose study, and are summarized in the table below, reproduced from the applicant's submission (Vol. 2, p 47).

	Treatment Group	
Body System ***Preferred Term***	*Oxycodone HCl 5 mg / Ibuprofen 400 mg* *N = 248* *n (%)*	*Oxycodone HCl 10 mg/ Ibuprofen 400 mg* *N = 244* *n (%)*
Number of patients with at least one AE leading to discontinuation	20 (8.1)	38 (15.6)
Digestive System		
Nausea	11 (4.4)	22 (9.0)
Vomiting	4 (1.6)	9 (3.7)
Constipation	1 (0.4)	2 (0.8)
Nervous System		
Dizziness	5 (2.0)	14 (5.7)
Somnolence	0	5 (2.0)
Body as Whole		
Headache	5 (2.0)	4 (1.6)

Body System Preferred Term	Treatment Group Oxycodone HCl 5 mg / Ibuprofen 400 mg N = 248 n (%)	Treatment Group Oxycodone HCl 10 mg/ Ibuprofen 400 mg N = 244 n (%)
Asthenia	0	5 (2.0)
Fever	0	2 (0.8)
Cardiovascular System		
Vasodilatation	1 (0.4)	2 (0.8)
Skin and Appendages		
Pruritus	0	2 (0.8)
Urticaria	0	2 (0.8)

The observation that the incidence was higher than the single-dose clinical study could be due to several reasons, including:

- If a study drug does have a particular adverse event in its profile, it is scientifically plausible that the adverse event will most likely manifest itself as one takes more of the study drug
- It is possible that a patient is less likely to discontinue from a single dose study when an adverse event is experienced since by definition, no additional doses are to be administered and therefore, they may be more willing to remain in the study
- The single dose studies had a shorter observation period than the multi-dose study, therefore an adverse event that occurred later in the time course is more likely to not be detected

Of note is that the types of adverse events that were associated with discontinuation in the multiple-dose study were consistent with adverse events seen with opioids.

7.1.4 Other Search Strategies

No additional search strategies were used in this review.

7.1.5 Common Adverse Events

The common adverse events, defined as those reported with an incidence of = 1%, were consistent with what was observed as adverse events that were associated with discontinuation, and the known adverse event profiles of opioids and NSAIDs. They are summarized in the table below, reproduced from the applicant's submission (Vol. 2, p 49).

Body System Preferred Term	Treatment Group Oxycodone HCl 5 mg /Ibuprofen 400 mg N = 923 n (%)	Treatment Group Ibuprofen 400 mg N = 913 n (%)	Treatment Group Oxycodone HCl 5 mg N = 286 n (%)	Treatment Group Placebo N = 315 n (%)
Patients with at least one TEAE	266 (28.8)	207 (22.7)	100 (35)	84 (26.7)
Digestive System				
Nausea	81 (8.8)	44 (4.8)	46 (16.1)	21 (6.7)
Vomiting	49 (5.3)	16 (1.8)	30 (10.5)	10 (3.2)
Constipation	7 (0.8)	9 (1.0)	3 (1.0)	6 (1.9)
Flatulence	9 (1.0)	7 (0.8)	3 (1.0)	0

Body System Preferred Term	Treatment Group Oxycodone HCl 5 mg /Ibuprofen 400 mg N = 923 n (%)	 Ibuprofen 400 mg N = 913 n (%)	 Oxycodone HCl 5 mg N = 286 n (%)	 Placebo N = 315 n (%)
Dry Socket	0	4 (0.4)	2 (0.7)	4 (1.3)
Nervous System				
Somnolence	67 (7.3)	38 (4.2)	12 (4.2)	7 (2.2)
Dizziness	47 (5.1)	21 (2.3)	17 (5.9)	8 (2.5)
Body as a Whole				
Headache	28 (3.0)	33 (3.6)	13 (4.5)	20 (6.3)
Fever	10 (1.1)	5 (0.5)	7 (2.4)	6 (1.9)
Pain abdominal	7 (0.8)	5 (0.5)	1 (0.3)	6 (1.9)
Skin and Appendages				
Pruritus	11 (1.2)	19 (2.1)	0	4 (1.3)
Sweat	15 (1.6)	7 (0.8)	4 (1.4)	1 (0.3)
Cardiovascular System				
Hypertension	0	4 (0.4)	4 (1.4)	6 (1.9)
Respiratory System				
Lung disorder	2 (0.2)	1 (0.1)	3 (1.0)	1 (0.3)

Adverse event incidence by age

The applicant evaluated the incidence of adverse event by age by assessing selected treatment-emergent adverse events. Presumably in order to increase the likelihood of detecting a relationship, the TEAEs selected were those with an incidence = 5% in one or more groups and at least twice the incidence of one or more of the other groups.

These TEAEs are summarized in the table below (reproduced from the applicant's submission, Vol. 2 p 53).

Preferred Term Treatment Group	Age Group = 17 years N	 n (%)	 18 - 64 years N	 n (%)	 =65 years N	 N (%)
Patients with at least one TEAE						
Oxycodone HCl 5 mg/Ibuprofen 400 mg	109	29 (26.6)	725	208 (28.7)	89	29 (32.6)
Ibuprofen 400 mg	107	18 (16.8)	721	155 (21.5)	85	34 (40)
Oxycodone HCl 5 mg	45	16 (35.6)	210	70 (33.3)	31	14 (45.2)
Placebo	39	6 (15.4)	242	64 (26.4)	34	14 (41.2)
Nausea						
Oxycodone HCl 5 mg/Ibuprofen 400 mg	109	15 (13.8)	725	60 (8.3)	89	6 (6.7)
Ibuprofen 400 mg	107	4 (3.7)	721	33 (4.6)	85	7 (8.2)
Oxycodone HCl 5 mg	45	11 (24.4)	210	32 (15.2)	31	3 (9.7)
Placebo	39	1 (2.6)	242	19 (7.9)	34	1 (2.9)
Vomiting						
Oxycodone HCl 5 mg/Ibuprofen 400 mg	109	12 (11.0)	725	35 (4.8)	89	2 (2.2)
Ibuprofen 400 mg	107	4 (3.7)	721	12 (1.7)	85	0
Oxycodone HCl 5 mg	45	9 (20)	210	20 (9.5)	31	1 (3.2)
Placebo	39	2 (5.1)	242	8 (3.3)	34	0
Somnolence						
Oxycodone HCl 5 mg/Ibuprofen 400 mg	109	4 (3.7)	725	60 (8.3)	89	3 (3.4)
Ibuprofen 400 mg	107	6 (5.6)	721	27 (3.7)	85	5 (5.9)
Oxycodone HCl 5 mg	45	1 (2.2)	210	10 (4.8)	31	1 (3.2)

Preferred Term *Treatment Group*	*Age Group*					
	= 17 years		*18 – 64 years*		*=65 years*	
	N	n (%)	N	n (%)	N	N (%)
Placebo	39	0	242	7 (2.9)	34	0
Fever						
Oxycodone HCl 5 mg/Ibuprofen 400 mg	109	0	725	7 (1.0)	89	3 (3.4)
Ibuprofen 400 mg	107	0	721	1 (0.1)	85	4 (4.7)
Oxycodone HCl 5 mg	45	0	210	4 (1.9)	31	3 (9.7)
Placebo	39	0	242	2 (0.8)	34	4 (11.8)

The overall impression is that treatment emergent adverse events increased with the patient's age in each of the four treatment groups. The increase in incidence appeared to be due primarily to fever and sweating; the incidence of nausea and vomiting tended to be higher in the younger age group.

The multiple dose data on the incidence of treatment emergent adverse events by age had similar results.

Adverse Event Incidence by Sex
Female patients had a higher incidence of treatment emergent adverse events than male patients, 32 % and 19 %, respectively. This difference persisted throughout all treatment groups. Somnolence, nausea, and vomiting were reported by female patients at twice or more the frequency than male patients.

Adverse Event Incidence by Ethnicity
The overall incidences of treatment emergent adverse events were comparable between whites and non-whites, 27.2% and 26%, respectively across all treatment groups. This similarity was maintained in the Oxycodone HCl 5 mg/Ibuprofen 400 mg treatment groups.

7.1.6 Less Common Adverse Events

The size of the safety database did not allow for assessment of less commonly occurring adverse events, particularly for the multiple-dose study.

7.1.7 Laboratory Findings

There were no new laboratory data submitted in this submission. From Dr. Comfort's review of the original NDA submission, the following potentially clinically significant laboratory abnormalities were previously identified in the original safety database:

- Increased serum cholesterol (9 subjects)
- Increased serum triglyceride (7 subjects)
- Increased serum glucose (3 subjects)
- Increased serum ALT/AST (1 subject on Oxycodone HCl 5 mg/Ibuprofen 400 mg, and 1 subject on Oxycodone HCl 10 mg/Ibuprofen 400 mg); increased serum total bilirubin (1 subject on Oxycodone HCl 5 mg/Ibuprofen 400 mg)

- Hematology changes: decreases in hemoglobin and lymphocytes, and increases in eosinophils.

For additional details, please refer to Dr. Comfort's review, but in summary, his overall conclusion after review of the data was there was no discernible safety signal in the laboratory abnormalities reported.

7.1.8 Vital Signs

Dr. Comfort's review of the original submission noted that the clinical pharmacology studies reported a mean decrease in the blood pressure and pulse rate compared to baseline, however no subjects experienced treatment-emergent adverse events related to blood pressure or heart rate changes.

The current submission noted that decreases in the diastolic blood pressure occurred more frequently in the oxycodone HCl 5 mg/Ibuprofen 400 mg group, and to a lesser extent in the ibuprofen alone treatment group, than in the other treatment groups. This is summarized in the table below, which is adapted from the applicant's submission (Vol. 2, p 59).

Potentially Clinically Significant Criteria	*Treatment Group*			
	Oxycodone HCl 5 mg /Ibuprofen 400 mg (N = 853) n (%)	*Ibuprofen 400 mg (N = 828) n (%)*	*Oxycodone HCl 5 mg (N = 252) n (%)*	*Placebo (N = 254) n (%)*
Systolic Blood Pressure (mm HG)				
Value = 200 and increase = 20	0	1 (0.1)	0	0
Value = 80 and decrease = 20	2 (0.2)	2 (0.2)	0	0
Diastolic Blood Pressure (mm Hg)				
Value = 110 and increase = 15	1 (0.1)	1 (0.1)	1 (0.4)	2 (0.8)
Value = 50 and decrease = 15	25 (2.9)	10 (1.2)	2 (0.8)	1 (0.4)
Pulse (beats/min)				
Value = 110 and increase = 15	3 (0.4)	8 (1.0)	1 (0.4)	1 (0.4)
Value = 50 and decrease = 15	8 (0.9)	4 (0.5)	1 (0.4)	3 (1.2)
Respiration (breaths/min)				
Value = 24 and increase = 6	9 (1.1)	6 (0.7)	1 (0.4)	5 (2.0)
Value = 12 and decrease = 3	46 (5,.4)	34 (4.1)	6 (2.4)	4 1(1.6)

N = the number of patients with a baseline and at least one post-baseline assessment
n = the number of patients with potentially clinically significant value at least once during any post-baseline assessment
Based on clinical studies OXY-MD3-96-01, OXY-MD-05, OXY-MD-06, OXY-MD-07, and OXY-MD-10

The applicant hypothesizes that the decrease may result from a reduction in the baseline pain in the patients treated with the combination or ibuprofen alone, compared to the patients treated with oxycodone alone or placebo. It is not clear whether this is a correct interpretation, however it is noted that no patient discontinued study drug due to changes in blood pressure or pulse rate.

7.1.9 Electrocardiograms (ECGs)

There were no new electrocardiographic data submitted with this submission. Dr. Comfort's review of the data in the original submission did not identify any clinically significant electrocardiographic abnormalities.

7.1.10 Immunogenecity

Formal studies to assess the immunogenic potential of the combination product were not performed conducted by the applicant.

7.1.11 Human Carcinogenecity

The Applicant indicated in the original NDA submission that carcinogenicity studies were not going to be conducted with the oxycodone/ibuprofen combination because their intention for the product was only for short term use. However, since oxycodone is a known mutagen, carcinogenicity data on the new combination would be desirable in the event that utilization patterns would change. Therefore, the need for carcinogenic evaluation of the combination was identified as one of the deficiencies in the Division's AE letter of October 18, 2002.

The applicant requested a Formal Dispute Resolution that eventually took this issue to the level of the Office of New Drugs (May 29, 2003). Dr. Jenkins concluded that the proposed new combination did not clearly trigger scientific issues that would require the submission of these data prior to approval or as a post-marketing study commitment. The applicant was encouraged by Dr. Jenkins to perform these studies, but the studies were no longer a requirement.

There is currently no adequate information available for inclusion in the package insert about the carcinogenic potential of oxycodone or ibuprofen at this time.

7.1.12 Special Safety Studies

No need for special safety studies has been identified.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The oxycodone in the combination formulation has the similar abuse liability as other μ agonist opioids. Therefore this combination product has the same abuse liability, potential for physical dependence and subsequently, withdrawal symptoms as any other oxycodone product.

The applicant has expressed their opinion in the submission that the abuse potential is limited by the low dose of oxycodone (5 mg), the inclusion of ibuprofen in the formulation, and the short-term indication. The applicant also notes that most oxycodone abusers attempt to increase the absorption of oxycodone by inhaling or injecting the drug product, but that the presence of ibuprofen makes this highly unlikely.

Although the applicant may have a valid point about the presence of ibuprofen in the formulation potentially having an effect on the abuse potential of their product, at this point in time it is entirely speculation by the applicant. In order to be able to assess whether these statements are true, formal evaluations, clinical and potentially non-clinical, will need to be performed.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women; therefore use of this combination product during pregnancy should only be considered when the potential benefits justify the potential risk to the fetus. In particular, because of the known effects that non-steroidal anti-inflammatory drugs can have on the ductus arteriosus, use during the third trimester should be avoided.

7.1.15 Assessment of Effect on Growth

The effect of the oxycodone HCl/ibuprofen combination on growth has not been assessed.

7.1.16 Overdose Experience

No cases of intentional or accidental overdoses with oxycodone HCl/ibuprofen have been reported in the drug development program. The applicant proposes to include language in the package insert that identifies the manifestation of acute overdosage with oxycodone or ibuprofen, as well as treatment guidelines.

7.1.17 Post-marketing Experience

There is no post-marketing experience with this formulation in the United States.

7.2 Adequacy of Patient Exposure and Safety Assessments

In the cumulative database of the oxycodone HCl/ibuprofen development program for this NDA, which would include nine clinical studies and six clinical pharmacology studies, 1741 patients have been exposed to an oxycodone/ibuprofen combination. In the safety database that was submitted in response to the AE letter, 1079 patients have been exposed to the to-be-marketed formulation, oxycodone HCl 5 mg/ibuprofen 400 mg. The multiple dose exposure data is generated from the extension study, Study OXY-MD-08, and the lead-in studies (OXY-MD-05, OXY-MD-06, or OXY-MD-07). The distribution of the number of patients that took a particular total number of doses is summarized in the table below, adapted from the applicant's submission (Vol. 2, p 38).

Total number of Doses	Oxycodone HCl/Ibuprofen (5 mg/400 mg) N = 334 n (%)
1	94 (28.1)
2 – 12	120 (35. 9)
13 – 24	88 (26.3)
25 – 28	32 (9.6)
Mean ± SD	10.0 ± 8.9
Median (Min, Max)	7.5 (1, 28)

Since the regimen allowed the combination tablet to be taken up to four times a day, the number of doses translated to a mean treatment duration of 3.8 days. There was no significance difference in the mean treatment duration based on gender or ethnicity (3.9 vs. 3.6 days for male and female patients, respectively, and 3.7 days for white patients and 4.0 days for non-white patients).

The safety assessments performed included physical examinations, electrocardiograms, laboratory investigations, and solicitation of reports of adverse experiences. The applicant's effort to assess safety data was adequate.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data sources used during this review are described in section *4.1 Sources of Clinical Data.*

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were utilized to evaluate the safety.

7.2.3 Adequacy of Overall Clinical Experience

The data submitted by the applicant was adequate to address the requirements stipulated by Dr. Galson at the conclusion of the Formal Dispute Resolution meeting. The applicant submitted the results from the post-operative gynecologic and abdominal pain study and safety data on multiple-dose exposure to the combination tablet.

7.2.4 Adequacy of Special Animal and/or *in vitro* Testing

The applicant was to submit the results of genotoxicity assessment for — — as part of the Complete Response, as requested in the AE letter. Please refer to Dr. Mamata De's review for complete details of the interpretation of the results from the *in vivo* mouse micronucleus assay and the mammalian microsomal reverse mutation assay submitted by the applicant.

7.2.5 Adequacy of Routine Clinical Testing

Based on the review conducted by Dr. Comfort during the first review cycle, and the study report submitted by the applicant with the resubmission, the applicant's efforts at monitoring laboratory parameters, vital signs, electrocardiograms, and adverse events appeared to be adequate. With respect to the study report included in this submission, OXY-MD-10, the study evaluations performed are denoted in section *6.1.3 Study Design*, of this review.

7.2.6 Adequacy of Metabolic, Clearance and Interaction Workup

No additional information was included in this resubmission, and no deficiencies were identified in the approvable letter dated October 18, 2002.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Neither of the components of the combination drug product was a new drug; the adverse event profile of both oxycodone and ibuprofen have been previously studied. The applicant's objective was to assess whether the concomitant administration of both components in one tablet resulted in a new adverse event profile, manifested as either a potentiation of either component's known adverse events, or a new adverse event.

The applicant's studies adequately evaluated for the potential adverse events with monitoring of laboratory investigations, electrocardiograms, physical examinations and vital sign assessment as appropriate, and solicitation of adverse event reporting.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the data available for review was adequate. The narratives, case report form, data output tabulations, study reports, and patient data listings were all legible, complete and relatively easy to navigate. The SAS® Software transport files that contained the safety data were acceptable.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions with this Complete Response from a clinical perspective.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The adverse events observed in the single dose OXY-MD-10 study were similar to what had been previously observed and submitted in the original NDA. The adverse events reported in the updated safety database in this submission were reflective of the previously observed safety profiles of opioids and NSAIDs. There were no new safety signals apparent in the current safety database.

7.4 General Methodology

This section was not applicable for the review of this submission, as the submission constituted a Complete Response to an approvable action letter and consisted of only one new clinical study report and a safety update of data that had, for the most part, already been reviewed during the first review cycle.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

In order to be reflect the clinical data submitted by the applicant in support of this application, the **Dosage and Administration** section of the label should state that the dosing regimen of the product should not exceed four tablets in a 24-hour time period. It should also state that the duration of treatment is not to exceed 7 days.

8.2 Drug-Drug interactions

Formal drug-drug interaction studies were not performed by the applicant with their combination product. However a significant amount of information is known about oxycodone and ibuprofen. The label will reflect such information as appropriate, including information from the referenced listed drugs. Specifically, the label will identify the drugs that might interact and potentiate the known adverse effects of opioids and/or nonsteroidal anti-inflammatory drugs.

8.3 Special Populations

The applicant has not performed any studies to specifically evaluate their combination product in special populations; specifically renally or hepatically impaired patients. However, a significant amount of information is known about oxycodone and ibuprofen in these patient populations, and the label will reflect such information as appropriate.

8.4 Pediatrics

The applicant has conducted two studies (OXY-MD-05 and OXY-MD-06) where the inclusion criteria allowed enrollment of patients as young as 12 years of age. The applicant has language in the **Pediatric Use** section of the proposed package insert that

. The applicant also proposes that no differences were noted in the efficacy and safety in patients younger than 17 years of age and those older than 17 years of age.

This assertion is an overstatement since there were only 109 patients identified in the database as being treated with the combination product and younger than 17 years of age. The youngest patient enrolled was 14, but the majority was between 15 and 17 years old.

Although the efficacy of the combination could not be assessed, it is appropriate to describe the safety findings noted in the group studied, since inferential statistics are not utilized when assessing safety data.

In the original submission, the applicant indicated their intention to conduct a study in pediatric patients between 7 and 12 years of age, and had requested a deferral for pediatric patients younger than 7 years of age. One of the reasons

cited for the request was a desire to confirm the safety and efficacy findings in adults and adolescents. The Division had previously expressed agreement regarding the appropriateness of a deferral at the Pre-NDA meeting (July 26, 2001), and Dr. Comfort's review reiterated that position.

However, the applicant now seeks a waiver from studying their fixed dose combination formulation in pediatric patients younger than 12, indicating they do not believe that the new formulation represents a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients. They also note that for a pediatric patient younger than 12, dosing is based on body weight, which would make it difficult to achieve using this fixed combination product.

The applicant has not provided any data to support the assertion that the combination formulation would not represent a meaningful therapeutic or that it is unlikely to be used in a substantial number of patients. Although they are potentially correct that the current combination formulation of oxycodone 5 mg/ibuprofen 400 mg may make it difficult to dose some of the younger patients, the absence of an age-appropriate formulation does not constitute sufficient rationale for a waiver. A deferral is recommended until such formulation is available. If a formulation can not be produced after an earnest attempt is made, then a waiver for a particular age group could be considered.

Therefore, with respect to the applicant's obligations under the Pediatric Research Equity Act, the applicant still needs to evaluate pediatric patients between the ages of 12 to 17 years. At the current time, a deferral is considered appropriate for pediatric patients between the ages of 2 to 12 years, pending the development of age-appropriate fixed combinations. However, as noted above, a waiver can be considered if the applicant is able to substantiate their position that their combination product is inappropriate for the 2 to 12 year age group. It is recommended that the requirement for studying the combination product in pediatric patients under the age of 2 years of age be waived.

8.5 Advisory Committee Meeting

Presentation at an Advisory Committee meeting was not necessary for this application.

8.6 Literature Review

The literature referenced by the applicant as part of this Complete Response were reviewed. Since the majority of the data in this submission had previously been reviewed and this review was a focused review of the new clinical study report and safety update, it was not necessary to conduct an extensive search and review of the literature.

8.7 Postmarketing Risk Management Plan

A formal postmarketing risk management plan is not needed for this combination product. The product's package insert should be adequate to convey the information to the prescriber and the patient what is known about the drug product.

Although this will be a controlled substance (Scheduled II), at this point in time there does not appear to be a need to institute a risk management plan for this formulation that would further address the issues of misuse, abuse, diversion, and intervention.

8.8 Other Relevant Materials
No additional materials were reviewed.

9 Overall Assessment

9.1 Conclusions

The applicant has submitted sufficient data to demonstrate the efficacy of a single dose of the oxycodone 5 mg /ibuprofen 400 mg combination tablet. Sufficient multiple-dose safety data has also been submitted to consider the requirements stipulated by Dr. Galson fulfilled.

9.2 Recommendation on Regulatory Action

It is recommended that the application be approved, with appropriate labeling to reflect the lack of efficacy data with a multiple dose regimen.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Designation as a controlled substance (Schedule II), appropriate labeling and routine post-marketing surveillance should be adequate risk management strategies. Additional risk management strategies, such as a boxed warning, medication guides, or a formal risk management program incorporating education, surveillance, and intervention do not appear necessary at this time.

9.3.2 Required Phase 4 Commitments

The applicant has indicated in the Complete Response their plans to submit the results of Segment I and Segment III reproductive toxicology studies as post-marketing commitments.

9.3.3 Other Phase 4 Requirements

Other than the requirements to fulfill their obligations under the Pediatric Research Equity Act, there are no other phase 4 commitments at this time.

9.4 Labeling Review

The label will be discussed with the applicant, and appropriate wording will be agreed upon and incorporated into the package insert to reflect the following:

- The indication is for the short term management of acute moderate to severe pain. Short term will be specifically identified to be no more than 7 days
- The results of the clinical studies that supported this action
- Multiple-dose studies evaluating the efficacy of the product have not been performed

9.5 Comments to the Applicant

Comments to be conveyed to the applicant include labeling requirements as well as Phase 4 study commitments and requirements, as noted above.

10 Appendices

Partial list of approved therapies indicated for the treatment of moderate to severe pain.

Name	Component
Numorphan injection	Oxymorphone hydrochloride
Avinza capsules	Morphine sulfate
Demerol syrup	Meperidine hydrochloride
Buprenex injectable	Buprenorphene hydrochloride
Dilaudid ampules	Hydormorphone hydrochloride
Kadian capsules	Morphine sulfate
MS Contin tablets	Morphine sulfate
MSIR oral solution concentrate	Morphine sulfate
Nubain injection	Nalbuphine hydrochloride
Oxycontin tablets	Oxycodone hydrochloride

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/s/

Rigoberto Roca
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DIVISION DIRECTOR'S REVIEW OF NDA AND BASIS FOR ACTION

NDA#	21-378
Sponsor	Forest Laboratories, Inc.
Generic name	Oxycodone HCl (5mg) and Ibuprofen (400 mg) Combination Tablet
Pharmacologic Class:	Opioid Analgesic
Indication:	Short term management of acute moderate to severe pain
Date of Submission	December 20, 2001

This review summarizes the basis for the Approvable action to be taken on the New Drug Application for the oxycodone HCl (5 mg) and ibuprofen (400 mg) combination tablet, for the treatment of moderate to severe pain.

The principal conclusions of the review team with which I concur are:

1. The application has failed to demonstrate adequately the safety and efficacy of oxycodone HCl (5 mg) and ibuprofen (400 mg) for acute and chronic pain.

2. The application has failed to provide confirmation for the dosing regimen described in the draft package insert.

3. The application has used an unapproved product as a reference drug for this 505(b)2 application for which the agency has not made finding of safety and efficacy.

Background

This is an application for an oxycodone (5 mg) product combined in a fixed dose with ibuprofen (400-mg). It is expected to fill the same niche as the oxycodone and aspirin combination tablet has filled for over 50 years, and oxycodone and acetaminophen more recently. The sponsor has indicated that it was interested in studying only short-term use in their development program. Based on the record of other combination products containing oxycodone it was predicted that this drug would be used in the treatment of chronic pain. Nevertheless the sponsor proposed to evaluate their product in a dental pain model only, and has requested a more general indication for acute, moderate to severe pain.

At a recent advisory committee meeting on Analgesics Drugs, there was great deal of support for the requirement that drug products be evaluated for both chronic and acute indications if the likely target population included both populations. While there have been discussions with Forest laboratories on this topic, the issue was never set to rest. In retrospect, this was an error.

The division and the sponsor had made an effort to strike a balance between the existing body of experience and data surrounding the other approved oxycodone combination products and the lack of experience with this unique combination. One of the division's main concerns was the potential for serious adverse safety consequences with similar patterns of use as the other combination products. This development plan did not strike that necessary balance.

While Forest Laboratories, Inc. was urged not to submit the NDA with only two single dose dental studies, the sponsor chose to do so regardless. The NDA was reviewed, found to be inadequate, and the sponsor was notified of the deficiencies on face. Due to a miscalculation of the "filing" date, the application was filed by default.

Regulatory

The sponsor used an unapproved drug product, Roxicodone™ 5 mg, as the reference listed product for this 505(b)2 application. While a linkage was attempted between the approved 15 mg Roxicodone and the 5 mg unapproved product, it must be noted that the Agency has never made a finding of safety and efficacy for a 5 mg oxycodone single entity product. Therefore this reference does not support the current application. The sponsor will need to perform a relative bioavailability study and provide the data that will allow the Agency to link the oxycodone HCl (5 mg) and ibuprofen (400 mg) combination product to an approved oxycodone product.

Efficacy

The sponsor provided two single dose trials in dental pain and, after filing, one in postoperative pain.

The first (Oxy-MD-05) was a classic factorial design study comparing oxycodone HCl (5 mg) and ibuprofen (400 mg) combination tablet with placebo, ibuprofen 400 mg, and oxycodone HCl 5 mg in patients who had two impacted third molar surgical removals. Patients underwent traditional pain evaluation and the results were compared based on $SPID_6$ (sum of pain intensity difference through 6 hours) and $TOTPAR_6$ (total pain relief through 6 hours) as the two primary efficacy measures. As noted by Drs. Comfort and Price, the study did not succeed on both prospective outcome measures. It was necessary to apply a *post-hoc* statistical method to the $TOTPAR_6$, in order to achieve a statistically significant difference from ibuprofen alone. Beyond that, it was clear that the effect of this combination failed to differ from ibuprofen alone after 3 hours. It appeared that the largest part of the effect was due to the contribution of ibuprofen. The effect of the combination drug in this trial cannot be discounted, however, this trial was not adequate by design to support the approval of this product for reasons that will be discussed below.

In a second study (Oxy-MD-07, Post-Operative Pain Study) no statistically significant difference between the oxycodone HCl/ibuprofen formulations and ibuprofen alone could be demonstrated.

A third study (Oxy-MD-06) compared oxycodone HCl (5 mg) and ibuprofen (400 mg) combination tablet with active controls ibuprofen 400 mg, oxycodone 5 and 10 mg, another fixed combination of oxycodone and ibuprofen, and placebo. The pain assessments and outcome measures were the same as those used in study Oxy-MD-05. In this study all relevant pairwise comparisons demonstrated a statistically significant difference between the combination drug and the individual components. As before, it is clear that the ibuprofen component is providing the largest effect. The effect, as in the previous study, is lost after three hours. While this third study was able to demonstrate a small statistically significant difference between the oxycodone HCl 5-mg and ibuprofen 400-mg tablet and each of the components and placebo, for the primary outcomes the difference was very small and not sustained over the entire dosing period.

The sponsor has also made additional claims regarding [redacted]. There was not confirmatory evidence across studies for this effect.

Although statistical differences in total pain relief and pain intensity from baseline between the combination drug product and ibuprofen alone are noted in the two single-dose trials, the studies were not designed adequately to evaluate the effectiveness of this combination drug in the manner of intended use.

It is important to note that only single-dose administration of this drug was studied in the two "pivotal trials" and in only one was the result positive, demonstrating a clinically small effect on the declared primary outcomes. In none of these was the proposed dosing regimen of q6 hours evaluated.

The division has taken into account the fact that this application could be ultimately filed under 505 (b) 2, relying on the Agency's prior finding of safety and efficacy of oxycodone made at the time of a DESI review. However, the sponsor has not supplied sufficient data on the efficacy and safety of this unique formulation to support an approval.

Pharmacokinetics

There were six pharmacokinetic studies provided in this NDA. These included a BE to Roxicodone study, food effect and a multiple dose study. The multiple dose study demonstrated that both ibuprofen and oxycodone dosed q 6 hours reached steady state after 3-1/2 days administration. Two efficacy studies measured PK parameters. No exposure response relationship was demonstrated.

Safety

Nonclinical

Nonclinical safety studies were reviewed for the individual components of this combination drug. The most significant findings were the GI ulcerations, renal papillary lesions, and pulmonary and hepatic lesions found with ibuprofen. Genotoxicity was reported with both individual drug components, and an impurity — — has potential mutagenicity. The combination product tested in dogs for 1-month did not demonstrate a more toxic profile than had been previously reported.

A full reproductive toxicology battery will be required and depending on when this application is resubmitted, may be done as a phase 4 commitment. Carcinogenicity testing should be required as this drug will likely be used in the chronic setting.

Clinical Safety

The sponsor has relied heavily on the safety of oxycodone in patients with dental pain for its demonstration of safety. There were 910 patients who received the current formulation in its ratio of oxycodone:ibuprofen::5:400. There were an additional nearly 500 patients who received this combination but in a different ratio. The vast majority of exposures were single dose.

Adverse events were largely non-serious, as one might expect from a relatively healthy outpatient dental population. The exceptions were the elderly patients in the orthopedic setting who received multiple dose oxycodone and ibuprofen combination tablets. These serious adverse events were largely postoperative complications, however some GI events such as bleeding ulcer and ileus may have had some relationship to the drug.

In general the treatment emergent adverse events reflected the presence of opioid in the combination drug. Most common were somnolence, nausea, dizziness, and vomiting.

The safety profile generated in this NDA is probably not reflective of the profile that might be expected in the broader acute pain population. While there are no serious signals identified in this database, there has been relatively little multiple dose exposure. The potential for serious GI side effects, combining a drug with known propensity to cause GI bleeding, with an opioid that reduces GI transit time, has not been explored.

Of particular concern is the fact that this combination product may have more potential usefulness in the chronic pain population than its counterparts, the oxycodone/ASA and oxycodone/APAP combinations. Escalating doses of this product, particularly with the development of tolerance, may occur more readily due to the lower perceived toxicity of ibuprofen. Therefore this may be seen as a product with greater flexibility and usefulness.

Chronic safety data should be provided if this product is to be approved in order to provide adequate labeling for a use that will most certainly occur.

Pediatric Development

The requirements of the pediatric rule will not be waived for this product in full, but rather study of children aged 2 months to 16 years will be deferred until more safety information is gained in adults.

Chemistry, Manufacturing, and Controls

There are numerous CMC deficiencies including a potentially genotoxic impurity found — which will require qualification. In general the impurity limits should be readjusted based on ICH guidelines.

Risks and Benefits

An informed assessment of the risks and benefits of this combination product cannot be made at this time, for the reasons described above. In order to evaluate this product fully, more data is needed. The sponsor will be asked to provide a controlled trial that demonstrates the effectiveness of this product used on a q 6-hr regimen for up to several weeks. In addition, the sponsor should provide additional safety data in the population of

projected use, including the chronic pain setting. Only then can an adequate assessment be made as to whether the small almost nominal effect achieved by this combination product weighs positively against the risks.

Action: Approvable with significant development work needed.

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Cynthia McCormick
10/17/02 04:48:35 PM
MEDICAL OFFICER

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MEDICAL OFFICER'S DRAFT REVIEW OF CLINICAL DATA

NDA # (serial):	**21-378**
Related IND(s):	**52,310**
Drug Name (generic):	**Oxycodone HCL (5/10 mg) / Ibuprofen Combination Tablet**
Sponsor:	**Forest Laboratories Inc.**
Indication:	**Short term management of acute/moderate to severe pain**
Type of Submission:	**NDA**
Date of Submission:	**20DEC01**
Date of Receipt (CDR):	**20DEC01**
Date of Review:	**10MAY02**
Material Reviewed:	**NDA Submission Documents**
Reviewer:	**Shaun M. Comfort, M.D.**
Project Manager:	**Lisa Basham-Cruz**

EXECUTIVE SUMMARY

CLINICAL REVIEW

ABBREVIATIONS & DEFINITIONS:

ABBREVIATION	DEFINITION
ADME	Absorption, Distribution, Metabolism, Excretion
AE(s)	Adverse Event
ANOVA	Analysis of Variance
BPI	Baseline Pain Intensity
CRF	Case Report Form
CRT	Case Report Tabulation
CVA	Cerebrovascular Accident
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ED 50	Effective Dose in 50%
E-R	Exposure-Response
GCP	Good Clinical Practice
GI	Gastrointestinal (System)
HTN	Hypertension
HV	Healthy Volunteers
Hx	History
IBP	Ibuprofen
ICH	International Committee on Harmonization
ITT	Intent to Treat
LD	Lethal Dose
LD 50	Lethal Dose in 50%
LOCF	Last Observation Carried Forward
LS	Least Squares
MAP	Mean Arterial Pressure
NOAEL	No Adverse Event Level (drug dosage)
OXY	Oxycodone
PBO	Placebo
PGA	Patient Global Assessment
PRID	Pain Relief – Pain Intensity Difference
PPR	Peak Pain Relief
LFT	Liver Function Test(s)
ISS	Integrated Summary of Safety
ISE	Integrated Summary of Efficacy
PK	Pharmacokinetics
PO	By Mouth
QoL	Quality of Life
QTc	Q-T Corrected Interval on ECG (msec)
SAE(s)	Serious Adverse Event

ABBREVIATION	DEFINITION
SBP	Systolic Blood Pressure
SPID	Sum of Pain Intensity Differences (at 3 or 6 hours)
SSD	Statistically Significant Difference
TEAE(s)	Treatment Emergent Adverse Event(s)
TESS	Treatment Emergent Signs and Symptoms
TOPR	Time of Onset of Pain Relief (Median)
TOTPAR	Total Pain Relief (at 3 or 6 Hours)
TTR	Time to Re-medication (Median)

EXECUTIVE SUMMARY

1 RECOMMENDATIONS:

1.1 Recommendations on Approvability:

Based on the clinical information submitted, I do not recommend approval of BRANDNAME. This recommendation is based the following conclusions:

1) The Sponsor has failed to demonstrate a meaningful difference in efficacy between the proposed Oxycodone HCL/Ibuprofen 5/400 mg tablet and Ibuprofen 400 mg alone. It should be noted that the Sponsor did meet 3 of 4 total endpoints ($TOTPAR_6$ and $SPID_6$) in the two pivotal studies. As discussed in conclusion #2, the Sponsor managed to achieve statistical significance after post-hoc transformation of the $TOTPAR_6$ data in the Oxy-MD-05 pivotal trial. If the post-hoc procedure is accepted then all four primary endpoints were met. However, in spite of achieving statistically significant differences in the primary endpoints, the overall clinical difference does not appear overwhelming. Specifically, the combination products difference from Ibuprofen is not apparent over the entire 6-hour study-time period, although there is some apparent efficacy difference over the initial 3-hours. In addition, a third non-dental pain trial (Oxy-MD-07 Post-Operative Pain Study) was also examined, and the results show no statistically significant difference between both of the BRANDNAME formulations and Ibuprofen alone. A third issue is that multiple comparisons are made without adjustment of the α significance levels. According to Dr. Price, this was not necessary in the Oxy-MD-05 trial because the Sponsor had to demonstrate superiority of the combination product versus each of its components. However, the Oxy-MD-06 trial had 6 total treatment arms and two combination formulations, that were also compared against each other. In this case adjustment for multiplicity was necessary and should have been performed. Dr. Price did recalculate this study's comparisons with an appropriate α level adjustment and did not observe that the outcomes were appreciably different.

2) The pivotal clinical trial (Oxy-MD-05) requires an unplanned (*post-hoc*) statistical procedure, in order to achieve a statistically significant difference from Ibuprofen alone for one of its primary endpoints. While the combination product shows a consistent superiority to placebo and oxycodone alone, the marginal statistical difference compared to Ibuprofen alone, does not suggest a convincing clinical efficacy over 6 hours.

3) The Sponsor uses Roxicodone™ 5 mg as the reference product (via NDA 21,011 for Roxicodone™, which does not cover this same 5 mg dosage). The use of the non-approved product means that the Agency has no supportive PK safety and efficacy data on this "particular" formulation/dosage. At the time of the NDA submission and this review, the Sponsor has not provided relative bioavailibility information that

would allow the Agency to link this product to the approved 15 and 30 mg Roxicodone™.

4) Both pivotal trials were conducted in dental pain. However, the Sponsor is proposing an acute, moderate to severe pain indication, which is broader than the studied condition. The Agency specifically stated in a meeting on July 26, 2001 that the study drug " [redacted] The sponsor's only non-dental pain trial was submitted after NDA filing date and showed no difference in efficacy between BRANDNAME and Ibuprofen alone. The Sponsor stated in a general correspondence letter (10/15/01) that it followed previous guidelines and was under the impression that replication in different painful conditions was not required.

5) The pivotal single-dose studies do not support the dosing interval for repeated dosing, from the efficacy perspective.

6) The Sponsor has not adequately addressed pediatric development in the younger 3-13 age group.

7) The Sponsor has not provided adequate justification for their belief that the BRANDNAME product will not be used chronically, in the larger population.

In summary, all of these deficiencies and problems support this reviewer's recommendation to not approve BRANDNAME.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps:

No clinical Phase 4 studies are recommended.

1.3 Deficiencies and Recommended Corrective Action:

1) The Sponsor should submit the results of two adequate and well-controlled clinical studies that demonstrate the effectiveness of multiple doses of BRANDNAME versus all its components, in the management of acute, moderate to severe pain for up to 2-3 weeks. The multiple dose evaluation is recommended because even "acute" pain opioid analgesics may be used chronically in the real world. It is recommended that this be performed in a non-dental pain condition such as Low Back Pain or Cancer Related Pain.

