

A compromise position, which I would recommend if the sponsor is dissatisfied, would be to add the following to the above paragraph (addition indicated by underlines):

Reducing dosage and stopping treatment

The decision to discontinue therapy with SUBUTEX after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

2.4.4 Administration Of Doses Requiring More Than Two Tablets In Combination

Based on review of pharmacokinetic data, the division proposed the following labeling language:

DOSAGE AND ADMINISTRATION

Method of administration

SUBOXONE tablets should be placed under the tongue until dissolved.

2.4.5 Response

The sponsor proposes the following language:

DOSAGE AND ADMINISTRATION

Method of administration

SUBOXONE tablets should be placed under the tongue until dissolved.

2.4.6 Assessment

The sponsor has not provided the necessary data to shed light on the proper method of dosing more than two tablets at a time. Because of the size limitations of the sublingual space and the large size of the tablets, lack of dose linearity is predicted and has been seen in some pharmacokinetic studies. Although PK data was provided from a clinical study in which various doses were used, the OCPB review team felt that this did not provide the necessary information to write informative labeling on the proper method of dosing.

The proposed labeling requires physicians to titrate to clinical effect without fully appreciating (or conveying to the patient) the possible impact of giving the same dose in different ways on different occasions. It is conceivable that a dose which seems adequate when given sequentially in the doctor's office may be inadequate when all of the necessary tablets are given simultaneously, as a patient might elect to do.

There is clearly a clinical need for the 2 mg tablet, and dosing instructions which did not include it would lack clinical practicality. The sponsor should generate the data previously requested. Once the necessary data is available to provide instructions on administering doses that require more than two tablets, the 2 mg tablet should be included in the labeling.

2.4.7 Conclusions/Labeling Review

If clinicians are to be expected to _____ they will certainly require information regarding the effects of simultaneous dosing of more than two tablets. Either the labeling proposed by the division should be retained, or approval of the 2 mg tablet should be withheld until adequate data are generated to support meaningful labeling.

3 OTHER ISSUES REQUIRING REVIEW

(Note that this section is identical to analogous sections in my review of the response to approvable for NDA 20-732.)

3.1 Hepatotoxicity

3.1.1 Background

Buprenorphine's potential to affect hepatic function was noted early in development. The review of the safety database on hepatic effects is summarized below (reproduced from my memo of November 16, 1999).

[Abnormal] LFTs were not unusual in the safety population. Baseline LFT abnormalities are common in this population, and are attributed to viral and chemical causes (e.g. drugs of abuse, alcohol). However, an effect of buprenorphine on LFTs was observed earlier in development, and Studies CR96/013, CR96/014, CR92/099, and CR92/100 defined LFTs >8x ULN as serious adverse events. In fact, this was the most commonly-reported SAE in the database (46 subjects). The relatedness of these events to buprenorphine treatment was assessed by identifying other contributing factors, which often included viral hepatitis and alcohol. Many subjects were seropositive at baseline for Hepatitis B and/or C. Elevations in enzymes in these subjects were occasionally attributed to exacerbation of pre-existing viral hepatitis, which, although plausible, does not argue convincingly against a drug effect. However, some seroconversions occurred during treatment, and these represent persuasive alternative explanations for acute transaminitides. Four of ten reports in CR96/013/014 can be thus explained. Insufficient detail is available to closely examine the relatedness of the 35 events in CR92/099/100 and the one in CR88/130, but the sponsor provided a table with brief comments on alternative etiologies for CR92/099/100. Thirteen of 35 listings offer an alternative explanation with some confidence. Therefore, over half of the reports of LFTs >8 x ULN might be attributed to buprenorphine, but lack of comparator makes this difficult to assess.

Analysis of shifts upwards or downwards from baseline in the four-week placebo-controlled study (CR96/013) showed no difference among Suboxone, Subutex, or placebo for AST, ALT, and LDH, with more shifts upwards than downward. The number of shifts from normal or high to "clinically abnormal" (possibly clinically significantly abnormal) was similar across groups for AST and ALT. For total bilirubin, four patients, two on each active treatment, showed shifts from normal to high or clinically abnormal, compared with none in the placebo group. For GGT, both active treatment had more downward shifts than upward shifts, compared to placebo which showed the opposite pattern. Shift tables from the 52-week extension (CR96/014) show that shifts from normal to abnormal appear to occur within the first four weeks and further shifts are not seen later in treatment. Similarly, the proportion of patients with possibly clinically significantly abnormal LFTs (about 1% at baseline) increases to about 4-5% by week 4 (the first measurement) and remains stable for the remaining weeks. Attrition does not seem to involve subjects with abnormal LFTs preferentially.

In the the solution studies, shifts from normal to abnormal AST occurred in 8-10% of buprenorphine subjects, without dose effect. By comparison, shifts were seen in 14% of methadone subjects. Shifts in ALT were seen in 8-17% of buprenorphine subjects, without dose effect, and in 16% of methadone subjects. As in the tablet study, an increase in the proportion of subjects with possibly clinically significantly abnormal LFTs occurred early in the study (within 8 weeks), but greater fluctuation was seen thereafter than in the tablet study. It did not appear that late-onset hepatotoxicity explained the fluctuations; rather it was a result of the changing denominator due to attrition from the study.

The labeling included in the last review cycle reads:

[Warnings section]

Hepatitis, hepatic events :

Recently, however, a publication in *The American Journal on Addictions* (Petry, N.M., Bickel, W.K., Piasecki, D., et al., Elevated Liver Enzyme Levels in Opioid-Dependent Patients with Hepatitis Treated with Buprenorphine, *The American Journal on Addictions* 9:265-269, 2000) has identified a particular vulnerability of patients with pre-existing hepatitis. Reckitt & Colman was asked to review the safety database to explore this question.