2) The Sponsor should establish a bioequivalence link between the unapproved Roxicodone™ 5 mg tablet and a Reference Listed Drug.

3) Appropriate information should be provided to justify the dosing regimen listed by the Sponsor.

4) If the Sponsor is unable to justify the assumption that this proposed product will not be used chronically, then further evaluations should be conducted to address possible chronic use. Specifically adequate and controlled trials should be performed according to the same criteria as "chronic pain" studies in that the duration of exposure should be for 12 weeks (3 months).

5) A satisfactory pediatric development program, or justification for why this is not possible, should be submitted for the younger age groups (3-13).

2 SUMMARY OF CLINICAL FINDINGS:

2.1 Brief Overview of Clinical Program

The clinical development program consisted of six Phase I Clinical Pharmacology studies, involving 144 subjects. Twenty-four of these study patients received single or multiple doses of an Oxycodone HCL/Ibuprofen combination while the remainder was exposed to single doses only. In addition to these studies, two clinical trials (MD-05 and MD3-96-01) measured both pharmacokinetic parameters and efficacy endpoints.

The clinical pharmacology studies were designed to assess the pharmacokinetics and bioequivalence of the combination product in healthy volunteers in the fed and fasted state. Special studies to assess drug-disease states, drug-drug interactions were not performed.

Eight randomized clinical studies were performed involving 3139 subjects (2651 unique subjects). One study (Oxy-MD-08) involved multiple doses of Oxycodone HCL/Ibuprofen combinations (5/400 mg and 10/400 mg). The total number of exposed clinical subjects consists of 2796 (2651 + 144) unique patients. The following table illustrates the Sponsor's clinical development program and subject distribution. Note, that the sums presented below are greater than 2796 due to crossover and subject participation in > one trial.

Table 2.1.1 Oxycodone/Ibuprofen Clinical Development Program

Phase	Exposure	Study Type/Population	Protocol #	N (# Treated)
I	Single Dose	Clinical Pharmacology – Crossover Trial	604-003-01	24
		Clinical Pharmacology – Crossover Trial	604-004-01	24
		Clinical Pharmacology – 3Way Crossover Trial	Oxy-PK1-96-01	24
		Clinical Pharmacology – 2Way Crossover Trial	Oxy-PK1-97-02	25
		Clinical Pharmacology – 2Way Crossover Trial	Oxy-PK-04	24
	Single/Multi-Dose	Clinical Pharmacology – 2Dose Crossover Study	Oxy-PK-03	24
		Total Clin/Pharm Subjects:	**Subtotal**	**144**
II	Single-Dose	Pilot Study: Dental Surgical Pain	604-001-01	117
		Pilot Study: Dental Surgical Pain	604-002-01	97
		Clinical Study: Dental Surgical Pain	Oxy-MD3-96-02	453
III	Single-Dose	Clinical Study: Dental Surgical Pain	Oxy-MD3-96-01	122
		Clinical Study: Dental Surgical Pain	Oxy-MD-05	498
		Clinical Study: Dental Surgical Pain	Oxy-MD-06	682
		Clinical Study: Post-Surgical Orthopedic Pain	Oxy-MD-07	682
	Multi-Dose	Clinical Study: Post-Surgical Ortho/Dental Pain Extended Double-Blind Study	Oxy-MD-08	488
		Total Clinical Subjects:	**Subtotal**	**3139**[++]
I, II, III		**TOTAL SUBJECTS:**	**TOTAL**	**3283**[++] **(2796)**

[++] Clinical subjects may be counted more than once due to crossover treatments from participation in the multi-dose Oxy-MD-08 study. Total # of unique subjects = 2796.
Source – 120 Day ISS Update, Vol. 4.8, pg. 3-23.

Of the 2796 total individual study subjects, 1572 were treated with an Oxycodone/Ibuprofen combination product. The majority of these subjects were exposed to single-doses of study drug. The 488 subjects in the Oxy-MD-08 multi-dose trial were exposed for an average of ~5 days (4.9 ± 2.9 days) with a range of 0 – 17 days total.

This efficacy review is based upon the results of the 2 Clinical Pivotal Phase III trials: Oxy-MD-05 and –06 (1180 subjects total). The safety review was conducted using the entire safety population of subjects, pooled from all of the trials.

2.2 Efficacy

Taken as a whole, the Oxycodone/Ibuprofen 5/400 mg combination did achieve a statistically significant difference (SSD) in primary outcome variables when compared to its individual components of Ibuprofen 400 mg, Oxycodone 5 mg, and Placebo. In addition, the majority of secondary variables tended towards SSD, if not actually achieving the specified α levels (0.05 % typically), when pair-wise comparisons were performed. However, detailed examination and review of the statistical findings suggests that the differences are mostly marginal in magnitude and do not suggest a meaningful

clinical benefit when BRANDNAME is compared to Ibuprofen 400 mg alone. On this basis the product is not recommended for approval. A more detailed discussion of the efficacy results follows.

The Oxy-MD-05 pivotal trial showed a SSD between the two primary outcome variables (Total Pain Relief at 6 hours - $TOTPAR_6$ and Sum of Pain Intensity Difference - $SPID_6$), for the 5/400 mg formulation when compared to its individual components. These metrics were computed using a simple integration of Least Square Mean Pain Relief (PR) scores and Pain Intensity Difference from Baseline (PID) scores, for each individual patient over the 6 hours of the single-dose study.

Examination of the Differences in scores of the different treatment groups demonstrates a clear difference in the combination vs. oxycodone alone and placebo. However, the 5/400 mg combination TOTPAR6 results were not SSD when compared to Ibuprofen alone (raw $p = 0.070$ for difference), unless the distribution of TOTPAR values for the combination was transformed to a more normal distribution using a *post-hoc* statistical procedure (resulting in $p = 0.012$). According to Dr. Price in Biostatistics, the statistical ANOVA procedure used for testing the hypothesis was robust enough to not require the unplanned transformation performed by the sponsor. Further examination of the time varying PR data (please see figures 6.1.1.5.1 and 6.1.1.5.2) shows that there is only a noticeable separation between Oxycodone/Ibuprofen 5/400 mg and Ibuprofen 400 mg PR scores during the .25 to 3 hour time frame. Even during this period there is a great deal of overlap in individual PR scores suggesting that there may not be much clinical difference in subject perceptions of pain relief (PR). Thus, the questionable necessity of performing further unplanned statistical procedures to achieve statistical significance in one of the primary outcome variables raises the possibility of bias being introduced into the results. It should be noted that the 2nd primary variable (SPID6) did not require "transformation" to achieve a SSD between the combination product and the individual components.

The secondary outcome variables (TOTPAR and SPID at 3 hours) did achieve a SSD for the combination vs. the individual components. Examination of the figures referred to above suggests a visible difference in mean PR scores being observed up to the 3-hour time point. Note that after 3 hours there appears to be no discernable difference between PR and PID scores. Other pertinent secondary outcome variables include the Time to Onset of Pain Relief (TOPR) and Time to Re-Medication (TTR). The sponsor's results demonstrate that the combination product (5/400 mg formulation) TOPR occurs at 21.4 minutes (95% CI 18.2 – 24.7 mins) for 50% of the treatment group subjects. The closest competing individual component (Ibuprofen 400 mg) has a TOPR time of 29.7 minutes (95% CI 25.6 – 33.6). This suggests an approximate 9-minute difference in median time to onset between the two with no overlap in confidence intervals. The clinical utility of this 9-minute onset difference is hard to gage, but it is presumed that this would be meaningful to individual patients in acute pain.

The median TTR for the Oxy-MD-05 study could not be estimated because less than 50 % of subjects in the combination and ibuprofen groups re-medicated. This suggests that over 6 hours there is no discernable difference in duration of pain relief between Oxy/Ibup 5/400 mg and Ibuprofen 400 alone, based upon this metric.

The Oxy-MD-06 study was similar in design, except that it included two additional treatment arms using Oxycodone/Ibuprofen 10/400 mg and Oxycodone HCL 10 mg treatments. This study specified similar primary outcome variables to the Oxy-MD-05 program. Here no unplanned *post-hoc* statistical procedures were necessary for the 5/400 mg combination product to show a SSD when compared to Ibuprofen alone ($p = 0.030$). However, examination of figures 6.1.2.5.1 and 6.1.2.5.2 again illustrate a similar time-course of PR scores when compared to Ibuprofen alone, in that there is separation of the combination product from its components only up to approximately 3-hours. After this time, the Mean PR vs. Time curves for the combination product and Ibuprofen Alone appear to be the same.

The 2nd primary variable (SPID6) also showed a similar pattern of significance, when compared to Ibuprofen alone ($p = 0.0389$). Both combinations and Ibuprofen alone showed a highly SSD compared to placebo and the oxycodone formulations. Note that no significant difference was found between the 5/400 mg and 10/400 mg Oxy/Ibuprofen formulations ($p = 0.9004$). All further discussion will focus on the 5/400 mg formulation, which the Sponsor is proposing for approval.

The secondary outcome variable results in Oxy-MD-06 were similar to the MD-05 study, in that the TOPR Combination Product/Ibuprofen difference was statistically different. However, the TOPR values for the 5/400 mg formulation and Ibuprofen alone treatments demonstrated only a 3 minute difference in median time of onset (25.35 mins with 95% CI [21.2 – 28.8 mins], and 28.03 mins with 95% CI [24.9 – 31.1 mins], respectively). The Sponsor states that the 10/400 mg formulation showed a 22.53 minute median onset time that was also SSD when compared to the Ibuprofen-alone treatment. In this case it is difficult to accept that the statistical difference in 3 minutes of median time to onset (for the particular treatment group) will translate into a clinically discernable difference for individual patients. This is especially so when it is noted that the 95% confidence intervals overlap. In contrast, the Oxy-MD-05 study showed a larger median TOPR difference of approximately 9 minutes (as discussed above) with non-overlapping confidence intervals. The Oxy-MD-05 difference appears large enough that some individuals might notice a clinical difference between treatments. The median Time to Re-Medication (TTR) again could not be estimated because the combination and Ibuprofen groups had less than 50% of their respective subjects requiring re-medication, during the 6-hour time-period of observation.

In conclusion, despite showing clear statistical differences between the efficacy of single-dose Oxycodone / Ibuprofen 5/400 mg vs. Oxycodone and Placebo, the statistical conclusions for the combination product vs. Ibuprofen alone are not as striking. In particular, the large degree of overlap in time course of pain relief scores, minimal

differences in onset of pain relief, and inability to determine median differences between times to re-medication for the two treatments, overall suggest that the statistical differences observed are less than impressive. It is this reviewer's opinion that the secondary variables $TOTPAR_3$ and $SPID_3$ suggest a more robust difference, compared to Ibuprofen, than the same primary metrics at 6 hours. In addition, the lack of any observed difference between pain relief and pain intensity differences between the two strength combination formulations (5/400 mg vs. 10/400 mg) suggest that increasing the Oxycodone strength does not improve the observed efficacy in the dental pain studies examined here.

2.2.1 Efficacy Addendum: Oxy-MD-07 Post-Operative Pain Study

The results of the study Oxy-MD-07 trial were not included in the efficacy analysis, because it was submitted after the NDA filing date. However, for completeness this study was reviewed in section 6.1.3, in detail. Because the results are pertinent to the efficacy discussion, they are briefly summarized here.

This trial examined similar $TOTPAR_6$ and $SPID_6$ primary outcome values for post-operative orthopedic pain for Oxy/Ibup 10/400 mg and 5/400 mg. These formulations were then compared against Ibuprofen 400 mg, Oxy 10, 5 mg, and placebo. Both combination products demonstrated a SSD when compared to Placebo or Oxycodone alone ($p < 0.001$). However, neither product (Oxy/Ibup 10/400 mg or 5/400 mg) showed a SSD when compared to Ibuprofen 400 mg alone ($p = 0.7163$ and $p=0.2967$ respectively for $TOTPAR_6$) for either $TOTPAR_6$ or $SPID_6$. This pattern of "no significant difference" was also see for all of the secondary variables examined (the same variables as in Oxy-MD-05 and –06). Thus this additional finding of "no statistically significant difference" between the combination product and Ibuprofen alone, support this reviewer's opinion that the proposed product BRANDNAME does not demonstrate superior efficacy to Ibuprofen.

2.3 Safety

As stated earlier, the entire safety population was used for the safety analysis. The safety population was defined as subjects treated with study drug. The safety review mainly consisted of evaluating the Integrated Summary of Safety (ISS) provided by the sponsor. In addition, the SAS Transport safety data base was interrogated to verify data tables, incidences, and integrity of the CRF → Electronic CRT → 120 Day Safety Update ISS results. The size of the safety data base was appropriate for analysis and drawing conclusions regarding short-term safety experience associated with both of the combination products: Oxy/Ibup 5/400 mg and 10/400 mg.

Overall the safety data integrity was good. However, one was found involving inappropriate coding of the following adverse event (AE) "Preferred Terms":

AMBLYOPIA, ASTHENIA, HYPERTONIA, and VASODILATION. Examination of several individuals CRFs and the respective Investigator Terms and Codes revealed that these items were chosen for the following patient complaints:

Patient Complaint/Investigator Term	Preferred Term Coding	Reviewer Comments
"feeling warm", "hot flashes"	VASODILATION	This seems inaccurate to label "feeling" hot this way
"fatigue", "tired"	ASTHENIA	FATIGUE would be a better choice
"muscle cramps", "muscle spasms"	HYPERTONIA	CRAMPS or SPASMS would be more appropriate, hypertonia implies neurologic dysfunction
"blurred vision"	AMBLYOPIA	VISION ABNORMAL, etc... would be preferable to this category

It may be that the COSTART system does not allow for easy categorization of these patient complaints, or there was confusion during the coding process. Regardless, the use of these terms for the listed patient symptoms appears clinically inaccurate. In particular, Amblyopia is a distinct clinical condition, not to be confused with the common symptom complaint of "blurred vision." Otherwise, review of the safety database revealed good agreement between investigator terms and the chosen AE codes.

Overall the safety analysis demonstrated no unusual safety "signals". There was only one death due to Pulmonary Embolus, which occurred approximately 2 weeks after the subject had completed participation in the study. It is unlikely that the study drug was a material contributor to this patient's death. The pattern of Serious Adverse Events (SAEs) appeared to be more related to the underlying morbidity of an elderly study population undergoing orthopedic procedures (most were in Oxy-MD-08) rather than being specifically attributable to the study drug used. The Treatment Emergent Adverse Events (TEAEs) and reported Adverse Events (AEs) occurred in the safety population in patterns similar to what might be expected for opioid related side effects. The five most frequent AEs reported for the 10/400 and 5/400 mg formulations were Nausea, Dizziness, Somnolence, Vomiting, and Headaches. Examination of Figure 7.9.3.1 illustrates this pattern graphically. Note that the "preferred term" AE categories of ASTHENIA and VASODILATION may be misleading due to the coding issues discussed above. Overall, across the 10 most common categories of complaints there was a clear pattern of the higher dose combination product producing more AEs than the proposed Oxy/Ibup 5/400 mg combination. Given this finding and the lack of difference between these formulations in terms of efficacy, this reviewer concludes that there is no benefit in using the higher oxycodone/ibuprofen formulation and indeed there is a corresponding price due to increased adverse events.

Laboratory, vital sign, and ECG related safety variables were also examined. No ECG evidence of QTc prolongation was found. Some clinical laboratory findings of mild LFT

changes were seen, most of which normalized during the study. One subject with LFT changes, and signs of myopathy had engaged in excessive weight lifting before the labs were drawn. Several cases of low hemoglobin and hematocrit were seen in the Oxy/Ibup 5/400 mg treatment group, however examination of the individual patient listings suggested that the abnormalities were mostly marginal in magnitude and in one case was related to a hemorrhage. The most frequent lab abnormality was mild Hypercholesterolemia, which was elevated at baseline in the majority of the 9 subjects examined. Vital sign changes were not prominent with the exception of a marginal decrease in Systolic and Diastolic Blood Pressure in approximately 5 patients.

In conclusion, the Oxycodone/Ibuprofen combination products appeared to have an unremarkable safety profile based upon the safety population experience of 1572 exposed subjects. The pattern of adverse events observed appear to reflect the underlying morbidity of the safety population and the typical side-effects that might be expected with many opioid medications. No significant laboratory abnormality patterns, documented QTc prolongation, severe vital sign changes, or patterns of clinical adverse events were reported that suggest the possibility of an unusual "safety signal."

2.4 Dosing

The proposed product is a fixed formulation Oxy/Ibuprofen 5/400 mg tablet for oral ingestion. An additional 10/400 mg formulation was also examined in several studies (Oxy-MD-06, Oxy-MD-07, and Oxy-MD-08). There were no studies specifically examining titration from the lower to higher dose formulation. However, the pharmacokinetic properties of Oxycodone/Ibuprofen seems to indicate that QID dosing for 7 days will not result in significant accumulation of drugs. Therefore, there is less of a safety concern with the proposed dosing regimen, based on the PK perspective. Dr. Lee of the OCPB Office determined that there is no obvious drug exposure-response relationship for BRANDNAME. Thus, there is no obvious efficacy or pharmacodynamic justification for the proposed dosing described in the draft package insert.

2.5 Special Populations

No significant drug-demographic interactions were identified in the safety review. Drug-drug interactions and Drug-disease interactions (e.g. renal and hepatic impairment) were not specifically studied. Specific pediatric studies have not been performed, although subjects ≤ 17 years of age, have been included in the clinical studies. There was no significant pattern of adverse events reported by age, due to the combination drug products, with the exception of a greater proportion of AEs for the 10/400 mg formulation compared to the 5/400 mg formulation. In addition, an increase in TEAE reports with increasing age, was observed in the placebo groups (see Figure 7.14.2.1).

CLINICAL REVIEW

1 INTRODUCTION AND BACKGROUND:

1.1 Proposed Indications:

The Sponsor's proposed indication for BRANDNAME, is described below:

> "BRANDNAME tablet is indicated for the short term management of acute, moderate to severe pain."

BRANDNAME is a fixed combination tablet for oral administration of the opioid analgesic agent, oxycodone HCL, with the nonsteroidal anti-inflammatory (NSAID) agent, ibuprofen. This product is for the control of acute, moderate to severe pain.

Oxycodone HCL is a centrally acting semi-synthetic mu-agonist opioid analgesic with multiple actions involving the CNS and smooth muscle. The exact mechanism of action is unknown. Oxycodone is rapidly absorbed after single dose administration with maximum plasma levels observed approximately 1.5 to 2 hours after administration. Oxycodone HCL is metabolized by the liver to noroxycodone (major circulating metabolite with weak analgesic activity) and oxymorphone (via CYP2D6).

Ibuprofen is an NSAID with analgesic and antipyretic properties. Its mechanism of action is thought to be related to inhibition of cyclooxygenase activity and prostaglandin synthesis. Ibuprofen is rapidly absorbed after oral administration and undergoes racemic interconversion to an S-isomer in plasma, before being metabolized to two forms of phenyl proprionic acid in the plasma.

The sponsor dosing recommendations suggest that BRANDNAME 5/400 mg should be taken no more than 4 times a day, for up to 7 days.

1.2 Milestones in Product Development:

— for Oxycodone/Ibuprofen combination tablets was filed on April 1, 1974 by —. The rights to the combination product were transferred to Forest Labs on October 3, 1996. On October 25, 1996 Forest Labs submitted — for Oxycodone HCL/Ibuprofen tablets, which was subsequently withdrawn without prejudice on November 20, 1996. On Dec. 20, 1996, Forest Labs submitted IND #52310 which is the effective IND for the currently submitted NDA.

The Sponsor and Agency interacted multiple times over the course of the development program (3/16/99, 6/16/99, 10/29/99, and 12/14/99).

Selected Meeting/Teleconference Highlights are discussed as follows:
1) 6/16/99 Meeting and 10/29/00 Tele-Conference –

- Any two positive studies, same pain condition or otherwise, would allow for approval for given dose of combination. (*Note that the Agency has actually specified that the study drug would only be approved in the pain condition studied*)
- ~ 1000 total subject exposures needed with ~ 500 exposed for 3 – 5 days

2) 9/19/00 Division letter – requested enrollment of pediatric subjects

3) 7/26/01 Pre-NDA Meeting –
   - Division would accept submission as 505(b)(2) application.
   - Pharm/Tox and Biopharm submission plans appeared acceptable.
   - Division requested justification for excluding certain studies from pooled ISE analysis.
   - Electronic SAS transport files for CRTs agreed upon.
   - Sponsor was requested to indicate how links were to be established between the multi- and single-dose studies.
   - Exposure numbers appeared acceptable. Results for Oxy-MD-07 would be submitted as part of the 120 Day Safety Data Base.
   - Pediatric Deferral Request to be included with NDA Submission.

   Note that the Agency was concerned about the single-dose study design being potentially inadequate for a short-term indication because of the potential for mult-dose/chronic use in the practice setting.

   The Final NDA was received by the Division on Dec. 20, 2001.

1.3 Foreign Marketing:

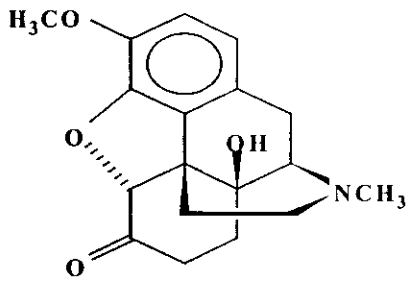
The Sponsor states that it has the exclusive worldwide rights to this product and has not licensed it to any other sponsor. To the best of the sponsor's knowledge, the product has not been marketed and has not had an application filed for marketing outside the U.S.

2 FINDINGS FROM OTHER REVIEW DIVISIONS OR CONSULTS:

2.1 Chemistry:

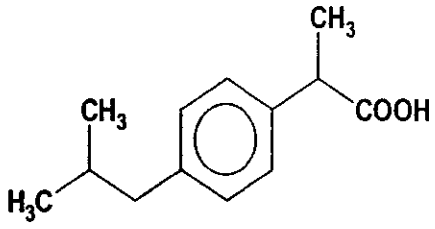
The active substances in BRANDNAME consist of Oxycodone HCL, USP 5 mg and Ibuprofen, USP 400 mg supplied in a fixed combination tablet. Oxycodone HCL is a centrally acting semi-synthetic mu-receptor opioid analgesic. Its chemical formula is $C_{18}H_{21}NO_4HCL$ with a molecular weight of 351.82. The structural formula is as follows:

Figure 2.1.1 Oxycodone HCL



Ibuprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Its chemical name is (±)-2-(p-isobutylphenyl) proprionic acid. Its chemical formula is $C_{13}H_{18}O_2$ and molecular weight is 206.29 Its structural formula is illustrated below:

Figure 2.1.2 Ibuprofen



The fixed combination tablet product also includes several inactive ingredients: sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, and calcium stearate.

The chemistry reviewer is finalizing his review at this time, and these results are pending. The interested reader is encouraged to consult Dr. Ravi Harapannhali's Chemistry Review, for more detail and an in-depth discussion.

2.2 Pharmacotoxicology:

The pharmacotoxicology of BRANDNAME, Oxycodone/Ibuprofen 5/400 mg is under review by Dr. Daniel Mellon/Pharmacology and the final results are pending.

The sponsor has investigated the toxicology findings of Oxycodone HCL, and their results are summarized here. Acute toxicity studies in rats demonstrate a highest non-LD of 150 mg/kg with a corresponding lowest LD of 225 mg/kg. Developmental and Repro toxicity studies in the rat and rabbit were negative, even at doses of 8 mg/kg and 125 mg/kg, respectively. There was no evidence of mutagenicity but there was genotoxicity observed only in the presence of metabolic activation, suggesting possible low genotoxic risk to humans.

The Sponsor notes that animal toxicity studies show the major effect of ibuprofen administration to be GI ulcerations, renal papillary lesions, and pulmonary/liver lesions. The highest tolerated ibuprofen doses were 300 mg/kg in mice, 180 mg/kg in rats, and 16 mg/kg in dogs. There was no evidence of carcinogenicity in mice and rats up through highest doses (300 – 100 mg/kg/day after 43 weeks) and 120 mg/kg/day. There was no mutagenicity noted in assay batteries but there was evidence of weak genotoxicity in mice bone marrow.

Acute rat toxicology studies of the combination product showed the highest non-LD to be 5/400 mg/kg and the lowest LD was 6.25/500 mg/kg. Two 1-month dog studies suggest that the combination drug had a toxicity profile no different than that of the individual constituents. A combination of Oxy/Ibup at 1:80 was no Teratogenic or maternally toxic in rats or rabbits.

For an in-depth discussion of the Pharmacology/Toxicology aspects of this submission, the reader is encouraged to read Dr. Mellon's review.

2.3 Clinical Pharmacology and Biopharmaceutics:

The Biopharmaceutics and clinical pharmacology review was conducted by Dr. David Lee of the Office of Clinical Pharmacology and Biopharmaceutics (CPB). Dr. Lee has concluded that the Human Pharmacokinetics and Bioavailability section of the NDA is acceptable provided that the Sponsor supplies the appropriate information necessary to link the Roxicodone™ 5 mg to an "approved" reference product. For an in-depth discussion of this issue, the reader is encouraged to consult Dr. Lee's review.

2.4 Controlled Substances Staff:

The Controlled Substances Staff (CSS) has stated that the product was to subject to CII regulations. Due to its low concentration of oxycodone it will not require a risk management plan or PPI. The CSS has not provided comments on the label due because the product is not recommended for approval.

2.5 Office of Post-Marketing Drug Risk Assessment:

At the time of this NDA review, the Sponsor has not supplied a BRANDNAME for the oxycodone/ibuprofen combination product and OPDRA has not been consulted.

2.6 Biostatistics:

Dr. Dionne Price from the Office of Biostatistics conducted a statistical review of the Sponsor's NDA submission. In discussion with her, it appears that the primary efficacy outcome variables (and the majority of the secondary outcome variables) did achieve a statistically significant difference between the combination products and the individual drug components. However, per Dr. Price, the levels of significance were marginal, over the ibuprofen-alone formulation over the six hour time period. Her opinion is that while the literal statistical goals (significance levels) have been met, a corresponding demonstration of clinical efficacy of the Oxycodone/Ibuprofen combination formulation may be less clear.

In addition to this overall conclusion, Dr. Price felt that the use of the statistical transformation of the TOTPAR data from study Oxy-MD-05 was not necessary and was an unplanned analysis. Dr. Price also suggested that the time to re-medication (TTR) metric is not be the best surrogate for "duration of pain relief" because it does not take into account the time needed for onset of pain relief. She suggested that the difference between these two times (TTR – TOPR) for each treatment, may be a more suitable measure of "duration of pain relief."

For a more in-depth discussion of the issues described here, the reader is encouraged to consult Dr. Price's Biostatistical Review.

3 HUMAN PHARMACOKINETCIS AND PHARMACODYNAMICS:

The Sponsor has submitted a total of 6 pharmacokinetic/biopharmaceutics

3.1 Pharmacokinetics:

Oxycodone is rapidly absorbed after single-dose administration of the Oxycodone/Ibuprofen 5/400 mg formulation. BRANDNAME shows an approximate T_{max} ranging from 1.3 to 2.1 hrs, with a corresponding C_{max} of 9.8 to 11.7 ng/mL. Dose proportionality was observed after increasing single doses. There was mild increase in C_{max} and AUC after a standard high-fat breakfast, that was deemed "not-clinically significant." Repeated administration (5/400 mg QID x 3.5 days) resulted in approximately 50% accumulation based upon the C_{max} for Oxycodone.

Ibuprofen was also rapidly absorbed after single-dose administration of the proposed product. The T_{max} ranged from 1.6 to 3.1 hrs. The rate of absorption for the total and S-racemic concentrations of ibuprofen was unaltered by the presence of oxycodone. The C_{max} and AUC values for total ibuprofen were unaltered by the presence of food. There was no accumulation with repeated doses of the proposed product.

Oxycodone is extensively distributed after oral and I.V. administration based upon the Sponsor's literature review. The Sponsor's literature findings suggest that oxycodone is ~38% protein bound at concentrations of 200 ng/mL with Ibuprofen showing > 99% binding to plasma proteins.

Oxycodone is metabolized via the P450 2D6 isozyme and the metabolic by-products oxycodone, noroxycodone and oxymorphone are excreted primarily in the urine. Ibuprofen is extensively conjugated and hydroxylated. The elimination half-life after a single dose of Oxy/Ibup 5/400 mg is 3.1-3.7 hrs.

3.2 Pharmacodynamics:

Oxycodone HCL is a centrally acting semi-synthetic mu-receptor opioid analgesic with similar clinical effects to morphine and other opioid medications. Ibuprofen is a non-steroidal anti-inflammatory (NSAID) agent.

The Sponsor did not undertake any specific investigation of the pharmacodynamic relationship between efficacy/safety measures and study drug concentration. Dr. Lee, in the Office of Clinical Pharmacology and Biopharmaceutics, performed a brief evaluation of the Sponsor's measured PK parameters with the primary outcome variables for Oxy-MD-05 subjects. His analysis did not indicate any clear pharmaco-dynamic (PD) relationship.

4 REVIEW METHODS:

4.1 Conduct of Review:

The review was conducted by initially determining that all applicable items in the clinical section were in place, and that the NDA was suitable for filing. This task was performed by Dr. Dal Pan. The Agency asked that the data files be compliant with the applicable guidance documents for electronic NDA submissions. The sponsor agreed to this request and submitted revised data files that were compliant with guidances. Once the filing date was passed the NDA review began.

The efficacy review consisted of a detailed analysis from the efficacy findings from the pivotal studies: Oxy-MD-05 and Oxy-MD-06. Each of these studies met statistical significance by the sponsor's criteria (Oxy-MD-05 required a data transformation of one primary variable to meet significance), and were thus chosen for review. The Sponsor

later submitted data from an orthopedic single-dose analgesic trial (Oxy-MD-07) and a multi-dose trial (Oxy-MD-08) that were not reviewed for clinical efficacy. The Agency had previously informed the sponsor that late submissions would be reviewed as part of the safety analysis, and not the efficacy portion.

The safety review consisted primarily of a review of the 120 Day Integrated Summary of Safety (ISS). In addition, the sponsor submitted electronic safety data base was used to supplement and verify findings from the ISS.

Requests for clarification and further data did not occur often. The few exceptions occurred later in the review cycle and are included as Appendix A of this document.

4.2 Materials Consulted:

The material consulted included the initial IND submission as well as the additional submissions provided by the Sponsor, summarized in the table below.

Date	Source Document
9/10/00	IND 52,310/GC-033 *Request for Clarification of Meeting Minutes*
8/3/01	IND 52,310 *7/26/01 Meeting Minutes*
12/20/01	NDA 21-378 *Submission Documents, Vols. > 50*
8/9/02	NDA 21-378 Response to Request for Information: Patient Disposition
8/8/02	NDA 21-378 Response to Request for Information: Clarification of Differences.

4.3 Evaluation of Data Quality and Integrity:

During the course of the review there were a few instances where difficulty was encountered finding some of the information mentioned in the study. The significant problems are discussed in more detail below. Overall, the electronic database integrity was quite good. Reconstruction of selected data tables, incidences, and quoted results for both efficacy and safety sections has been successfully performed by the reviewer. In addition, selected patient reports have been examined in all three formats (table listing, CRF, and electronic CRT) with good agreement in all selected cases. The values and ranges of laboratory values from the PK studies appears to be physically plausible without obvious "non-sense" values indicating errors, when the electronic data is queried. Dr. Price in Biostatistics has also confirmed that she has been able to reproduce the Sponsor's efficacy results using SAS software.

The sponsor discusses several protocol violations with subject numbers, in Oxy-MD-06. When the reference tables were consulted to obtain further information on the subjects, they could not be found. This problem was reported to the Sponsor on 7/31/02 with a request for correction of this. The Sponsor replied to the Agencies questions with the requested documentation on 8/9/02.

The sponsor also refers to a table listing the approved anesthetics in Oxy-MD-06. However, this table was not listed as described, when the appropriate volume was consulted. The sponsor was notified of the deficiency on 8/15/02 and the Agency is awaiting a response.

Note that the problems with inaccurate/inappropriate coding of AE Preferred Terms have already been discussed in section 2.3.

4.4 Financial Disclosure:

To comply with 21CRF 312.54 (c)(4) Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interest and arrangements of the BRANDNAME clinical investigators for all the clinical studies: Oxy-MD-05, Oxy-MD-06, Oxy-MD-07 (submitted as part of the 120 Day Safety Update Apr 30th, 2002) and Oxy-MD-08 as of the time of NDA Submission on Dec. 19th, 2002.

The sponsor notes that study sites 3 and 12 of Oxy-MD-07 did not receive study drug and the study sites were not initiated. Oxy-MD-07 certification was not included at the time of NDA submission. The final certification and disclosure, along with the finalized safety data from Oxy-MD-08 (multi-dose safety data), was submitted as part of the 120 Day Safety Update.

In summary, all of the supplied certifications show that no financial arrangements were made with the listed investigators whereby the value of compensation could be affected by the study outcome. The submitted documentation appears to be acceptable.

5 DESCRIPTION OF DATA SOURCES:

The primary source of data for this NDA review consisted of the NDA clinical volumes submitted by the Sponsor on Dec. 19, 2001, as well as the electronic data sets submitted to the Agency Electronic Document Room (EDR).

5.1 Primary Source Data:

Source data consisted of SAS Transport files containing study subject Case Report Tabulations. These files were accessible through the EDR for data verification and evaluation of the Sponsor's efficacy results. The 120 Day Safety Update files were also submitted to the Agency and were reviewed electronically. In addition to these electronic data sets there were also patient listings, patient narratives, and data file print outs in the paper NDA submission.

5.2 Postmarketing Experience:

No formulations of BRANDNAME Oxycodone HCL/Ibuprofen 5/400 mg tablets are currently marketed.

5.3 Literature Search:

The Sponsor has conducted an extensive review of the literature and has supplied copies of numerous articles referenced within the report. Clinical topics covered by the articles submitted include methods of measuring pain, pain onset, the time course of pain relief, and current practices regarding single-dose pain studies and pain relief.

6 INTEGRATED REVIEW OF EFFICACY:

6.1 Individual Review of Studies (by indication)

6.1.1 Study OXY-MD-05:

A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCL 5mg/Ibuprofen 400 mg Compared to Ibuprofen 400 mg Alone and Oxycodone HCL 5mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery.

6.1.1.1 Findings vs. Labeling Claims:

No review of the Package Insert and Proposed Labeling was performed because the Sponsor failed to show convincing evidence of efficacy of the proposed product.

6.1.1.2 Study Plan:

6.1.1.3 Population, Design, and Objectives

The protocol-specified objective of the study was:

> "To evaluate the analgesic efficacy of a single dose of a combination tablet of oxycodone HCL/ibuprofen 5/400 mg relative to ibuprofen 400 mg alone, oxycodone HCL 5 mg alone and placebo using the third-molar-extraction pain model."

The protocol was designed as a multi-site, double-blind, double-dummy, randomized, parallel-group, single-dose, placebo and active-controlled design. Subjects were to have undergone surgical removal of at least two ipsilateral, bony impacted third molars. Patients meeting these criteria for the study were to be enrolled based upon their post-surgery pain intensity measured by the Baseline Pain Intensity (PI) scale and Visual Analog Scale (VAS). The PI is a 4 level ordinal scale that allows subjects to rate their pain as integers between "0" and "4." The VAS is a continuous visual scale 100 mm total length that corresponds to "no" pain to "severe" at 100 mm. Subjects mark their current perceived pain level on this scale, which is measured proportionally. Potential subjects rated their BPI as moderate to severe and their VAS as greater than 50. They were then to have been randomized into one of 4 treatment groups: (1) Oxycodone HCL/ibuprofen 5/400 mg, (2) Ibuprofen 400 mg, (3) Oxycodone HCL 5 mg, and (4) placebo.

The study had planned for a total sample size of 448 patients to have been randomized in a 3:3:1:1 ratio (168:168:56:56 patients) to the respective study groups outlined above. In addition, a PK subgroup was also planned. This was to consist of 32 patients randomly drawn from the four treatment groups. These patients were to have had blood samples drawn at each time point, after efficacy and safety evaluations were performed.

Potential subjects were to have had the purpose and procedure of the trial explained to them. Subjects that agreed to participate were supposed to complete an informed consent, undergo a physical examination, a review of their medical history, and to remain NPO for 8 hours prior to their planned surgery. Female patients of childbearing potential were to perform a urine pregnancy screening test on the day of planned surgery. All subjects meeting the inclusion and exclusion criteria were to undergo further instruction on how to complete their diary. A listing of these criteria follows this section.

Potential subjects were to be chosen from patients undergoing third-molar extraction. The sponsor states that this model had well established utility in analgesic evaluation due to:

- The surgical procedure caused uniform pain production.
- There was low inter-subject variability due to etiology of the pain.
- The model demonstrated good assay sensitivity for discrimination between active drugs.

All potential subjects had to meet the following inclusion criteria:

- Ability to provide written informed consent (parental approval for <18 years of age).
- All patients must be healthy male or female outpatients at least 12 years of age.
- All childbearing potential females must have negative urine pregnancy tests on day of surgery.
- Patients must be alert and able to communicate.
- Patients must be able to complete the study as instructed.
- All patients must abstain from all ETOH, caffeine, and smoking for 8 hours prior to surgery to the end of the post-dosing period.
- All patients must be scheduled to have at least two ipsilateral, bony impacted 3rd molars removed. No additional surgery must be performed.
- All patients must remain on-site during the post dosing period.

The exclusion criteria were:

- Pregnant or lactating females.
- Patients who had taken the following medications:

- Short-Acting analgesics (ASA, acetaminophen, etc...) within 6 hours prior to surgery
- Ibuprofen within 10 hours of surgery
- Long-Acting NSAIDs or any opiate analgesic within 48 hours prior to surgery.
- Steroids within 72 hours prior to surgery

- Use of any psychoactive drug (e.g. antidepressants, phenothiazines, hypnotics, anti-anxiety agents) or opioid antagonists within 72 hours prior to surgery.

- Use of surgical anesthesia and/or antiemetics not in the approved protocol.

- Patients with significant co-existing medical condition (e.g. GI, hematologic, neurologic, renal, cardiovascular disorders, etc...)

- Patients receiving investigational drug or in a clinical trial within 30 days prior to this study.

- Patients who were employees, relatives of employees or prior participants in this study.

- Patients with known allergies or reactions to opioid or NSAID medications, including the two active study compounds.

- Current drug or alcohol abuse.

- Concurrent medication use that could affect quantifying analgesia.

- Medical conditions compromising ability to swallow, absorb, metabolize, or excrete the study medication.

- Significant pre-existing pain condition unrelated to teeth.

Surgery was to be performed with approved anesthesia. The Sponsor provided an analysis of the distribution of anesthetics used during surgery for the different study populations. Examination of Table 2.6 (Vol. 51, pg. 108) shows a similar distribution of treatment frequencies from highest to lowest, across groups: Midazolam (78.5%), Mepivacaine (77.5%), NO_2 (72.5%), Lidocaine (62.7%), Brevital (43.2%), and Fentanyl (15.5%). No obvious significant difference in usage of these surgical medications was noted.

Post-Surgery enrollees were to be placed in an observation area by study staff, for up to 5 hours. Patients were to notify study personnel when their pain reached the threshold for randomization into the study, using VAS and Baseline Pain Intensity (PI). The threshold criteria for randomization was to consist of a PI score of "moderate" to "severe" pain and

VAS score ≥ 50 mm, within the 5 hour post-op period. If potential subjects did not develop sufficient pain levels as defined above, within 5 hours, they were to be classified as ineligible for study continuation.

Table 6.1.1.3.1 Approved Anesthesia

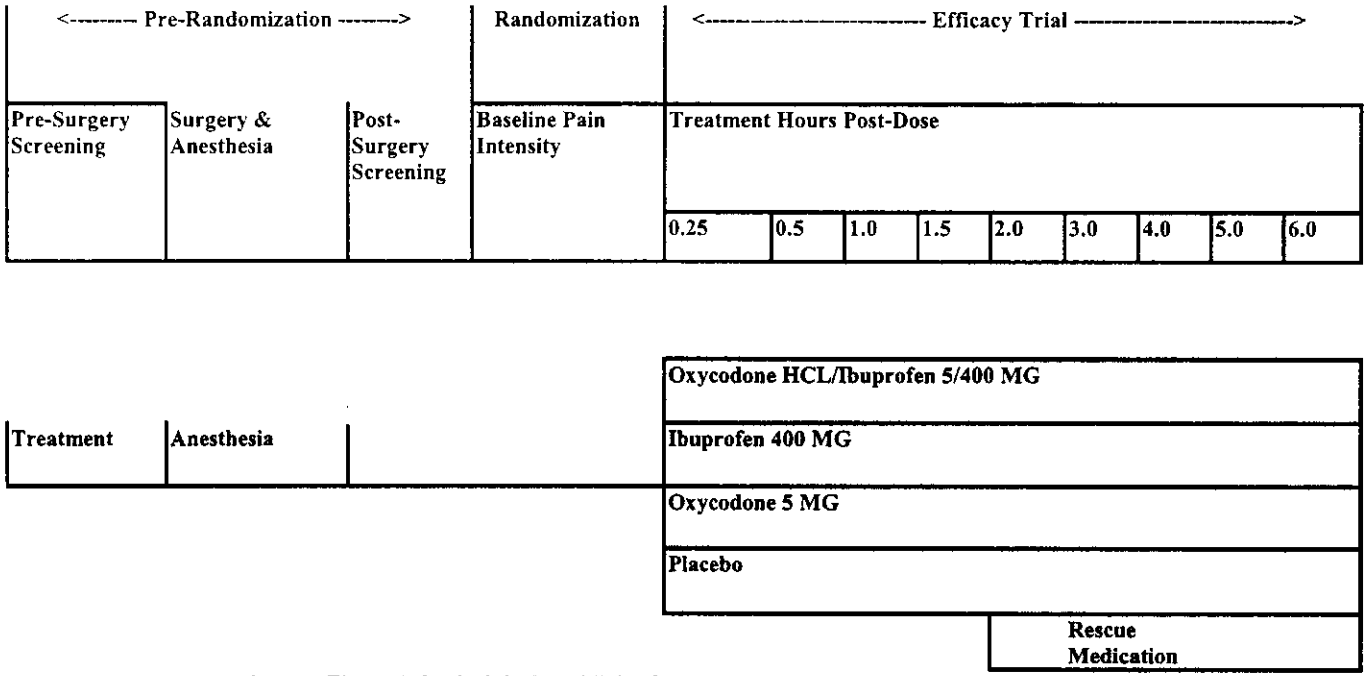
Allowable Anesthetic/Antiemetic Medications for 3rd Molar Extraction	
Nitrous Oxide/O_2	Citanest forte
Diazepam	Tigan
Atropine	Mepivacaine HCL 3%
Fentanyl	Other, Specify
Lidocaine HCL 2% w/ Epinephrine	Lidocaine HCL 2% w/ Epinephrine

Source: OXY-MD-05 Annotated CRF

Subjects that met the pain criteria were to be randomly assigned to their respective treatment groups and then study medication could be provided. PK subgroup participants were to provide a blood sample immediately prior to dosing. All patients were to remain at the study location for 6 hours post dosing. Subjects were to be encouraged to remain awake during the 6 hour post-dose period. If a patient's pain were to become severe they could request "rescue" medication, in addition to their dosing of study medication. Subjects were to be encouraged to wait at least 2 hours post-dosing before requesting "rescue" medication. The following figures were adapted from the Oxycodone/Ibuprofen Comparative Efficacy Study vol. 51, and illustrate the proposed study outline and schedule of evaluations.

Note that study participants could have been discontinued from the study at any time. This could have been due to occurrence of an adverse event (AE), poor therapeutic response, protocol violations, withdrawal of consent, or administrative reasons.

Figure 6.1.1.3.1 Oxycodone/Ibuprofen Comparative Efficacy Study Schematic



Source: Figure 1. Study Schedule OXY-MD-05, NDA, Vol. 1-51, 24

Table 6.1.1.3.2 Schedule of Evaluation

	PRE-SURGERY	POST-SURGERY DOSING										
		Surgery	PRE-DOSING	Dosing	POST-DOSING (HOURS)							
	SCREEN-ING		Baseline		0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Randomization			X											
Medical/Medication History	X													
Concomitant Meds	X		X		At Any Time									X
Physical Exam, VSS	X		X							X				X
Urine Preg. Test			X											
Patient Diary			X		X	X	X	X	X	X	X	X	X	X
Global Rating														X
Adverse Events			X		At Any Time									X
Patient Diary Review														X
PK			X		X	X	X	X	X	X	X	X	X	X

Source: Figure 1. Study Schedule OXY-MD-05, NDA, Vol. 1-51, p 34

6.1.1.3.1 Treatment Summary

Patients were to be randomized to one of four groups, in a 3:3:1:1 ratio in order to receive Study Combination Drug, Ibuprofen, Oxycodone, or placebo, respectively. The "double dummy" method was to be used to maintain a study blind by administering treatment in groups of one and two tablets. Each site was to have administered the study drug to each enrolled patient. These were to be in identical blister packs that should not have indicated their contents. The following table illustrates the proposed drug information and dosing. Each blister pack was to be labeled with the protocol number, randomization number, space for patient initials, and instructions. Patients were to be assigned the randomization number on the study drug label. These sequential numbers were to be matched with randomization codes generated and kept in a secure area at Forest Laboratories.

Table 6.1.1.3.1.1 Study Drug and Dosing Regimen

Group	Treatment	Tablet/Capsule Strength	Lot Number	Dispensed As:		
1	Oxycodone HCL/ Ibuprofen	5 mg / 400 mg	99229K	1 x 5 mg Oxycodone + 400 mg Ibuprofen tablet	1 x Placebo Capsule	1 x Placebo Capsule
2	Ibuprofen	200 mg	119960	1 x Placebo tablet	1 x 200 mg Ibuprofen Capsule	1 x 200 mg Ibuprofen Capsule
3	Oxycodone HCL	5 mg	119959	1 x 5 mg Oxycodone tablet	1 x Placebo Capsule	1 x Placebo Capsule
4	Placebo X	0 mg	99247L	1 x Placebo tablet	1 x Placebo Capsule	1 x Placebo Capsule
	Placebo Y	0 mg	119958	1 x Placebo tablet	1 x Placebo Capsule	1 x Placebo Capsule

Source: 6.2.2 Panel 1, pg. 30 & 6.2.5 Panel 2, pg. 32; Vol. 1-51

Medications were to be administered with 4 ounces of water. Each combination of one tablet/two capsules was to be identical in appearance for all groups of patients. All medications were to be consumed.

The associated patient randomization number and assigned treatment was to be generated and maintained by the Forest Laboratories Department of Biostatistics. Bottles of identical "double-blind" medication were to be labeled with a two-part, three-panel label. The first part was to remain on the bottle at the time of administration. The other 2 panels were to be placed in the patent's CRF. In the event of emergency the 3rd panel could have been broken to reveal the patient's treatment.

Any patients concurrently taking medication that could have confounded the analgesia analysis were to be excluded from the study at screening. For study patients, the following concomitant medications and treatments were to have been prohibited throughout the entire study period.

- NSAIDs, salicylates, propoxyphene, acetaminophen, steroids, codeine, hydroxyzine, pentazacine or other medications that could confound quantifying analgesia EXCEPT as rescue medication for those requiring it
- Mood altering drugs within 72 hours prior to surgery
- Alcohol
- Caffeine
- Smoking

Rescue medication was to be available upon patient request in the post-dosing period, as stated earlier. All patients were to be encouraged to wait at least 2 hours after the study medication, before requesting "rescue". The type of rescue medication was to be at the discretion of the Investigator, unless the patient was also participating in the PK study. PK subgroup patients were to be provided Darvocet-N® 50 (propoxyphene napsylate 50 mg/acetaminphen 325 mg) or acetaminophen 1000 mg as rescue medication.

6.1.1.3.2 Assessments

Several efficacy measures were to be recorded by participating patients, during this study:

- Pain Intensity (PI) at baseline and scheduled intervals
- Visual Analog Scale (VAS)
- Pain Intensity (PI), Pain Relief (PR)
- Pain Half Gone
- Patient's Global Assessment.

The Baseline PI and VAS scale were to be entered into their respective patient diary just before dosing with the study medication. The other self-rated scales were to be entered into diary cards at each sampling time. All time measures were to be relative to the dosing time, recorded by the study coordinator. The scales (excluding VAS) are illustrated below:

Baseline PI	My starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
PI	My pain at this time is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
PR	My relief from starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
Pain Half Gone	My pain at this time is half gone: 0 = "NO" 1 = "YES"
Patient's Global Assessment	My starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"

Note that potential subjects were supposed to have a BPI rated moderate to severe and have a VAS Baseline Pain score of ≥ 50 mm within 5 hours postoperatively.

Effectiveness time measures were to be determined relative to the dosing time. Patients were to be given two stopwatches and instructions for stopping the individual watches as defined in below:

Measure	Definition	Patient Action
Onset of First Perceptible Pain Relief	The time when first pain relieving effect of medication noticed	1. Stop 1st Stopwatch 2. Record Time Interval 3. Reset Stopwatch to 0
Onset of Meaningful Pain Relief	The time when patient felt pain relief was meaningful	1. Stop 2nd Stopwatch 2. Record Time Interval 3. Reset Stopwatch to 0

Source: NDA 21-378, OXY-MD-05 Study, Vol.: 1-51

In addition to the efficacy measures discussed above, blood samples were also to be drawn from patients enrolled in the PK study sub-group. Samples were to be drawn just prior to dosing and after each subsequent safety/efficacy evaluation times (15, 30, 45 mins, 1, 1.5, 2, 3, 4, 5, 6 hrs) for a total of 11 blood specimens per patient. The time of blood draws was to be recorded in the respective CRF.

6.1.1.3.3 Analysis Plan

Three analysis populations were defined in the protocol. The randomized population was specified to consist of all patients randomized to the study. The safety population was to consist of all treated patients within the study. The intent-to-treat (ITT) population was to consist of all randomized patients taking the study drug and having ≥ 1 post-baseline efficacy measure.

The protocol specified primary efficacy endpoints for statistical analysis was to consist of two measures calculated from self-rated patient pain scales:

1. Sum of Pain Intensity Difference through 6 Hours ($SPID_6$).
   - Define PID = difference between pain intensity at a given time and the baseline pain intensity (e.g. PID(t) = PI(t) – BPI).
   - SPID = the AUC of PID vs. time from 0 – 6 hours.

2. Total Pain Relief through 6 hours ($TOTPAR_6$)
   - Defined as the area under the curve (AUC) of pain relief (PR) vs. time from 0 – 6 hours.

The primary analyses of efficacy were to be based on the ITT population, with the last observation carried forward (LOCF) to extrapolate any missing PI or PR values. Statistical testing was specified to use two-tailed analysis with 5 % and 10 % significance levels respectively, for the main and interaction term effects. The protocol specified sample sizes calculations were to be based upon an expected difference in $SPID_6$ values for the Oxycodone HCL/ibuprofen and ibuprofen alone groups. The sample size assumptions were stated as follows:

- $SPID_6$ difference as defined above = 1.35 (based upon OXY-MD3-96-01 results)
- Each $SPID_6$ group standard deviation = 4.2
- Two tailed t-test at 0.05 significance level
- 83 % power needed to detect difference

Sample size was calculated to be 168 for these two groups. There was a large expected difference in $SPID_6$ groups for oxycodone alone and ibuprofen alone, and as a result only 56 patients per group were to be enrolled in those categories. This was to result in a total of 448 patients in a 3:3:1:1 (168:168:56:56) proportion. Similar calculations for TOTPAR resulted in smaller sample sizes required, however the larger number quoted here was to be used for both groups.

Primary analyses were to be the comparison of the effects of the combination product treatment to individual analgesic components alone, for $SPID_6$ and $TOTPAR_6$. Pairwise comparisons across treatment groups were to have been analyzed using ANOVA techniques with treatment, study site, and BPI as effects. Comparability among treatment groups was to be tested using ANOVA with treatment as the continuous variable factor. The Cochran-Mantel-Haenszel (CMH) test was to be used for testing comparability among treatment groups by categorical variables.

Several secondary efficacy parameters were also specified in the protocol:

- TOTPAR 3 and SPID 3 – Defined and analyzed similarly to the 6 hour primary parameters.

- PR – analyzed at each time point using ANOVA with treatment and study site as effects.

- PID - analyzed at each time point using ANOVA with treatment, study site, and BPI as effects. Pair-wise comparisons performed using Fisher's protected LSD procedure.

- PRID = RI + PID. Combined pain relief analyzed similar to PID.

- Peak PR and Patient's Global Rating at 6 Hours (LOCF). Analyzed using ANOVA.

- Proportion of Patients Reporting Pain Half Gone. Data analyzed at each time point using the CMH test stratified by study site.

- Onset of PR – Defined as time from medication dosing to time 1st stopwatch stopped, for patients who also stopped the second stopwatch during the observation period. Patients who did not stop the second watch had onset time defined as a censored value at the last PI or PR measurement. This endpoint was analyzed using the log rank test for censored data. Median time to PR was calculated using the Kaplan-Meier product limit estimator.

- Time to Re-medication – Defined as elapsed time from dosing to time rescue medication administered. This was analyzed similar to Onset of PR.

No interim analyses were to be performed. All statistical computations were to be performed using SAS version 6.12.

Pharmacokinetic analyses were to be performed on data from the PK subgroup. Principal parameters were specified to be the bioavailability of ibuprofen and oxycodone in the combination, oxycodone alone, and ibuprofen alone groups. All assays and measurements were to be performed in the Bioanalytical Department of Forest Laboratories. Resulting plasma concentration vs. time curves was to be used to derive the appropriate PK metrics. AUC_{0-t}, C_{max}, and T_{max}. C_{max} and T_{max} were to be determined observationally as the peak concentration for the respective subject. AUC was to be calculated using a numerical integration technique.

6.1.1.3.4 Protocol Amendments and Changes in the Planned Analyses

There were two protocol amendments to Protocol OXY-MD-05:

Amendment #1 Dated 1/1/2000, provided the following changes:

1. **Increase in minimum subject age** from 12 to 16 years old.

Amendment #2 Dated 8/1/2000, provided the following changes:

1. **Increase in the number of study sites** from 1 to at least 2 sites

2. Modifications of the analysis of primary and secondary efficacy endpoints **to include study site effect**.

There were no other changes made to the Statistical Analysis Plan.

The restriction of subject age does limit the applicability of study efficacy findings to pediatric age groups, however it does not appear to materially affect the study design. The increase in study sites should not have had any particular biased effect on the study outcome. Inclusion of a "study site effect" is a common feature of many analyses. Overall, these protocol changes are not judged to have a significant effect on the study results, other than limiting applicability to pediatrics.

6.1.1.4 Study Conduct

In the Study Report (Section 6.7.9), the Sponsor lists the following measures to assure the data quality:

- Pre-trial meetings with Investigators to familiarize them with CRFs, diary cards, protocol
- Pre-trial review meetings with each individual Investigator to review study procedures
- CRFs customized for data collection in this study
- CRFs 100% reviewed against source documents by clinical monitors
- CRF data double-entered into validated database system
- Answering all data clarifications or queries, with changes made to database, by Forest Labs to update new or changed information
- Database was locked and treatment codes un-blinded after all issues resolved.

The sponsor notes that study was performed at 3 sites in the US. Each study center Principal Investigator was responsible for ensuring that the study was conducted according to the Protocol, Investigator Agreements, the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

6.1.1.4.1 Patient Disposition

The study report does not indicate how many patients were screened for admission to the study and were not accepted. In addition, the sponsor does not state how many patients were screened and never achieved the pain levels necessary to be enrolled, during the 6 hour post surgery time limit. A request for this information was faxed to the Sponsor on 7/23/02 and the results were received by the Agency on 8/9/02. The Sponsor states that there were 142 Screening Failures in Oxy-MD-05. There were 17 patients screened that were never randomized due to insufficient pain levels. The sponsor indicates that 498 patients were randomized into the four study groups:

Oxycodone HCL / Ibuprofen 5/400 mg	Ibuprofen 400 mg	Oxycodone 5 mg	Placebo
187	186	63	62

Source: NDA 21,378, Vol. 51, Oxy-MD-05, pg. 35.

Panel 6 of the study report summarizes patient dispositions, completions, discontinuation, and major reasons for dropping out of the study. Note that any patient taking rescue medication did not record any subsequent efficacy measures. 254 (51%) total patients completed the study. Both the combination and ibuprofen treatment groups experienced ~36 % discontinuation due to insufficient therapeutic response. The Oxycodone and Placebo groups experienced ~ 83% discontinuation due to lack of response. Two patients withdrew due to vomiting and/or nausea. 1 patient discontinued after withdrawing consent. The patient disposition summary is included below.

Table 6.1.1.4.1.1 Patient Completion and Discontinuation

	Oxy/Ibu 5/400 mg N=187	Ibu 400 mg N=186	Oxycodone 5 mg N=63	Placebo N=62	Total N=498
Completed	118 (63.1%)	115 (61.8%)	11 (17.5%)	10 (16.1%)	254 (51.0%)
Discontinued	69 (36.9%)	71 (38.2%)	52 (82.5%)	52 (83.9%)	244 (49.0%)
Discontinuation Reason					
AE(s)	2 (1.1%)	0	0	0	2 (0.4%)
Insufficient Response	67 (35.8%)	70 (37.6%)	52 (82.5%)	52 (83.9%)	241 (48.4%)
Withdrawal of Consent	0	1 (0.5%)	0	0	1 (0.2%)

Source: NDA 21,378, Vol. 51, Oxy-MD-05, pg. 36.

Inspection of the disposition table demonstrates ~ 36 % discontinuation in the Oxy/Ibup and Ibuprofen alone groups, due to insufficient therapeutic response. The Oxycodone alone and Placebo show even greater discontinuation. Patients that discontinued had their missing data imputed as LOCF. The large proportions of "drop outs" may skew the data results to some degree. The sponsor did not perform a "completers analysis" to show the effect of inclusion of such a large percentage of discontinuing subjects.

6.1.1.4.2 Protocol Deviations and Violations:

The sponsor notes that there were no protocol deviations.

6.1.1.4.3 Data Sets Analyzed

The Intent-to-Treat population was defined as all randomized patients taking the study medication with ≥ 1 post-baseline efficacy assessment. Efficacy analysis was performed on the ITT group. The last observation carried forward (LOCF) was used to extrapolate missing data. The Randomized population consisted of all patients randomized to the

study. One patient from the Randomized population was excluded from the ITT population.

The safety population consisted of all patients treated with study medication. The safety analysis was performed on this population.

6.1.1.4.4 Demographics/Group Comparability

Baseline characteristics and other demographic variables are summarized in the sponsor's table, which is reproduced below:

Table 6.1.1.4.4.1 Patient Demographics and Baseline Characteristics

	Oxy/Ibu 5/400 mg N=187	Ibuprofen 400 mg N=186	Oxycodone 5 mg N=63	Placebo N=62	Total N=498
Age (Years)					
Mean (Std Dev)	24.7 (5.31)	24.1 (5.1)	24.3 (5.19)	24.8 (5.5)	24.5 (5.23)
Sex, N (%)					
Male	69 (36.9)	85 (45.7)	30 (47.6)	35 (56.5)	219 (44)
Female	118 (63.1)	101 (54.3)	33 (52.4)	27 (43.5)	279 (56)
Race, N (%)					
White	116 (62)	138 (74.2)	48 (76.2)	48 (77.4)	350 (70.3)
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 (Std Dev)	154.7 (39.9)	159.6 (36.9)	158.8 (28.3)	163.8 (35.9)	158.2 (34.8)
Height (in)					
Mean (Std Dev)	66.5 (4.4)	67.1 (4.3)	67.6 (3.7)	67.4 (3.5)	67.0 (4.2)
Baseline Pain Intensity, N (%)					
Moderate	169 (90.4)	173 (93)	58 (92.1)	56 (90.3)	456 (91.6)
Severe	18 (9.6)	13 (7)	5 (7.9)	6 (9.7)	42 (8.4)
Baseline VAS (mm)					
Mean (Std Dev)	59.0 (8.8)	58.0 (7.2)	57.8 (7.2)	58.5 (8.6)	58.4 (8.0)

Source: NDA 21,378, Panel 7 Vol. 51, Oxy-MD-05, pg. 39.

Inspection of the abbreviated demographics table shows generally similar characteristics across groups. The exception is that of race and sex. There was a greater proportion of females than males (63.1% vs. 36.9%) in the combination group. There was also a lessor proportion of white subjects, compared to other groups. The sponsor states that adjusting analysis for sex and race indicates that these variables had no effect on treatment efficacy.

6.1.1.4.5 Treatment Compliance:

All participating subjects in this single-does study received medication directly from the Study coordinator. No other compliance measurements were necessary.

6.1.1.4.6 Unplanned Analyses

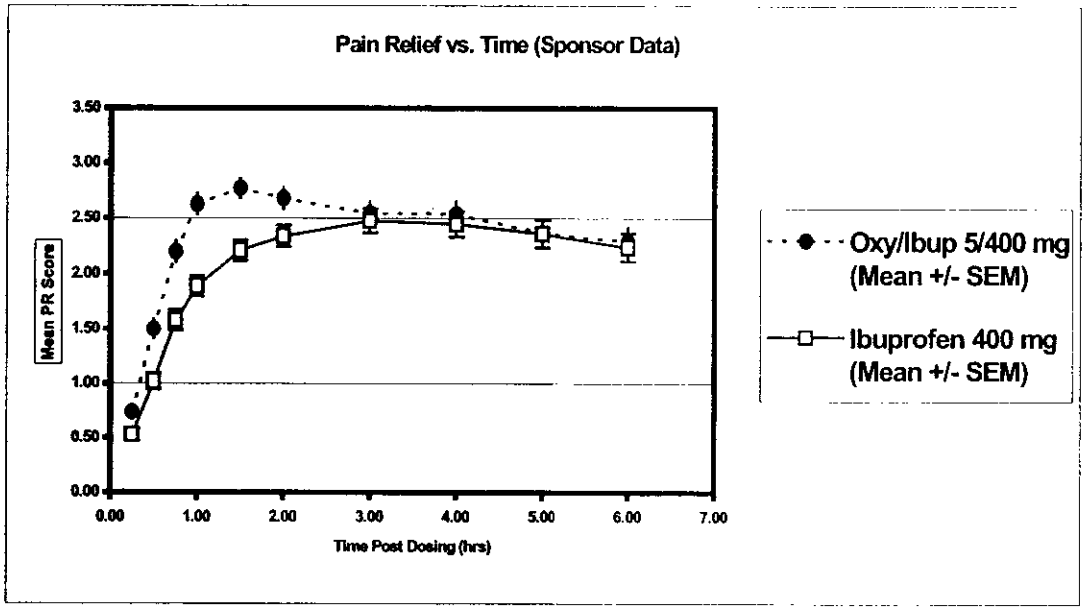
There were no unplanned analyses.

6.1.1.5 Sponsor's Efficacy Results for OXY-MD-005:

6.1.1.5.1 Primary efficacy Variables:

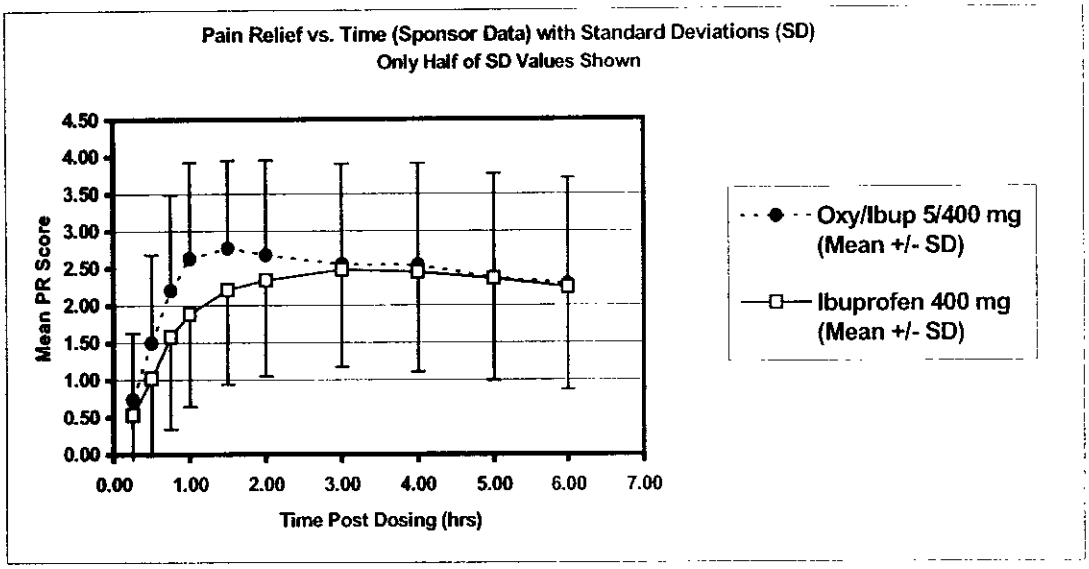
The primary efficacy variables were calculated metrics for "total pain relief at 6 hours" and the "sum of pain intensity differences at 6 hours": $TOTPAR_6$ and $SPID_6$ respectively. Both are derived from the Area Under the Curve (AUC) for the Mean Pain Relief (PR) and Pain Intensity Difference (PID), as a function of time. The Mean PR values over the time of the trial are illustrated here for visual inspection in Figure 6.1.1.5.1. and 2.

Figure 6.1.1.5.1 Oxy-MD-05 Mean PR Scores with Standard Errors



These graphs are Excel plots of PR efficacy data from the sponsor's analysis results, in Table 5.3, Vol. 51, pg. 115. Only half of the standard deviation (SD) error bars are shown, for clarity. Note that the time curves show a great deal of overlap when the actual standard deviation is included.

Figure 6.1.1.5.2 Oxy-MD-05 Mean PR Scores with Standard Deviations



Note that $TOTPAR_6$ is derived from the LS Mean data illustrated in these two curves. Given the large overlap in Oxy/Ibup and Ibuprofen standard deviations, it suggests that there is little difference in pain relief over the given study time, especially beyond 3 hours.

The difference in Between-Treatment-Group Least Squares (LS) Means for $TOTPAR_6$ was compared using ANOVA. The Sponsors results for $TOTPAR_6$ are summarized below:

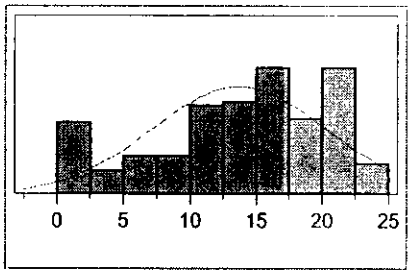
Table 6.1.1.5.1.1 $TOTPAR_6$ Results for ITT Population

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

*Raw p value 0.070, statistical significance achieved after normalizing the $TOTPAR_6$ data
Source: NDA 21-378, OXY-MD-05, Panel 8, Vol. 51, pg. 45.

The most important pair-wise comparison is between the combination study drug (Oxy/Ibuprofen) and its individual component Ibuprofen. The clinical trial was designed with sufficient statistical power to detect a difference between these two treatment groups for $SPID_6$. This resulted in even greater power for detecting differences in $TOTPAR_6$. The sponsor noted that the model residuals for $TOTPAR_6$ were not normally (gaussian) distributed, based upon the Shapiro-Wilks test. In addition, the ANOVA comparison of the raw data did not reach statistical significance ($p = 0.070$), although the "raw p value" is not far from the standard level ($\alpha = 0.05$) of significance. The raw TOTPAR6 data is shown below in frequency histograms with a fitted normal function, for visual inspection.

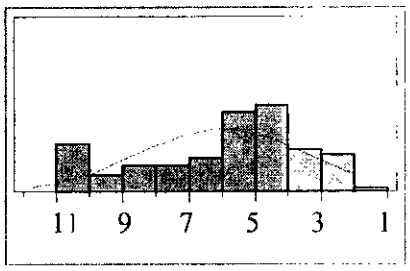
Figure 6.1.1.5.3 Raw TOTPAR6 Histogram for Oxycodone/Ibuprofen (5/400 mg)



Moments

Mean	13.771451
Std Dev	6.6057867

Figure 6.1.1.5.2 Raw TOTPAR6 Histogram for Ibuprofen-Alone 400 mg



Moments

Mean	12.585122
Std Dev	6.4067047

Note that both distributions demonstrate a large frequency bar near zero. This is presumably due to "non-responders" having their respective LOCF throughout the calculation. The visual data does show some departure from normality, but note that these graphs are of the TOTPAR data and not the residuals.

The sponsor used the BLOM formula to normalize this data set, and statistical significance was then achieved ($p = 0.012$). This data transformation was performed on TOTPAR6 across all treatments, however the resultant p value was shown only for the Combination vs. Ibuprofen pair-wise comparison.

I discussed the data transformation further with Dr. Dionne Price/Biostatistics Reviewer. She stated that the BLOM transformation was not necessary because ANOVA is a robust procedure capable of handling moderately non-normal data, under many conditions. In addition, there is no mention of possible "normalization procedures" within the analysis plan of the original protocol.

The second primary efficacy variable is $SPID_6$ and it was analyzed similarly to $TOTPAR_6$, described above. The normality assumption for the SPID6 combination drug residuals was also not met. Again, the sponsor used the BLOM transformation procedure to correct for this. However, it appears that the data set comparison of Mean LS Group Differences for the Combination vs. Ibuprofen was statistically significant before and after normalization (raw $p = 0.007$, normal $p = 0.002$). All other groups showed statistically significant differences with the exception of Oxycodone vs. Placebo. The summary table is shown below.

Table 6.1.1.5.1.2 $SPID_6$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Combination	186	6.54	0.42	5.71, 7.37	< 0.001
Ibuprofen 400 mg	186	5.41	0.44	4.56, 6.27	
Oxycodone 5 mg	63	0.14	0.60	-1.03, 1.31	
Placebo	62	0.32	0.59	-0.85, 1.48	
Pair-wise Comparisons:		**LS Mean Difference**		**95% CI for LS Mean Diff.**	**p-value**
Combination vs. Ibuprofen 400 mg		1.13	0.41	0.31, 1.94	0.002*
Combination vs. Oxycodone 5 mg		6.4	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

*(Raw p value = 0.007) Source: NDA 21-378, OXY-MD-05, Panel 9, Vol. 51, pg. 47.

6.1.1.5.2 Secondary Efficacy Variables:

Various secondary variables were analyzed in this study. Four of the variables appear to have the greatest relevance to the sponsor's labeling claims: $TOTPAR_3$, $SPID_3$, Time to Onset of PR (TOPR), and Time to Re-medication (TTR). $TOTPAR_3$ and $SPID_3$ are the three-hour versions of the 2 primary outcome variables.

$TOTPAR_3$ LS means are summarized in the following table. ANOVA analysis of the results between treatment groups demonstrates statistically significant differences in all pair-wise comparisons except Oxycodone vs. Placebo. Note that no data normalization was necessary.

Table 6.1.1.5.2.1 $TOTPAR_3$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Combination	186	6.43	0.24	5.97, 6.90	< 0.001
Ibuprofen 400 mg	186	5.35	0.24	4.89, 5.81	
Oxycodone 5 mg	63	2.17	0.37	1.44, 2.90	
Placebo	62	2.03	0.38	1.29, 2.77	
Pair-wise Comparisons:		**LS Mean Difference**		**95% CI for LS Mean Diff.**	**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	0.805

Source: NDA 21-378, OXY-MD-05, Panel 10, Vol. 51, pg. 49.

$SPID_3$ LS means are summarized in the following table. Analysis shows that between treatment mean scores were significantly different at three hours. The exception is again the Oxycodone vs. Placebo group, which did not demonstrate a significant difference in mean SPID scores.

Table 6.1.1.5.2.2 $SPID_3$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Combination	186	3.19	0.19	2.83, 3.56	< 0.001
Ibuprofen 400 mg	186	2.43	0.19	2.05, 2.81	
Oxycodone 5 mg	63	0.27	0.26	-0.25, 0.79	
Placebo	62	0.24	0.26	-0.27, 0.75	
Pair-wise Comparisons:		**LS Mean Difference**		**95% CI for LS Mean Diff.**	**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	0.805

Source: NDA 21-378, OXY-MD-05, Panel 11, Vol. 51, pg. 50.

This is presumably measured by the **Time to Onset of PR (TOPR)**. This is compared across treatment groups using Kaplan-Meier Survival Curves, with a pair-wise log rank test to assess differences between the treatments. The sponsor states that the results show the combination product provided the most rapid onset of pain relief. The pair-wise comparisons did demonstrate that the combination shows the fastest median onset of PR ($p < 0.05$). The results are as follows:

- Combination (Oxycodone/Ibuprofen) median TOPR: 21.4 mins
- Ibuprofen 400 mg median TOPR: 29.7 mins
- Oxycodone 5 mg median TOPR: not estimated b/c < 50% of subjects achieved PR
- Placebo median TOPR: not estimated b/c < 50% of subjects achieved PR

It is presumed that **Time to Re-medication (TTR)** was used as a surrogate metric for "duration of pain relief". TTR was estimated using Kaplan-Meier statistics. Fewer than 50% of the Combination product and Ibuprofen groups re-medicated over the 6-hour period. This prevented estimation of the median TTR for these groups. K-M cumulative curves demonstrate that 36.6%, 37.6%, 82.5%, and 83.9% of subjects in the Compound, Ibuprofen, Oxycodone, and Placebo groups, required re-medication over the 6 hours, respectively. The mean TTR was 2.1 hrs and 2.0 hrs for the Oxycodone and Placebo groups, respectively.

6.1.1.5.3 Other Secondary Outcome Variables:

Various other secondary outcome measures were also examined, as specified in the protocol analysis plan. Each result will be discussed in turn in this section.

The **Pain Relief (PR) Scores at Each Timepoint** was compared for the different treatments, using an ANOVA model. The "least-squares mean" value for the treatment group PR is assigned a letter value (A – D) indicating the ranking of most effective to least effective treatment. PR scores with different letters are significantly different from one another, at the $\alpha = 0.05$ (5%) level. The results show some significant difference between the combination product and ibuprofen from 0.25 to 2 hours, after which there is no discernable difference in efficacy. This pattern can also be seen by examining figures 6.1.1.5.1 and 6.1.1.5.2. The sponsor states that this demonstrates significantly greater pain relief with the combination products over the individual components, at the earliest time periods.

The **Pain Intensity Difference (PID) Scores at Each Timepoint** was compared in a similar fashion to the PR scores discussed above. Again there is a statistical difference between the combination product (5/400 mg) ranked as "A or most efficacious" and ibuprofen 400 mg ranked as "B or less efficacious" over the time period of 0.5 to 2 hours. Note that after 2 hours there is no difference between ibuprofen PID scores and the combination products.

The **Sum of PR + PID (PRID) Scores at Each Timepoint** was compared similarly to the above secondary outcome variables. The time varying scores show a similar pattern of statistically significant difference in superior rated "mean" PRID scores of the combination product vs. ibuprofen. The time period of significant difference again is seen from 0.25 to 2 hours, after which there is no discernable difference noted.

The **Peak PR Score** is determined as the maximum least squares mean PR Score during the 6 hours post-dose. The combination product showed statistically superior mean peak PR scores ($p < 0.05, < 0.001, < 0.001$) compared to ibuprofen, oxycodone, and placebo, respectively.

The **Peak PID Score** is determined as the maximum least squares mean PID score during the 6 hours post-dose. Again, Oxy/Ibup 5/400 showed greater mean Peak PID scores than all other comparisons ($p < 0.01$).

The **Peak PRID Score** is defined similarly to the Peak PR and Peak PID scores. The combination product showed significantly greater peak PRID than subjects in all other treatment groups ($p < 0.01$ for all comparisons).

Patient's Global Evaluation (PGE) Score was the least squares mean score for each group at 6 hours post-dose. Note that these scores are partly based on the LOCF for those subjects not completing the trial. The sponsor's analysis shows that the PGE scores

across groups indicated that the Oxy/Ibup 5/400 combination showed significantly higher scores when compared to all other treatment groups ($p < 0.01$ for all comparisons).

Proportion of Patients Reporting Pain Half-Gone (PGH) is calculated at each time point. The sponsor notes that both combination products show approximately 64% of subjects reporting PHG by .75 hours post-dose. This is compared to 43%, 15%, and 18% respectively in the ibuprofen 400 mg, oxycodone 5 mg, and placebo groups respectively. This difference is shown in the early phase of treatment. The sponsor notes that this difference is sustained from 0.5 through 2 hours post-dose.

6.1.1.5.4 Summary Discussion of Efficacy Findings for OXY-MD-005:

6.1.1.5.4.1 Primary Outcome Variables:

The $SPID_6$ variable result demonstrates a significant difference from Ibuprofen (and all other comparisons) without normalization. However, the $TOTPAR_6$ variable relies upon a normalization procedure applied to the Oxy/Ibuprofen data, in order to achieve statistical significance when compared to Ibuprofen-alone. Examination of the time course of the Mean PR scores illustrates the large amount of overlap (figure 6.1.1.5.2) for Oxy/Ibup and Ibuprofen. Since the TOTPAR scores are derived from this, it suggests that there may not be a significant difference between the Combination product and Ibuprofen.

In addition to the significant overlap in PR scores, it must also be noted that the normalization procedure was not planned procedure in the protocol defined statistical analysis plan (NDA 21-378, Vol. 52, pg. 17-20). Thus, the normalization and subsequent ANOVA of the transformed $TOTPAR_6$ data can be considered a "post hoc" analysis. Thus efficacy would have to be based upon the raw $TOTPAR_6$ comparisons which did not demonstrate a convincing difference, from Ibuprofen-alone treatment at the 5% ($\alpha = 0.05$) level of significance. The significance finding of the $SPID_6$ outcome variable suggests that there is some degree of greater pain intensity difference of the combination product, over Ibuprofen treatment. In summary, the disagreement in the significance of the two primary variables makes the claim of clear superior efficacy over Ibuprofen difficult to support.

6.1.1.5.4.2 Secondary Outcome Variables:

In contrast, review of the efficacy results does demonstrate highly statistically significant differences (SSDs) between the Combination product and Ibuprofen, for some of the secondary outcome variables. The $TOTPAR_3$ and $SPID_3$ metrics appear to clearly demonstrate significant differences, when compared to Ibuprofen.

The median **Time to Onset of PR (TOPR)** does appear to show a statistically significant difference between treatments. Specifically these are 21.4 min (Oxy/Ibup) and 29.7 min (Ibup), respectively. The **Time to Re-medication (TTR)** could not be estimated for either the Combination product or Ibuprofen. This suggests that there may not be a distinguishable clinical difference between their respective 6-hour pain profiles, at least enough to warrant subject re-medication. In discussion with our Biostatistician, the TTR may not be the most adequate measure for duration of pain relief. Per Dr. Price, a more robust metric would be the difference between the TOPR and the TTR time periods. This would measure the duration of pain relief from the onset to the time of re-medication.

The other secondary metrics including the time varying **PR**, **PID**, **PRID** scores showed a SSD when compared to ibuprofen alone, during the early period after dosing (up to approximately 3 hours). The **Peak PR, Peak PID**, and **Peak/Maximum PRID** Scores showed statistically significant differences compared to ibuprofen, during the early period post-dosing. The **PGE** score was SSD for the 5/400 combination, compared to ibuprofen. The **Pain Half-Gone** metric showed a separation between the combination products and ibuprofen alone from 0.75 hours to approximately 3 hours. Overall, the majority of secondary outcome measures show a trend towards SSD when compared to ibuprofen, up to approximately 3 hours post-dosing.