Materials received from the sponsor on 11/16/00 include correspondence between Dr. Bickel and Reckitt&Colman dating back several years, and individual patient data from Dr. Bickel's lab. Dr. Bickel provided baseline and on-treatment AST and ALT data for 120 patients. Of these, 48 had no history of hepatitis and 72 had a history of hepatitis (type not indicated). The sponsor analyzed Dr. Bickel's data and concluded, based on group means, that no significant difference between the groups existed, particularly after discarding data from two patients with significant increases in their LFTs on treatment.

3.1.2 Assessment

3.1.2.1 Dr. Bickel's Data

Examination of the line listings for Dr. Bickel's data reveals that significant increases in LFTs were more likely to occur among the patients with hepatitis history.

The table below lists the subjects who demonstrated a change from baseline of >100 U/L in AST and/or ALT. The grayed-out cells represent changes not meeting that criterion.

Patient #	Baseline AST	On-treatment	Difference	Baseline ALT	On-treatment	Difference
Hepatitis-negative (N = 48)						
BUP078	43	220	177	29	261	232
Hepatitis-positive (N = 72)						
BUP009				294	411	117
BUP017				121	284	163
BUP021				25	310	285
BUP028	38	154	116	32	182	150
BUP035	31	798	767	36	569	533
BUP042	50	158	108	103	395	292
BUP053	51	210	159	74	292	218
BUP076				156	360	204
BUP087	22	2005	1983	23	2100	2077
BUP099	115	286	171	160	288	128
BUP116	215	358	143			
BUP118				83	186	103

While 17% of the subjects positive for hepatitis had changes from baseline of at least 100 U/L in either AST or ALT, only 1 of 48 (2%) of the hepatitis-negative subjects had a change of this magnitude. The specific hepatitis serology of the patients was not given (e.g. B vs. C) for this dataset. Hepatitis C has a fluctuating course, and the elevations seen in this population may or may not be related to buprenorphine. Clearly, the hepatitis-positive subgroup is more prone to significant shifts in liver enzymes, but without a placebo comparison the role of buprenorphine is difficult to interpret.

3.1.2.2 Sponsor's Data

Reckitt & Colman was asked to reassess the data from the safety database for the NDA to address the possibility that hepatitis-positive patients may be more vulnerable to buprenorphine-related hepatic damage than patients without viral hepatitis history. The materials sent reveal that only one dataset, from Study CR96/013 and its companion/follow-on CR96/014, included routine determination of hepatitis serology for all subjects. Therefore, only this dataset was analyzed.

The dataset includes 314 subjects from the 4-week double-blind portion of the study who had hepatitis serologic status documented at baseline (nine of the 323 subjects in the study had one or more missing serology determinations).

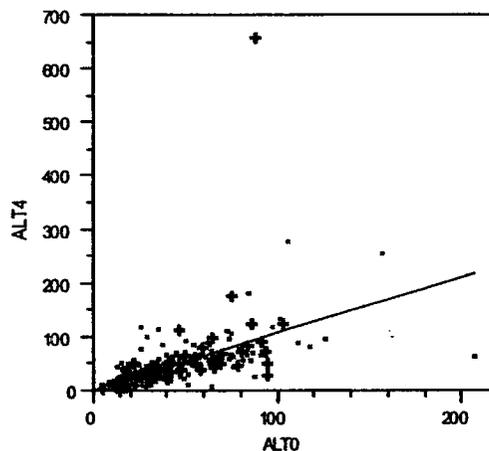
The serologic status by treatment group was as follows:

	Buprenorphine/ naloxone	Buprenorphine	Placebo	Total
Negative for B&C	37	35	40	112
Positive for B only	10	8	10	28
Positive for C only	19	21	21	61
Positive for B & C	40	36	37	113
Total	106	100	108	314

Slightly fewer of the subjects positive for Hepatitis C than subjects negative for Hepatitis C were still participating in the fourth week of the study. Overall, 83% of the "negative" group were dosed during the fourth week, while 82% of the "B only" group, 61% of the "C only" and 78% of the "B&C" group.

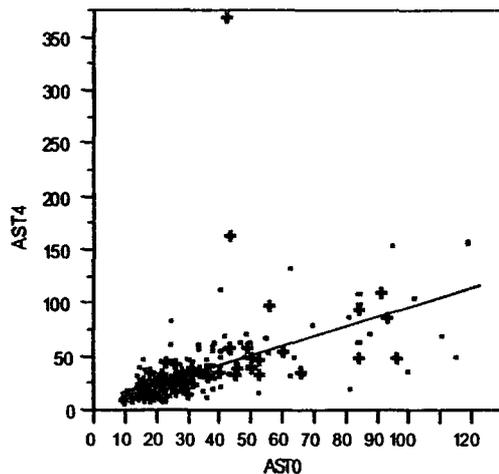
I examined the data for the four-week placebo-controlled period by graphing baseline vs. Week 4 for four different laboratory values associated with hepatic function (AST, ALT, GGT, and Total Bilirubin).

The figure below shows ALT at baseline on the X axis vs. ALT at week 4 on the Y axis. Subjects represented by crosses are on placebo and subjects represented by square markers are on buprenorphine. Not visible in a black-and-white document is the color coding for hepatitis status. Only three of the outliers are hepatitis negative; all three had baseline ALT <50 and week 4 ALT approximately 100. All of the other outliers were positive for Hepatitis C, either alone or in combination with Hepatitis B.