In conclusion, while the Oxy/Ibup formulation achieves a SSD from Placebo and Oxycodone alone, it demonstrates a questionable difference when compared to Ibuprofen. Specifically the OXY-MD-05 primary variable $TOTPAR_6$ for Oxy/Ibup 5/400 mg shows a questionably significant indication of efficacy (if the "normalization procedure" is not used). In contrast, SPID6 and the secondary outcome variables appear to show generally supportive signals regarding efficacy, especially in the early time period post-dosing up to 3 hours.

6.1.2 Study OXY-MD-06-00:

A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCL 5mg/Ibuprofen 400 mg and Oxycodone HCL 5 mg/Ibuprofen 400 mg compared to Ibuprofen 400 mg Alone, Oxycodone HCL 10 mg Alone and Oxycodone HCL 5mg Alone in Patients with Moderate to Severe Pain Following Dental Surgery.

6.1.2.1 Findings vs. Labeling Claims:

No review of the Package Insert and Proposed Labeling was performed because the Sponsor failed to show convincing evidence of efficacy of the proposed product.

6.1.2.2 Study Plan:

6.1.2.3 Population, Design, and Objectives

The protocol-specified objective of the study was:

> "To evaluate the analgesic efficacy and safety of a single dose of a combination tablet of oxycodone HCL/ibuprofen 5/400 mg or oxycodone HCL/ibuprofen 10/400 mg relative to ibuprofen 400 mg alone, oxycodone HCL 5 mg alone, oxycodone HCL 10 mg alone, and placebo using the third-molar-extraction pain model."

The protocol was designed as a multi-site, double-blind, double-dummy, randomized, parallel-group, single-dose, placebo and active-controlled design. Subjects were to have undergone surgical removal of at least two ipsilateral, bony impacted third molars. Patients meeting these criteria for the study were to be enrolled based upon their post-surgery pain intensity measured by the baseline Pain Intensity (PI) scale and Visual Analog Scale (VAS). The PI is a 4 level ordinal scale that allows subjects to rate their pain as integers between "0" and "4." The VAS is a continuous visual scale 100 mm total length that corresponds to "no" pain to "severe" at 100 mm. Subjects mark their current perceived pain level on this scale, which is measured proportionally. Potential subjects had to rate their BPI as moderate - severe and their VAS as greater than 50. They were then to have been randomized into one of 5 treatment groups:

(1) Oxycodone HCL /ibuprofen 5/400 mg
(2) Oxycodone HCL/ibuprofen 10/400 mg
(3) Ibuprofen 400 mg
(4) Oxycodone HCL 5 mg
(5) Oxycodone HCL 10 mg
(6) Placebo.

Potential subjects were to have had the purpose and procedure of the trial explained to them. Subjects that agreed to participate were supposed to complete an informed consent, undergo a physical examination, a review of their medical history, and to remain NPO for 8 hours prior to their planned surgery. Female patients of childbearing potential

were to perform a urine pregnancy screening test on the day of planned surgery. All subjects meeting the inclusion and exclusion criteria were to undergo further instruction on how to complete their diary. A listing of these criteria follows this section.

Potential subjects were to be chosen from patients undergoing third-molar extraction. The sponsor states that this model had well established utility in analgesic evaluation due to:

- The surgical procedure caused uniform pain production.
- There was low inter-subject variability due to etiology of the pain.
- The model demonstrated good assay sensitivity for discrimination between active drugs.

All potential subjects had to meet the following inclusion criteria:

- Ability to provide written informed consent (parental approval for <18 years of age).
- All patients must be healthy male or female outpatients at least 12 years of age.
- All childbearing potential females must have negative urine pregnancy tests on day of surgery.
- Patients must be alert and able to communicate and able to complete the study as instructed.
- All patients must abstain from all ETOH, caffeine, and smoking for 8 hours prior to surgery to the end of the post-dosing period.
- All patients must be scheduled to have at least two ipsilateral, bony impacted 3rd molars removed. No additional surgery must be performed.
- All patients must be willing remain on-site during the post dosing period (6 hours total).

The exclusion criteria were:

- Pregnant or lactating females.
- Patients who had taken the following medications:
  - Short-Acting analgesics (ASA, acetaminophen, etc…) within 6 hours prior to surgery
  - Ibuprofen within 10 hours of surgery
  - Long-Acting NSAIDs or any opiate analgesic within 48 hours prior to surgery
  - Steroids within 72 hours prior to surgery

- Use of any psychoactive drug (e.g. antidepressants, phenothiazines, hypnotics, anti-anxiety agents) or opioid antagonists within 72 hours prior to surgery.

- Use of surgical anesthesia and/or antiemetics not in the approved protocol.

- Patients with significant co-existing medical condition (e.g. GI, hematologic, neurologic, renal, cardiovascular disorders, etc...)

- Patients receiving investigational drug or in a clinical trial within 30 days prior to this study.

- Patients who were employees, relatives of employees or prior participants in this study.

- Patients with known allergies or reactions to opioid or NSAID medications, including the two active study compounds.

- Current drug or alcohol abuse.

- Concurrent medication use that could affect quantifying analgesia.

- Medical conditions compromising ability to swallow, absorb, metabolize, or excrete the study medication.
- Significant pre-existing pain condition unrelated to teeth.

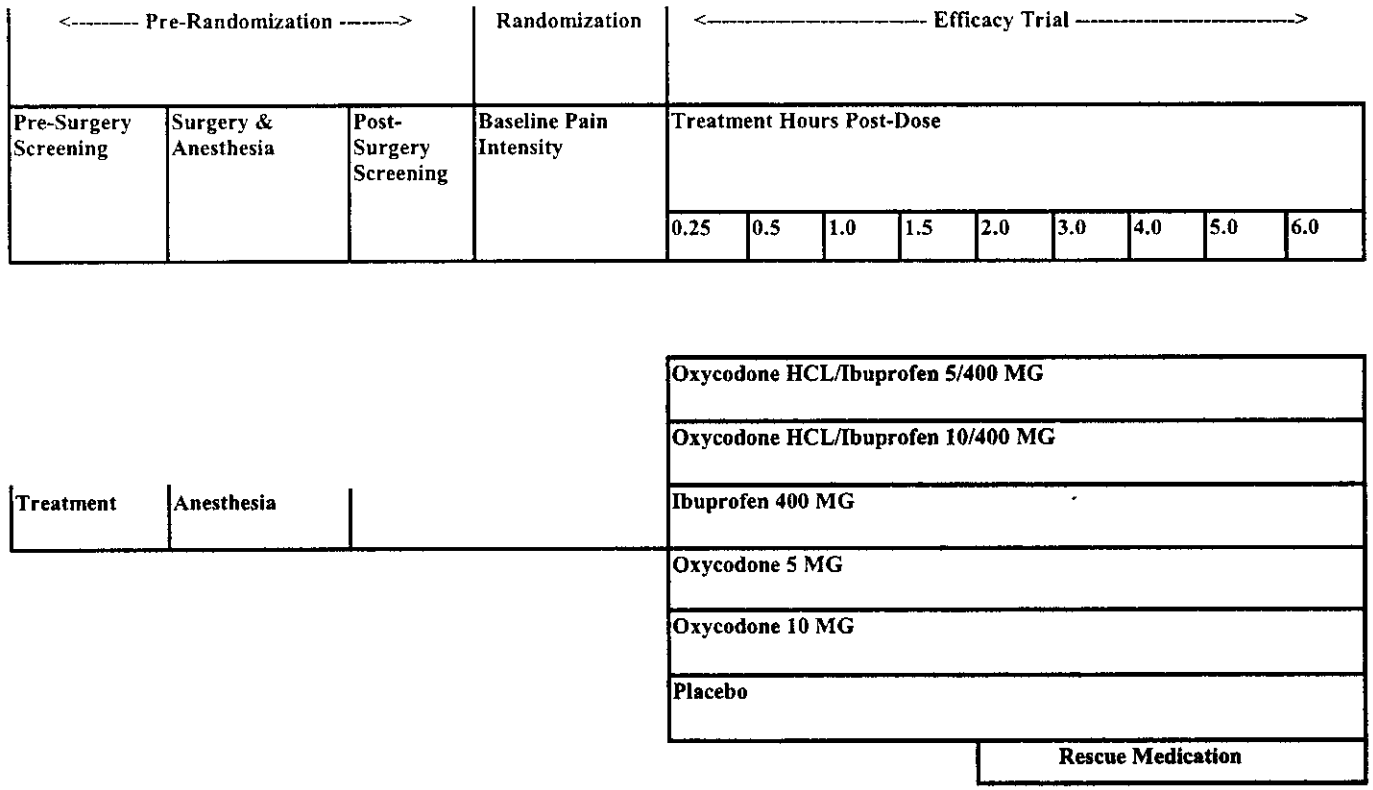
Surgery was to be performed with approved anesthesia (Note that the Sponsor has referenced a table of approved anesthetics that was to have been provided. A request has been submitted to Forest Labs on 8/15/02 for this information. On 9/3/02 the Sponsor subsequently provided a listing of the approved anesthesia that was identical to that used in Oxy-MD-05 Table 6.1.1.3.1). The Sponsor has provided an analysis of the distribution of anesthetics/medications used during surgery for the different study populations. Examination of Table 2.6 (Vol. 58, pg. 106) shows a similar distribution of treatment frequencies from highest to lowest, across groups (note that subjects could have > 1 medication): Lidocaine (99.9%), Fentanyl (96.0%), Brevital (92.8%), NO2 (87.8%), Midazolam (71.7%), and Atropine (53.5%). The only obvious significant difference in usage of these surgical medications was Mepivacaine and Tigan, which was used in 4.7% and 0.6% of the Oxy/Ibup 5/400 mg group and 9.4-14.0%, 2.3-5.3% in the other groups. The Oxy/Ibup 10/400 mg group had a more frequent use of these two medications, similar to the pattern with Oxycodone, Ibuprofen, and Placebo. These differences were not seen in the more commonly listed medications and were not felt to significantly bias the results.

Post-Surgery enrollees were to be placed in an observation area by study staff, for up to 5 hours. Patients were to notify study personnel when their pain reached the threshold for randomization into the study, using VAS and Brief Pain Intensity (PI). The threshold

criteria for randomization was to consist of a Baseline PI score of "moderate" to "severe" pain and VAS score ≥ 50 mm, within the 5 hour post-op period. If potential subjects did not develop sufficient pain levels as defined above, within 5 hours, they were to be classified as ineligible for study continuation.

Subjects that met the entry pain criteria were to be randomly assigned to their respective treatment groups and then study medication could be provided. All patients were to remain at the study location for 6 hours post dosing. Subjects were to be encouraged to remain awake during the 6 hour post-dose period. If a patient's pain were to become severe they could request "rescue" medication, in addition to their dosing of study medication. Subjects were to be encouraged to wait at least 2 hours post-dosing before requesting "rescue" medication. The following figures were adapted from the Oxycodone/Ibuprofen Comparative Efficacy Study vol. 58, and illustrate the proposed study outline and schedule of evaluations.
Note that study participants could have been discontinued from the study at any time. This could have been due to occurrence of an adverse event (AE), poor therapeutic response, major protocol violations, withdrawal of consent, or administrative reasons.

Figure 6.1.2.3.1 Oxycodone/Ibuprofen Comparative Efficacy Study Schematic



Source: Figure 1. Study Schematic OXY-MD-06, NDA, Vol. 58.

Table 6.1.2.3.2 Schedule of Evaluation

	PRE-SURGERY	POST-SURGERY DOSING										
		Surgery	PRE-DOSING	Dosing	POST-DOSING (HOURS)							
	SCREEN-ING		Baseline		0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Randomization			X											
Medical/Medication History	X													
Concomitant Meds	X		X		At Any Time									X
Physical Exam, VSS	X		X							X				X
Urine Preg. Test			X											
Patient Diary			X		X	X	X	X	X	X	X	X	X	X
Global Rating														X
Adverse Events			X		At Any Time									X
Patient Diary Review														X

Source: Panel 3. Study Schedule OXY-MD-06, NDA, Vol. 58.

6.1.2.3.1 Treatment Summary

Patients were to be randomized to one of six groups, in a 3:3:3:1:1:1 ratio (168:168:168:56:56:56 subjects respectively) in order to receive Study Combination Drugs, Ibuprofen, Oxycodone, or placebo, respectively. The total study population target was to be 674 analyzable subjects. The "double dummy" method was to be used to maintain a study blind by administering treatment in groups of one and two tablets. Each site was to have administered the study drug to each enrolled patient. These were to be in identical blister packs that should not have indicated their contents. The following table illustrates the proposed drug information and dosing. Each blister pack was to be labeled with the protocol number, randomization number, space for patient initials, warning information, and instructions. Patients were to be assigned the randomization number on the study drug label. These sequential numbers were to be matched with randomization codes generated and kept in a secure area at Forest Laboratories.

Table 6.1.2.3.1.1 Study Drug and Dosing Regimen

Group	Treatment	Tablet/Capsule Strength	Lot Number	Dispensed As:		
1	Oxycodone HCL/ Ibuprofen	5 mg / 400 mg	99229K	1 x 5 mg Oxycodone + 400 mg Ibuprofen tablet	1 x Placebo Capsule	1 x Placebo Capsule
2	Oxycodone HCL/ Ibuprofen	10 mg / 400 mg	99230K	1 x 10 mg Oxycodone + 400 mg Ibuprofen tablet	1 x Placebo Capsule	1 x Placebo Capsule
3	Ibuprofen	200 mg	119959	1 x Placebo tablet	1 x 200 mg Ibuprofen Capsule	1 x 200 mg Ibuprofen Capsule
4	Oxycodone HCL	5 mg	119960	1 x 5 mg Oxycodone tablet	1 x Placebo Capsule	1 x Placebo Capsule
5	Oxycodone HCL	10 mg	119960	1 x 5 mg Oxycodone tablet	1 x 5 mg Oxycodone tablet	1 x Placebo Capsule
6	Placebo X or Y	0 mg	99247K 119958	1 x Placebo tablet	1 x Placebo Capsule	1 x Placebo Capsule
	Placebo Y	0 mg	119958	1 x Placebo tablet	1 x Placebo Capsule	1 x Placebo Capsule

Source: 6.2.2 Panel 1 and Panel 2, Vol. 58.
Oxycodone 10 mg dose consists of two 5 mg dose capsules

Medications were to be administered with 4 ounces of water. Each combination of one tablet/two capsules was to be identical in appearance for all groups of patients. All medications were to be consumed.

The associated patient randomization number and assigned treatment was to be generated and maintained by the Forest Laboratories Department of Biostatistics. Bottles of identical "double-blind" medication were to be labeled with a two-part, three-panel label. The first part was to remain on the bottle at the time of administration. The other 2 panels were to be placed in the patent's CRF. In the event of emergency the 3rd panel could have been broken to reveal the patient's treatment.

Any patients concurrently taking medication that could have confounded the analgesia analysis were to be excluded from the study at screening. For study patients, the following concomitant medications and treatments were to have been prohibited throughout the entire study period.

- NSAIDs, salicylates, propoxyphene, acetaminophen, steroids, codeine, hydroxyzine, pentazacine or other medications that could confound quantifying analgesia EXCEPT as rescue medication for those requiring it
- Mood altering drugs within 72 hours prior to surgery
- Alcohol, Caffeine, and Smoking

Rescue medication was to be available upon patient request in the post-dosing period, as stated earlier. All patients were to be encouraged to wait at least 2 hours after the study medication, before requesting "rescue." The type of rescue medication was to a "standard analgesic."

6.1.2.3.2 Assessments

Several efficacy measures were to be recorded by participating patients, during this study:

- Pain Intensity (PI) at baseline and at scheduled intervals.
- Visual Analog Scale (VAS)
- Pain Intensity (PI), Pain Relief (PR)
- Pain Half Gone
- Patient's Global Assessment.

The PI and VAS scale were to be entered into their respective patient diary just before dosing with the study medication. The other self-rated scales were to be entered into diary cards at each sampling time. All time measures were to be relative to the dosing time, recorded by the study coordinator. The scales (excluding VAS) are illustrated below:

Table 6.1.2.3.2.1 Efficacy Scale Descriptions

Baseline PI	My starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
PI	My pain at this time is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
PR	My relief from starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"
Pain Half Gone	My pain at this time is half gone: 0 = "NO" 1 = "YES"
Patient's Global Assessment	My starting pain is: 0 = "NONE" 1 = "SLIGHT" 2 = "MODERATE" 3 = "SEVERE"

Note that potential subjects were supposed to have a Baseline PI rated moderate to severe and have a VAS Baseline Pain score of ≥ 50 mm within 5 hours postoperatively.

Effectiveness time measures were to be determined relative to the dosing time. Patients were to be given two stopwatches and instructions for stopping the individual watches as defined in below:

Table 6.1.2.3.2.2 Stopwatch Instructions

Measure	Definition	Patient Action
Onset of First Perceptible Pain Relief	The time when first pain relieving effect of medication noticed	1. Stop 1st Stopwatch 2. Record Time Interval 3. Reset Stopwatch to 0
Onset of Meaningful Pain Relief	he time when patient felt pain relief was meaningful	1. Stop 2nd Stopwatch 2. Record Time Interval 3. Reset Stopwatch to 0

Source: NDA 21-378, OXY-MD-06

6.1.2.3.3 Analysis Plan

Three analysis populations were defined in the protocol. The randomized population was specified to consist of all patients randomized to the study. The safety population was to consist of all treated patients within the study. The intent-to-treat (ITT) population was to consist of all randomized patients taking the study drug and having ≥ 1 post-baseline efficacy measure.

The protocol specified primary efficacy endpoints for statistical analysis was to consist of two measures calculated from self-rated patient pain scales:

1. Sum of Pain Intensity Difference through 6 Hours ($SPID_6$).

- Define PID = difference between pain intensity at a given time and the baseline pain intensity (e.g. PID(t) = PI(t) – Baseline PI).
- SPID = the AUC of PID vs. time from 0 – 6 hours.

2. Total Pain Relief through 6 hours (**$TOTPAR_6$**)
   - Defined as the area under the curve (AUC) of pain relief (PR) vs. time from 0 – 6 hours.

The primary analyses of efficacy were to be based on the ITT population, with the last observation carried forward (LOCF) to extrapolate any missing PI or PR values. Primary analyses were to be the comparison of the effects of the combination product treatment to individual analgesic components alone, for $SPID_6$ and $TOTPAR_6$. Statistical testing was specified to use two-tailed analysis with 5 % and 10 % significance levels respectively, for the main and interaction term effects. The comparisons of the two primary efficacy variables across treatment groups were to be performed using an ANOVA model with treatment and study site as effects. Comparability among treatment groups was to be tested using ANOVA with treatment as the continuous variable factor. The Cochran-Mantel-Haenszel (CMH) test was to be used for testing comparability among treatment groups by categorical variables.

The protocol specified sample sizes calculation was to be based upon an expected difference in $SPID_6$ values for the Oxycodone HCL/ibuprofen 5/400 mg and ibuprofen alone group. This expected difference was determined from a previous single-site study: OXY-MD3-96-01. The sample size assumptions that were to be used are stated as follows:

- $SPID_6$ difference as defined above = 1.35 (based upon OXY-MD3-96-01 results)
- Each $SPID_6$ group standard deviation = 4.2
- Two tailed t-test at 0.05 significance level
- 83 % power needed to detect difference

The resulting sample size was projected to be 168 for these two groups. It was assumed that a similar sample size would suffice for the oxycodone/ibuprofen 10/400 mg group. There was a large expected difference in $SPID_6$ groups for oxycodone alone and ibuprofen alone, and as a result only 56 patients per group were to be enrolled in those categories. This was to result in a total of 672 patients in a 3:3:3:1:1:1 (168:168:168:56:56:56) proportion, as listed earlier in this review. Similar calculations for TOTPAR resulted in smaller required sample sizes, however the larger number quoted here was to be used for both groups.

Several secondary efficacy parameters were also specified in the protocol:

- TOTPAR 3 and SPID 3 – Defined and analyzed similarly to the 6 hour primary parameters.

- PR – analyzed at each time point using ANOVA with treatment and study site as effects.

- PID - analyzed at each time point using ANOVA with treatment, study site, and BPI as effects. Pair-wise comparisons performed using Fisher's protected LSD procedure.

- PRID = PR + PID. Combined pain relief analyzed similar to PID.

- Peak PR and Patient's Global Rating at 6 Hours (LOCF). Analyzed using ANOVA.

- Proportion of Patients Reporting Pain Half Gone. Data analyzed at each time point using the CMH test stratified by study site.

- Onset of PR – Defined as time from medication dosing to time 1st stopwatch stopped, for patients who also stopped the second stopwatch during the observation period. Patients who did not stop the second watch had onset time defined as a censored value at the last PI or PR measurement. This endpoint was analyzed using the log rank test for censored data. Median time to PR was calculated using the Kaplan-Meier product limit estimator.

- Time to Re-medication – Defined as elapsed time from dosing to time rescue medication administered. This was analyzed similar to Onset of PR.

No interim analyses were to be performed. All statistical computations were to be performed using SAS version 6.12.

6.1.2.3.4 Protocol Amendments and Changes in the Planned Analyses

There were no amendments to the protocol or changes to the Statistical Analysis Plan.

6.1.2.4 Study Conduct

The sponsor notes that this study was performed at 2 sites in the US. Each study center Principal Investigator was responsible for ensuring that the study was conducted according to the Protocol, Investigator Agreements, the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

In the Study Report (Section 6.7.9), the Sponsor lists the following measures used to assure data quality:

- Pre-trial meetings with Investigators to familiarize them with CRFs, diary cards, protocol
- Pre-trial review meetings with each individual Investigator to review study procedures
- CRFs customized for data collection in this study
- CRFs 100% reviewed against source documents by clinical monitors
- CRF data double-entered into validated database system

- Answering all data clarifications or queries, with changes made to the database, by Forest Labs to update new or changed information
- Database was locked and treatment codes un-blinded after all issues resolved.

6.1.2.4.1 Patient Disposition

The study report does not indicate how many patients were screened for admission to the study and were not accepted. In addition, the sponsor does not state how many patients were screened and never achieved the pain levels necessary to be enrolled, during the 6 hour post surgery time limit. A request for this information was faxed to the Sponsor on 7/23/02 and the results were received by the Agency on 8/9/02. The Sponsor states that there were 52 Screening Failures in Oxy-MD-06. There were 5 patients screened that were never randomized due to insufficient pain levels.

The sponsor indicates that 682 patients were randomized into the six study groups. One (1) patient was excluded from the ITT group and the efficacy analysis, due to no post-dose efficacy evaluation. Therefore the ITT efficacy total was 681 subjects.

Table 6.1.2.4.1.1 Patient Disposition Summary:

Oxycodone HCL / Ibuprofen 5/400 mg	Oxycodone HCL / Ibuprofen 10/400 mg	Ibuprofen 400 mg	Oxycodone 5 mg	Oxycodone 10 mg	Placebo
170	169	171	57	57	57

Source: NDA 21,378, Vol. 58, Oxy-MD-06, pg. 35.

Panel 6 of the study report summarizes patient dispositions, completions, discontinuation, and major reasons for dropping out of the study. 519 (76.1%) patients completed the study. Both of the combination groups had approximately 12 % discontinuation with the ibuprofen treatment group showing a 13.5 % discontinuation due to insufficient therapeutic response. The Oxycodone alone groups experienced approximately 44 – 49 % discontinuation while the Placebo group had a 64.9 % withdrawal due to lack of therapeutic response.

Six (6) patients withdrew from the study due to AEs: 1 each in the oxycodone/ibuprofen 5/400 mg and placebo groups, two each in the ibuprofen and oxycodone 10 mg alone groups. Review of the After-Text listing1.2, of AEs causing discontinuation reveals that nausea, emesis/vomiting were the listed causes across treatment categories. The following table summarizes the findings of this section.

Table 6.1.1.4.1.2 Patient Completion and Discontinuation

	Oxy/Ibu 5/400 mg N=171	Oxy/Ibu 10/400 mg N=169	Ibu 400 mg N=171	Oxycodone 10 mg N=57	Oxycodone 5 mg N=57	Placebo N=57	Total N=682
Completed	149 (87.1%)	147 (87.0%)	146 (85.4%)	29 (50.9%)	30 (52.6%)	18 (31.6%)	519 (76.1%)
Discontinued	22 (12.9%)	22 (13.0%)	25 (14.6%)	28 (49.1%)	27 (47.4%)	39 (68.4%)	163 (23.9%)
Adverse Events (AEs)	1 (0.6%)	0	2 (1.2%)	0	2 (3.5%)	1 (1.8%)	6 (0.9%)
Poor Response	21 (12.3%)	21 (12.4%)	23 (13.5%)	28 (49.1%)	25 (43.9%)	37 (64.9%)	155 (22.7%)
Withdraw Consent	0	0	0	0	0	1 (1.8%)	1 (0.1%)
Other	0	1 (0.6%)	0	0	0	0	1 (0.1%)

Source: Panel 6, NDA 21,378, Vol. 58, Oxy-MD-06, pg. 36.

6.1.2.4.2 Protocol Deviations and Violations:

The sponsor notes that there were six (6) protocol deviations, from the inclusion/exclusion criteria.

- Inclusion Criteria Violations:
  1) Non-Ipsilateral Molar extraction. This occurred in four (4) subjects (02374, 02765, 02370, and 02254). Note that a request was sent to the sponsor to obtain the correct PIDs. The Sponsor replied on 8/9/02 with the following corrections to the PIDs: 020374, 020765, 020370, and 020254. Examination of the provided summaries shows that 2 subjects (020765 & 020370) were both in the Oxy/Ibup 5/400 mg treatment group, while the other two subjects were in the Placebo and Ibuprofen groups. The review concern is that if there is a difference in pain thresholds or response to analgesia, then a disproportion of these subjects in one treatment group could possibly bias the efficacy conclusions. A request has been forwarded to the sponsor (8/15/02) to address whether the "non-ipsilateral" molar surgeries are similar enough in pain intensity and analgesia response to add the two subjects to the Oxy/Ibup 5/400 mg group. The Sponsor replied on 9/3/02 stating that 3 subjects (020374-PBO, 020370-Oxy/Ibup 5/400 mg, and 020254-Ibu 400 mg) had all 4 wisdom teeth extracted but the bony impacted ones (two in each case) were contralateral rather than ipsilaterally placed. The fourth subject (020765-Oxy/Ibup 5/400 mg) met all study criteria but had an additional dental procedure performed. The distribution of these subjects across treatments does not suggest an obvious bias that might affect the outcome of the trial.

2) Protocol-excluded surgical medication in one (1) patient (02369).

3) Unapproved surgery (Tubal ligation) and no urine pregnancy test result in one (1) patient (01976). Note that a request was sent to the sponsor regarding this patient. It appears the patient had a different PID (010976) and did have the required dental surgery but had Tubal Ligation 2 years previously. The protocol violation in this case was that the subject did not have a screening urine pregnancy test, which is unlikely to have materially affected the study by including her.

The sponsor did not exclude the data from these patients from the safety or efficacy analysis because the violations were thought to have no relevant effect on the study outcome.

6.1.2.4.3 Data Sets Analyzed

The Intent-to-Treat population was defined as all randomized patients taking the study medication with ≥ 1 post-baseline efficacy assessment. Efficacy analysis was performed on the ITT group. The last observation carried forward (LOCF) was used to extrapolate missing data. The Randomized population consisted of all patients randomized to the study. One patient from the Randomized population was excluded from the ITT population.

The safety population consisted of all patients treated with study medication. The safety analysis was performed on this population.

6.1.2.4.4 Demographics/Group Comparability

Baseline characteristics and other demographic variables are summarized in the sponsor's table, which is reproduced here:

Table 6.1.2.4.4.1 Patient Demographics and Baseline Characteristics

	Oxy/Ibu 5/400 mg N=171	Oxy/Ibu 10/400 mg N=169	Ibuprofen 400 mg N=171	Oxycodone 5 mg N=57	Oxycodone 10 mg N=57	Placebo N=57	Total N=682
Age (yrs):							
Mean (SD)	18.9 (4.15)	18.4 (2.71)	18.4 (3.36)	18.1 (2.41)	18.7 (2.74)	18.2 (2.47)	18.5 (3.26)
Sex: N (%)							
Male	85 (49.7)	89 (52.7)	93 (54.4)	24 (42.1)	31 (54.4)	27 (47.4)	349 (51.2)
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)

	Oxy/Ibu 5/400 mg N=171	Oxy/Ibu 10/400 mg N=169	Ibuprofen 400 mg N=171	Oxycodone 5 mg N=57	Oxycodone 10 mg N=57	Placebo N=57	Total N=682
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.}: N (Std. Dev)							
Mean (SD)	146.8 (29.95)	151.2 (33.23)	150.4 (29.64)	148.3 (36.62)	149.5 (33.28)	151.4 (32.59)	149.5 (31.74)
Height {in}: N (Std. Dev)							
Mean (SD)	67.6 (3.82)	68.3 (4.07)	67.9 (3.91)	67.2 (3.76)	68.0 (4.26)	67.9 (3.60)	67.9 (3.92)
Baseline Pain Intensity: N (Std. Dev)							
Moderate	97 (56.7)	92 (54.4)	99 (57.9)	36 (63.2)	34 (59.6)	36 (63.2)	394 (57.8)
Severe	74 (43.3)	77 (45.6)	72 (42.1)	21 (36.8)	23 (40.4)	21 (36.8)	288 (42.2)
Baseline Pain Visual Analog Scale (VAS): N (Std. Dev)							
Mean (SD)	74.9 (10.54)	75.8 (10.05)	74.4 (10.93)	74.3 (11.08)	74.2 (10.86)	73.6 (12.26)	74.8 (10.73)

Source: NDA 21,378, Panel 7 Vol. 58, Oxy-MD-06, pg. 39.

6.1.2.4.5 Treatment Compliance:

All participating subjects in this single-dose study received medication directly from the Study coordinator. No other compliance measurements were necessary.

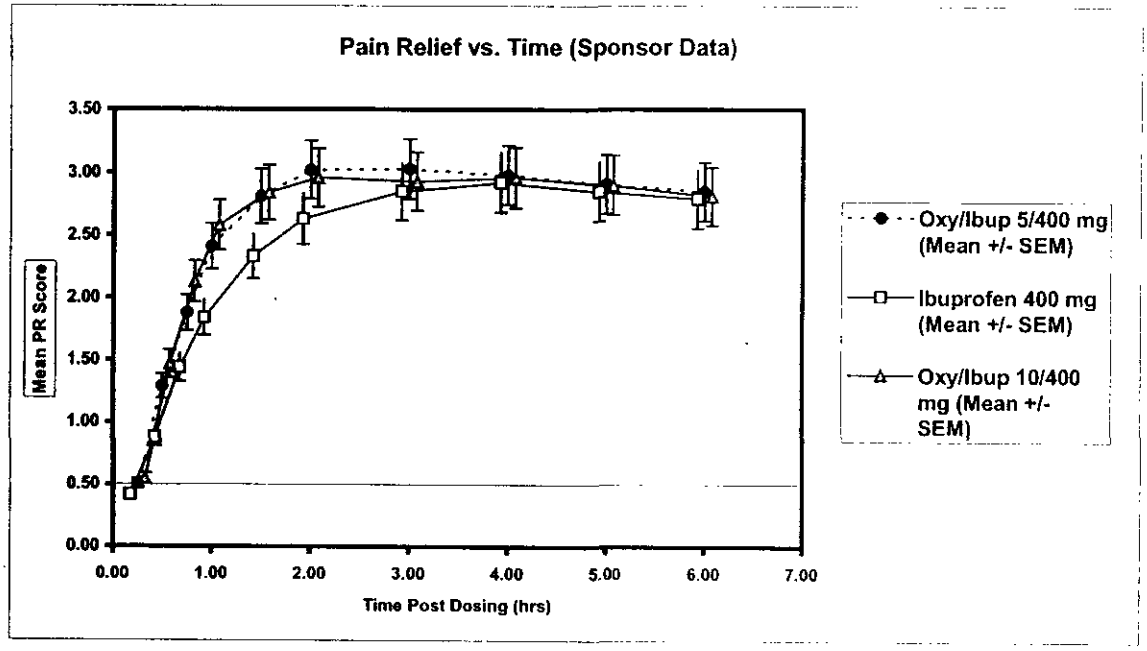
6.1.2.4.6 Unplanned Analyses:

There were no interim analyses.

6.1.2.5 Sponsor's Efficacy Results for OXY-MD-06:

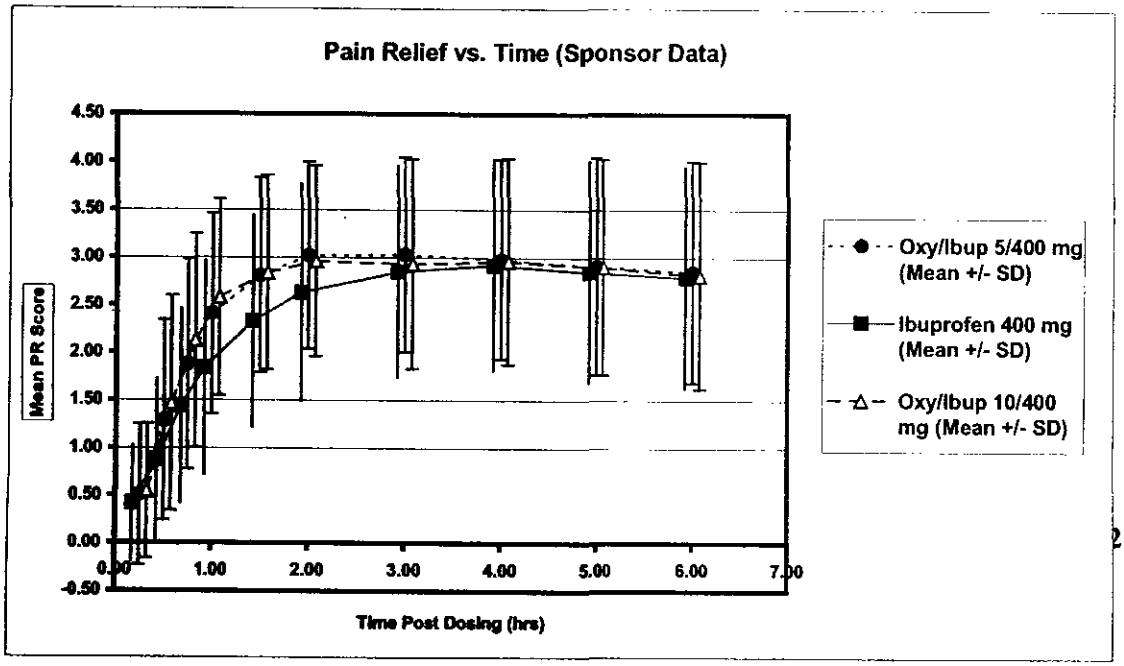
The primary efficacy variables were calculated metrics for "total pain relief at 6 hours" and the "sum of pain intensity differences at 6 hours:" $TOTPAR_6$ and $SPID_6$ respectively. Both are derived from the Area Under the Curve (AUC) calculations for the Mean Pain Relief (PR) and Pain Intensity Difference (PID), as a function of time. The Mean PR values over the time of the trial are illustrated here for visual inspection in Figure 6.1.2.5.1.1 and 2.

Figure 6.1.2.5.1 Oxy-MD-06 Mean PR Scores with Standard Errors



These graphs are Excel plots of PR efficacy data from the sponsor's analysis results, in Table 5.3, Vol. 58, pg. 113. Note that the time curves show a great deal of overlap when the actual standard deviation is included.

Figure 6.1.2.5.2 Oxy-MD-06 Mean PR Scores with Standard Deviations



Note that $TOTPAR_6$ is derived from the LS Mean data illustrated in these two curves. Given the large overlap in Oxy/Ibup 10/400 mg, Oxy/Ibup 5/400 mg and Ibuprofen standard deviations, it suggests that there is little difference in pain relief over the given study time.

The difference in Between-Treatment-Group Least Squares (LS) Means for $TOTPAR_6$ was analyzed using a "pair-wise comparison" test. The selected results for $TOTPAR_6$ are summarized below:

Table 6.1.2.5.1 Selected $TOTPAR_6$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Oxy/Ibup 5/400 mg	170	15.76	0.42	14.93, 16.59	< 0.001
Oxy/Ibup 10/400 mg	168	15.68	0.43	14.85, 16.52	
Ibuprofen 400 mg	169	14.46	0.43	13.63, 15.30	
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	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**95% CI for LS Mean Diff.**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		1.3	0.60	0.13, 2.47	0.030
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		7.14	0.84	5.49, 8.79	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		1.22	0.60	0.05, 2.40	0.0412
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		6.77	0.85	5.11, 8.44	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		0.07	0.60	-1.10, 1.25	0.9004
Versus Placebo					
Oxy/Ibup 5/400 mg		9.49	0.85	7.83, 11.15	< 0.001
Oxy/Ibup 10/400 mg		9.42	0.85	7.75, 11.08	< 0.001
Ibup 400 mg		8.19	0.85	6.53, 9.85	< 0.001

Source: NDA 21-378, OXY-MD-06, Panel 8, Vol. 58, pg. 45.

The most relevant pair-wise comparisons are between the combination study drugs (Oxy 5 and 10 mg/Ibuprofen) and the individual component Ibuprofen. Both of the combination products showed a statistically significant difference (SSD) in mean $TOTPAR_6$ (at $\alpha = 0.05$ level) when compared to Ibuprofen alone.

The second primary efficacy variable is $SPID_6$ and it was analyzed similarly to $TOTPAR_6$, described above. Again, both combination product mean $SPID_6$ values showed a SSD when compared to Ibuprofen alone. Both Oxycodone/Ibuprofen combination product mean SPID scores show no SSD.

Table 6.1.2.5.2 $SPID_6$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Oxy/Ibup 5/400 mg	170	8.28	0.31	7.68, 8.89	< 0.001
Oxy/Ibup 10/400 mg	168	8.27	0.31	7.66, 8.88	
Ibuprofen 400 mg	169	7.39	0.31	6.78, 8.00	
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	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**95% CI for LS Mean Diff.**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		0.89	0.43	0.05, 1.74	0.0389
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		4.98	0.61	3.79, 6.18	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		0.88	0.43	0.03, 1.73	0.0430
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		4.90	0.61	3.70, 6.11	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		0.02	0.43	-0.83, 0.87	0.9720
Versus Placebo					
Oxy/Ibup 5/400 mg		6.54	0.61	5.34, 7.75	< 0.001
Oxy/Ibup 10/400 mg		6.53	0.61	5.32, 7.73	< 0.001
Ibup 400 mg		5.65	0.61	4.44, 6.85	< 0.001

Source: NDA 21-378, OXY-MD-06, Panel 9, Vol. 58, pg. 47.

6.1.2.5.1 Secondary Efficacy Variables:

Various secondary variables were analyzed in this study. Four of the variables appear to have the greatest relevance to the sponsor's labeling claims: $TOTPAR_3$, $SPID_3$, Time to Onset of PR (TOPR), and Time to Re-medication (TTR). $TOTPAR_3$ and $SPID_3$ are the three-hour versions of the 2 primary outcome variables: $TOTPAR_6$ and $SPID_6$.

$TOTPAR_3$ LS means are summarized in the following table. ANOVA analysis of the results demonstrates an overall statistically significant difference (SSD) between groups. In addition, pair-wise comparisons using "*t*-tests"demonstrate SSD between combination products and Ibuprofen alone. Note that the mean TOTPAR score for Oxy/Ibup 10/400 mg and Oxy/Ibup 5/400 mg show no SSD.

Table 6.1.2.5.3 $TOTPAR_3$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Oxy/Ibup 5/400 mg	170	6.98	0.19	6.61, 7.35	< 0.001
Oxy/Ibup 10/400 mg	168	7.05	0.19	6.67, 7.42	
Ibuprofen 400 mg	169	5.92	0.19	5.55, 6.29	
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	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**95% CI for LS Mean Diff.**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		1.07	0.27	0.55, 1.59	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		3.31	0.37	2.58, 4.05	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		1.13	0.27	0.61, 1.65	< 0.001
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		3.22	0.38	2.47, 3.96	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		-0.06	0.27	-0.58, 0.46	0.815
Versus Placebo					
Oxy/Ibup 5/400 mg		4.31	0.38	3.58, 5.05	< 0.001
Oxy/Ibup 10/400 mg		4.38	0.38	3.64, 5.12	< 0.001
Ibup 400 mg		3.25	0.38	2.51, 3.99	< 0.001

Source: NDA 21-378, OXY-MD-06, Panel 10, Vol. 58, pg. 49.

$SPID_3$ group means are summarized in the following table. Analysis shows that between treatment mean scores were significantly different at three hours, for the treatments of clinical interest. Note that no obvious SSD was found between the combination Oxy/Ibup means.

Table 6.1.2.5.4 $SPID_3$ Results for ITT Population

Treatment Group	N	LS Mean	SE	95% CI	Overall Treatment p-value
Oxy/Ibup 5/400 mg	170	3.57	0.14	3.31, 3.84	< 0.001
Oxy/Ibup 10/400 mg	168	3.66	0.14	3.39, 3.93	
Ibuprofen 400 mg	169	2.92	0.14	2.65, 3.18	
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	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**95% CI for LS Mean Diff.**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		0.66	0.19	0.29, 1.03	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		2.29	0.27	1.77, 2.82	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		0.74	0.19	0.37, 1.12	< 0.001
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		2.23	0.27	1.70, 2.76	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		-0.08	0.19	-0.46, 0.29	0.663
Versus Placebo					
Oxy/Ibup 5/400 mg		2.90	0.27	2.37, 3.43	< 0.001
Oxy/Ibup 10/400 mg		2.99	0.27	2.45, 3.52	< 0.001
Ibup 400 mg		2.24	0.27	1.71, 2.77	< 0.001

Source: NDA 21-378, OXY-MD-06, Panel 11, Vol. 58, pg. 51.

Time to Onset of PR (TOPR) calculates the median time of onset of pain relief. This value is calculated using Kaplan-Meier Survival Curves from the Pain Relief Score over time. Comparisons between different treatment curves are performed using the pair-wise log rank test. The sponsor states that the results show that the Oxy/Ibup 10/400 mg product provided a more rapid onset of pain relief, compared to Ibuprofen alone ($p < 0.050$). The combination treatments shared the "most effective" treatment status. Median values of TOPR could not be determined for the placebo group because < 50 % achieved pain relief. The results are summarized in the following table.

Table 6.1.2.5.5 TOPR Results for ITT Population

Treatment	N	Median TOPR (mins)	95 % CI (mins)
Oxy/Ibup 5/400 mg	170	25.35^{AB}	21.17, 28.80
Oxy/Ibup 10/400 mg	168	22.53^{A}	19.95, 24.97
Ibuprofen	169	28.03^{B}	24.93, 31.07
Oxy 5 mg	57	67.3^{C}	27.08, N/A
Oxy 10 mg	56	63.37^{D}	37.40, N/A
Placebo	56	N/A	134.00, N/A

Source: NDA 21-378, OXY-MD-06, Table 5.6, Vol. 58, pg. 116.
A,B,C,D – Letter A indicates the most effective treatment based on long-rank pairwise testing, B is the second best and so forth. Treatments sharing the same letter do not have SSD at the 5 % level.

While both combination products do appear to demonstrate significance at the 5 % level using pairwise log-rank testing, compared to Ibuprofen alone, the issue of clinical significance becomes important. It is difficult to see a clinical benefit in a treatment that has a difference of 3 – 6 minutes in onset of pain relief, over the most active individual constituent.

Time to Re-medication (TTR) is presumably used as a surrogate metric for "
TTR was also estimated using Kaplan-Meier statistics. The estimated median time to re-medication could not be estimated for any of the active treatment groups because < 50% of the subjects in these groups requested rescue. This prevented estimation of the TTR for these groups.

6.1.2.5.2 Other Secondary Outcome Variables:

Various other secondary outcome measures were also reported, that were specified in the protocol analysis plan. Each result will be discussed in turn in this section.

The **Pain Relief (PR) Scores at Each Timepoint** was compared for the different treatments, using an ANOVA model. The "least-squares mean" value for the treatment group PR is assigned a letter value (A – D) indicating the ranking of most effective to least effective treatment. PR scores with different letters are significantly different from one another, at the $\alpha = 0.05$ (5%) level. The results show some significant difference between the combination products and ibuprofen from 0.5 to 2 hours, after which there is no discernable difference in efficacy. This pattern can also be seen by examining figures 6.1.2.5.1 and 6.1.2.5.2.

The **Pain Intensity Difference (PID) Scores at Each Timepoint** was compared in a similar fashion to the PR scores discussed above. Again there is a statistical difference between the combination products (5/400 and 10/400 mg) ranked as "A or most efficacious" and ibuprofen 400 mg ranked as "B/C or less efficacious" over the time period of 0.5 to 2 hours. Note that after 2 hours there is no difference between ibuprofen PID scores and the combination products.

The **Sum of PR + PID (PRID) Scores at Each Timepoint** was compared similarly to the above secondary outcome variables. The time varying scores show a similar pattern of statistically significant difference in superior rated "mean" PRID scores of the combination products vs. ibuprofen. The time period of significant difference again is seen from 0.5 to 2 hours, after which there is no discernable difference noted.

The **Peak PR Score** is determined as the maximum least squares mean PR Score during the 6 hours post-dose. Both combination products showed borderline statistically superior mean peak PR scores compared to ibuprofen (5/400 w/ $p = 0.090$, 10/400 w/ $p = 0.074$).

The **Peak PID Score** is determined as the maximum least squares mean PID score during the 6 hours post-dose. Again, both combination products (Oxy/Ibup 5/400 and 10/400 mg) showed borderline statistically significant differences ($p = 0.059$ and $p = 0.051$ respectively) when compared to ibuprofen 400 mg alone.

The **Peak PRID Score** is defined similarly to the Peak PR and Peak PID scores. The combination products showed borderline statistically significant differences when compare to ibuprofen alone ($p = 0.073$ and $p = 0.059$).

Patient's Global Evaluation (PGE) Score was the least squares mean score for each group at 6 hours post-dose. Note that these scores are partly based on the LOCF for those subjects not completing the trial. The sponsor's analysis shows that the PGE scores across groups indicated that the Oxy/Ibup 5/400 combination showed borderline statistically significant difference (SSD) to ibuprofen ($p = 0.066$) while the 10/400 combination showed significance at the $\alpha = 5\%$ level ($p = 0.049$). Both combinations showed SSD when compared to oxycodone and placebo.

Proportion of Patients Reporting Pain Half-Gone (PGH) is calculated at each time point. The sponsor notes that both combination products show approximately 50% of subjects reporting PHG by .75 hours post-dose. This is compared to 31%, 11%, and 13% respectively in the ibuprofen 400 mg, oxycodone 5 mg, and oxycodone 10 mg groups respectively. This difference is shown in the early phase of treatment. Inspection of the After-Text Table 6.5 indicates that the separation between the combination products and ibuprofen disappears after 3 hours.

6.1.2.5.3 Summary Discussion of Efficacy Findings for OXY-MD-06:

6.1.2.5.3.1 Primary Outcome Variable Efficacy Findings:

Both of the primary outcome variables demonstrated significant differences for the combination products (Oxy 5 & 10/Ibup 400 mg) vs. Ibuprofen alone, at the 5 % level. However, the two combination products could not be distinguished from each other on the basis of $TOTPAR_6$ or $SPID_6$. Examination of the time course of the Mean PR scores demonstrates significant overlap (figure 6.1.2.5.2) in PR values for Oxy/Ibup (5 & 10/400 mg) and Ibuprofen alone. Similar degrees of variation are assumed for PID scores vs. time. Since the TOTPAR and SPID scores are derived from these time varying scores, it suggests that there may not be a significant clinical difference between the Combination products and Ibuprofen. The large degree of overlap in PR scores between the combination products and Ibuprofen also suggests the possibility that Oxy/Ibuprofen derives the majority of it's analgesic effect from Ibuprofen.

In summary, the primary variables do meet the statistical criteria for significance and from this perspective can be construed as supporting efficacy for both of the combination products versus Ibuprofen. However:

- Inability to detect a significant difference between the Oxy/Ibup 10/400 mg and Oxy/Ibup 5/400 mg suggests that there may be no additional therapeutic benefit to the higher dose Oxycodone combination product.

- Significant visual overlap in PR scores for all three active products suggests the possibility that the SSDs between treatments may not equal "clinically" significant differences.

6.1.2.5.3.2 Secondary Outcome Variable Efficacy Findings:
Several of the efficacy results for selected secondary outcome variables, also demonstrate statistically significant differences between the Combination products and Ibuprofen.

$TOTPAR_3$ and **$SPID_3$** demonstrate smaller p-values for differences between the combination products and Ibuprofen alone, that the values for the 6 hour TOTPAR/SPID results. Examination of the sponsor graphs (Vol. 58, pg. 46 & 48) as well as Figures 6.1.2.5.1 & 2 in this review, demonstrate a larger dispersion in mean PR scores and mean PID scores (Sponsor graph pg. 48) up to 3 hours. Even the large overlapping variation in PR scores demonstrated in Figure 6.1.2.5.2, are less pronounced during the 0 to 3 hour period. This suggests the possibility that there may be a more obvious clinical difference in analgesic efficacy of the Combination products vs. Ibuprofen, during the first 3 hours post dose.

The $TOTPAR_3$ and $SPID_3$ scores for the two combination Oxycodone/Ibuprofen products, were not significantly different at the 5% level. Again, this suggests that there is no obvious treatment benefit caused by the higher Oxycodone dosage treatment.

The median **Time of Onset of Pain Relief (TOPR)** estimated using Kaplan-Meier methods do not appear to be so different for the combination vs. Ibuprofen curves, as visually shown on pg. 57 of the Sponsor's Efficacy Study. However, the pairwise log-rank tests suggest such a difference. It is questioned whether this result would translate into clinically significant differences in time to pain relief.

Note again that there is no distinguishable difference between the median times for the two Oxycodone combination doses.

The **Time to Re-medication (TTR)** could not estimate values for either of the Combination products or Ibuprofen, because < 50 % of these group subjects requested rescue medication. This suggests that there may not be a distinguishable clinical difference between their respective 6-hour pain profiles, at least not enough to warrant subject re-medication. It is assumed that this metric is used as a surrogate to estimate "duration of pain relief". Dr. Price has suggested that this may not be an adequate measure of this time interval because TTR measures from the time of dosing to re-medication. She has suggested that a more robust way to determine this time would be to calculate the difference between the TTR and the Time of Onset of Pain Relief (TOPR).

This would give an estimation of the time a subject felt the medication was working, until re-medication was required to sustain analgesia.

The other secondary metrics including the time varying **PR**, **PID**, **PRID** scores showed a SSD when compared to ibuprofen alone, during the early period after dosing (.75 to approximately 3 hours). The **Peak PR**, **Peak PID**, and **Peak/Maximum PRID** Scores showed borderline statistically significant differences compare to ibuprofen, during the early period post-dosing. The **PGE** score was borderline SSD for the 5/400 combination product and marginally SSD for the 10/400 combination, compared to ibuprofen. The **Pain Half-Gone** metric showed a separation between the combination products and ibuprofen alone from 0.75 hours to approximately 3 hours. Overall, the majority of secondary outcome measures show a trend towards SSD (or "near" SSD) when compared to ibuprofen, up to approximately 3 hours post-dosing.

6.1.2.5.3.3 Conclusion:
The OXY-MD-06 primary and majority of secondary outcome variables reviewed here, appear to show statistically significant support for superior efficacy of aggregate Oxycodone / Ibuprofen combination products, when compared to Ibuprofen alone. In aggregate, Total Pain Relief, the Sum of Pain Intensity Differences, and the majority of secondary metrics appear to be more significantly different in the first 3 hours of treatment, rather than the later portions of the study. The differences in treatment associated "time to onset of pain relief" appear clinically unimpressive, although there are significant differences between the combinations and ibuprofen, at the 5 % level. The re-medication time could not be calculated for the three active combination and Ibuprofen treatments, suggesting that there may not be a "clinical" difference that results in needing rescue medication.

Thus there is a majority of both primary and secondary outcome variables that support a statistical difference in combination and Ibuprofen alone responses to treatment, early in the post-dosing period. However, it is questioned if these results indicate a true clinical superior difference, especially for the 6-hour variables. This reviewer suggests that the 3 hour secondary variables show a more compelling display of differences in efficacy than the primary outcome variables. Although, the 6-hour combination product outcome variables achieve a SSD from Ibuprofen, the clinical benefit of this is questionable.

In contrast, there is no obvious statistically significant difference between the Oxy/Ibup 5/400 mg treatment and Oxy/Ibup 10/400 mg formulation. Visual examination of the provided data and graphs also do not suggest a significant subjective difference, to the reviewer. There is no obvious rationale to support use of the Oxy/Ibup 10/400 mg treatment, given this result.

As a final comment, Dr. Price in Biostatistics has pointed out that the multiple pairwise *t*-test comparisons used in Oxy-MD-006, may actually be producing spurious significant differences due to inflation of Type-I errors. This statistical issue suggests the possibility

that the differences seen in this review may not be as significant as they appear to be. This issue will be addressed in more detail in Dr. Price's Statistical Review.

APPEARS THIS WAY
ON ORIGINAL

6.1.3 Study OXY-MD-07:

A Double-Blind, Placebo-Controlled, Single-Dose Parallel Study of the Analgesic Efficacy and Safety of Oxycodone HCL 5mg/Ibuprofen 400 mg and Oxycodone HCL 5 mg/Ibuprofen 400 mg compared to Ibuprofen 400 mg Alone, Oxycodone HCL 10 mg Alone and Oxycodone HCL 5mg Alone in Patients with Moderate to Severe Post-Orthopedic Surgical Pain.

6.1.3.1 Findings vs. Labeling Claims:

No review of the Package Insert and Proposed Labeling was performed because the Sponsor failed to show convincing evidence of efficacy of the proposed product.

6.1.3.2 Study Plan:

Note that this study was submitted as part of the 120 Day Safety Update and not as part of the NDA efficacy submission. A brief review of the study and the relevant findings is included for completeness.

6.1.3.3 Population, Design, and Objectives

The protocol-specified objective of the study was:

> "To evaluate the analgesic efficacy and safety of a single dose of a combination tablet of oxycodone HCL/ibuprofen 5/400 mg or oxycodone HCL/ibuprofen 10/400 mg relative to ibuprofen 400 mg alone, oxycodone HCL 5 mg alone, oxycodone HCL 10 mg alone, and placebo using the post-orthopedic surgical pain model."

The protocol was designed as a multi-site, double-blind, double-dummy, randomized, parallel-group, single-dose, placebo and active-controlled design. Subjects were to have undergone surgical orthopedic procedures including a unilateral or bilateral total knee or hip joint replacement, revision of prior joint replacement, or another orthopedic procedure involving periostial elevation and bony manipulation. Patients meeting these criteria for the study were to be enrolled based upon their post-surgery pain intensity measured by the Baseline Pain Intensity (PI) scale (immediately after surgery) and Visual Analog Scale (VAS). The PI is a 4 level ordinal scale that allows subjects to rate their pain as integers between "0" and "4." The VAS is a continuous visual scale 100 mm total length that corresponds to "no" pain to "severe" at 100 mm. Subjects were to have marked their current perceived pain level on this scale, which is measured proportionally. Potential subjects were to have rated their BPI as moderate - severe and their VAS as greater than 50. They were then to have been randomized into one of 6 treatment groups:

1) Oxycodone HCL /ibuprofen 5/400 mg
2) Oxycodone HCL/ibuprofen 10/400 mg
3) Ibuprofen 400 mg
4) Oxycodone HCL 5 mg

5) Oxycodone HCL 10 mg
6) Placebo.

Potential subjects were to have had the purpose and procedure of the trial explained to them at the screening visit, which was to occur 1 week prior to surgery. Subjects that agreed to participate were to complete an informed consent, undergo a physical examination, a review of their medical history, and to remain NPO for 8 hours prior to their planned surgery. Female patients of childbearing potential were to perform a urine pregnancy test on the day of planned surgery. All subjects meeting the inclusion and exclusion criteria were to undergo further instruction on how to complete their diary. A listing of these criteria follows this section.

Potential subjects were to be chosen from patients about to undergo specified orthopedic procedures. The sponsor states that this pain model had established utility in analgesic evaluation due to:

- The surgical procedures caused fairly uniform pain production.
- There was relatively low inter-subject variability.

All potential subjects had to meet the following inclusion criteria:

- Ability to provide written informed consent (parental approval for <18 years of age).
- All patients must be in good general health of either sex or race and ≥12 years of age.
- All potential childbearing females must have negative urine pregnancy tests prior to dosing.
- Patients must be alert and able to communicate with study personnel, able to complete the study as instructed, and able to ingest and absorb oral medication.
- All patients must abstain from all ETOH, caffeine, and smoking for 8 hours prior to surgery to the end of the post-dosing period.
- All patients must be scheduled to have either unilateral or bilateral total knee or hip joint replacement, revision of prior joint replacement, or another orthopedic procedure involving periostial elevation and bony manipulation
- All patients were to be dosed at least 24 hours post-op but not longer than 72 hours post-op.

The exclusion criteria were:

- Pregnant or lactating females.
- Patients who had taken the following medications:

- Short-Acting analgesics (ASA, acetaminophen, etc...) within 6 hours prior to surgery
- Ibuprofen within 10 hours of surgery
- Long-Acting NSAIDs or any opiate analgesic within 48 hours prior to surgery
- Steroids within 72 hours prior to surgery
- Any opiate analgesic via PCA within 1 hour or epidural or IM Opiate analgesia within 4 hours of study medication.

- Use of any psychoactive drug (e.g. TCA antidepressants, MAO Inhibitors, phenothiazines) or opioid antagonists within 72 hours prior to surgery.

- Use of sedative/hypnotics/anti-anxiety agents not part of a stable home regimen OR given as part of preop anesthesia preparation.

- Use of surgical anesthesia and/or antiemetics (other than Reglan, Zofran, or Kytril) during the study period.

- Patients with significant co-existing medical condition (e.g. GI, hematologic, neurologic, renal, cardiovascular disorders, etc...)

- Patients receiving investigational drug or in a clinical trial within 30 days prior to this study.

- Patients who were employees, relatives of employees or prior participants in this study.

- Patients with known allergies or reactions to opioid or NSAID medications, including the two active study compounds.

- Current drug or alcohol abuse.

- Concurrent medication use that could affect quantifying analgesia.

- Medical conditions compromising ability to swallow, absorb, metabolize, or excrete the study medication.

- Laboratory values deviating from the normal ranges and judged clinically significant by the investigator.

Surgery was to be performed with approved anesthesia. The Sponsor provided an analysis of the distribution of anesthetics used during surgery for the different study populations. Examination of Table 2.6 (Vol. 4.2, pg. 111) shows a similar distribution of frequency of the following treatments from highest to lowest, across groups: Oxygen

(77.6%), Propofol (73.5%), Fentanyl (66.4%), Midazolam (58.1%), NO_2 (55.3%), Sevoflurane (37.8%), and Lidocaine (35.8%). No obvious significant differences in frequency of use of these surgical medications, were noted.

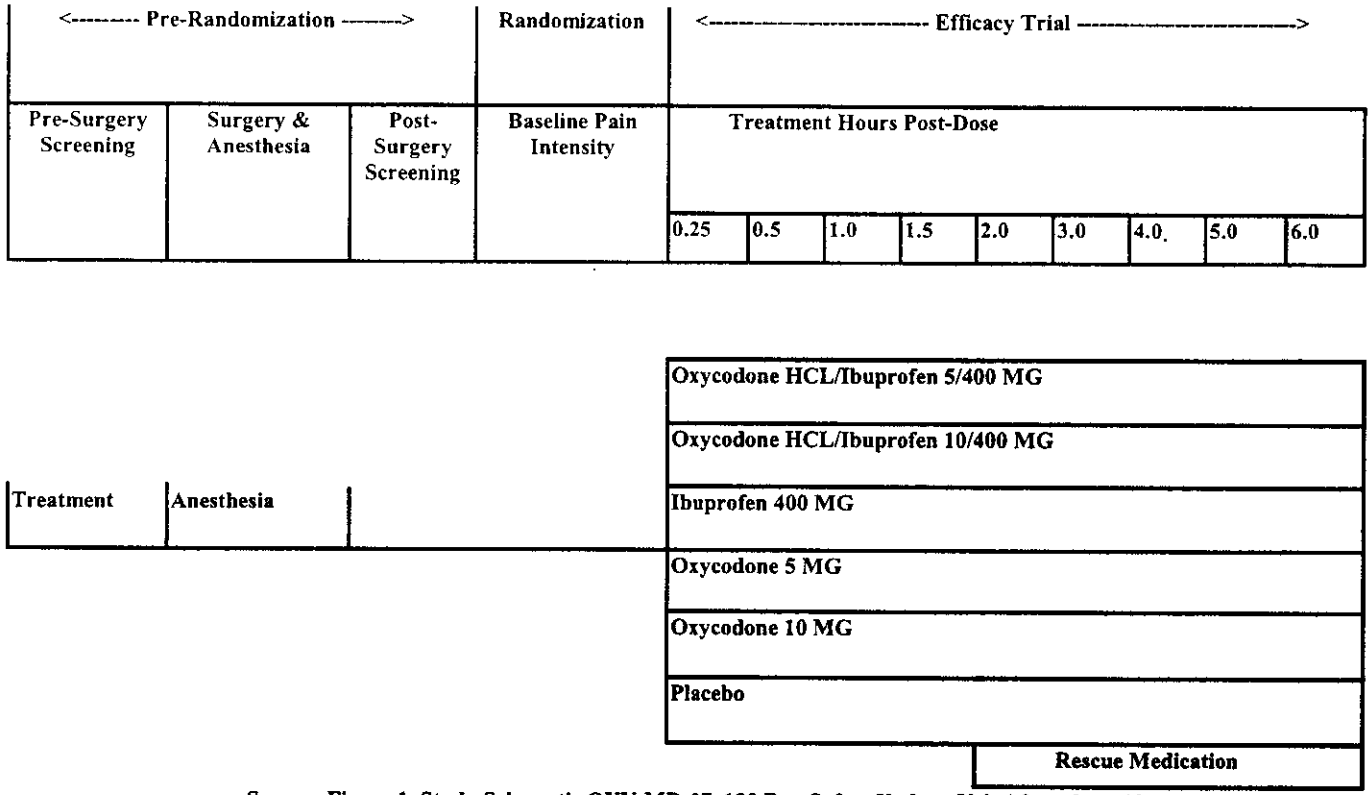
Post-Surgery enrollees were to be placed in an observation area by study staff, for up to 5 hours. Patients were to notify study personnel when their pain reached the threshold for randomization into the study, using VAS and Brief Pain Intensity (PI). The threshold criteria for randomization was to consist of a Baseline PI score of "moderate" to "severe" pain and VAS score $\geq$ 50 mm, within the 5 hour post-op period. If potential subjects did not develop sufficient pain levels as defined above, within 5 hours, they were to be classified as ineligible for study continuation.

Subjects that met the entry pain criteria were to be randomly assigned to their respective treatment groups and then study medication could be provided. All patients were to remain in the hospital for 6 hours post dosing. Subjects were to be encouraged to remain awake during the 6-hour post-dose period. Patients not experiencing adequate pain relief from study medication could request "rescue" medication. Subjects were to be encouraged to wait at least 2 hours post-dosing before requesting "rescue" medication. These subjects then completed the next efficacy evaluation and continued to be monitored for AEs throughout the full 6-hour post-dosing period.

Note that study participants could have been discontinued from the study at any time. This could have been due to occurrence of an adverse event (AE), poor therapeutic response, major protocol violations, withdrawal of consent, or administrative reasons.

The following figures illustrate the proposed study outline and schedule of evaluations.

Figure 6.1.3.3.1 Oxycodone/Ibuprofen Comparative Efficacy Study Schematic



Source: Figure 1. Study Schematic OXY-MD-07, 120 Day Safety Update, Vol. 4.2, and pg. 10.

Table 6.1.3.3.2 Schedule of Evaluation

	PRE-SURGERY	POST-SURGERY DOSING											
		Surgery	PRE-DOSING	Dosing	POST-DOSING (HOURS)								
	SCREEN-ING		Baseline		0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Randomization			X											
Medical/Medication History	X													
Concomitant Meds	X		X		At Any Time									X
Physical Exam, VSS	X		X							X				X
Urine Preg. Test			X											
Patient Diary			X		X	X	X	X	X	X	X	X	X	X
Global Rating														X
Adverse Events			X		At Any Time									X
Patient Diary Review														X

Source: Panel 3. Study Schedule OXY-MD-07, 120 Day Safety Update, Vol. 4.8, pg. 29.

6.1.3.3.1 Treatment Summary

Patients were to be randomized to one of six groups, in a 3:3:3:1:1:1 ratio (168:168:168:56:56:56 subjects respectively) in order to receive Study Combination Drugs, Ibuprofen, Oxycodone, or placebo, respectively. The total study population target was to be 674 analyzable subjects. The "double dummy" method was to be used to maintain a study blind by administering treatment in groups of one and two tablets. Each site was to have administered the study drug to each enrolled patient. These were to be in identical blister packs that should not have indicated their contents. The following table illustrates the proposed drug information and dosing. Each blister pack was to be labeled with the protocol number, randomization number, space for patient initials, warning information, and instructions. Patients were to be assigned the randomization number on the study drug label. These sequential numbers were to be matched with randomization codes generated and kept in a secure area at Forest Laboratories.

Table 6.1.3.3.1.1 Study Drug and Dosing Regimen

Group	Treatment	Tablet/Capsule Strength	Lot Number	Dispensed As:		
1	Oxycodone HCL/ Ibuprofen	5 mg / 400 mg	99229K	1 x 5 mg Oxycodone + 400 mg Ibuprofen tablet	1 x Placebo Capsule	1 x Placebo Capsule
2	Oxycodone HCL/ Ibuprofen	10 mg[##] / 400 mg[**]	99230K	1 x 10 mg Oxycodone + 400 mg Ibuprofen tablet	1 x Placebo Capsule	1 x Placebo Capsule
3	Ibuprofen	200 mg	119959	1 x Placebo tablet	1 x 200 mg Ibuprofen Capsule	1 x 200 mg Ibuprofen Capsule
4	Oxycodone HCL	5 mg	119960	1 x 5 mg Oxycodone tablet	1 x Placebo Capsule	1 x Placebo Capsule
5	Oxycodone HCL	10 mg	119960	1 x 5 mg Oxycodone tablet	1 x 5 mg Oxycodone tablet	1 x Placebo Capsule
6	Placebo X or Y	0 mg	99247K 119958	1 x Placebo tablet	1 x Placebo Capsule	1 x Placebo Capsule

Source: 6.2.2 Panel 1 and Panel 2, 120 Day Safety Update, Vol. 4.8, pg. 24 & 26.
[##] Oxycodone 10 mg dose consists of two 5 mg dose capsules
[**] Ibuprofen 400 mg consisted of two 200 mg dose capsules

Medications were to be administered with 4 ounces of water. Each combination of one tablet/two capsules was to be identical in appearance for all groups of patients. All medications were to be consumed.

The associated patient randomization number and assigned treatment was to be generated and maintained by the Forest Laboratories Department of Biostatistics. Bottles of identical "double-blind" medication were to be labeled with a two-part, three-panel label. The first part was to remain on the bottle at the time of administration. The other 2 panels were to be placed in the patent's CRF. In the event of emergency, the 3rd panel could have been broken to reveal the patient's treatment.

Any patients concurrently taking medication that could have confounded the analgesia analysis were to be excluded from the study at screening. For study patients, the following concomitant medications and treatments were to have been prohibited throughout the entire study period.

- NSAIDs, salicylates, propoxyphene, acetaminophen, steroids, codeine, hydroxyzine, pentazacine or other medications that could confound quantifying analgesia EXCEPT as rescue medication for those requiring it
- Mood altering drugs within 72 hours prior to surgery
- Alcohol, Caffeine, and Smoking

Rescue medication was to be available upon patient request in the post-dosing period, as stated earlier. All patients were to be encouraged to wait at least 2 hours after the study medication, before requesting "rescue". The type of rescue medication was to a "standard analgesic".

6.1.3.3.2 Assessments

Several efficacy measures were to be recorded by participating patients, during this study:

- Pain Intensity (PI) at baseline and at scheduled intervals.
- Visual Analog Scale (VAS)
- Pain Intensity (PI), Pain Relief (PR)
- Pain Half Gone
- Patient's Global Assessment.

The PI and VAS scale were to be entered into their respective patient diary just before dosing with the study medication. The other self-rated scales were to be entered into diary cards at each sampling time. All time measures were to be relative to the dosing time, recorded by the study coordinator. The scales (excluding VAS) are illustrated below:

Note that detailed discussion of these metrics has already been covered in section 6.1.2.3.2 of this review, regarding Oxy-MD-06. Thus, redundant tables and information will not be included here.

6.1.3.3.3 Analysis Plan

Three analysis populations were defined in the protocol. The randomized population was specified to consist of all patients randomized to the study. The safety population was to consist of all treated patients within the study. The intent-to-treat (ITT) population was to consist of all randomized patients taking the study drug and having ≥ 1 post-baseline efficacy measure.

The protocol specified primary efficacy endpoints for statistical analysis was to consist of two measures calculated from self-rated patient pain scales:

3. Sum of Pain Intensity Difference through 6 Hours (**$SPID_6$**).
   - Define PID = difference between pain intensity at a given time and the baseline pain intensity (e.g. PID(t) = PI(t) – Baseline PI).
   - SPID = the AUC of PID vs. time from 0 – 6 hours.

4. Total Pain Relief through 6 hours (**$TOTPAR_6$**)
   - Defined as the area under the curve (AUC) of pain relief (PR) vs. time from 0 - 6 hours.

The primary analyses of efficacy were to be based on the ITT population, with the last observation carried forward (LOCF) to extrapolate any missing PI or PR values. Primary analyses were to be the comparison of the effects of the combination product treatment to individual analgesic components alone, for $SPID_6$ and $TOTPAR_6$. Statistical testing was specified to use two-tailed analysis with 5 % and 10 % significance levels respectively, for the main and interaction term effects. The comparisons of the two primary efficacy variables across treatment groups were to be performed using an ANOVA model with treatment and study site as effects. Comparability among treatment groups was to be tested using ANOVA with treatment as the continuous variable factor. The Cochran-Mantel-Haenszel (CMH) test was to be used for testing comparability among treatment groups by categorical variables.

The protocol specified sample sizes calculation was to be based upon an expected difference in $SPID_6$ values for the Oxycodone HCL/ibuprofen 5/400 mg and ibuprofen alone group. This expected difference was determined from a previous single-site study: OXY-MD3-96-01. The sample size assumptions that were to be used are stated as follows:

- $SPID_6$ difference as defined above = 1.35 (based upon OXY-MD3-96-01 results)
- Each $SPID_6$ group standard deviation = 4.2
- Two tailed t-test at 0.05 significance level
- 83 % power needed to detect difference

The resulting sample size was projected to be 168 for these two groups. It was assumed that a similar sample size would suffice for the oxycodone/ibuprofen 10/400 mg group. There was a large expected difference in $SPID_6$ groups for oxycodone alone and

ibuprofen alone, and as a result only 56 patients per group were to be enrolled in those categories. This was to result in a total of 672 patients in a 3:3:3:1:1:1 (168:168:168:56:56:56) proportion, as listed earlier in this review. Similar calculations for TOTPAR resulted in smaller required sample sizes, however the larger number quoted here was to be used for both groups.

Several secondary efficacy parameters were also specified in the protocol:

- TOTPAR 3 and SPID 3 – Defined and analyzed similarly to the 6 hour primary parameters.

- PR – analyzed at each time point using ANOVA with treatment and study site as effects.

- PID - analyzed at each time point using ANOVA with treatment, study site, and BPI as effects. Pair-wise comparisons performed using Fisher's protected LSD procedure.

- PRID = PR + PID. Combined pain relief analyzed similar to PID.

- Peak PR and Patient's Global Rating at 6 Hours (LOCF). Analyzed using ANOVA.

- Proportion of Patients Reporting Pain Half Gone. Data analyzed at each time point using the CMH test stratified by study site.

- Onset of PR – Defined as time from medication dosing to time 1st stopwatch stopped, for patients who also stopped the second stopwatch during the observation period. Patients who did not stop the second watch had onset time defined as a censored value at the last PI or PR measurement. This endpoint was analyzed using the log rank test for censored data. Median time to PR was calculated using the Kaplan-Meier product limit estimator.

- Time to Re-medication – Defined as elapsed time from dosing to time rescue medication administered. This was analyzed similar to Onset of PR.

No interim analyses were to be performed. All statistical computations were to be performed using SAS version 6.12.

6.1.3.3.4 Protocol Amendments and Changes in the Planned Analyses

There were no amendments to the to the Statistical Analysis Plan. There was one protocol amendment (#1 dated 3/33/2000) which eliminated the investigator requirement to draw hematology and chemistry samples at screening. Labs drawn as part of pre/post-surgery requirements were to be reviewed and clinically significant abnormalities were to be excluded from the study.

6.1.3.4 Study Conduct

The sponsor notes that this study was performed at 12 sites in the US. Each study center Principal Investigator was responsible for ensuring that the study was conducted according to the Protocol, Investigator Agreements, the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

The Sponsor utilized the same measures to insure data quality as were employed in Oxy-MD-07. These methods will not be repeated again here.

6.1.3.4.1 Patient Disposition

The study report does not indicate how many patients were screened for admission to the study and were not accepted. In addition, the sponsor does not state how many patients were screened and never achieved the pain levels necessary to be enrolled, during the 6 hour post surgery time limit.

The sponsor indicates that 684 patients were randomized into the six study groups. One (2) patients were excluded from the ITT/Safety group before any dosing occurred (1 randomized to PBO and the other to Ibuprofen alone). Therefore, the ITT efficacy total was 682 subjects.

Table 6.1.3.4.1.1 Patient Disposition Summary:

Oxycodone HCL / Ibuprofen 5/400 mg	Oxycodone HCL / Ibuprofen 10/400 mg	Ibuprofen 400 mg	Oxycodone 5 mg	Oxycodone 10 mg	Placebo
175	169	171	58	56	55

Source: NDA 21,378, Panel 5, Oxy-MD-07, 120 Day Safety Update, pg. 47.

Panel 6 of the study report summarizes patient dispositions, completions, discontinuation, and major reasons for dropping out of the study. 423 (61.8%) patients completed the study. The combination groups had approximately 32 % (Oxy/Ibup 5/400 mg) and 22.5 % (10/400 mg) discontinuation rates compared to the ibuprofen treatment group showing a 29.8 % discontinuation due to insufficient therapeutic response. The Oxycodone alone groups experienced approximately 66 & 57 % discontinuation while the Placebo group had a 67.3 % withdrawal due to lack of therapeutic response.

Five (5) patients withdrew from the study due to AEs: 1 each in the oxycodone/ibuprofen 5/400 mg and ibuprofen groups, three in the oxycodone/ibuprofen 10/400 mg group. Two subjects were coded with the AE of increased pain (1 in each oxy/ibup group) which should have actually been coded as discontinuing due to insufficient efficacy. The following table summarizes the findings of this section.

Table 6.1.3.4.1.2 Patient Completion and Discontinuation

	Oxy/Ibu 5/400 mg N=175	Oxy/Ibu 10/400 mg N=169	Ibu 400 mg N=171	Oxycodone 5 mg N=58	Oxycodone 10 mg N=56	Placebo N=55	Total N=684
Completed	117 (66.9%)	127 (75.1%)	118 (69.0%)	20 (34.5%)	24 (42.9%)	17 (30.9%)	423 (61.8%)
Discontinued	58 (33.1%)	42 (24.9%)	53 (31.0%)	38 (65.6%)	32 (57.1%)	38 (69.1%)	261 (38.2%)
Discontinuation Reason							
Adverse Events (AEs)	1 (0.6%)	3 (1.8%)	1 (0.6%)	0	0	0	5 (0.7%)
Poor Response	56 (32.0%)	38 (22.5%)	51 (29.8%)	38 (65.5%)	32 (57.1%)	37 (67.3%)	252 (36.8%)
Withdraw Consent	1 (0.6%)	1 (0.6%)	0	0	0	0	2 (0.3%)
Other	0	0	1 (0.6%)	0	0	1 (1.8%)	2 (0.3%)

Source: Panel 6, NDA 21,378, Vol. 4.2, Oxy-MD-07, 120 Day Safety Update, pg. 48.

6.1.3.4.2 Protocol Deviations and Violations:

The sponsor notes that there were two (2) protocol deviations, from the inclusion/exclusion criteria. One occurred in the oxy/ibup 5/400 mg group and the other was in the oxy/ibup 10/400 mg group. Both subjects were discontinued because they received prohibited medications, however their results were still included in the ITT analysis.

6.1.3.4.3 Data Sets Analyzed

The Intent-to-Treat population was defined as all randomized patients taking the study medication with ≥ 1 post-baseline efficacy assessment. Efficacy analysis was performed on the ITT group. The last observation carried forward (LOCF) was used to extrapolate missing data. The Randomized population consisted of all patients randomized to the study.

The safety population consisted of all patients treated with study medication. The safety analysis was performed on this population.

6.1.3.4.4 Demographics/Group Comparability

Baseline characteristics and other demographic variables are summarized in the sponsor's table, which is reproduced here:

Table 6.1.3.4.4.1 Patient Demographics and Baseline Characteristics

	Oxy/Ibu 5/400 mg N=175	Oxy/Ibu 10/400 mg N=169	Ibuprofen 400 mg N=170	Oxycodone 5 mg N=58	Oxycodone 10 mg N=56	Placebo N=54	Total N=682
Age (yr.):							
Mean (SD)	60.5 (15.38)	60.8 (14.44)	61.9 (14.17)	63.0 (14.05)	59.5 (15.25)	64.5 (15.24)	61.4 (14.72)
Sex: N (%)							
Male	96 (54.9)	88 (52.1)	86 (50.6)	29 (50.0)	22 (39.3)	30 (55.6)	351 (51.5)
Female	79 (45.1)	81 (47.9)	84 (49.4)	29 (50.0)	34 (60.7)	24 (44.4)	331 (48.5)
Race: N (%)							
White	155 (88.6)	146 (86.4)	136 (80.0)	52 (89.7)	46 (82.1)	44 (81.5)	579 (84.9)
Black	15 (8.6)	123 (7.7)	19 (11.2)	4 (6.9)	4 (7.1)	6 (11.1)	61 (8.9)
Other	5 (2.9)	10 (5.9)	14 (8.2)	2 (3.4)	5 (8.9)	4 (7.4)	40 (5.9)
Weight {lbs.}: N (Std. Dev)							
Mean (SD)	191.7 (43.75)	193.9 (46.26)	192.1 (43.14)	196.4 (51.20)	180.7 (44.92)	191.0 (42.54)	191.8 (44.89)
Height {in}: N (Std. Dev)							
Mean (SD)	67.2 (4.40)	67.0 (4.56)	67.2 (4.18)	67.5 (4.36)	66.6 (3.62)	67.1 (4.91)	67.1 (4.35)
Baseline Pain Intensity: N (Std. Dev)							
Moderate	136 (77.7)	127 (75.1)	129 (75.9)	40 (69.0)	41 (73.2)	37 (68.5)	510 (74.8)
Severe	39 (22.3)	42 (24.9)	40 (23.5)	18 (31.0)	15 (26.8)	17 (31.5)	171 (25.1)
Baseline Pain Visual Analog Scale (VAS): N (Std. Dev)							
Mean (SD)	67.9 (12.93)	68.3 (13.56)	69.2 (13.41)	69.6 (13.68)	68.6 (13.74)	71.6 (14.52)	68.8 (13.45)

Source: NDA 21,378, Panel 7, Vol. 4.2, Oxy-MD-07, 120 Day Safety Update, pg. 50.