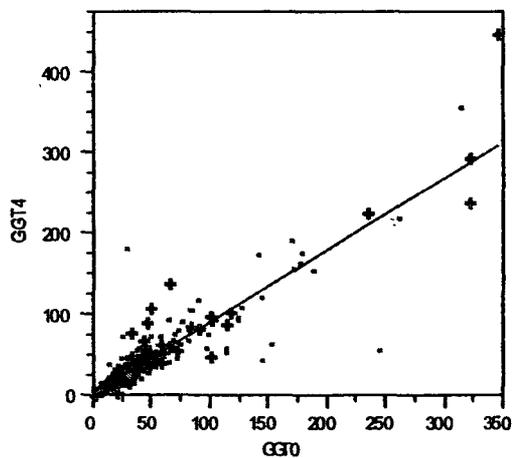


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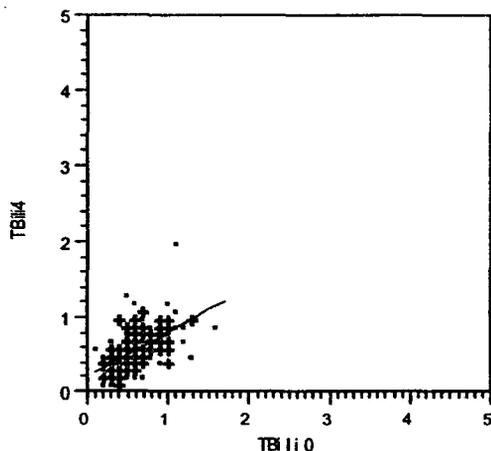
The figure below shows AST at baseline on the X axis vs. AST at week 4 on the Y axis. Subjects represented by crosses are on placebo and subjects represented by square markers are on buprenorphine. One outlier (cross at left center of graph) is a hepatitis-negative subject. All others are positive for Hepatitis C, with or without Hepatitis B.



The figure below shows GGT at baseline on the X axis vs. GGT at week 4 on the Y axis. Subjects represented by crosses are on placebo and subjects represented by square markers are on buprenorphine. Among the outliers, only the subject at the far upper right and one subject (baseline GGT 51; week 4 GGT 109) are negative for hepatitis. All other outliers are positive for Hepatitis C, with or without Hepatitis B.



The figure below shows GGT at baseline on the X axis vs. GGT at week 4 on the Y axis. Subjects represented by crosses are on placebo and subjects represented by square markers are on buprenorphine. Shifts from baseline were small and there are few significant outliers. Among the outliers, only one subject was negative for hepatitis (baseline TBili 0.5, week 4 Tbili 1.3). All others were positive for Hepatitis C, with or without Hepatitis B.



These data show that even within the first four weeks of treatment, significant fluctuations in LFTs are seen, particularly in subjects positive for Hepatitis C. These fluctuations occurred both in subjects on buprenorphine and in subjects on placebo. It should be noted when examining these figures that twice as many subjects were randomized to buprenorphine as to placebo.

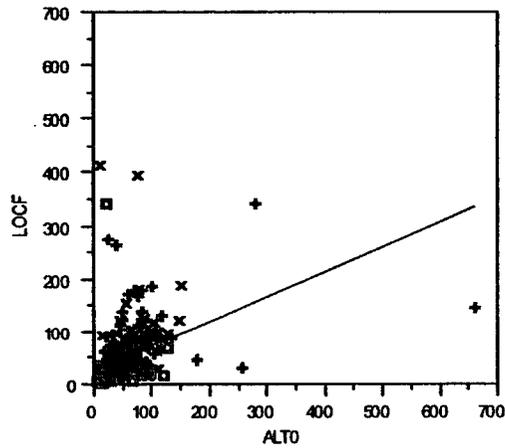
Data was also provided for the year-long, open-label, flexible dose study. This dataset encompasses 472 subjects, with serology status shown below:

Serology	# (%) of subjects
Negative for B&C	147 (31%)
Positive for B only	48 (10%)
Positive for C only	86 (18%)
Positive for B&C	183 (39%)

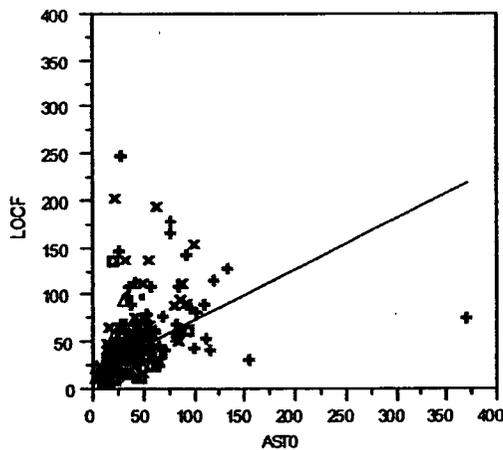
Of the 472 subjects, 291 had missing values at week 44. Dropout tended to occur early, with 71 subjects having missing values by the first follow-up at week 4, and 226 subjects having missing values by week 24. Because transient, spontaneously-resolving elevations in LFTs were not thought to be of interest, an analysis was conducted graphing the baseline value against the last observed value.

In these figures, hepatitis status is indicated by marker shape. Hepatitis-negative subjects are indicated by a square marker; subjects positive for Hepatitis B only are indicated by a triangle. Subjects positive for Hepatitis C only are indicated by an X and subjects positive for both B and C are indicated by a cross.

The figure below shows ALT at baseline on the X axis, graphed against the last observed value on the Y axis. Subjects with no follow-up values are not included.

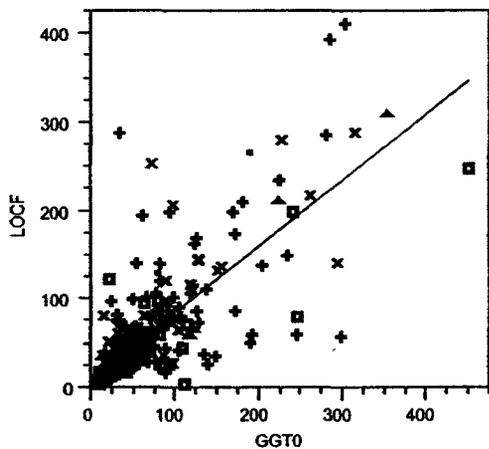


The figure below shows AST at baseline on the X axis, graphed against the last observed value on the Y axis. Subjects with no follow-up values are not included.

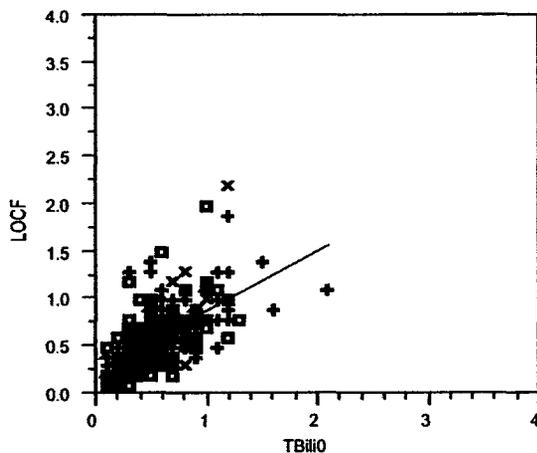


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The figure below shows GGT at baseline on the X axis, graphed against the last observed value on the Y axis. Subjects with no follow-up values are not included.



The figure below shows TBili at baseline on the X axis, graphed against the last observed value on the Y axis. Subjects with no follow-up values are not included.



From this analysis, it is evident, as was suggested by Dr. Bickel's data, that subjects with hepatitis at entry (particularly Hepatitis C) are more likely to have significant elevations from baseline in all LFTs. However, without comparators it is difficult to determine the role of buprenorphine in these changes.

**APPEARS THIS WAY
ON ORIGINAL**

3.1.2.3 Post-marketing Data

The MedWatch database has over 1000 AE reports identifying buprenorphine as the suspect drug. The vast majority of these have been reported to Reckitt & Colman by Schering, who markets the drug abroad, and are reports of foreign AE's, primarily from France where Subutex is marketed for opiate agonist maintenance treatment. Reports of 21 hepatic AEs were reviewed by Martin Pollock, Ph.D., of OPDRA.

Two deaths were reported in subjects using low doses of buprenorphine chronically, apparently for pain. In neither case did the deaths appear to be due to hepatic events (one cancer death; one pneumonia/sepsis). Thirteen reports involved events requiring hospitalization occurred. Elevations in LFTs and jaundice occurred in patients both with and without viral hepatitis. At least one event documents the resolution of transaminitis in a patient who continued to use buprenorphine sublingually (but stopped injecting it intravenously).

3.1.3 Conclusions/Labeling Review

A careful re-evaluation of all available data should be requested of the sponsor, with analyses focused on extreme values, rather than group means. There may be more controlled data available from studies sponsored by NIDA and conducted under investigator INDs.

The current labeling reads:

[Warnings section]

Hepatitis, hepatic events :

[]

There is little evidence that monitoring for changes in LFTs offers protection from drug-induced hepatic events. Furthermore, the majority of the data are uncontrolled and offer no clear indication that buprenorphine, rather than hepatitis itself, is responsible for the changes seen. At this time, it is not clear that there is value in recommending ongoing monitoring. No specific changes in the label wording are recommended based on review of the data provided.

4 OTHER ISSUES RAISED BY SPONSOR

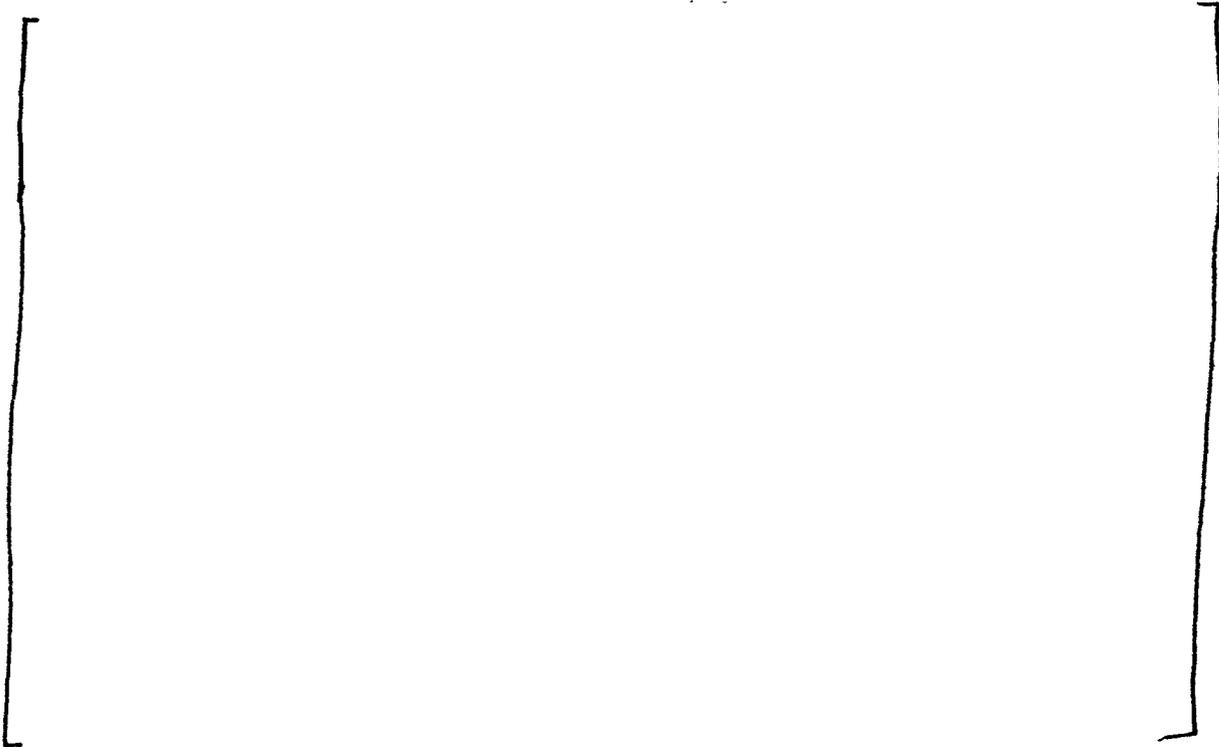
In the labeling proposed by the sponsor, various insertions and deletions were made which, in some cases, amount to new claims or assertions of safety and/or efficacy. These are reviewed below.