6.1.3.4.5 Treatment Compliance:

All participating subjects in this single-dose study received medication directly from the Study coordinator. No other compliance measurements were necessary.

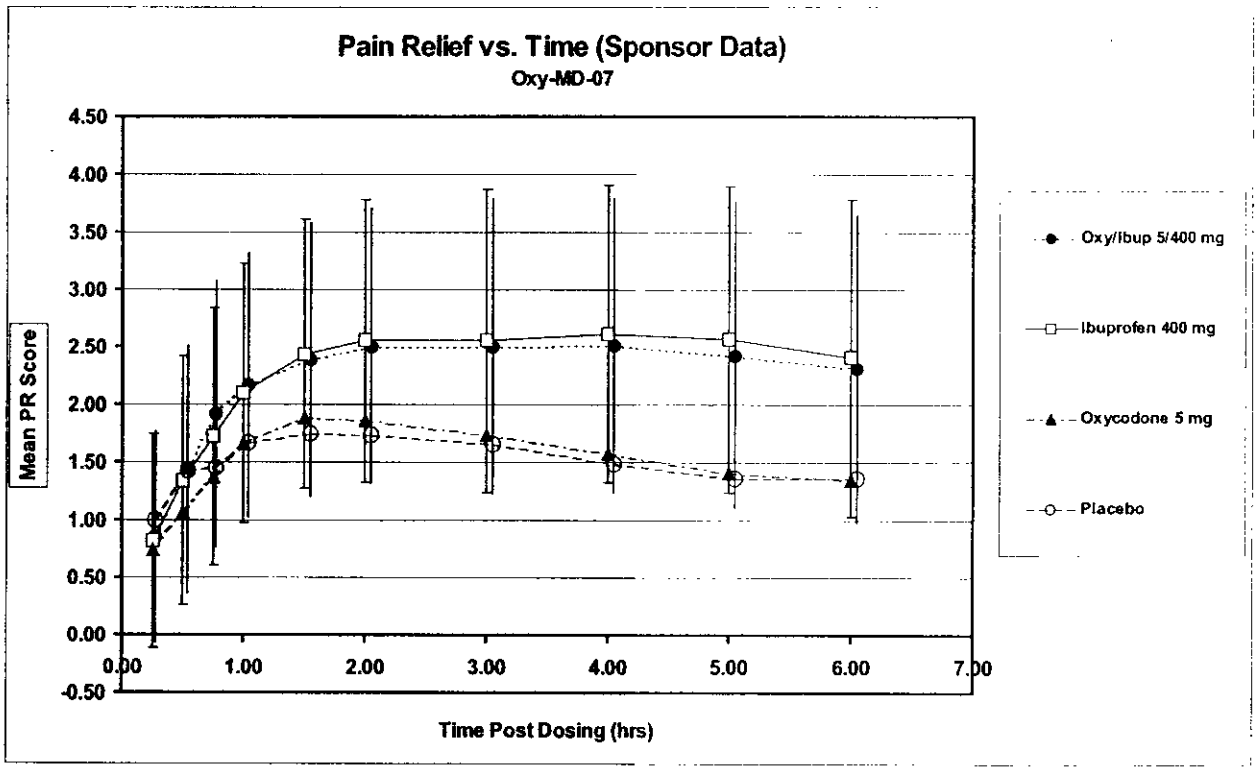
6.1.3.4.6 Unplanned Analyses:

There were no interim unplanned analyses.

6.1.3.5 Sponsor's Efficacy Results for OXY-MD-07:

The primary efficacy variables were calculated metrics for "total pain relief at 6 hours" and the "sum of pain intensity differences at 6 hours:" $TOTPAR_6$ and $SPID_6$ respectively. Both are derived from the Area Under the Curve (AUC) calculations for the Mean Pain Relief (PR) and Pain Intensity Difference (PID), as a function of time. The Mean PR values over the time of the trial are illustrated here for visual inspection in Figure 6.1.3.5.1.1 . This graph is an Excel plots of PR efficacy data from the sponsor's analysis results, in Table 4.1, Vol. 4.2, pg. 124. Note that the great deal of overlap when the actual standard deviation is included.

Figure 6.1.3.5.2 Oxy-MD-07 Mean PR Scores with Standard Deviations



Note that $TOTPAR_6$ is derived from the LS Mean data illustrated in these two curves. There was no difference between Oxy/Ibup 10/400 mg, Oxy/Ibup 5/400 mg and Ibuprofen treatments, based on the results presented by the sponsor.

The difference in Between-Treatment-Group Least Squares (LS) Means for $TOTPAR_6$ was analyzed using a "pair-wise comparison" test. The selected results for $TOTPAR_6$ are summarized below:

Table 6.1.3.5.1 Selected $TOTPAR_6$ Results for ITT Population

Treatment Group	N	LS Mean	SD	Overall Treatment p-value
Oxy/Ibup 5/400 mg	175	12.84	6.45	0.0000
Oxy/Ibup 10/400 mg	169	13.81	6.26	
Ibuprofen 400 mg	169	13.08	6.44	
Oxycodone 5 mg	58	8.32	6.16	
Oxycodone 10 mg	56	9.05	6.81	
Placebo	54	8.12	5.98	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		- 0.24	0.66	0.7163
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		4.53	0.93	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		0.70	0.67	0.2967
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		4.66	0.95	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		- 0.94	0.66	0.1571

Source: NDA 21-378, OXY-MD-07, Table 4.1, 120 Day Safety Update, Vol. 4.2, pg. 124.

The most relevant pair-wise comparisons are between the combination study drugs (Oxy 5 and 10 mg/Ibuprofen) and the individual component Ibuprofen. Both of the combination products failed to show a statistically significant difference (SSD) in mean $TOTPAR_6$ (at $\alpha = 0.05$ level) when compared to Ibuprofen alone.

The second primary efficacy variable is $SPID_6$ and it was analyzed similarly to $TOTPAR_6$, described above. Again, both combination product mean $SPID_6$ values failed to show a SSD when compared to Ibuprofen alone. Both Oxycodone/Ibuprofen combination product mean SPID scores show no SSD, when compared to each other.

Table 6.1.3.5.2 $SPID_6$ Results for ITT Population

Treatment Group	N	LS Mean	SD	Overall Treatment p-value
Oxy/Ibup 5/400 mg	175	5.42	4.77	< 0.001
Oxy/Ibup 10/400 mg	169	6.24	4.47	
Ibuprofen 400 mg	169	5.84	4.35	
Oxycodone 5 mg	58	2.77	3.75	
Oxycodone 10 mg	56	3.06	4.81	
Placebo	54	2.66	4.56	
Pair-wise Comparisons:		**LS Mean Difference**	**SE**	**p-value**
Oxy/Ibup 5/400 mg vs. Ibuprofen 400 mg		- 0.41	0.45	0.3617
Oxy/Ibup 5/400 mg vs. Oxy 5 mg		2.86	0.63	< 0.001
Oxy/Ibup 10/400 mg vs. Ibup 400 mg		0.34	0.45	0.4528
Oxy/Ibup 10/400 mg vs. Oxy 10 mg		3.14	0.64	< 0.001
Oxy/Ibup 5/400 mg vs. Oxy/Ibup 10/400 mg		- 0.75	0.45	0.0954

Source: NDA 21-378, OXY-MD-07, Table 4.2, 120 Day Safety Update, Vol. 4.2, pg. 125.

6.1.3.5.1 Secondary Efficacy Variables:

Various secondary variables were analyzed in this study, similarly to study Oxy-MD-06. All of the secondary variables showed similar results to the primary variables. The Oxy/Ibup products showed statistically significant differences compared to Placebo and Oxycodone alone.

However, the combination products did not show a statistically significant difference when compared to Ibuprofen alone for any secondary variable (TOTPAR3, SPID3, TOPR, TTR, Peak Pain Relief, PRID, or Patient Global Rating). The individual comparisons and associated p-values are not shown here.

6.1.3.5.1.1 Conclusion:

The OXY-MD-07 primary and secondary outcome variables reviewed here, appear to show no support for superior efficacy of aggregate Oxycodone / Ibuprofen combination products, when compared to Ibuprofen alone in Post-Operative Orthopedic Pain. Both combinations did show a significant difference to both oxycodone formulations and placebo alone, suggesting that the combination product does act as an analgesic.

The sponsor states that the prior use of narcotics before surgery may have caused this population to have a partial tolerance to narcotic analgesics prior to inclusion in the study. They base this on the fact that the primary AEs of nausea and vomiting were seen more frequently in the dental-pain studies, when subjects were exposed to oxycodone. They argue that the low report of these AEs suggest a "partial tolerance."

Another alternative is that the primary driving analgesic is actually Ibuprofen and the studied doses of oxycodone may not provide any improvement in efficacy.

6.1.4 Study OXY-MD-08-00:

A Randomized, Double-Blind, Multiple Dose Evaluation of the Analgesic Efficacy and Safety of Oxycodone HCL 5 mg/Ibuprofen 400 mg and Oxycodone HCL 10 mg/Ibuprofen 400 mg in Patients with Moderate to Severe Pain following Dental or Orthopedic Surgery.

6.1.4.1 Regulatory History:

This follow-on multi-dose study was not included as a pivotal trial to support the sponsor's acute pain indication. The sponsor was informed that the results from this would not be submitted in time to be considered as part of the efficacy review (see Memorandum: IND 52,310, DalPan MD, 2/6/02). The sponsor continued this multi-dose study and submitted the results from Oxy-MD-08 as part of the 120-day safety update.

6.1.4.2 Brief Study Description:

This study was designed as a multi-dose, multi-site optional follow-on to eligible subjects completing three prior single dose studies: Oxy-MD-05, Oxy-MD-06, and Oxy-MD-07. Studies 05 and 06 have been discussed at length in the previous sections of this NDA review and will not be covered here.

Study Oxy-MD-07 was a multi-site, double-blind, randomized, parallel-group, single-dose, placebo- and active-controlled study comparing treatments given to subjects with moderate to severe orthopedic post-operative pain. Subjects had to have undergone unilateral or bilateral total knee (TKA) or total hip joint (THA) replacement/revision. Other allowed orthopedic procedures had to involve peri-ostial elevation and bony manipulation. The parallel single-dose treatments and protocol design were to be the same as described in the 2nd pivotal trial: Oxy-MD-06. However, this was designed as an active control trial and not as a placebo-control. This feature prevents interpretation of the benefit of the combined products due to lack of assay sensitivity (measured against placebo).

The multi-dose Oxy-MD-08 trial was to begin subsequent to the single-dose studies. Eligible patients were to have successfully completed the 6-hour post-dose observation periods in the three Oxy-MD studies: 05, 06, and 07. Subjects then were to be randomized to either Oxy/Ibup 5/400 mg or 10/400 mg. The subjects were to be given blinded medication to take up to 7 days, with the stipulation of dosing no more often than every 6 hours. Efficacy measures, adverse events, and other information were to be recorded in patient diaries that were to be returned at the final follow-up visit.

7 INTEGRATED REVIEW OF SAFETY:

7.1 Findings vs. Labeling Claims:

7.2 Adequacy of Exposure and Safety Assessment:

The Safety data comes from 8 Phase II/III studies and 6 Phase I studies. A large portion of the safety database was submitted to the Agency as part of the 120-day safety update. This specifically included further exposure data from multi-dose patients (Oxy-MD-08) and the results of Oxy-MD-07, that were not included as part of the Review of Efficacy. A total of 2796 subjects are included in the database with 1572 patients exposed to one of the oxycodone/ibuprofen combination products. The total exposure by study is summarized in Table 7.2.1, derived from the sponsor trial summaries.

Table 7.2.1 ISS Oxycodone/Ibuprofen Combination Exposure

Phase	Exposure	Study Type/Population	Protocol #	# Exposed to Oxy/Ibup Combination
I	Single Dose	Clinical Pharmacology – Crossover Trial	604-003-01	24
		Clinical Pharmacology – Crossover Trial	604-004-01	23
		Clinical Pharmacology – 3Way Crossover Trial	Oxy-PK1-96-01	24
		Clinical Pharmacology – 2Way Crossover Trial	Oxy-PK1-97-02	25
		Clinical Pharmacology – 2Way Crossover Trial	Oxy-PK-04	24
	Single/Multi-Dose	Clinical Pharmacology – 2Dose Crossover Study	Oxy-PK-03	24
		Total Clin/Pharm Exposure:	**Subtotal**	**144**
II	Single-Dose	Pilot Study: Dental Surgical Pain	604-001-01	50
		Pilot Study: Dental Surgical Pain	604-002-01	39
		Clinical Study: Dental Surgical Pain	Oxy-MD3-96-02	82
III	Single-Dose	Clinical Study: Dental Surgical Pain	Oxy-MD3-96-01	171
		Clinical Study: Dental Surgical Pain	Oxy-MD-05	187
		Clinical Study: Dental Surgical Pain	Oxy-MD-06	340
		Clinical Study: Post-Surgical Orthopedic Pain	Oxy-MD-07	344
	Multi-Dose	Clinical Study: Post-Surgical Ortho/Dental Pain Extended Double-Blind Study**	Oxy-MD-08	215**
		Total Clinical Exposure:	**Subtotal**	**1428**
I, II, III		**TOTAL SUBJECT EXPOSURE:**	**TOTAL**	**1572**

** This is # of patients from previous single-dose studies that received Oxy/Ibup combination for the 1st time. Actual # of subjects participating in this trial = 488 (273 were previously on combination treatment)
Source – ISS, Vol. 4.8, pg. 3-23.

A total of 2796 individual patients were treated in all of the trials. The Clin/Pharm Studies enrolled a total of 145 normal subjects with 144 treated with one of the combination products. The Clinical Studies included 2651 total subjects. The distribution of patients exposed to each treatment was similar regardless of age, sex, or race. The number of subjects by treatment is as follows:

Treatment:	Oxy/Ibup Comb	Ibuprofen	Oxycodone	Placebo
# Subjects	1428	816	347	275

Source: ISS Update, Vol. 4.8, Section 2.0, pg. 3.

Some patients received more than 1 treatment (i.e. changed during transition from single-dose to the multi-dose study). Thus the total subject number (2651) is less than the sum of patients in each treatment group (2866 total).

The distribution of treated patients among all the studies utilizing Oxycodone/Ibuprofen 5/400 mg is illustrated in table 7.2.2. Many of the subjects participated in crossover studies or an extension clinical trial and received more than 1 treatment. As of 1/3/2002 2651 subjects received study drug in the oxycodone/ibuprofen clinical studies: 910 treated with Oxy/Ibup 5/400 mg, 527 with Oxy/Ibup 10/400 mg, 121 with other Oxy/Ibup combinations, 816 with ibuprofen alone, and 275 with placebo. Subjects in Oxy-MD-08 may be counted twice, once for lead-in study treatment and again for treatment in Oxy-MD-08.

Table 7.4.1 Distribution of Treated Subjects
(All Studies of Oxy/Ibup 5/400 mg)

Study Groups	Oxy/Ibup 5/400 mg	Ibuprofen 400 mg	Oxycodone 5 mg	Placebo	Total *
Clinical Studies					
Placebo Control					
604-001-01	50	43	0	24	117
Oxy-MD3-96-01	171	168	56	58	453
Oxy-MD-05	187	186	63	62	498
Oxy-MD-06	171	171	57	57	456
Oxy-MD-07	175	170	58	54	457
Active Control (no Placebo)					
Oxy-MD-08	(156)+	0		0	(156)+
*Total Clinical**	754 (156)++	738	234	255	1981
Clinical Pharmacology Studies (Active controls only)					
604-003-01	24	0	0	0	24
604-004-01	23	(23)**	1 (23)**	0	24
Oxy-PK1-96-01	24	(24)**	(24)**	0	24
Oxy-PK1-97-02	25	0	0	0	25
Oxy-PK-03	24	0	0	0	24
Oxy-PK-04	24	0	0	0	24
Total ClinPharm	144	(47)**	1(47)**	0	145
TOTAL*	898 (156)**	738 (47)**	235 (47)**	255	2126

* Subjects counted once only in each treatment group, including those exposed to ≥ 1 treatment

** The number in ( ) = number of subjects counted in a previous row or column

\+ ( ) represents the subjects in Oxy-MD-08 not previously administered Oxy/Ibup 5/400 during the lead-in studies.

++ 910 unique subjects received Oxy/Ibup 5/400 mg combination in the clinical studies

Source: NDA 21-378 ISS Update, Vol. 4.8, Panel 8, pg. 35 (pg. 47 of Vol.)

Similar data regarding the other Oxycodone/Ibuprofen combination products (10/400, 5/200, 10/200) was also provided. Table 7.2.3 illustrates the results.

Table 7.4.2 Distribution of Treated Subjects
(All Studies of other Oxy/Ibup Combinations)

Study Groups	Oxy/Ibup 5/200 mg	Oxy/Ibup 10/200 mg	Oxy/Ibup 10/400 mg	Ibup 200 mg	Oxy 10 mg	Placebo	Total *
Clinical Studies							
Placebo Control							
604-001-02	39	0	0	38	0	20	97
Oxy-MD-06	0	0	169	0	57	0 (57)**	226
Oxy-MD-07	0	0	169	0	56	0 (54)**	225
Active Control Only							
Oxy-MD3-96-01	41	41	0	40	0	0	122
Oxy-MD-08	0	0	(189)+	0	0	0	(189)+
*Total Clinical**	80	41	338 (189)++	78	113	20 (111)**	670
Clin-Pharm Studies, Active Control Only							
Oxy-PK1-97-02	0	0	(24)**	0	0	0	(24)**
Oxy-PK-03	0	0	(12)**	0	0	0	(12)**
Total ClinPharm	0	0	(36)**	0	0	0	(36)**
TOTAL*	80	41	338 (225)**	78	113	20 (111)**	670

* Subjects counted once only in each treatment group, including those exposed to ≥ 1 treatment

** The number in ( ) = number of subjects counted in a previous row or column

\+ ( ) represents the subjects in Oxy-MD-08 not previously administered Oxy/Ibup 10/400 during the lead-in studies.

++ 910 unique subjects received Oxy/Ibup 5/400 mg combination in the clinical studies

Source: NDA 21-378 ISS Update, Vol. 4.8, Panel 8, pg. 35 (pg. 47 of Vol.)

7.2.1 Extent and Duration of Exposure in Clinical Trials:

As described above, 2651 total patients (some with > 1 treatment) were enrolled in the clinical trials. In Oxy-MD-08 the time/extent of exposure was determined as the sum of exposures in the lead-in (single-dose) and extension (multi-dose) studies. The single-dose lead-in studies include subjects from Oxy-MD-05, Oxy-MD-06, and Oxy-MD-07. Extent of exposure was not calculated for the single-dose studies alone due to their brief dosing period (< 1 day). In the table that follows, patients are counted separately for each treatment. Table 7.2.1.1 illustrates the summary of treatment duration for the multi-dose oxycodone/ibuprofen combination products.

Table 7.2.1.1 Duration of Exposure by Treatment Group (Multiple Dose Study)

Duration (Days)	Oxy/Ibu 5/400 mg: N (%)	Oxy/Ibu 10/400 mg: N (%)	Totals*: N (%)
0	94 (28.1)	64 (22.2)	18 (3.7)
1-3	73 (21.9)	82 (28.5)	160 (32.5)
4-6	81 (24.3)	62 (21.5)	141 (28.7)
7-9	76 (22.8)	70 (24.3)	151 (30.7)
≥ 10	10 (3.0)	10 (3.5)	22 (4.5)
Mean	3.8	3.9	4.9
SD	3.3	3.2	2.9
Range	0 - 17	0 - 14	0 - 17
Total	**334**	**288**	**492***

Source: ISS 120-Day Update, Vol.4.8, Table 3.2, pg. 116.
* Only counts the unique patients!

Extent of exposure by dosage (total # of new doses taken) for the multi-dose subjects in Oxy-MD-08 was also summarized for the two combination products:

Table 7.2.1.2 Extent of Exposure by Treatment Group (Multiple Dose Study)

Total Doses (tablets)	Oxy/Ibu 5/400 mg: N (%)	Oxy/Ibu 10/400 mg: N (%)	Totals*: N (%)
1	94 (28.1)	64 (22.2)	18 (3.7)
2-12	120 (35.9)	126 (43.8)	254 (51.6)
13-24	88 (26.3)	68 (23.6)	156 (31.7)
25-28	32 (9.6)	30 (10.4)	64 (33.0)
Mean	10.0	10.0	12.7
SD	8.9	8.8	8.5
Range	1 - 28	1 - 28	1 - 28
Total	**334**	**288**	**492***

Source: ISS 120-Day Update, Vol.4.8, Table 3.3, pg. 120.
* Only counts the unique patients!

7.2.2 Evaluation of Exposure Conclusion:

The distribution of exposure to the two proposed combination products versus the individual components is due to the study design. The different studies were powered to show efficacy differences between the combination products and the main active individual ingredient: Ibuprofen. Thus the majority of patient exposure data is in the Oxycodone/Ibuprofen 5/400 mg and 10/400 mg groups. The numbers of exposed subjects and duration of exposure appears to be adequate to make an assessment of safety findings. Selected exposure information displayed in the tables was verified using JMP 4.0 to summarize the multiple dose duration data (supplied as SAS Transport files).

7.3 Methods for Review of Safety:

The safety review consisted primarily of a review of the Integrated Summary of Safety (ISS) document, with review of selected elements of the safety sections (CRTs and CRFs) when further information was required. The Sponsor's SAS Transport electronic database was also utilized during the safety review.

7.4 Subject Disposition:

The frequencies of premature discontinuation among the single-dose oxydocone / ibuprofen treatment groups ranged from 18.9% to 38.8% and were lower than other treatment groups. The sponsor notes that 33.7% of subjects treated with oxy/ibup 5/400 mg discontinued prematurely compared to 37.3% and 72.6% of those treated with ibuprofen 400 mg alone and oxycodone 5 mg alone. The greatest rate of premature discontinuation was in the placebo groups (77.6 – 85%), followed by oxycodone alone (52.2 – 72.6%) and ibuprofen alone (37.3 – 42.3%). The majority of discontinuations in the single-dose studies were due to insufficient therapeutic response.

Table 7.4.1 Discontinuations in All Single-Dose Oxy/Ibup 5/400 mg Clinical Studies

	Treatment Group				
	Oxy/Ibup 5/400 mg (N=754) n (%)	Ibup 400 mg (N=738) n (%)	Oxy 5 mg (N=234) n (%)	Placebo (N=255) n (%)	Total (N=1981) n (%)
# Completions	500 (66.3)	463 (62.7)	64 (27.4)	57 (22.4)	1084 (54.7
# Discontinuations	254 (33.7)	275 (37.3)	170 (72.6)	198 (77.6)	897 (45.3)
Reason for Discontinuation					
AE	6 (0.8)	4 (0.5)	0	2 (0.8)	12 (0.6)
Insuff. Response	245 (32.5)	267 (36.2)	169 (72.2)	194 (76.1)	875 (44.2)
Protocol Violation	1 (0.1)	0	0	0	1 (0.1)
W/D Consent	0	3 (0.4)	1 (0.4)	1 (0.4)	5 (0.3)
Other	2 (0.3)	1 (0.1)	0	1 (0.4)	4 (0.2)

N = # treated with study drug
Source: ISS Update, Vol. 4.8, Panel 9, pg. 37 (pg. 49 of Vol.).

Table 7.4.2 Discontinuations in All "Other" Single-Dose Oxy/Ibup Clinical Studies

	Treatment Group						
	Oxy/Ibup 5/200 mg (N=80) n (%)	Oxy/Ibup 10/200 mg (N=41) n (%)	Oxy/Ibup 10/400 mg (N=338) n (%)	Ibup 200 mg (N=78) n (%)	Oxy 10 mg (N=113) n (%)	Placebo (N=20) n (%)	Total (N=670) n (%)
# Completions	49 (61.3)	31 (75.6)	274 (81.1)	54 (47.8)	3 (15.0)	3 (15.0)	456 (68.1)
# Discontinuations	31 (38.8)	10 (24.4)	64 (18.9)	59 (52.2)	17 (85.0)	17 (85.0)	214 (31.9)
Reason for Discontinuation							
AE	0	1 (2.4)	3 (0.9)	2 (1.8)	0	0	7 (1.0)
Insuff. Response	31 (38.8)	9 (22.0)	59 (17.5)	31 (39.7)	57 (50.4)	17 (85.0)	204 (30.4)
Protocol Violation	0	0	1 (0.3)	0	0	0	1 (0.1)
W/D Consent	0	0	0	0	0	0	0
Other	0	0	1 (0.3)	0	0	0	2 (0.3)

N = # treated with study drug
Source: ISS Update, Vol. 4.8, Panel 10, pg. 38 (pg. 50 of Vol.).

In the multi-dose trial (Oxy-MD-08) 22.4% discontinued prematurely (19.8% in the 5/400 mg group and 25.0% in the 10/400 mg group). The most frequent reason for discontinuation was AEs (8.1% and 15.6% respectively). A total of 6.1% discontinued due to insufficient therapeutic response (7.3 and 4.9 % respectively).

Table 7.4.3 Completion/Discontinuation in the Multi-Dose Oxy/Ibup Clinical Studies

	Treatment		
	Oxy/Ibup 5/400 mg (N=248) n (%)	Oxy/Ibup 10/400 mg (N=244) n (%)	Total (N=492) n (%)
# Completions	199 (80.2)	183 (75.0)	382 (77.6)
# Discontinuations	49 (19.8)	61 (25.0)	110 (22.4)
Reason for Discontinuation			
AE	20 (8.1)	38 (15.6)	58 (11.8)
Insuff. Response	18 (7.3)	12 (4.9)	30 (6.1)
Protocol Violation	2 (0.8)	5 (2.0)	7 (1.4)
W/D Consent	1 (0.4)	1 (0.4)	2 (0.4)
Lost to F/U	0	2 (0.8)	2 (0.4)
Other	8 (3.2)	3 (1.2)	11 (2.2)

N = # treated with study drug
Source: ISS Update, Vol. 4.8, Table 1.1c, pg. 110.

There appeared to be a larger percentage of discontinuations (15.6% vs. 8.1%) due to AEs in the higher oxycodone/ibuprofen combination group. In contrast, the discontinuation rate due to insufficient response in the Oxy/Ibup 10/400 mg group was 4.9% compared to the 7.3% rate in the Oxy/Ibup 5/400 mg group. The higher rate of AEs

could be expected in the 10/400 mg treatment arm because these subjects would be exposed to 2x the Oxycodone dose of the 5/400 mg group, resulting in a higher incidence of opioid related AEs. The same rate for the 10/400 product group in the single-dose studies is much less (0.9%), however this may be misleading because there is less exposure (1 dose only).

7.5 Demographic and Other Baseline Characteristics:

Table 7.2.1.1 illustrates the global distribution of subjects among all clinical studies for the demographic variables: age, sex, and race. Note that in this summary patients receiving multiple treatments are counted only once, resulting in slightly lower numbers of subjects in the oxycodone/ibuprofen multi-dose groups. The initial tables split the demographic profile into Single-Dose studies with the Oxy/Ibup 5/400 mg formulation and similar studies with all other Oxy/Ibup formulations.

Table 7.5.1 Demographic Profile by Treatment Group (All Single-Dose Clinical Studies for Oxy/Ibup 5/400 mg)

Demographic Variable	Treatment Group				
	Oxy/Ibup 5/400 mg (N=754) n (%)	Ibup 400 mg (N=738) n (%)	Oxy 5 mg (N=234) n (%)	Placebo (N=255) n (%)	Total (N=1981) n (%)
Age (Years)					
Mean ± SD	30.9 ± 18.5	31.0 ± 18.8	31.7 ± 19.8	31.0 ± 19.3	31.1 ± 18.9
Range	14 - 89	14 - 96	13 - 87	14 - 88	13 - 96
Age Group (N, %)					
≤ 17 years	109 (14.5)	107 (14.5)	45 (19.2)	39 (15.3)	300 (15.1)
17 < years < 65	563 (74.7)	547 (74.1)	158 (67.5)	183 (71.8)	1451 (73.2)
≥ 65 years	82 (10.9)	84 (11.4)	31 (13.2)	33 (12.9)	230 (11.6)
Sex					
Male	370 (49.1)	372 (50.4)	109 (46.6)	130 (51.0)	981 (49.5)
Female	384 (50.9)	366 (49.6)	125 (53.4)	125 (49.0)	1000 (50.5)
Race (N, %)					
Caucasian	626 (83.0)	623 (84.4)	204 (87.2)	222 (87.1)	1675 (84.6)
Non-Caucasian	128 (17.0)	115 (15.6)	30 (12.8)	33 (12.9)	306 (15.4)
Weight (lbs.)					
N	754	738	234	254	1980
Mean ± SD	162.3 ± 39.2	162.3 ± 39.2	164.9 ± 42.1	165.5 ± 38.7	164.9 ± 42.1
Range	90 - 338	90 - 346	98 - 355	101 - 300	90 - 355
Height (in)					
N	754	738	234	254	1980
Mean ± SD	67.3 ± 4.2	67.5 ± 4.0	67.5 ± 3.8	67.6 ± 3.9	67.4 ± 4.0
Range	52 - 78	51 - 80	58 - 76	55 - 76	51 - 80

Source: ISS Update, Vol. 4.8, Panel 11, pg. 40 (pg. 52 of Vol.).

Examination of Table 7.5.1 shows that the proportions of subjects are distributed approximately equally across sex, weight, and height variables. There is a preponderance

of caucasian subjects in the trial (84.6% vs. 15.4%). The age groups are proportional across treatments with the majority of subjects in the 17 – 65 age group.

Table 7.5.2 Demographic Profile by Treatment Group ("Other" Combination Single-Dose Clinical Studies)

Demographic Variable	Treatment Group						
	Oxy/Ibup 5/200 mg (N=80) n (%)	Oxy/Ibup 10/200 mg (N=41) n (%)	Oxy/Ibup 10/400 mg (N=338) n (%)	Ibup 200 mg (N=78) n (%)	Oxy 10 mg (N=113) n (%)	Placebo (N=20) n (%)	Total (N=670) n (%)
Age (Years)							
Mean ± SD	20.5 ± 4.7	17.9 ± 2.6	39.6 ± 23.6	20.6 ± 5.0	38.9 ± 23.2	25.3 ± 5.2	33.2 ± 21.4
Range	14 - 36	14 - 29	13 - 93	14 - 36	14 - 89	17 - 35	13 - 93
Age Group (N, %)							
≤ 17 years	24 (30.)	19 (46.3)	62 (18.3)	22 (28.2)	20 (17.7)	1 (5.0)	148 (22.1)
17 < years < 65	56 (70.0)	22 (53.7)	203 (60.1)	56 (71.8)	72 (63.7)	19 (95.0)	428 (63.9)
≥ 65 years	0	0	73 (21.6)	0	21 (18.6)	0	94 (14.0)
Sex (N, %)							
Male	40 (50.0)	23 (56.1)	177 (52.4)	43 (55.1)	53 (46.9)	9 (45.0)	345 (51.5)
Female	40 (50.0)	18 (43.9)	161 (47.6)	35 (44.9)	60 (53.1)	11 (55.0)	325 (48.5)
Race (N, %)							
Caucasian	74 (92.5)	39 (95.1)	307 (90.8)	77 (98.7)	101 (89.4)	16 (80.0)	614 (91.6)
Non-Caucasian	6 (7.5)	2 (4.9)	31 (9.2)	1 (1.3)	12 (10.6)	4 (20.0)	56 (8.4)
Weight (lbs.)							
N	80	41	336	78	113	20	668
Mean ± SD	152.3 ± 26.4	147.4 ± 30.6	172.7 ± 45.6	156.8 ± 35.7	165.0 ± 42.3	157.2 ± 26.5	165.0 ± 41.6
Range	104 - 210	88 - 235	87 - 357	90 - 293	100 - 290	110 - 210	87 - 357
Height (in)							
N	80	41	336	78	113	20	668
Mean ± SD	68.6 ± 3.4	68.0 ± 4.1	67.7 ± 4.4	68.2 ± 3.9	67.3 ± 4.0	68.2 ± 4.5	67.8 ± 4.1
Range	61 - 77	60 - 76	57 - 80	60 - 77	60 - 78	57 - 80	57 - 80

Source: ISS Update, Vol. 4.8, Panel 12, pg. 41 (pg. 53 of Vol.).

Table 7.5.2 reveals more disparities among the different treatment groups in the various demographic categories of age distribution, sex ratios, race distribution, height, and weight. These differences may be due chance variation that is more noticeable due the small sample sizes (i.e. Placebo has only 20 subjects total). In spite of this, the age distribution is still unimodal with the majority in the 17 – 65 age group, as in the Oxy/Ibup 5/400 mg studies. The race distribution is slightly more (Caucasian/Other 91.6/8.4% vs. 84.6/15.4% respectively) pronounced in the caucasian category, when compared to the Oxy/Ibup 5/400 mg studies.

The multi-dose studies compared Oxy/Ibup 5/400 mg vs. 10/400 mg formulation and drew subjects from the single-dose trials. The demographic profile for this category of studies is illustrated below.

Table 7.5.3 Demographic Profile by Treatment Group (Multi-Dose Clinical Studies)

Demographic Variable	Treatment Group		
	Oxy/Ibup 5/400 mg (N=334) n (%)	Oxy/Ibup 10/400 mg (N=288) n (%)	Total (N=492*) n (%)
Age (Years)			
Mean ± SD	34.6 ± 20.9	35.0 ± 21.2	35.0 ± 21.1
Range	14 - 89	13 - 87	13 - 89
Age Groups (N, %)			
≤ 17 years	58 (17.4)	47 (16.3)	84 (17.1)
17 < years < 65	222 (66.5)	196 (68.1)	329 (66.9)
≥ 65 years	54 (16.2)	45 (15.6)	79 (16.1)
Sex (N, %)			
Male	176 (52.7)	158 (54.9)	266 (54.1)
Female	158 (47.3)	130 (45.1)	226 (45.9)
Race (N, %)			
Caucasian	279 (83.5)	251 (87.2)	417 (84.8)
Non-Caucasian	55 (16.5)	37 (12.8)	75 (15.2)
Weight (N, %)			
N	332	286	489
Mean ± SD	168.1 ± 43.8	167.6 ± 42.5	168.5 ± 42.5
Range	87 - 355	87 - 338	87 - 355
Height (N, %)			
N	332	286	489
Mean ± SD	67.7 ± 4.2	67.7 ± 4.3	67.7 ± 4.2
Range	52 - 77	52 - 80	52 - 80

Source: ISS Update, Vol. 4.8, Table 2.1c, pg. 113

The multi-dose study tended to show a slightly older mean age group (35.0 vs. 33.2 and 31.1 years, respectively) in the other single-dose demographic distributions. There was an increase in the proportion of male subjects in the multi-dose study (54.1%) as compared to the single-dose groups (49.5 and 51.5%).

The different demographic subgroups were collectively compared vs. their corresponding treatment categories, across all studies. This information is presented in Table 7.5.4. Note that some subjects may be counted > 1 time due to crossover into different treatment categories.

Table 7.5.4 Total Exposure by Treatment Group and Demographic Sub-Groups (All Completed Clinical Studies)

Treatment	Overall N (%)*	Age			Sex		Race	
		≤ 17 yrs	17 to < 65	≥ 65	Male	Female	White	Non-White
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Oxy/Ibuprofen								
5/200 mg	80 (3.0)	24 (5.4)	56 (3.0)	0 (0.0)	40 (3.0)	40 (3.0)	74 (3.2)	6 (1.7)
10/200 mg	41 (1.5)	19 (4.2)	22 (1.2)	0 (0.0)	23 (1.7)	18 (1.4)	39 (1.7)	2 (0.6)
5/400 mg**	910 (34.3)	133 (29.7)	664 (35.3)	113 (34.9)	446 (33.6)	464 (35.0)	762 (33.3)	148 (40.9)
10/400 mg**	527 (19.9)	93 (20.8)	339 (18.0)	95 (29.3)	273 (20.6)	254 (19.2)	471 (20.6)	56 (15.5)
Subtotal***	1428 (53.9)	248 (55.4)	992 (52.8)	188 (58.0)	714 (53.8)	714 (53.9)	1233 (53.9)	195 (53.9)
Ibuprofen								
200 mg	78 (2.9)	22 (4.9)	56 (3.0)	0 (0.0)	43 (3.2)	35 (2.6)	77 (3.4)	1 (0.3)
400 mg	738 (27.8)	107 (23.9)	547 (29.1)	84 (25.9)	372 (28.1)	366 (27.6)	623 (27.2)	115 (31.8)
Subtotal	816 (30.8)	129 (28.8)	603 (32.1)	84 (25.9)	415 (31.3)	401 (30.3)	700 (30.6)	116 (32.0)
Oxycodone								
5 mg	234 (8.8)	45 (10.0)	158 (8.4)	31 (9.6)	109 (8.2)	125 (9.4)	204 (8.9)	30 (8.3)
10 mg	113 (4.3)	20 (4.5)	72 (3.8)	21 (6.5)	53 (4.0)	60 (4.5)	101 (4.4)	12 (3.3)
Subtotal	347 (13.1)	65 (14.5)	230 (12.2)	52 (16.0)	162 (12.2)	185 (14.0)	305 (13.3)	42 (11.6)
Placebo	275 (10.4)	40 (8.9)	202 (10.8)	33 (10.2)	139 (10.5)	136 (10.3)	238 (10.4)	37 (10.2)
Grand Total	**2651**	**448**	**1879**	**324**	**1326**	**1325**	**2289**	**362**

* Percentage based upon Grand Total

** % Includes patients in multi-dose study OXY-MD-08 who received Oxy/Ibup for the 1st time.

*** Patients who received multiple treatments are counted only once.

Source: Oxycodone/Ibuprofen NDA 21-378 ISS, Vol. 76, Table 3.1A, pg. 114.

Multiple Clinical Pharmacology studies were performed, that are also included as part of the safety database. These consist of single- and multi-dose PK studies. Table 7.5.5 illustrates the demographic and baseline characteristics of the subjects in these studies.

Table 7.5.5 Demographic Profile by Treatment Group (Single/Multi-Dose Clinical Pharmacology Studies)

Demographic Variable	Treatment Group				
	Oxy/Ibup 5/400 mg (N=144) n (%)	Oxy/Ibup 10/400 mg (N=36) n (%)	Ibuprofen 400 mg (N=47) n (%)	Oxy 5 mg (N=48) n (%)	Total (N=145) n (%)
Age (Years)					
Mean ± SD	27.0 ± 5.2	28.5 ± 4.4	27.1 ± 5.8	27.1 ± 5.7	27.0 ± 5.2
Range	18 - 39	19 - 35	18 - 39	18 - 39	18 - 39
Sex					
Male	101 (70.1)	19 (52.8)	35 (74.5)	36 (75.0)	102 (70.3)
Female	43 (29.9)	17 (47.2)	12 (25.5)	12 (25.0)	43 (29.7)
Race (N, %)					
Caucasian	98 (68.1)	14 (38.9)	37 (78.7)	38 (79.2)	99 (68.3)
Non-Caucasian	46 (31.9)	22 (61.1)	10 (21.3)	10 (20.8)	46 (31.7)
Weight (lbs.)					
N	144	36	47	48	145
Mean ± SD	159.72 ± 24.23	153.12 ± 22.52	160.51 ± 23.60	160.96 ± 23.56	159.87 ± 24.22
Range	97.2 – 231.5	102.3 – 204.4	117.1 – 231.5	117.1 – 231.5	97.2 – 231.5
Height (in)					
N	144	36	47	48	145
Mean ± SD	68.01 ± 4.56	65.76 ± 4.35	68.24 ± 4.40	68.28 ± 4.36	68.03 ± 4.55
Range	57.1 – 77.2	57.9 – 72.8	57.1 – 76.0	57.1 – 76.0	57.1 – 77.2

Source: ISS Update, Vol. 4.8, Table 6.2A, pg. 40 (pg. 355 of Vol.).