**APPEARS THIS WAY
ON ORIGINAL**

4.1 Medically assisted withdrawal

4.1.1 Sponsor's Proposal

The sponsor has added a section describing the use of Subutex in



The labeling language proposed by the division was:

Reducing dosage and stopping treatment

The decision to discontinue therapy with SUBUTEX should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

The sponsor now proposes:

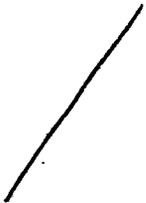




4.1.2 Assessment

The language inserted in the section on the _____ is, again, based on the _____ which was felt inadequate to support labeling language previously. I do not feel it is appropriate to include _____ in the text based on _____





It remains accurate to say, as the division proposed, that both abrupt and gradual discontinuation have been used. Clearly, clinicians' judgment will be the determining factor in how this product is used in this phase of treatment. The label, as proposed by the division, neither warns against the use of buprenorphine in detoxification, nor provides insufficiently-supported dosing instructions.

4.1.3 Conclusions/Labeling Review

The label should remain as proposed by the division:

Reducing dosage and stopping treatment

The decision to discontinue therapy with SUBUTEX should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

A compromise position, which I would recommend if the sponsor is dissatisfied, would be to add the following to the above paragraph (addition indicated by underlines):

Reducing dosage and stopping treatment

The decision to discontinue therapy with SUBUTEX after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

4.2 Relative abuse potential of buprenorphine vs buprenorphine + naloxone

4.2.1 Sponsor's proposal

The sponsor has inserted the following language in the Dosage and Administration section of the label:

[

]

4.2.2 Assessment

No specific references in support of this claim have been provided. However, a variety of studies have examined the subjective effects of buprenorphine with and without naloxone. Some have shown no difference (i.e. studies of sublingual administration, as would be predicted from the low sublingual bioavailability of naloxone). Others have shown, as expected, that suitable combinations of buprenorphine and naloxone precipitate withdrawal in subjects dependent on full agonists while buprenorphine alone may be perceived as an agonist in some subjects. The naloxone has not been shown to alter the subjective effects of buprenorphine in non-dependent subjects. The term — is somewhat vague, particularly in this context.

4.2.3 Conclusions/Labeling Review

More accurate language is recommended, specifically:

[

]

5 RISK MANAGEMENT/POST-MARKETING SURVEILLANCE PLAN

The recently-enacted Drug Abuse Treatment Act of 2000 (DATA) creates a new context for opiate maintenance treatment outside the existing methadone and LAAM clinic system. The current system, under the Narcotic Addict Treatment Act, requires a separate registration for practitioners dispensing narcotics for the treatment of narcotic addiction, and also requires adherence with treatment standards established by the Secretary of Health and Human Services. The legislation amends the Controlled Substances Act to waive the requirement for separate registration for practitioners (meeting certain requirements) who wish to prescribe Schedule III-V narcotic drugs that are approved for the treatment of narcotic addiction. The law requires that the physician interested in a waiver must submit a notification that certifies qualifications and indicates that the physician has the capacity to refer for ancillary services as needed, and agrees to treat no more than 30 patients.

The law permits prescribing limited only by the provisions of Schedule III-V of the CSA which permit telephone orders, refills, and prescriptions of large supplies of medication. It provides no standards for treatment or treatment guidelines, and in fact precludes the federal government from “interfering with the practice of medicine” in this regard. Buprenorphine treatment standards, analogous to those proposed for methadone in the proposed rule, but accommodating the differences between methadone and buprenorphine, were developed by the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA). These standards (in the form of a proposed rule) are not permissible under the law unless the drug is the subject of “an adverse determination” by the Secretary. CSAT is now creating treatment “guidelines” which will be provided through educational efforts undertaken in cooperation with professional organizations.

The precise legal meaning of “adverse determination” in this context is not fully understood. However, it is evident that the intent of the law is to allow buprenorphine to

be used with minimal regulatory interference (in stark contrast to the use of methadone) unless and until such time as it has been established that this practice is unwise.