As expected the age range for the clinical pharmacology studies is younger than for the clinical studies (31.1 ± 18.9 and 33.2 ± 21.4 versus 27.0 ± 5.2), due to these being Phase I studies primarily in healthy volunteers. The racial mix is more balanced for the clinical pharmacology studies (68.3/31.7 % vs. 91.6/8.4 %). Height appears to be roughly similar across all groups (clinical and PK studies), while weight varies more for the clinical studies. In spite of the small differences in age, the Clinical PK study samples appear appropriate for addition to the overall safety data-base.

7.6 Deaths:

One death occurred as of January 3, 2002 in a patient taking a combination Oxycodone/Ibuprofen. This is the only death reported out of 1572 total patients receiving a combination product.

Patient 080071, a 66-year-old female, was enrolled in the multi-dose study Oxy-MD-08 after undergoing a total right knee replacement and completing Oxy-MD-07 (orthopedic pain trial). The subjected initially was randomized to ibuprofen 400 mg in the single-dose study and then received 6 days of prn treatment (one dose/day) of combination treatment (Oxycodone/Ibuprofen 5/400 mg). The patient developed a pulmonary embolism (PE) and died suddenly at home on [redacted] This occurred 14 days

after completing dosing in study Oxy-MD-08. The subject received a total of 7 doses over 6 days of combination treatment starting on —— In addition to the study medication, the patient was also taking Enoxaparin from —— for clot prophylaxis after surgery.

The subject's clinical event occurred 2 weeks after finishing the multiple-dose study. Elderly post-op patients can have increased risks of thrombo-embolic events, especially with decreased movement and prolonged bed-rest. Per the patient narrative it appears that the anti-thrombotic medication Enoxaparin was discontinued on the same day as the study medication. It is unclear if the patient was on any other anti-platelet agent or anti-coagulant. Her ambulatory status at the time of the PE is also unknown. However, the prolonged time (multiple half-lives of Oxycodone or Ibuprofen) between the last dose of study medication and the PE makes it difficult to ascribe a causal role of the study drug, in the patient's death.

7.7 Non-Fatal Serious Adverse Events:

Other serious adverse events (SAEs) were defined as serious adverse events other than death, including those temporally associated with or preceding death. No SAEs occurred in the Clinical Pharmacology studies.

SAEs were reported in a total of 28/2796 (1.0%) of subjects. 22/1572 (1.4%) of the SAEs was reported in patients receiving an Oxycodone/Ibuprofen combination product. One subject reported an SAE (cholecystistis/cholelithiasis) who received ibuprofen 400 mg (Oxy-MD3-96-01). All other subjects experiencing SAEs did so during the single-dose orthopedic study (Oxy-MD-07) or the multi-dose extension trial (Oxy-MD-08). A listing of the SAEs by Study Protocol and Treatment is shown in Table 7.7.1, taken from the sponsor's panel listing in the ISS Update discussion.

Table 7.7.1 List of Individual Serious Adverse Events (SAEs)

Treatment Study Number (Lead-in Number)	Patient ID	Age/Sex	AE Preferred Term	Study Day of AE Start
Oxycodone/Ibuprofen 5/400 mg				
Oxy-MD-07	060293	49/M	Fever	0
Oxy-MD-07	130678	85/F	Ileus	3
Oxy-MD-08 (Oxy..05)	010015	33/M	Infection	7
Oxy-MD-08 (Oxy..05)	010223	26/F	Bacterial Infection	6
Oxy-MD-08 (Oxy..07)	080027	75/M	Joint Disorder	14
Oxy-MD-08 (Oxy..07)	080042	71/M	DVT	4
Oxy-MD-08 (Oxy..07)	**080071****	**66/F**	**PE**	**21**
Oxy-MD-08 (Oxy..07)	080375	78/F	DVT	13
Oxy-MD-08 (Oxy..07)	090106	37/F	Infection	11
Oxycodone/Ibuprofen 10/400 mg				
Oxy-MD-07	050017	42/F	Joint Disease	11
			Paralysis	80
Oxy-MD-07	050202	53/M	Injection Site Inflammation	6
Oxy-MD-07	050465	76/M	Cerebral Ischemia	6
			Hyponatremia	19
			Hypotension	19
			Hypovolemia	19
			Syncope	19
Oxy-MD-07	080606	77/F	Cardiovascular Disorder	28
Oxy-MD-07	080729	62/M	Afib	7
Oxy-MD-08 (Oxy..07)	080013	73/F	Bacterial Infection	3
Oxy-MD-08 (Oxy..07)	080059	59/F	Pneumonia	3
Oxy-MD-08 (Oxy..07)	080059	59/F	DVT	5
Oxy-MD-08 (Oxy..07)	080064	62/M	Cellulitis	5
			Edema	5
Oxy-MD-08 (Oxy..07)	080207*	76/M	Intestinal Obstruction*	5
Oxy-MD-08 (Oxy..07)	080217	36/M	Cellulitis	38
Oxy-MD-08 (Oxy..07)	080357	80/F	Urinary Retention	3
Oxy-MD-08 (Oxy..07)	090312*	86/F	Anemia*	4
			Encephalopathy*	5
			Hypoxia*	4
			Melena*	3
			Pre-renal Azotemia	4
			Stomach Ulcer Hemorrhage	3
Ibuprofen 400 mg				
Oxy-MD3-96-01	010227	18/F	Cholecystitis	10
			Cholelithiasis	10
Oxy-MD-07	050781	59/M	Dehydration	30
			Syncope	30
Oxy-MD-07	060118	59/M	Ileus	1
Oxy-MD-07	060500	49/F	Abscess	9
Oxycodone 5 mg				
Oxy-MD-07	050464	67/F	Fever	4
Oxycodone 10 mg				
Oxy-MD-07	010581	59/M	DVT	2

* Discontinue due to SAE

** Death occurred 2 weeks after study stop of PE

AE Start = SAE start date – study drug start date + 1
Source: ISS Update, Vol. 4.8, Panel 15, pg. 48 (pg. 60 of Vole).

The individual listing of SAEs demonstrates that the majority of events occurred in older subjects (> 50). Thirteen (1.9%) patients experience 19 SAEs during the orthopedic post-op pain study Oxy-MD-07. SAEs reported included fever; ileus; joint disease and paralysis; injection site inflammation; cerebral ischemia; hyponatremia; hypotension; syncope; and atrial fibrillation. The sponsor felt that all of these SAEs were consistent with typical complications following substantial orthopedic surgery. Two patients from the Oxycodone/Ibuprofen 10/400 mg group were discontinued after developing SAEs (ileus in 080207; anemia, encephalopathy, hypoxia, melena, azotemia, and bleeding gastric ulcer in 090312). Selected SAE narratives for combination product administration are examined in more detail below, by the reviewer. These events are then classified by their potential relationship to the SAE.

Study / Patient ID	Treatment	SAE Term	Reviewer Comments
Oxy-MD-08 / 080071	Oxy/Ibup 5/400 mg	PE, DEATH (later)	**PLEASE SEE DEATH SUMMARY SECTION FOR DISCUSSION OF THIS Subject's SAE.**
Oxy-MD-08, 080207	Oxy/Ibup 10/400 mg	Intestinal Obstruction	75-year-old male with right total knee replacement receiving study drug for two days along with metoclopramide & ondansetron, for nausea. The subject developed severe GI distress for 3 days that resulted in discontinuation from the study. Colonoscopic decompression for cecal volvulus, was performed. The subject recovered and was discharged from the hospital on — . The investigator judged there was no association with the SAE and the study drug. *However, narcotic analgesics are associated with decreased smooth muscle activity and constipation, suggesting a POSSIBLE relationship.*
Oxy-MD-08, 090312	Oxy/Ibup 10/400 mg and Enoxaparin 60 mg qd	UGI Bleed, Azotemia, Encephalopathy,	86-year-old female treated with study drug prn for 3 days, after undergoing ORIF of a right femoral FX. The patient was also on enoxaparin 60 mg daily until hospitalization with UGI bleeding, severe melena, hypoxemai, and azotemia. Study drug and trial participation was discontinued at that time. AEs resolved by — and the patient was discharged to rehab on — . *The Study Drug / SAE relationship is UNLIKELY.*
Oxy-MD-08 / 080217	Oxy/Ibup 10/400 mg	HA, Cellulitis	36 M receiving study drug prn x 7 days after L Calcaneous FX repair. Subject D/C'd from study for persistent mild HA for the two initial days of the study. During f/u call the subject reported a left foot infection occurring 5 days after last study dose, Rx'd by his surgeon. Subject was later re-hospitalized for Rx of cellulitis, which later resolved. *Study Drug / SAE (HA) judged POSSIBLE, SAE (Cellulitis) UNLIKELY.*
Oxy-MD-08 / 090106	Oxy/Ibup 5/400 mg	Dizziness, Nausea, Infection	37 F receiving study drug prn x 8 days after laminectomy procedure. Subject reported severe dizziness + Nausea 5 days into study. Subject was D/C'd from study due to SAEs after 8 days and all Sx's resolved on day of discontinuation. 2 days later subject was hospitalized due to post-op wound infection

Study / Patient ID	Treatment	SAE Term	Reviewer Comments
			and underwent I&D, after which the subject recovered. *Study Drug / SAE (Dizziness, Nausea) relationship judged POSSIBLE, SAE (Infection) judged UNLIKELY.*
Oxy-MD-08, 080059	Oxy/Ibup	DVT, Pneumonia	This 59-year-old female developed pneumonia during hospitalization, extending her stay. She developed a DVT DX'd by venous doppler 5 days later and was started on warfarin. Later discharged. Took study drug prn for 3 days (contiguous with development of pneumonia). *Narcotic associated decreased respiratory effort/drive can increase the risk of pneumonia and thus the study drug / SAE has a POSSIBLE relationship.*
Oxy-MD-08 / 080357	Oxy/Ibup 10/400 mg	Urinary Retention	80 F receiving study drug prn x 10 days after L TKA. Subject developed severe urinary retention 2 days after starting study, which extended hospitalization. Subject was D/C'd with catheter and later reported continued abnormal voiding requiring self-catheterization which resolved ~ 1 month later. *Study Drug / SAE relationship judged POSSIBLE.*
Oxy-MD-07 / 010581	Oxy 10 mg	DVT	59 male w/ h/o HTN took 1 dose of study drug 2 days post-op after right TKA. The next day patient developed R leg pain and was DX'd with DVT of RLExtremity. *Study Drug / SAE relationship judged UNCLEAR.*
Oxy-MD-07 / 050017	Oxy/Ibup 10/400 mg	Joint Disorder Paralysis	42 F w/ h/o LLeg pain and PE due to DVTs received study drug x 1 for post-op pain [redacted] after L THA. On [redacted] was re-hospitalized for surgical revision for intermittent dislocations. Subject had ongoing LLExt hemiparalysis (due to pain?) and sciatica. *Given history, multiple surgeries, and complications study drug / SAE relationship is UNLIKELY.*
Oxy-MD-07 / 050202	Oxy/Ibup 10/400 mg	Edema	53 M had study drug x 1 after L2/L3 laminectomy. Developed surgical site inflammation and was readmitted 5 days later for further treatment. *Study Drug/SAE relationship UNLIKELY.*
Oxy-MD-07 / 050464	Oxy 5 mg	Fever	67 F received study dose x 1 for post-op pain from L TKA, and was D/C'd same day. Re-admitted 3 days later for Fever of Unknown Origin. Sxs resolved 2 days later. *Study Drug / SAE relationship UNCLEAR.*
Oxy – MD-07 / 050465	Oxy/Ibup 10/400 mg	CVA	76 M w/ h/o memory changes, 1st Degree AV Block received study drug x 1 for post-op pain from R TKA. In phone f/u patient reported CVA 5 days later (1 day after D/C) affecting his memory. ER w/u showed negative CT but was DX'd as TIA. *Study Drug / SAE relationship UNCLEAR.*
Oxy-MD-07 / 050486	Oxy/Ibup 10/400 mg	Syncope, Hyponatremia, Hypotension	75 M w/ h/o IDDM, Heart Murmur received study drug x 1 for post-op pain from R TKA. Following administration pt. Experienced syncope, hypotension, and hyponatremia. 18 days later patient was hospitalized for these Sxs and autonomic dysfunction was DX'd due to Diabetes. Sx's resolved during hospitalization. *Study Drug / SAE relationship UNLIKELY.*
Oxy-MD-07 / 060293	Oxy/Ibup 5/400 mg	Fever	49 M received study drug x 1 for post-op lumbar laminectomy pain. Patient had intermittent fever b/f study drug administration and this continued afterwards, eventually resolving. *Study Drug / SAE relationship UNLIKELY.*
Oxy-MD-07 / 080606	Oxy/Ibup 10/400 mg	R Heart Failure,	77 F w/ h/o CVA, HTN, Vascular Dz. received single dose of study drug 2 days after R THA. ~ 1 mo. Later patient was

Study / Patient ID	Treatment	SAE Term	Reviewer Comments
		Cardiovascular Dz.	hospitalized for SOB/Dyspnea and CHF. Patient was DX'd with 3 Vessel CAD at that time and D/C'd for outpatient therapy. *Study Drug / SAE relationship UNLIKELY.*
Oxy-MD-07 / 080729	Oxy/Ibup 10/400 mg	Afib	62 M received study drug x 1 two days after Bil TKA. 6 days later patient showed asymptomatic 180 BPM Afib, and underwent medical therapy for this. The SAE prolonged hospitalization. *Study Drug / SAE relationship UNLIKELY.*
Oxy-MD-07 / 130678	Oxy/Ibup 5/400 mg	Ileus	86 F w/ h/o Colon CA, colectomy, and colostomy received study drug x 1 one day after L THA. Patient developed N/V with ileus 3 days later, which later resolved. *Although narcotic agents (such as the study drug) are associated with decreased bowel motility, a single dose causing problems 3 days later appears UNLIKELY.*
Oxy-MD-08 / 010015	Oxy/Ibup 5/400 mg	Infection	33 M taking study drug prn x 8 days and completing the study. During study subject developed L facial swelling requiring I & D 4 days into the study. Subject again developed L Mandibular swelling and went to ER and was DX'd w/ R Buccal Space Infection. Subject was hospitalized and underwent I&D + ABX therapy, Oxycodone/APAP, and Chlorhexidine Gluconate. Subject was D/C'd on oral ABX. *Post-surgical infections are not uncommon and the Study Drug / SAE relationship is judged UNLIKELY.*
Oxy-MD-08 / 010223	Oxy/Ibup 5/400 mg	Infection	26 F receiving study drug prn x 4 days. Subject underwent surgical debridement + Clindamycin 5 days after surgery. Subject went to ER the same day and was hospitalized for Neck Abscess and R Submandibular Buccal Space Abscess. Subject Rx'd with I&D, ABX, and Oxycodone/APAP and discharged after resolution of Sxs. *Study Drug / SAE relationship judged UNLIKELY.*
Oxy-MD-08 / 080013	Oxy/Ibup 10/400 mg	Infection	73 F taking study drug prn x 7 days for L THA pain. On study day #5 subject developed post-op nosocomial L hip surgical wound infection. Subject treated with Vanco and D/C'd after 5 days and then re-admitted for further ABX therapy. By 2 months wound infection resolved. *Study Drug / SAE relationship judged UNLIKELY.*
Oxy-MD-08 / 080027	Oxy/Ibup 5/400 mg	Joint Dislocation	75 M received study drug prn x 8 days. 5 days after completing study subject was re-admitted for R Hip Dislocation and nonserious nosocomial wound infection. Subject was Rx'd and Sx's resolved. *Study Drug / SAE relationship judged UNLIKELY.*
Oxy-MD-08 / 080042	Oxy/Ibup 5/400 mg	DVT	71 M receiving study drug prn x 9 days after R TKA. 3 days into study subject developed R calf DVT and was Rx'd with enoxaparin & warfarin. Per patient's primary care physician he recovered and warfarin was stopped. *Study Drug / SAE relationship judged UNCLEAR.*
Oxy-MD-08 / 080059	Oxy/Ibup 10/400 mg	Pneumonia, DVT	59 F w/ h/o RAD, Bronchitis, Pneumonia, and COPD was taking study drug prn x 3 days after R TKA. 1 day into study subject developed pneumonia Rx'd with ABX. 1 day after stopping study drug subject DX'd with DVT of R leg with femoral thrombus. Subject was switched from enoxaparin to warfarin and heparin. After resolution of pneumonia, subject

Study / Patient ID	Treatment	SAE Term	Reviewer Comments
			D/C'd on warfarin and DVT resolved 4 months later. *Study Drug / SAE relationship UNCLEAR.*
Oxy-MD-08 / 080064	Oxy/Ibup 10/400 mg	Cellulitis, Edema	62 M receiving study drug prn x 13 days after R THA. 4 days into study subject hospitalized for surgical site pain/swelling and was Rx'd with Morphine and ABX. Sx's resolved and subject later D/C'd. *Study Drug / SAE relationship UNLIKELY.*
Oxy-MD-08 / 080375	Oxy/Ibup 5/400 mg	DVT	78 F receiving study drug prn x 6 days after L TKA. Subject did not complete study due to protocol violation (dosing with oxycodone,etc... in addition to study drug). 7 days after D/C'd from study subject was hospitalized for LLeg swelling x two days. Subject DX'd with L DVT and Rx'd with warfarin and enoxaparin. DVT resolved. *Study Drug / SAE relationship UNLIKELY.*

Source: ISS Update, Vol. 4.9, Patient Narratives, pg. 198-226.

Note that the listed SAEs are for the clinical studies only. There were no deaths or SAEs reported in any of the six clinical pharmacology studies.

The overall impression of the SAEs, after reviewing the individual narratives, is that most are likely related to typical post-op complications typically seen among a predominantly elderly population with multiple medical problems. There are several events (e.g. ileus, etc...) where the study drug may have a possible relationship to the event. There does not appear to be an obvious safety "signal" in terms of event type, frequency of occurrence or severity that can be easily discerned from the data.

7.8 Other Significant Adverse Events:

7.8.1 Adverse Events That Led to Discontinuation of Study Drug:

The incidence of AEs by treatment group and body system that led to study drug discontinuation was summarized in Sponsor Panel's 16 and 17, for the single-dose clinical studies. These tables are reproduced below:

Table 7.8.1.1 AE Incidence Associated with Discontinuation for Single-Dose Clinical Studies of Oxy/Ibup 5/400 mg

Body System Preferred Term	Treatment Group			
	Oxy/Ibup 5/400 mg (N = 754) n (%)	Ibup 400 mg (N = 738) n (%)	Oxy 5 mg (N = 234) n (%)	Placebo (N = 255) n (%)
Patients with ≥ 1 AE leading to discontinuation	7 (0.9)	4* (0.5)	0	3 (1.2)
Digestive System				
Vomiting	4 (0.5)	2 (0.3)	0	1 (0.4)
Nausea	2 (0.3)	0	0	0
Body as a Whole				
HA	2 (0.3)	1 (0.1)	0	1 (0.4)
Pain	1 (0.1)	0	0	0
Nervous System				
Somnolence	0	0	0	1 (0.4)
Skin and Appendages				
Sweat	1 (0.1)	0	0	0

* One subject in Oxy-MD3-96-01 recorded as discontinued due to AE, but no AE was recorded in the CRF.
N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 16, pg. 51 (pg. 63 of Vol.).

Table 7.8.1.2 AE Incidence Associated with Discontinuation for Single-Dose Clinical Studies (other Oxy/Ibup Combinations)

Body System Preferred Term	Treatment Group					
	Oxy/Ibup 5/200 mg (N = 80) n (%)	Oxy/Ibup 10/200 mg (N = 41) n (%)	Oxy/Ibup 10/400 mg (N = 338) n (%)	Ibuprofen 200 mg (N = 78) n (%)	Oxy 10 mg (N = 113) n (%)	Placebo (N = 20) n (%)
Patients with ≥ 1 AE leading to discontinuation	0	1 (2.4)	3 (0.9)	1 (1.3)	2 (1.8)	0
Digestive System						
Vomiting	0	1 (2.4)	2 (0.6)	1 (1.3)	2 (1.8)	0
Nausea	0	1 (2.4)	0	1 (1.3)	1 (0.9)	0
Body as a Whole						
Pain	0	0	1 (0.3)			0
Nervous System						
Confusion	0	0	1 (0.3)			0

N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 17, pg. 52 (pg. 64 of Vol.).

Subjects discontinuing in the single-dose studies due to AEs was 0.9% in the Oxy/Ibup 5/400 mg group, 0.9% in the 10/400 mg group, 0.5% in the ibuprofen alone, 0 % in the oxy 5 mg alone, 1.8% in the oxy 10 mg alone, and 0 – 1.2 % in the placebo groups. A total of 21 subjects reported AEs associated with discontinuation from the single-dose studies. Note that one subject was reported as having an AE resulting in discontinuation

from study OXY-MD3-96-01 treated with Ibuprofen 400mg. However, the Sponsor states that no AE was recorded in the associated subject's CRF, when they examined it. The Sponsor did not provide the individual subject ID number, so that inspection of this CRF could not be performed.

The frequency of reasons for discontinuation can be viewed by body system. GI complaints were the most frequent reason; due to nausea and vomiting. This was most frequent in the Oxy 10 mg group (0.9% and 1.8% respectively). Another reason for discontinuation was HA: 2 subjects in the combination groups, 1 ibuprofen, and 1 placebo patient. The overall crude incidence for these events was < 1 %.

Table 7.8.1.2 AE Incidence Associated with Discontinuation (> 1 Subject in Any Treatment Group) – Clinical Multi-Dose & Lead-In Studies

Body System Preferred Term	Treatment Group	
	Oxy/Ibup 5/400 mg (N = 248) n (%)	Oxy/Ibup 10/400 mg (N = 244) n (%)
Patients with ≥ 1 AE leading to discontinuation	20 (8.1)	38 (15.6)
Digestive System		
Nausea	11 (4.4)	22 (9.0)
Vomiting	4 (1.6)	9 (3.7)
Constipation	1 (0.4)	2 (0.8)
Nervous System		
Dizziness	5 (2.0)	14 (5.7)
Somnolence	0	5 (2.0)
Body as a Whole		
HA	5 (2.0)	4 (1.6)
Asthenia	0	5 (2.0)
Fever	0	2 (0.8)
Cardiovascular System		
Vasodilation	1 (0.4)	2 (0.8)
Skin and Appendages		
Pruritus	0	2 (0.8)
Urticaria	0	2 (0.8)

N = # subjects treated with study drug
n = # subjects discontinued due to AEs.
Subjects receiving different doses of oxy/ibup in the lead-in and multi-dose studies are counted separately for each dose.
Source: ISS Update, Vol. 4.8, Panel 18, pg. 53 (pg. 65 of Vol.).

The sponsor notes that the crude incidence of AEs associated with discontinuation was greater for the multi-dose study, as illustrated in table 7.8.1.2. Twenty subjects (8.1%) in the Oxy/Ibup 5/400 mg group and 38 (15.6%) in the 10/400 mg groups reported AEs causing discontinuation. This results in an overall number of 58 subjects (11.8%) reporting > 1 AE leading to D/C. The most frequent AEs for Oxy/Ibup 5/400 & 10/ 400

were GI disorders (4.8% and 10.7%), Nervous System Disorders (2.0% and 8.6%), and Events involving the Body as a Whole (2.0 and 4.1% respectively). The higher oxycodone dose combination product appeared to have a larger percentage of GI and Nervous System associated AEs. These AEs appear typical of narcotic associated side effects. No obvious excess increased numbers of cases are seen among the combination treatment groups suggesting an adverse safety signal.

In the clinical pharmacology studies, there was only one discontinuation due to an adverse event. This was coded as RASH and PRURITUS in Subject 013, in Study Oxy-PK1-97-02. This 29 year-old female subject developed her rash symptoms after one dose of Oxycodone/Ibuprofen 5/400 mg. The event was rated as MILD and POSSIBLY RELATED. The subject was discontinued from the study and was treated for this AE.

7.9 Overall Evaluation of Adverse Events:

7.9.1 Approach to Eliciting AEs in the Development Program:

Adverse Events were volunteered by the subject or observed by the investigator and recorded throughout the study period, after the 1st administration of study drug. AEs were defined as "any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug" whether or not considered related to the study drug. The investigator provided an assessment of the seriousness, severity, timing, causal relationship to study drug, and event outcome. All events were recorded.

Treatment Emergent Adverse Events (TEAEs) were defined as an AE starting after dosing with study drug or present before dosing, and worsening after dosing. For the combined single- and multi-dose AE dataset, a TEAE is defined as an event starting post 1st dose of combination treatment, either in lead-in or in the extension study, or an ongoing AE that worsened after treatment with a combination product. Subjects switching combination treatment from lead-in to the extension study had AEs associated with whatever combination treatment they had in the lead-in study.

7.9.2 Appropriateness of AE Categorization and Preferred Terms:

Review of the pooled 120-Day ISS Safety Database was notable for some mismatch between the investigator term and the preferred coded term. "Feeling Hot", "Feeling Warm" and "Hot Flashes" were coded as the cardiovascular body term VASODILATION. Multiple investigator statements of "blurred vision" or "visual change" were coded as AMBLYOPIA instead of the preferable term ABNORMAL VISION. "Muscle spasms" and "leg cramps" were both coded as HYPERTONIA, while in other subjects "muscle spasm" were coded as SPASM GENERAL. All reviewed investigator designations of "fatigue", "tiredness", etc... in the electronic safety data base were coded as ASTHENIA, which is more of a diagnosis than a symptom.

In contrast, the majority of the other examined investigator terms and AE coded terms appeared to agree reasonably well. As an exercise, the reviewer correlated the AE preferred term with the electronic entries and the sponsor provided CRFs, for selected subjects. In all the examined cases, there was reasonable agreement between the three documents.

In conclusion, the majority of AE categorization appeared to be appropriate for determining the frequency of AEs accurately. There appeared to be rare problems in the particular cases mentioned above with inaccurate and inconsistent coding of the investigator terms. The reviewer notes that these problems appeared to be associated only with investigator terms like "feeling warm", "hot flashes", muscle spasm, shaking", "fatigue", and "blurred vision". The observed mismatch suggests that some of the resulting AE incidence analyses using these terms (particularly categories ASTHENIA, AMBLYOPIA, and VASODILATION) may not have much validity.

7.9.3 Analyses and Explorations:

The sponsor has reported AEs by number (percentage) by treatment group, body system, and preferred term. For clinical studies, crude incidence tables of TEAEs are also presented by treatment group, body system, and preferred term stratified by age group, sex, and race.

The overall crude incidence of TEAEs for the single-dose trials is illustrated in tables 7.9.3.1 and 7.9.3.2 by treatment group, body system, and preferred term for the oxy/ibup 5/400-combination compared to the other oxy/ibup combinations, respectively. The single-dose studies show a range of TEAE frequencies for combination treatments: 26.1% in the 5/400 group to 58.5% in the 10/200-mg group. The corresponding frequencies for oxy/ibup 10/400-mg, ibuprofen 400 mg alone, ibuprofen 200 mg alone, and placebo were 46.7%, 18.0%, 24.4%, and 19.6% respectively.

Somnolence (8.6%), Nausea (7.6%), Dizziness (5.8%), and Vomiting (5.2%) were the most frequent TEAEs reported in the oxy/ibup 5/400-mg treated group. This incidence was > 2x that seen in the corresponding placebo group (2.4, 3.5, 2.4, and 2.4% respectively). Somewhat greater percentages of Nausea and Vomiting were seen in the oxycodone alone 5 mg group, suggesting that these are related to oxycodone administration.

Table 7.9.3.1 TEAE Crude Incidence (≥ 1 %) for Clinical Studies – (All Single-Dose Oxy/Ibup 5/400 mg Studies)

Body System Preferred Term	Treatment Group			
	Oxy/Ibup 5/400 mg (N = 754) n (%)	Ibup 400 mg (N = 738) n (%)	Oxy 5 mg (N = 234) n (%)	Placebo (N = 255) n (%)
Patients with ≥ 1 AE	197 (26.1)	133 (18.0)	77 (32.9)	51 (20.0)
Digestive System				
Nausea	57 (7.6)	22 (3.0)	34 (14.5)	9 (3.5)
Vomiting	39 (5.2)	9 (1.2)	25 (10.7)	6 (2.4)
Dry Socket	0	4 (0.5)	2 (0.9)	4 (1.6)
Nervous System				
Somnolence	65 (8.6)	33 (4.5)	12 (5.1)	6 (2.4)
Dizziness	44 (5.8)	16 (2.2)	16 (6.8)	6 (2.4)
Body as a Whole				
HA	19 (2.5)	23 (3.1)	8 (3.4)	13 (5.1)
Fever	6 (0.8)	4 (0.5)	3 (1.6)	4 (1.6)
Asthenia	8 (1.1)	1 (0.1)	1 (0.4)	1 (0.4)
Cardiovascular System				
Hypertension	0	4 (0.5)	4 (1.7)	6 (2.4)
Skin and Appendages				
Sweat	15 (2.0)	7 (0.9)	4 (1.7)	1 (0.4)

* One subject in Oxy-MD3-96-01 recorded as discontinued due to AE, but no AE was recorded in the CRF.
N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 19, pg. 56 (pg. 68 of Vol.).

Much greater percentages of Nausea were seen in the oxy/ibup 10/200 mg (41.5%), 5/200 mg (22.5%), 10/400 mg (17.5%), and oxycodone 10 mg (16.8%), compared to placebo (5.0%). Somnolence and Dizziness also appeared to be more common among the oxy/ibup combinations when compared to ibuprofen 200 mg alone and placebo.

Table 7.9.3.2 TEAE Crude Incidence (≥ 1 %) for Clinical Studies – (All Other Single-Dose Oxy/Ibup Combination Studies)

Body System Preferred Term	Treatment Group					
	Oxy/Ibup 5/200 mg (N = 80) n (%)	Oxy/Ibup 10/200 mg (N = 41) n (%)	Oxy/Ibup 10/400 mg (N = 338) n (%)	Ibuprofen 200 mg (N = 78) n (%)	Oxy 10 mg (N = 113) n (%)	Placebo (N = 20) n (%)
Patients with ≥ 1 AE	33 (41.3)	24 (58.5)	158 (46.7)	19 (24.4)	48 (42.5)	3 (15.0)
Digestive System						
Nausea	18 (22.5)	17 (41.5)	59 (17.5)	10 (12.8)	19 (16.8)	1 (5.0)
Vomiting	5 (6.3)	12 (29.3)	50 (14.8)	6 (7.7)	17 (15.0)	0
Nervous System						
Somnolence	6 (7.5)	0	48 (14.2)	3 (3.8)	15 (13.3)	1 (5.0)
Dizziness	10 (12.5)	4 (9.8)	27 (8.0)	3 (3.8)	8 (7.1)	0
Body as a Whole						
HA	5 (6.3)	2 (4.9)	10 (3.0)	3 (3.8)	2 (2.7)	1 (5.0)
Skin and Appendages						
Sweat	0	0	17 (5.0)	0	3 (2.7)	0

N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 20, pg. 57 (pg. 69 of Vol.).

In the multi-dose study TEAEs occurred in 58.4% of the 5/400 group and 78.8% of the 10/400 group. The most frequently reported AEs were similar to the single-dose studies including Nausea (25.4 and 35.4%), Dizziness (19.2 and 33.7%), Somnolence (17.4 and 21.5%), and HAs (10.2 and 10.4%) respectively. The 10/400-mg group had a generally greater frequency of narcotic associated side-effect AEs (nausea, vomiting) than the lower 5/400-mg group.

Table 7.9.3.3 TEAE Crude Incidence (≥ 5 %) for Clinical Studies – (Multi-Dose and Lead-In Study Experiences)

Body System Preferred Term	Treatment Group	
	Oxy/Ibup 5/400 mg (N = 334) n (%)	Oxy/Ibup 10/400 mg (N = 288) n (%)
Patients with ≥ 1 AE	195 (58.4)	227 (78.8)
Digestive System		
Nausea	85 (25.4)	102 (35.4)
Vomiting	15 (4.5)	50 (17.4)
Constipation	15 (4.5)	15 (5.2)
Nervous System		
Dizziness	64 (19.2)	97 (33.7)
Somnolence	58 (17.4)	62 (21.5)
Body as a Whole		
HA	34 (10.2)	30 (10.4)
Asthenia	11 (3.3)	22 (7.6)
Pain	17 (5.1)	14 (4.9)

Body System Preferred Term	Treatment Group	
	Oxy/Ibup 5/400 mg (N = 334) n (%)	Oxy/Ibup 10/400 mg (N = 288) n (%)
Cardiovascular System		
Vasodilation (Warm Feeling)	10 (3.0)	16 (5.6)
Skin and Appendages		
Pruritis	11 (3.3)	33 (11.5)
Urticaria	14 (4.2)	21 (7.3)

N = # subjects treated with study drug
n = # subjects discontinued due to AEs.
Subjects receiving different doses of oxy/ibup in the lead-in and multi-dose studies are counted separately under both doses.
Source: ISS Update, Vol. 4.8, Panel 21, pg. 58 (pg. 70 of Vol.).

The sponsor notes that the multi-dose study did not include a placebo or single ingredient comparator, making interpretation of the incidence rates difficult. However, given the placebo incidence rates seen in the single-dose trials, it would seem reasonable that similar placebo AE frequencies would also have been seen in the multi-dose trial. This suggests that the combination treatments would have an excess of AEs compared to placebo, as might be expected. The episodes of pruritis and urticaria may be unique to the multi-dose combination products, as it was not reported as frequently in the single-dose groups.

In summary, the typical TEAEs seen in the single-dose clinical studies (Nausea, Vomiting, Dizziness, Somnolence, etc...) are what one could expect to see as side effects of narcotic treatment. In addition, the higher combination doses of oxycodone/ibuprofen appear to have a greater predominance of these TEAEs. This constellation of TEAEs is certainly greater than that for Placebo, as would be expected. In contrast, the single-dose studies show approximately equal crude incidence frequencies of HAs and Fevers, when compared to the Placebo group. Interestingly, episodes of HTN are seen more frequently in the Placebo arm, possibly due to post-surgical pain?

TEAEs did occur in the clinical pharmacology studies, to a lesser degree. Crude incidence of AEs is shown in Table 7.9.3.4 for the single-dose studies, by preferred term and treatment. A similar listing is also included for the multi-dose clinical pharmacology studies. Of note, a total of 41% and 61% of subjects treated with Oxy/Ibup 5/400 mg and 10/400 mg respectively, reported TEAEs. This roughly similar to the clinical study proportions. The most common occurrences (> 5%) included Dizziness, Nausea, HA, Somnolence, and Vomiting. This was similar to the profile of TEAEs by preferred term, reported in the clinical studies.

Table 7.9.3.4 TEAE Crude Incidence (≥ 3 %) for Clinical-Pharmacology Studies (Single-Dose Exposure)

Body System Preferred Term	Treatment Group			
	Oxy/Ibup 5/400 mg (N = 132) n (%)	Ibup 400 mg (N = 36) n (%)	Oxy 5 mg (N = 47) n (%)	Placebo (N = 48) n (%)
Patients with ≥ 1 AE	53 (40.2)	22 (61.1)	2 (4.3)	11 (22.9)
Dizziness	41 (31.1)	18 (50.0)	0	5 (10.4)
Nausea	12 (9.1)	12 (33.3)	0	4 (8.3)
HA	8 (6.1)	2 (5.6)	0	2 (4.2)
Somnolence	7 (5.3)	4 (11.1)	0	0
Vomiting	7 (5.3)	6 (16.7)	0	2 (4.2)
Asthenia	6 (4.5)	3 (8.3)	0	0
Pruritus	2 (1.5)	3 (8.3)	0	0

N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 25, pg. 72 (pg. 84 of Vol.), Cross-Reference Table 6.3B.

A similar pattern of AE reports was seen in the multi-dose clinical pharmacology studies of Oxy/Ibup 5/400 mg treatment. This is illustrated in the following table.

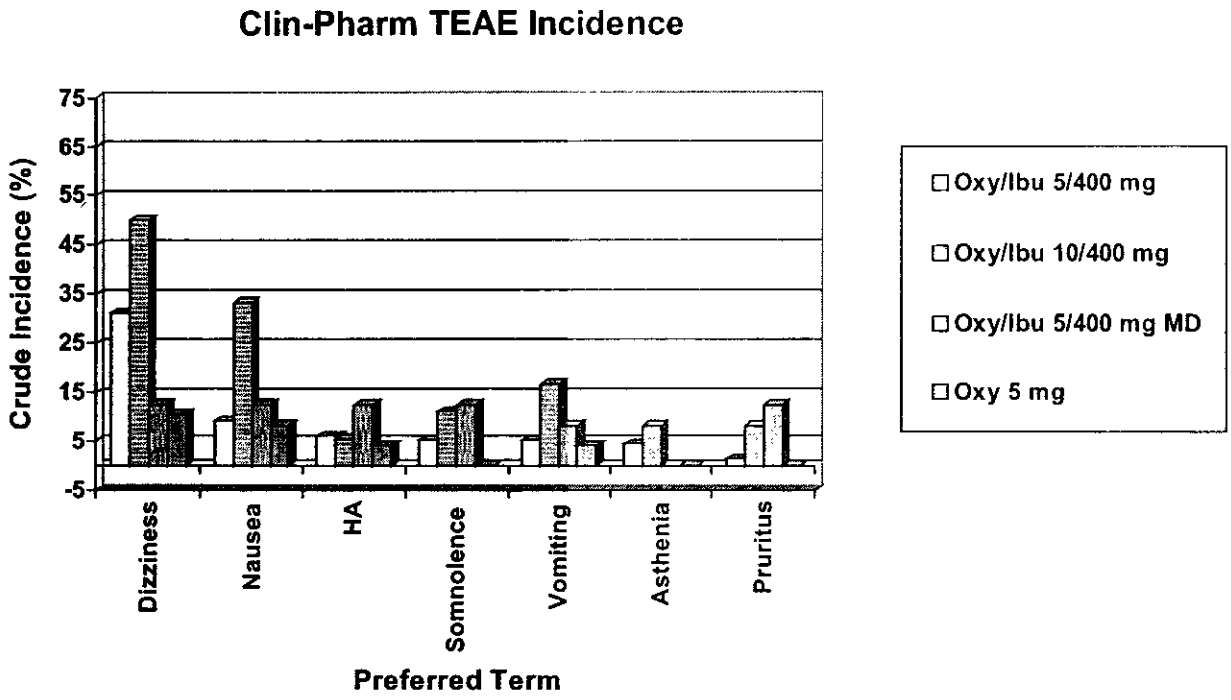
Table 7.9.3.5 TEAE Incidence (≥ 1 Patient) for Clinical-Pharmacology Studies (Multi-Dose Exposure)

Body System Preferred Term	Treatment Group: Oxy/Ibup 5/400 mg (N = 24) n (%)
Patients with ≥ 1 AE	12 (50.0)
Dizziness	3 (12.5)
Somnolence	3 (12.5)
HA	3 (12.5)
Nausea	3 (12.5)
Pruritus	3 (12.5)
Vomiting	2 (8.3)
Vasodilation	2 (8.3)

N = # subjects treated with study drug; n = # subjects discontinued due to AEs.
Source: ISS Update, Vol. 4.8, Panel 26, pg. 73 (pg. 85 of Vol.), Cross-Reference Table 6.3C.