Most physicians, it is hoped, will follow treatment guidelines to be provided by CSAT, but compliance is voluntary. It is not yet clear whether the requirements of the DATA are sufficient to ensure a treatment system that strikes the best balance between access to treatment and protection of public health. It should be noted that France, which has had Subutex available for several years for addiction treatment, has recently moved to limit pharmacies to dispensing no more than a seven-day supply of medication at a time.

The main risks presented by the buprenorphine sublingual tablet products include overdose, which may be lethal if combined with other depressants, and diversion. Diversion refers to the introduction of buprenorphine into the illicit market either by patients or by individuals who obtain the drug through theft from patients or pharmacies. This diversion may lead to new addicts using buprenorphine as the primary drug of abuse, and overdose risk in this population is likely to be greater than that in the population in treatment. Because the naloxone in the combination tablet precipitates withdrawal in individuals dependent on heroin, methadone, or other full agonists, the combination tablet is expected to be less likely to be diverted for intravenous abuse.

The sponsor should develop a plan to proactively minimize the likelihood of abuse and diversion, and should establish an active surveillance program to identify and intervene in cases of abuse and diversion. Potential features of such a program include:

- Development of a patient package insert and an education program for patients in _____ addressing the importance of keeping the medication in a secure place, the risks of combining the medication with other depressants, and the danger the medication presents to other household members
- _____
- _____
- Development of a computerized database so that pharmacies can ensure that only prescriptions from a _____ physician are filled

In addition, surveillance components to be requested of the sponsor include:

- Surveys of pharmacies to determine prescription size and number of refills
- Media surveillance to include print and internet

- Establishment of a network of “key informants” and ethnographers to identify trends in street use of buprenorphine
- Regular monitoring of publicly-available databases/surveys including:
 - Drug Abuse Warning Network (DAWN)—monitors the frequency at which a drug is mentioned in association with emergency room visits or medical examiner reports
 - Toxic Exposure Surveillance System (TESS)—monitors contacts to poison control centers
 - Drug Evaluation Network System (DENS)—monitors drugs used by patients presenting for drug treatment at a sample of centers nationwide
 - Monitoring the Future Study—surveys drug use by students in grades 7-12
 - Community Epidemiology Working Groups (CEWG)—monitors trends in street drug use in 20 cities nationwide

The sponsor should regularly monitor these sources of information and make quarterly reports to FDA.

A risk management plan should be established prior to launch of either this product, or its companion product, Subutex

6 CONCLUSIONS

The sponsor has provided insufficient stability data to permit approval of the application. Adequate PK data needed to write dosing instructions was not provided. Other issues revisited in this submission (transfer from methadone, detoxification) may be cautiously included in labeling with language suggested above. Further examination of the potential for buprenorphine-associated hepatotoxicity and approaches to prevention and management are needed.

7 RECOMMENDATIONS

In addition to any chemistry deficiencies identified on review, the following should be included as issues to be addressed prior to approval of this application (deficiencies):

- *Data should be provided from a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, e.g. comparing simultaneous dosing vs. sequential dosing at various intervals.*
- *A safety update should be provided, including a complete review of all existing safety data, including data from ongoing and completed studies sponsored by Reckitt & Colman’s CRADA partner, NIDA, and its grantees. This update should specifically examine the potential for buprenorphine-induced hepatotoxicity, the role of viral hepatitis in increasing vulnerability to hepatotoxicity, and the proper approach to prevention and management of hepatic adverse events. Analyses should focus on outliers and extreme values, rather than measures of central tendency, and should compare the course seen in uncontrolled studies of buprenorphine to the natural history of hepatic enzyme fluctuation in viral hepatitis. In addition, the safety data should be examined for any cases of acute allergic reaction to buprenorphine.*

- *A risk management and active surveillance plan should be designed to minimize the likelihood of abuse and diversion of buprenorphine, and to identify and intervene if such abuse and diversion occurs.*
- *A common package insert should be created, including both products on a single label.*

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Celia Winchell
1/10/01 04:36:12 PM
MEDICAL OFFICER

Cynthia McCormick
1/12/01 05:39:44 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel: (301) 827-7410

MEDICAL OFFICER REVIEW

NAD: 20,733

Ref. Pediatric Study

The majority of opioid-dependence occurs in adult (≥ 16 year old) although cases less than 16 year old have been reported. It is anticipated that Suboxone will not be used in pediatric population. Therefore, there is no need to conduct clinical study in this population.

[/S/]
Chang Q. Lee, MD, DrPH
Medical Review Officer

] 12/8/97

I concur that, at present, the epidemiology of this disorder is such that little use in patients < age 16 is anticipated, and, therefore, studies supporting pediatric labeling need not be required. [/S/]

12/8/99



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HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301)827-7410

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA #: 20-733;

Sponsor: Reckitt & Colman Pharmaceuticals Inc.

Drug Name

Generic Name: Buprenorphine and Naloxone Sublingual Tablets;

Trade Name: Suboxone

Drug Categorization

Pharmacological Class: Narcotic Agonist/Antagonist

Proposed Indication: Treatment of Opiate Dependence

NDA Classification: 3 S

Dosage Forms: 2 mg buprenorphine + 0.5 mg naloxone and
8 mg buprenorphine + 2.0 mg naloxone tablets

Route: Sublingual

Reviewer Information

Clinical Reviewer: Chang Q. Lee, MD, M.S.H.A., Dr.PH

Peer Medical reviewer: Celia Winchell, MD, Team Leader

Original Receipt Date: June 7, 1999

Completion Date: October 29, 1999

SECTION 1.0	MATERIAL UTILIZED IN REVIEW	4
SECTION 2.0	Background	4
SECTION 2.1	INDICATION	5
SECTION 2.2	RELATED IND'S AND NDA'S	5
SECTION 2.3	ADMINISTRATIVE HISTORY	5
SECTION 2.4	PROPOSED DIRECTIONS FOR USE	7
SECTION 2.5	FOREIGN MARKETING	8
SECTION 3.0	Chemistry	9
SECTION 4.0	Animal Pharmacology/Toxicology	10
SECTION 5.0	Description of Clinical Data Sources	12
SECTION 5.1	STUDY TYPE AND DESIGN/PATIENT ENUMERATION	12
SECTION 5.2.	DEMOGRAPHICS	16
SECTION 5.3	EXTENT OF EXPOSURE	18
SECTION 6.0	Human Pharmacokinetics	18
SECTION 7.0	Efficacy Findings	20
SECTION 7.1	Overview of Efficacy	20
SECTION 7.2	SUMMARY OF STUDIES PERTINENT TO EFFICACY	21
SECTION 7.2.1	STUDY CR96/013 (1008A)	22
SECTION 7.2.2	STUDY CR88/130	41
SECTION 7.2.3	STUDY CR92/099	47
SECTION 7.2.4	STUDY 92/102	55
SECTION 7.2.5	—	58
SECTION 7.2.6	—	68
SECTION 7.2.7	EFFECTIVE DOSE RANGE	70
SECTION 7.2.8	—	70
SECTION 8.0	SAFETY FINDINGS	72
SECTION 8.1	METHODS	72
SECTION 8.2	SERIOUS ADVERSE EVENTS	74
SECTION 8.2.1	DEATHS	74
SECTION 8.2.2	NON-FATAL SERIOUS ADVERSE EVENTS	79
SECTION 8.2.3	OVERDOSE EXPERIENCES	84
SECTION 8.3	ASSESSMENT OF DROPOUTS	85
SECTION 8.3.1	BUPRENORPHINE EXPOSURE	85
SECTION 8.3.2	ADVERSE EVENTS	88
SECTION 8.4	OTHER ADVERSE EVENTS	92
SECTION 8.4.1	ADVERSE EVENTS OVERALL	92
SECTION 8.4.2	ADVERSE EVENTS BY GENDER	100
SECTION 8.4.3	ADVERSE EVENTS BY AGE	104
SECTION 8.4.4	ADVERSE EVENTS BY RACE	104
SECTION 8.4.5	ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY	107

SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH RENAL INSUFFICIENCY..... 109
SECTION 8.4.7 ADVERSE EVENTS RELATED PREGNANCY, NURSING, LABOR AND
DELIVERY 109
SECTION 8.5 OTHER SAFETY FINDINGS 115
SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS..... 115
SECTION 8.5.2 VITAL SIGNS..... 125
SECTION 8.5.3 BODY WEIGHT 126
SECTION 8.6 DOSE-RESPONSE ADVERSE EXPERIENCE INFORMATION..... 128
SECTION 8.7 DRUG-DRUG INTERACTIONS 129
SECTION 8.8 ADVERSE EFFECTS IN LONG TERM USE 129
SECTION 8.9 FOREIGN MARKETING EXPERIENCES 134
SECTION 8.10 EFFECTS OF SUBLINGUAL NALOXONE IN OPIOID
DEPENDENT SUBJECTS 137
SECTION 8.11 SUMMARY OF EFFICACY AND SAFETY 150
SECTION 9.0 CONCLUSIONS..... 155
SECTION 10.0 RECOMMENDATIONS..... 156

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SECTION 1.0 MATERIAL UTILIZED IN REVIEW**NDA Hard Copy of Clinical Data: 265 Volumes**

<u>Volume</u>	<u>Contents</u>
69	Background and Overview of Clinical Investigations, Draft labeling,
70	Clinical data summary, risk/benefit
71- 91	Clinical pharmacology studies, including PK studies and published references
92-168	Clinical Trials
92	Overview of Controlled Clinical Trials
93	Placebo Controlled Studies with CRFs
	93 - 112 <u>Study CR96/013 and CR96/014 (Bup/Nal Combination)</u>
	113 - 114 <u>STUDY CR92/102 (BUPRENORPHINE SUBLINGUAL SOLUTION)</u>
115-120	Methadone Comparison Studies and Published References
120 - 143	Dose Ranging Studies
144 - 146	Uncontrolled Clinical Studies and Published References
147	Other Studies/Published References and Information
148 - 151	Post-marketing Experience of Buprenorphine Sublingual Tablets
152	Summary of Effectiveness
153 - 166	Integrated Summary of Safety
167 - 168	Drug Abuse and Overdose Section

169-333 Case Report Forms (All deaths, cases with serious AE and other adverse events were examined based upon review needs).

Electronic Data: 10 diskettes: safety data for Study 1008 and the pooled solution studies. MS Word Text for the Integrated Summary of Safety and Labeling.

A safety update on NDA 20-733 and NDA 20-732 was submitted on October 12, 1999. Literature search was conducted for new publications between May 1998 and August 1999. Updated post-marketing adverse event data for Subutex tablets covers the period between January 1, 1999 and July 31, 1999. Serious adverse events in an ongoing clinical study were reported until July 31, 1999.

SECTION 2.0 BACKGROUND

The traditional treatment for opiate dependency has been methadone, administered commonly as oral solution in clinics with approved methadone maintenance programs. FDA approved a newer drug, levo-alpha-acetylmethadol or levomethadyl acetate hydrochloride (LAAM) in June 1993 as an orally administered, longer-acting, alternative mu agonist to methadone in the treatment of opiate dependence.