Selected results from the Clin-Pharm tables, are illustrated graphically below. Note that the multi-dose Oxy/Ibup 5/400 mg doses are also included.

Figure 7.9.3.1 Clin-Pharm TEAE Incidence by Preferred Term



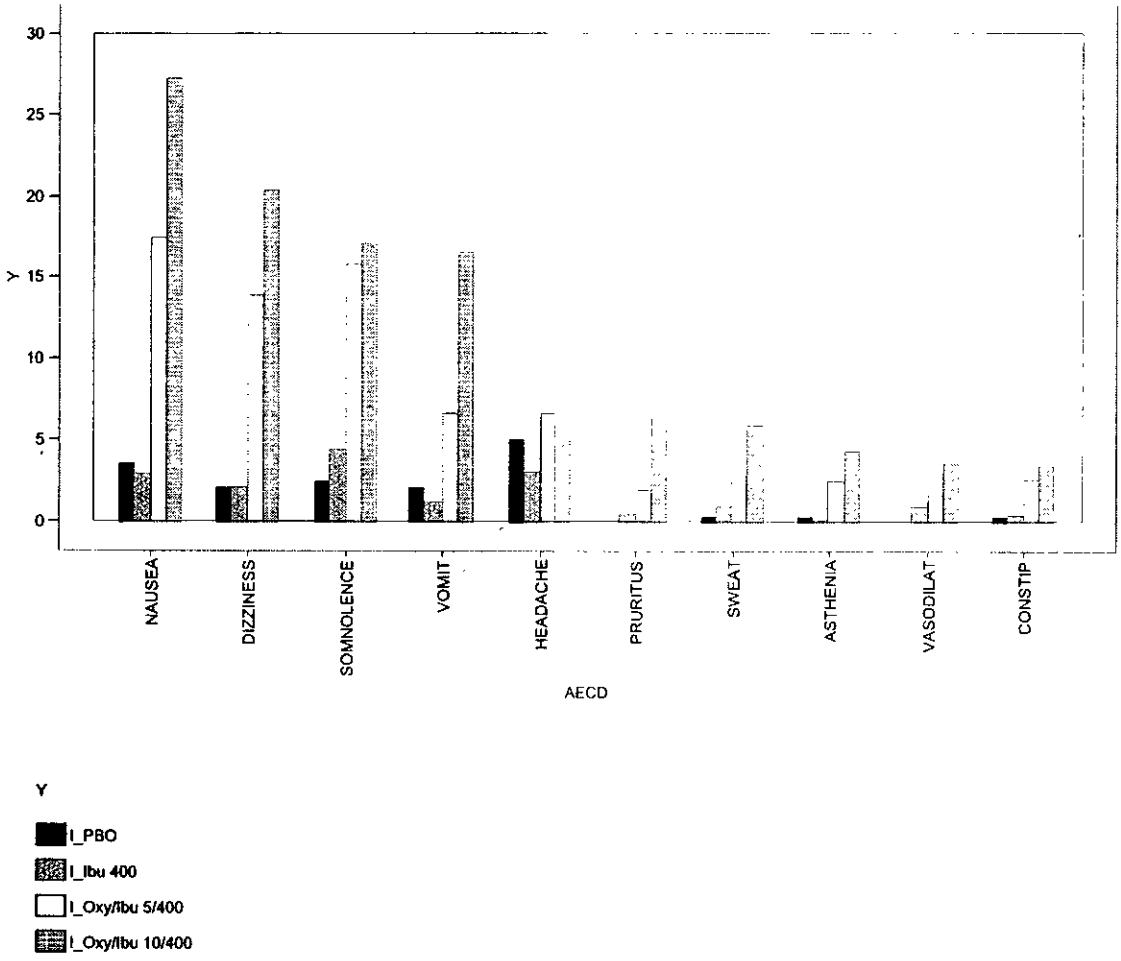
Overall, the TEAEs reported in the clinical pharmacology studies appear to be similar in frequency and preferred term to the clinical studies.

7.9.4 Oxycodone/Ibuprofen Combination-Placebo Differences in AE Rates:

Another way of looking at the summary results is by examination of the following figure. Here the reviewer pooled all the clinical studies and then calculated the crude incidence of the 10 most frequent AEs, using JMP 4.0. Note that subjects may be counted > 1 time by going from the single-dose groups to the multi-dose study. The graphic bar chart easily illustrates the greater preponderance of the top 4 AEs (Nausea, Vomiting, Dizziness, and Somnolence) to the two combination products. The frequency of HA is more evenly distributed. The frequency of pruritis, sweating, vasodilation, asthenia, and constipation appear to clearly be associated with the combination products with the greatest frequency in all cases corresponding to the Oxycodone/Ibuprofen 10/400 mg group. Again the results do not appear to be greatly different in AE frequency than one might expect for opioid type medications. Note that duration of exposure is not taken

into account with this crude incidence technique, presented graphically here. Since both the 10/400 and 5/400 mg groups had multiple doses (up to approximately 1 week) associated with them, the corresponding *incidence density* (# AEs/treatment/person-time exposed) would probably lower the AE rate compared to the other treatments (that were only single-dose).

Figure 7.9.4.1 Ten Most Frequent AEs (%) by Treatment (All Clinical Studies Pooled)



7.9.5 Adverse Events by Severity:

The number of subjects in the single-dose clinical studies with TEAEs listed by severity were analyzed by the sponsor and listed in Table 4.5A, B, and C. All AEs were classified by the investigator as "mild, moderate, or severe" and form the basis for the severity

classification used by the sponsor. In the Oxy/Ibup 5/400 mg single-dose clinical studies the majority of AEs were mild (233/1981) and moderate (205/1981), with a few rated as severe (20/1981). The most common "body system" category rated as severe was "body as a whole" with HA (4/1981 with ½ from Placebo) and PAIN (6/1981 with 5 from Oxy/Ibup and Ibup groups) events. The "Nervous System" and "Digestive System" were the next most frequent with the primary AE symptoms of "Somnolence, dizziness, nausea, 1 episode of ileus and 1 of cholecystitis/lithiasis".

The single-dose clinical trials of all other oxycodone/ibuprofen combination products shows a more frequent occurrence of severe events (38/670). This is primarily due to the higher dose combination products association with nausea (10/200 mg → 7/41 cases, 10/400 mg → 3/348 cases, Ibu 200 mg → 4/78 cases) and vomiting (10/200 mg → 4/41 cases, Ibu 200 mg → 2/78 cases). The most frequent severely rated AEs in the Nervous System were Dizziness (4/670) and Somnolence (1/670). Both of these AEs were found in the Oxy/Ibup 5/200 mg and 10/400 mg groups.

Incidence of TEAE in the multi-dose studies showed that the majority were rated as "mild" (170/492) and "moderate" (156/492); with a smaller number (70/492) rated as "severe". The majority of "severe" events were confined to the Nervous System (23/70) with Dizziness (8/23) and Somnolence (12/23) being the main AEs. Of these, the greater proportion was in the 10/400 mg group (15/44 vs. 8/26) compared to the 5/400 mg combination group. Similarly to the single-dose clinical trials, both the Digestive System (25/70) and the "Body as a Whole" (16/70) were the other main systems accounting for AEs. Within these categories the most frequent AEs were: Nausea, Vomiting, Constipation, HA, Asthenia, and Pain. Of particular note, there was only 1 episode of Pruritus ranked "severe" and no similarly ranked episodes of Urticaria.

In summary, AEs by severity were similarly distributed by body system, preferred term, and treatment, when compared to the overall incidence of AEs. The majority of cases were rated mild and moderate; and were primarily seen among the oxycodone and oxycodone combination groups. These oxycodone combination groups overall had a significantly greater proportion of AEs than the Placebo group, consistent with typical opioid type side effects.

7.9.6 Adverse Events Judged to be Related to Treatment:

Investigators assess the relationship of study drug to an adverse event as "not related", "possibly related", or "related". The sponsor analyzed the number of TEAEs by relationship, body system, preferred term, and treatment. These results are tabulated in Tables 4.6A. In total, the separate relationship categories were reported:

- Not Related 106/1981
- Possibly Related 339/1981
- Related 13/1981

The Oxy/Ibu 5/400 mg group had 9/754 Related, 159/754 Possibly Related, and 29/754 Not Related classifications by the study investigators. The Oxy/Ibu 10/400 mg group had 1/338 Related, 134/338 Possibly Related, and 23/338 Not Related event classifications. In contrast, the largest Placebo grouping (255 subjects) had 0/255 Related, 32/255 Possibly Related, and 19/255 Not Related classifications. This shows a clearly higher frequency of Related/Not Related AEs in the two combination groups. In the combination groups the Body System Categories and Preferred Terms accounting for the reported AEs by relationship occur in roughly similar proportions to those seen in section 7.9.5.

7.9.7 Relationship of Dose to Adverse Events:

Examination of AE frequencies and proportions by several approaches discussed in the previous sections shows that the combination dosage level is associated with differences in reported AEs. Figure 7.9.4.1 illustrates this graphically, along with the corresponding Placebo and Ibuprofen 400 mg associated AEs. Overall, the larger combination dose (Oxy/Ibup 10/400 mg) is most often associated with a greater frequency of the most common AEs when analyzed by Preferred Term, Body System, and Severity. The analysis of AEs by relatedness does not distinguish as easily between the two dosage categories.

7.10 Laboratory Findings:

7.10.1 Extent of Laboratory Testing in the Development Program:

Laboratory data was collected during the clinical pharmacology studies: 604-003-01, 604-004-001, Oxy-PK1-96-01, Oxy-PK1-97-02, Oxy-PK-03, and Oxy-PK-04. The results were compared at baseline (pre-treatment) and the end of the study.

7.10.2 Clinical Laboratory Values over Time:

Summary statistics for the laboratory data are presented as "change from baseline." The sponsor states that there were no notable "mean" changes from baseline for any laboratory parameter.

7.10.3 Shift Tables of Laboratory Values:

The sponsor created tables to summarize the percentage lab values characterized as Potentially Clinically Significant (PCS). PCS lab values in the Metabolic Tests and Liver Functions Values were most frequently noted for:

- Increased serum cholesterol (9 subjects)
- Increased triglyceride (7 subjects)

- ↑ glucose (3 subjects)
- ↑ ALT (2 subjects)[subject 1, 2], ↑ AST (2 subjects)[subject 1, 2], ↑ Total BILI (1 subject)[subject3]

  Subject 1 – AST/ALT increase seen at baseline (Oxy/Ibu 5/200 mg and Oxy/Ibu 5/400 mg) and post-treatment and was associated with CPK increase due to excessive weight lifting.
  Subject 2 – AST/ALT reported after Rx with Oxy/Ibu 10/400 mg with no concurrent TEAEs.
  Subject 3 – Isolated elevated bilirubin reported following treatment with Oxy/Ibu 5/400 mg.

Table 7.10.1 illustrates this information by laboratory group as follows.

Table 7.10.1 Number (%) Subjects with PCS Post-Treatment Laboratory Values

Lab Group	Parameter	Units	PCS Low Limit	PCS High Limit	Overall n/N (%)
HEMATOLOGY					
	Basophils	%		> 2*ULN	0/143 (0.0)
	Eosinophils	%		> 2*ULN	5/143 (3.5)
	Hematocrit	%	< 0.9*LLN		2/143 (1.4)
	Hemoglobin	G/dl	< 0.9*LLN		6/143 (4.2)
	Lymphocyte	%	≤ 0.8*LLN		4/143 (2.8)
	Lymphocyte	%		> 1.5*ULN	0/143 (0.0)
	Monocyte	%		> 1.5*ULN	0/120 (0.0)
	Neutrophil	%	≤ 0.8*LLN		0/143 (0.0)
	Neutrophil	%		> 1.2*ULN	1/143 (0.7)
	Platelet	Thou/mm^3	≤ 75	≥ 700	0/143 (0.0)
	Red Blood Cells	mil/mm^3	< 0.9*LLN		4/143 (2.8)
	Red Blood Cells	mil/mm^3		> 1.1*ULN	0/143 (0.0)
	White Blood Cells	Thou/mm^3	≤ 2.5	≥ 15	0/143 (0.0)
CLINICAL CHEMISTRY					
Electrolytes					
	Sodium	Meq/dl	< 0.9*LLN	> 1.1*ULN	0/143 (0.0)
	Chloride	Mmol/l	< 0.9*LLN	> 1.1*ULN	0/96 (0.0)
	Potassium	Meq/dl	< 0.9*LLN	> 1.1*ULN	0/143 (0.0)
	Creatinine	Mg/dl	< 0.9*LLN	> 1.3*ULN	0/143 (0.0)
Liver Functions					
	ALT (SGPT)	IU/L		≥ 3*ULN	2/143(1.4)
	Alk Phos	IU/L		≥ 3*ULN	0/143 (0.0)
	AST (SGOT)	IU/L		≥ 3*ULN	2/143 (1.4)
	Total Bilirubin	Mg/dl		≥ 3*ULN	1/143 (0.7)
	Serum Protein	G/dl	< 0.9*LLN	> 1.1ULN	0/143 (0.0)
Metabolic Labs					
	Glucose	Mg/dl	< 0.8*LLN		0/143 (0.0)
	Glucose	Mg/dl		> 1.2ULN	3/143 (2.1)
	Calcium	Mg/dl	< 0.9*LLN	> 1.1ULN	0/96 (0.0)
	Albumin	G/dl	< 0.9*LLN	> 1.1ULN	0/143 (0.0)
	Cholesterol	Mg/dl		> 1.1ULN	9/96 (9.4)
	Triglycerides	Mg/dl		> 1.1ULN	7/49 (14)
URINALYSIS					
	Specific Gravity			> 1.1ULN	0/96 (0.0)
	Urine pH		< 0.9*LLN	> 1.1ULN	0/96 (0.0)

Source: 120 Day ISS Update, Vol. 4.8, Table 6.10, pg. 384-385.

Examination of the summary table shows several observations of abnormal PCS Hematology values including:

> Hemoglobin (↓ in 6 subjects), eosinophils (↑ in 5 subjects), lymphocytes (↓ in 4 subjects), RBCs (↓ in 4 subjects), Hct (↓ in 2 subjects), and neutrophils (↑ in 1 subject).

All of these abnormalities were seen after treatment with Oxy/Ibup 5/400 mg combination product. The one exception was a single subject with a low Hgb after dosing with Oxy 5 mg. This subject had a TEAE of hemorrhage, which had resolved at the time of the PCS laboratory. No other hematology changes were associated with a TEAE.

7.10.4 Individual PCS Laboratory Discussion:

Examination of the individual Hematology line listings demonstrates that the subjects with eosinophilia (3.5%) appeared to have dizziness, HAs, and nausea frequently. In addition, the majority of values decreased towards normal post-treatment. The majority of subjects with Hgb decreases reported nausea, dizziness, and vomiting as AEs. The lab values were relatively mild, with the most exceptional Hgb decrease being 11.2 to 9.8 g/dl, in subject 016 (Oxy-PK-03). Of note, the one subject with a TEAE of HEMORRHAGE had an Hgb decrease from 11.7 to 10.1 g/dl. Overall, these values do not seem severely abnormal. One of the 4 subjects with lymphocyte decrease, demonstrated the most marked decrease starting from 31 → 15 %, post-treatment. This subject reported DIZZINESS and HAs as AEs. All of the subjects with low RBCs appear to have demonstrated baseline low levels with minimal change over the treatment period.

The Hepatic laboratory abnormalities have already been discussed briefly. Subject 001 from study 604-003-01 demonstrated ALT & AST elevations of 146 and 594 at baseline, respectively. This reduced to 62 and 33 respectively as the patient was followed over time. This subject had several AEs coded referring to ACCID INJURY, HEMATURIA, etc... due to excessive weight-lifting. The subject with elevated Bilirubin (19 W Male) showed an increase from 1.4 → 1.7 over the treatment period, and AEs of SOMNOLENCE and HA.

The subjects with elevated cholesterol are summarized in the following table, due the relatively larger numbers of these subjects.

Table 7.10.4.1 Cholesterol Abnormalities

Laboratory	Study/Subj. #	Demog	Units	Baseline	Post-Rx
Cholesterol	604-004-01/001	37 W M	Mg/dl	309 H	256 H
	604-004-01/004	19 W M	Mg/dl	213 H	225 H
	Oxy-PK1-96-01/008	29 W F	Mg/dl	199	221 H
	Oxy-PK1-96-01/014	24 W F	Mg/dl	235 H	227 H
	Oxy-PK1-96-01/012	30 W M	Mg/dl	229 H	242 H
	Oxy-PK1-97-02/002	32 W M	Mg/dl	260 H	331 H
	604-003-01/009	21 W M	Mg/dl	233 H	236 H
	604-003-01/006	22 W M	Mg/dl	250 H	222 H
	604-003-01/021	38 B M	Mg/dl	247 H	241 H
	604-004-01/001	37 W M	Mg/dl	309 H	282 H

Source: 120 Day ISS Update, Vol. 4.8, Table 6.11, pg. 397-398.

Examination of the cholesterol values shows moderate/elevated baseline levels with minimal changes over the dosing period of the trials. Much of this may be biologic variability over the time of the trial, superimposed on baseline cholesterol elevations.

There were no PCS abnormal values noted for electrolytes or urinalysis parameters.

In summary, no obvious discernable "safety signal" is noted by examining the laboratory profiles of subjects with PCS values. The sponsor did not report any discontinuations due to laboratory abnormalities.

7.11 Vital Signs:

Summary statistics for vital sign data collected during the clinical pharmacology studies at baseline and the end of the study, are summarized in the Sponsor's data table reproduced here.

Table 7.11.1 Vital Sign Changes

Parameter (units)	Pre-Rx (Mean ± SD)	End of Study (Mean ± SD)	Change (Mean ± SD)	Abnl Criteria	Overall n/N (%)
SBP (mm Hg)	116.4 (10.2)	108.7 (12.4)	-7.7 (11.4)	≥ 200 and ↑ ≥ 20	0/145 (0.00)
				≤ 80 and ↓ ≥ 20	2/145 (1.38)
DBP (mm Hg)	75.2 (7.3)	70.5 (8.5)	-4.7 (8.6)	≥ 110 and ↑ ≥ 15	0/145 (0.00)
				≤ 50 and ↓ ≥ 15	4/145 (2.76)
HR (bpm)	69.5 (8.2)	69.2 (8.5)	-0.3 (10.0)	≥ 120 and ↑ ≥ 15	0/145 (0.00)
				≤ 50 and ↓ ≥ 15	4/145 (2.76)

Source: 120 Day ISS Update, Vol. 4.8, Table 6.13, pg. 399-400.

Inspection of Table 7.11.1 demonstrates that recorded subjects showed mean decreases in blood pressure and pulse rate from baseline, although the results are somewhat difficult to interpret due to the crossover designs of the studies. The Sponsor did not think any of these mean changes were clinically important.

Eight total subjects had PCS vital sign measurements indicating decreases in blood pressures and pulse rates. No subjects experienced TEAEs related to BP or HR changes.

7.12 Physical Examination Findings:

7.13 Electrocardiograms:

Summary statistics for ECG data collected during the clinical pharmacology studies at baseline and the end of the studies, are presented in the following table. Note that Oxy-PK-04 subjects are excluded because there were no post-treatment measurements made. No clinically important changes from baseline were observed and no patients had PCS parameters at any time during the study.

Table 7.11.1 ECG Changes

Parameter (units)	Pre-Rx (Mean ± SD)	End of Study (Mean ± SD)	Change (Mean ± SD)	Abnl Criteria	Overall n/N (%)
Heart Rate (bpm)	63.2 (10.2)	64.2 (11.6)	0.9 (8.6)		0/120 (0.0)
PR Interval (msec)	155.4 (17.8)	153.7 (19.0)	-1.7 (13.1)	≥ 250	0/120 (0.0)
QRS Interval (msec)	80.6 (11.1)	80.0 (10.8)	-0.6 (6.5)	≥ 150	0/120 (0.0)
QTC Interval (msec)	383.1 (24.8)	380.5 (22.2)	-2.6 (23.7)	≥ 500	0/120 (0.0)

Source: 120 Day ISS Update, Vol. 4.8, Table 6.13, pg. 399-400.

A shift table is included by the sponsor for subjects in Oxy-PK-03, 604-003-01, and 604-004-01 clinical pharmacology studies. The sponsor states that Oxy-PK-04 subjects are not included due to no "end of study" measurements and Oxy-PK1-96-01 and 97-02 are excluded due to distinct classification of ECG results. The shift table for the 71 subjects is reproduced below:

Table 7.11.1 ECG Shift Table

	End of Study			
Pre-Treatment	**Normal (%)**	**Abnl (NCS) (%)**	**Abnl (CS) (%)**	**Total (%)**
Normal (%)	56 (79)	2 (3)	0 (0)	58 (82)
Abnl (NCS) (%)	1 (1)	12 (17)	0 (0)	13 (18)
Abnl (CS) (%)	0 (0)	0 (0)	0 (0)	0 (0)
Total (%)	57 (80)	14 (20)	0 (0)	71 (100)

Source: 120 Day ISS Update, Vol. 4.8, Table 6.18, pg. 409.
NCS – not clinically significant, CS – Clinically Significant.

Examination of the shift table shows that 1 subject initially classified as normal was later classed as abnormal (not clinically significant). One subject initially classed as abnormal (not clinically significant) was moved to the normal class by the end of the study. Tables of individual subject ECG values, classed as "abnormal", are not provided for inspection by the sponsor. No subject ECG values were classed as clinically significant.

7.14 Drug-Demographic Interactions:

To assess drug-demographic interactions, the Sponsor assessed the influence of age, sex, and race on the incidence of TEAEs.

7.14.1 Gender Differences:

TEAE incidence for the single-dose clinical studies is presented by body system, preferred term, treatment group, and sex (see 120-Day ISS Supplement, Tables 4.8A, 4.8B). The multi-dose clinical study TEAE incidence is presented separately (Table 4.8C).

Females reported a higher TEAE incidence rate than males (27.6 vs. 18.6%) in the single-dose clinical studies. This was most common in subjects receiving Oxy/Ibup 5/400 mg (31.8% of females and 20.3% of males) and those receiving Oxy 5 mg (36% females vs. 29.4 % males). Females reported the following TEAEs at 2x the frequency of males in the Oxy/Ibup 5/400 mg combination group: somnolence (13.5 vs. 3.5%), nausea (10.7 vs. 4.3%), and vomiting (7.6 vs. 2.7%). Similar trends were observed in the placebo group with females reporting somnolence, nausea, and vomiting more frequently (4.8%, 5.6%, and 3.2% vs. 0, 1.5, and 1.5%, respectively).

Females reported TEAEs at 86.7% vs. 75.2% frequency in males, in the multi-dose study. Females reported vomiting (7.0 vs. 2.3%) at 2x the frequency of males, in this study.

Overall TEAEs were reported more frequently by females than males, although the sponsor notes that the relative incidence rates for individual TEAEs were roughly similar for both sexes.

7.14.2 Age Group Differences:

The sponsor assessed the frequency of TEAE reports separately for the single- and multi-dose studies. This information is presented in the enclosed tables by body system, preferred term, treatment group and age.

Table 7.14.2.1 Selected* TEAEs by Age Group and Treatment: Oxy/Ibup 5/400 mg, Oxy/Ibup 10/400 mg, and Placebo Treatments (Single Dose Studies)

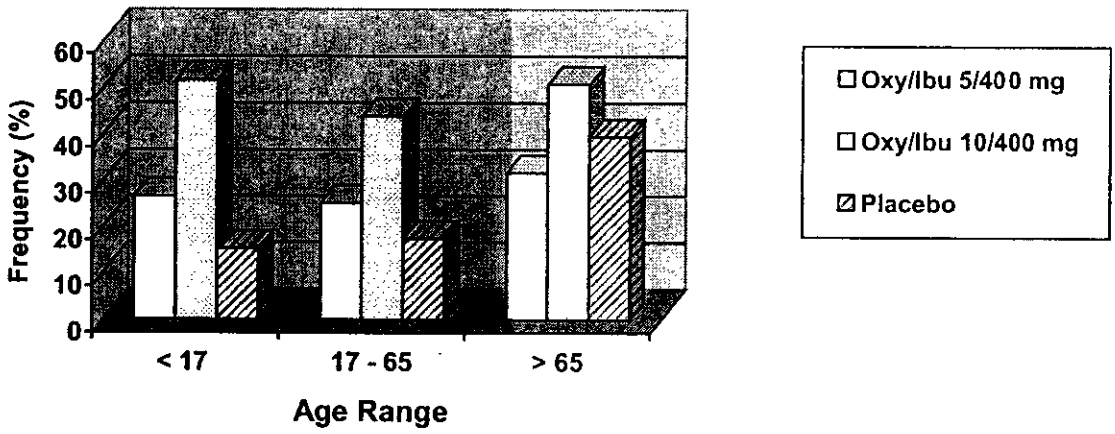
Preferred Term Treatment Group	Age Group					
	≤ 17 Years		> 17 to < 65 Years		≥ 65 Years	
	N	N (%)	N	N (%)	N	N (%)
All TEAEs	300	69 (23.0)	1451	302 (20.8)	230	87 (37.8)
Oxy/Ibup 5/400 mg	109	29 (26.6)	653	142 (25.2)	82	26 (31.7)
Oxy/Ibup 10/400 mg	62	32 (51.6)	203	89 (43.8)	73	37 (50.7)
Placebo	39	6 (15.4)	183	32 (17.5)	33	13 (39.4)
Vomiting						
Oxy/Ibup 5/400 mg	109	12 (11.0)	563	26 (4.6)	82	1 (1.2)
Oxy/Ibup 10/400 mg	62	22 (35.5)	203	25 (12.3)	73	3 (4.1)
Placebo	39	2 (5.1)	183	4 (2.2)	33	0
Nausea						
Oxy/Ibup 5/400 mg	109	15 (13.8)	563	37 (6.6)	82	5 (6.1)
Oxy/Ibup 10/400 mg	62	20 (32.3)	203	35 (17.2)	73	4 (5.5)
Placebo	39	1 (2.6)	183	8 (4.4)	33	0
Dizziness						
Oxy/Ibup 5/400 mg	109	6 (5.5)	563	36 (6.4)	82	2 (2.4)
Oxy/Ibup 10/400 mg	62	4 (6.5)	203	16 (7.9)	73	7 (9.6)
Placebo	39	0	183	3 (1.6)	33	3 (9.1)
Somnolence						
Oxy/Ibup 5/400 mg	109	4 (3.7)	563	58 (10.3)	82	3 (3.7)
Oxy/Ibup 10/400 mg	62	10 (16.1)	203	27 (13.3)	73	11 (15.1)
Placebo	39	0	183	6 (3.3)	33	0
Sweating						
Oxy/Ibup 5/400 mg	109	0	563	10 (1.8)	82	5 (6.1)
Oxy/Ibup 10/400 mg	62	2 (3.2)	203	8 (3.9)	73	7 (9.6)
Placebo	39	0	183	0	33	1 (3.0)

Source: ISS Update, Vol. 4.8, Panel 22, pg. 61 (pg. 73 of Vol.).
*TEAEs with ≥ 5% incidence in ≥ 1 age group, and 2x the incidence of one or more of the other groups.

Inspection of the single-dose study table shows that the overall incidence of TEAEs was greater in the > 65 year-old age group (37.8 vs. 23.0 and 20.8% in the < 17 and 17-65 groups, respectively). In most cases the combination products produced greater

frequencies of TEAEs in the older age groups, compared to placebo. However, the trend for placebo-associated TEAEs also increases with age and TEAEs are more frequent than those reported for the Oxy/Ibup 5/400 mg group at the > 65 year-old category. This is illustrated in the following figure.

Figure 7.14.2.1 Overall TEAE Incidence
(Single-Dose Studies)



In the combination groups the incidence of nausea and vomiting decreased with increasing age, whereas sweating occurred with greater frequency in patients ≥ 65 years of age. Dizziness was reported in 5.5% and 6.4% of the Oxy/Ibup 5/400 < 17 and 17-65 age groups. The incidence in the > 65 group was decreased to 2.4% of subjects. This pattern was not seen in the Oxy/Ibup 10/400 mg group. Dizziness was also more frequently reported in the Placebo group with increasing age. However, the small numbers in the placebo category (3/33 or 9.1%) make it difficult to interpret this as little more than small sample "noise", when compared to the larger combination product groups.

The multi-dose groups were not compared to placebo. The higher dose Oxy/Ibuprofen combination had the greatest frequency of reported TEAEs in the majority of categories, especially in the > 65 age group. The main exception occurred with Constipation. Here there did not appear to be an appreciable difference in frequency of TEAE report, base on dosage and age category. Figure 7.14.2.2 illustrates the overall difference in frequency of reporting, as a function of age category. Of note, the frequency in the Oxy/Ibup 5/400 mg treatment group shows a decrease in TEAE reports over the age range.

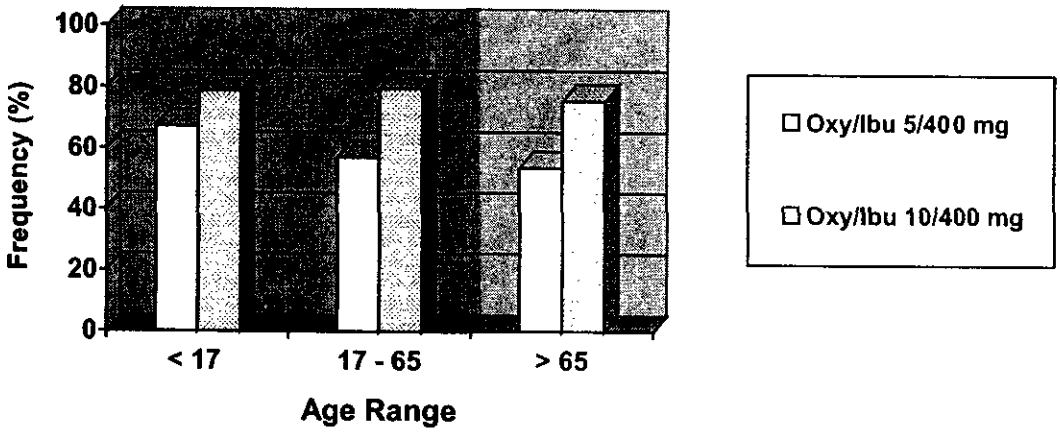
Table 7.14.2.2 Selected* TEAEs by Age Group and Treatment: Oxy/Ibup 5/400 mg, Oxy/Ibup 10/400 mg (Multi-Dose Study)

Preferred Term Treatment Group	Age Group					
	≤ 17 Years		> 17 to < 65 Years		≥ 65 Years	
	N	N (%)	N	N (%)	N	N (%)
All TEAEs	84	71 (84.5)	329	267 (81.2)	79	58 (73.4)
Oxy/Ibup 5/400 mg	58	39 (67.2)	222	127 (57.2)	54	29 (53.7)
Oxy/Ibup 10/400 mg	47	37 (78.7)	196	156 (79.6)	45	34 (75.6)
Dizziness						
Oxy/Ibup 5/400 mg	58	21 (36.2)	222	41 (18.5)	54	2 (3.7)
Oxy/Ibup 10/400 mg	47	26 (55.3)	196	64 (32.7)	45	7 (15.6)
Somnolence						
Oxy/Ibup 5/400 mg	58	14 (24.1)	222	43 (19.4)	54	1 (1.9)
Oxy/Ibup 10/400 mg	47	14 (29.8)	196	44 (22.4)	45	4 (8.9)
Headache (HA)						
Oxy/Ibup 5/400 mg	58	13 (22.4)	222	20 (9.0)	54	1 (1.9)
Oxy/Ibup 10/400 mg	47	7 (14.9)	196	23 (11.7)	45	0
Vomiting						
Oxy/Ibup 5/400 mg	58	5 (8.6)	222	9 (4.1)	54	1 (1.9)
Oxy/Ibup 10/400 mg	47	8 (17.0)	196	37 (18.9)	45	5 (11.1)
Sweating						
Oxy/Ibup 5/400 mg	58	2 (3.4)	222	9 (4.1)	54	3 (5.6)
Oxy/Ibup 10/400 mg	47	0	196	17 (8.7)	45	4 (8.9)
Constipation						
Oxy/Ibup 5/400 mg	58	1 (1.7)	222	7 (3.2)	54	7 (13.0)
Oxy/Ibup 10/400 mg	47	1 (2.1)	196	8 (4.1)	45	6 (13.3)

Source: ISS Update, Vol. 4.8, Panel 22, pg. 63 (pg. 75 of Vol.). Cross-reference Table 4.7C

*TEAEs with ≥ 5% incidence in ≥ 1 age group, and 2x the incidence of one or more of the other groups.

Figure 7.14.2.2 Overall TEAE Incidence (Multi-Dose Study)



7.14.3 Racial Differences:

The majority of patients/subjects in the clinical development program were white, accounting for over 84.6% of the single-dose clinical studies of Oxy/Ibup 5/400 mg and > 91.6% of the single-dose studies of other combination products. The small number of non-whites and the lack of further subdivision of non-whites (this is not a specific racial category), make it difficult to interpret the frequency of AEs by racial groups. The sponsor tables (4.9C) show that whites and non-whites had similar overall frequencies of TEAEs (23.3 vs. 21.9%) in the single-dose studies. The multi-dose studies showed that whites had a > rate of TEAEs to non-white patients (82.5% vs. 69.3%) for Oxy/Ibup 5/400 mg subjects. The sponsor also note that diarrhea and pruritus was reported in a greater percentage of non-white patients (7.3 and 7.3% respectively) vs. white patients (1.1% and 2.5% respectively).

Otherwise no obvious significant differences in TEAE incidence frequencies were observed.

7.15 Drug-Drug Interactions:

Drug interaction studies were not performed and consequently, no review of this topic is possible.

7.16 Drug-Disease Interactions:

In discussion with the Biopharmaceutics Reviewer, Dr. David Lee, it appears that the Sponsor has performed no independent evaluations of BRANDNAME (Oxy/Ibup 5/400 mg) tablets in specifically targeted disease states. Given this, no review comments regarding studies of BRANDNAME use in hepatic or renal impaired subsets is possible.

8 USE IN SPECIAL POPULATIONS:

8.1 Adequacy of By-Gender Investigation and Analyses:

The Sponsor has included adequate numbers of subjects and patients of both genders in the clinical development program. The Sponsor has also performed adequate by-gender analyses. While some of the common opioid-related side effects are more common in women than in men, the overall safety data do not suggest any substantial gender differences.

8.2 Elderly Patients:

The sponsor notes that approximately 320 subjects ≥ 65 years were exposed to oxycodone/ibuprofen combinations during the initial safety/efficacy evaluation. 79/320

subjects were exposed to multiple doses with average duration of 6.1 days. The sponsor planned to submit additional exposure data from 241 elderly subjects not enrolled in the multi-dose study, from the completion of the Oxy-MD-07 trial as part of the 120 Day Safety Update.

8.3 Pediatric Program Evaluation:

The Sponsor's Pediatric Development plan has consisted of the following, so far:

- Approximately 240 pediatric patients between the ages of 13 – 17 were exposed to oxycodone/ibuprofen combination product as part of the safety evaluation. Of these subjects approximately 80/240 were exposed to multiple doses of the product with an average duration of 4 days (range 1 – 8 days).

- The Sponsor submitted a Pediatric Study Request to conduct a [redacted] study to address the pediatric age group 7 – 12 years of age [redacted]

On Dec. 19, 2001 the Sponsor submitted a Pediatric Deferral Request as part of the NDA submission, to cover other pediatric age groups. This Deferral Request has the following features.

1) Ages requested are neonates, infants, and children 2 – 6 years

2) Reasons for not including these subjects:
   - IRB restriction of enrollment of pediatric patients due to potential safety concerns of ≥ 5 mg Oxycodone doses and possibility of pediatric patients being randomized to placebo arms of trial.

   - The ability of children ≤ 12 years to understand how to assess pain using stopwatches and the VAS metric is limited.

3) Reasons for Deferring Pediatric Studies:
   - The completed safety and efficacy trials already include a robust number of pediatric patients 13 – 17 years of age.

   - Sponsor has already proposed a PK study (8/29/01) in pediatric subjects 7 – 12.

   - The Sponsor wants to confirm safety and efficacy findings in the above populations before attempting studies in younger patients.

The Sponsor notes that a final study report of the Pediatric PK results in 7 – 12 year olds will be available ~ 9 months after study completion.

While the Pediatric PK study results will be useful, it is unclear if the reasons for not enrolling subjects below 6 years of age is adequate for a deferral to be granted. In particular, the 3 – 6 year age range may still be suitable for testing as these patients certainly can experience pain and may potentially benefit from new therapeutic analgesics for appropriate conditions. In addition, it may be possible to perform efficacy studies in the 3 – 17 age ranges, which would be useful to help determine the appropriate dosing in these different groups. The Agency does note that the Sponsor's concerns regarding may be appropriate for the neonate to ~ 2 – 3 years of age.

In conclusion, the Sponsor's request for Pediatric Deferral is reasonable in the youngest age groups listed above. However, the 3 – 6 age range may still be appropriate for evaluation. This reviewer recommends that the Sponsor include this group in its Pediatric PK trial or provide more compelling arguments for why this should not be done. In addition, potential efficacy trials in the 3 – 17 ages should also be considered.

8.4 Abuse Liability:

The Sponsor notes that Oxycodone is a Schedule II controlled substance and these products are commonly abused. The sponsor states that the abuse potential of this product is limited by the low dose of Oxycodone (5 mg), the short-term indication, and the inclusion of ibuprofen. The sponsor notes that the inclusion of ibuprofen in the fixed combination product makes potential alternate routes of administration (nasal or injection) highly unlikely. There was no evidence of misuse, incremental use, or drug seeking behavior noted in the completed clinical studies.

The Sponsor note that there was no evidence of drug-withdrawal-related concerns with acute use of the combination product in this submission, as reflected in the TEAE/SAE safety profiles.

Overdose toxicity is different for the different components of the Oxycodone/Ibuprofen tablets. Ibuprofen component has had serious toxicity and death reported in the medical literature, from overdose. Typical findings are abdominal pain, nausea, vomiting, lethargy, HA, tinnitus, and Seizures. Hypotension, bradycardia, tachycardia and Afib have also been reported.

In contrast, Oxycodone toxicity is usually associated with respiratory depression, somnolence, muscle flaccidity, constricted pupils, bradycardia, and hypotension. In severe cases, death may also occur.

9 REVIEW OF PACKAGE INSERT:

No review of the Package Insert and Proposed Labeling was performed because the Sponsor failed to show convincing evidence of efficacy of the proposed product.

10 APPENDIX:

10.1 Appendix A

This section lists the Sponsor provided documentation, requested by the Agency during the review process. The interested reader may obtain the listed documents by using the associated N-000-BM designation and listed Document Date.

1) Clarification of differences in data presented in the ISS and the 120-Day Safety Update Database. NDA 21-378, N-000-Minor Medical Document Amendment (BM), Doc. Date: 8-7-02.

2) Patient disposition in studies OXY-MD-05 & OXY-MD-06. NDA 21-378, N-000-Minor Medical Document Amendment (BM), Doc. Date: 8-9-02.

3) Response to FDA Request for Information: request received August 15, 2002 from the FDA clinical reviewer. NDA 21-378, N-000-Minor Medical Document Amendment (BM), Doc. Date: 8-30-02.

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/s/

Shaun Comfort
9/23/02 03:52:23 PM
MEDICAL OFFICER

Bob, This is the Oxy/Ibup NDA review, you've already ok'd for entry into DFS.

Bob Rappaport
9/23/02 05:08:33 PM
MEDICAL OFFICER