Buprenorphine is a mu-opiate partial agonist that produces morphine-like subjective effects and cross-tolerance to the effects of other opiates. A parenteral dosage form

(Buprenex) is marketed in the United States as a sterile injection in ampoules containing 1ml of a 0.3mg / ml solution of buprenorphine HCl under the trade name of Buprenex[®] (NDA 18-401) since 1982 for the relief of moderate to severe pain in doses up to 0.3 mg IV and 0.6 mg IM.

In other parts of the world buprenorphine is marketed by Reckitt & Colman or their licensed distributors as sublingual analgesic tablets (0.2mg and 0.4mg) and as a sterile injection under the brand names of Temgesic[®] and Buprex[®]. In Japan buprenorphine is also available as a suppository under the brand name of Lepetan[®].

SECTION 2.1 INDICATION

The proposed indication for Suboxone is:

“Suboxone is indicated for the treatment of opiate dependence.”

The sponsor also proposes other potential indications under “Dosage and Administration” section, including for _____, maintenance and _____.

SECTION 2.2 RELATED IND'S AND NDA'S

There are over 40 separate INDs for investigational use of buprenorphine, reflecting the long history of development primarily sponsored through grant-making by the National Institute on Drug Abuse. Many of the INDs involved the use of buprenorphine sublingual solution, or buprenorphine sublingual tablets without naloxone (Subutex).

Data cited in this review was conducted under the following INDs:

IND Number	Formulation	Sponsor
35,877	Suboxone	NIDA Medications Development Division
45,220	Suboxone	Reckitt & Colman

IND-45,219 and NDA 20-732 are related to Subutex (Buprenorphine HCl Sublingual Tablets). NDA 20-732 for Subutex contains much of the same safety and efficacy data and may be regarded as a “companion” to this NDA.

SECTION 2.3 ADMINISTRATIVE HISTORY

The sponsor opened the IND 45,220 for Suboxone on May 2, 1994. The National Institute on Drug Abuse (NIDA) and Reckitt & Colman have entered a Cooperative Research and Development Agreement (CRADA) to develop buprenorphine products for the treatment of narcotic addiction in the USA since then. Through NIDA-funded

studies, buprenorphine has been studied as a treatment for opiate dependence (under over 40 different INDs) over two decades.

The sublingual route for the treatment of opiate dependency was chosen based on experience with low dose buprenorphine analgesic tablets that are administered effectively by this route. Oral administration was not chosen because of the marked first-pass metabolism of buprenorphine by a mixture of intestinal and hepatic enzymes. Parenteral administration was not chosen because of the aim to move addicts away from injecting drugs.

The initial formulation used for opiate dependency in clinical studies was sublingual solutions of buprenorphine dissolved in 30% ethanol / water. For some studies unit doses in 1ml of solution were enclosed in  containers. The sublingual solution has been tested over 1,000 patients. Treatment duration ranged from 3 days to 9 weeks in detoxification studies not involving abrupt withdrawal, and 1 month to 1 year in maintenance studies. Treatment dose ranges were from 1 to 32 mg/day. However,

 A new formulation of buprenorphine sublingual tablets ("Mono" tablets, Subutex) was then developed by Reckitt & Colman. In addition, the sponsor developed a combination of buprenorphine/naloxone ("combo" tablets, Suboxone) for sublingual administration (under IND 45,220 opened May 2, 1994). The rationale for the development of the combination product is that naloxone has faster onset than buprenorphine at the μ -opioid receptor and has a poor sublingual absorption. It is hoped that the naloxone in this product will limit the parenteral abuse liability when the product is used in the treatment of narcotic abuse. Based on clinical pharmacology studies, the sponsor predicts that a dependent subject injecting the product may rapidly experience opioid withdrawal symptoms followed by later by attenuated opioid agonist effects. Conversely, the sponsor predicts that naloxone is not expected to precipitate withdrawal following sublingual administration because of the poor absorption of naloxone. NIDA and Reckitt & Colman envision that Suboxone would be used as the primary maintenance drug, and that its predicted low abuse potential would make it suitable for use outside the methadone clinic setting. They envision that the primary use of the mono product would be for initial transfer from street drugs or methadone ("induction") or for use in pregnant addicts to prevent unnecessary exposure to naloxone.

The FDA Drug Abuse Advisory Committee reviewed clinical studies of the buprenorphine sublingual solution as an incomplete data set under IND #35,877, and recommended that buprenorphine (as a sublingual solution) was generally safe and effective for the management of opiate dependency on December 5, 1994. A plan to link the new formulation pharmacokinetically to the formulation tested in the efficacy studies was endorsed. However, the doses of buprenorphine sublingual tablets are not bioequivalent to the sublingual solutions used in the previous clinical studies; the bioavailability was approximately 50% relative to the sublingual solution in single-dose

[]

[]

Maintenance:

[]

Reducing dosage and stopping treatment

[]

[]

[]

SECTION 2.5 FOREIGN MARKETING

Suboxone has not been marketed in any country. Low dose buprenorphine sublingual tablets for the relief of moderate to severe pain, manufactured by Reckitt & Colman, are currently sold in over 30 countries. The usual daily analgesic dose is in the range 0.2 mg to 1.2 mg per day. Buprenorphine sublingual tablets containing 8mg, 2mg and 0.4mg for the treatment of opioid dependence were approved with the brand name of Subutex® in France in July 1995. Tablets are currently marketed in France (from February 1996) and the United Kingdom (from Feb 1999). To date an estimated 100,000 patients have been and are being treated with these tablets in France. Marketing authorization for Subutex has been granted in Argentina, Finland, Luxembourg and Switzerland. Subutex is under review in

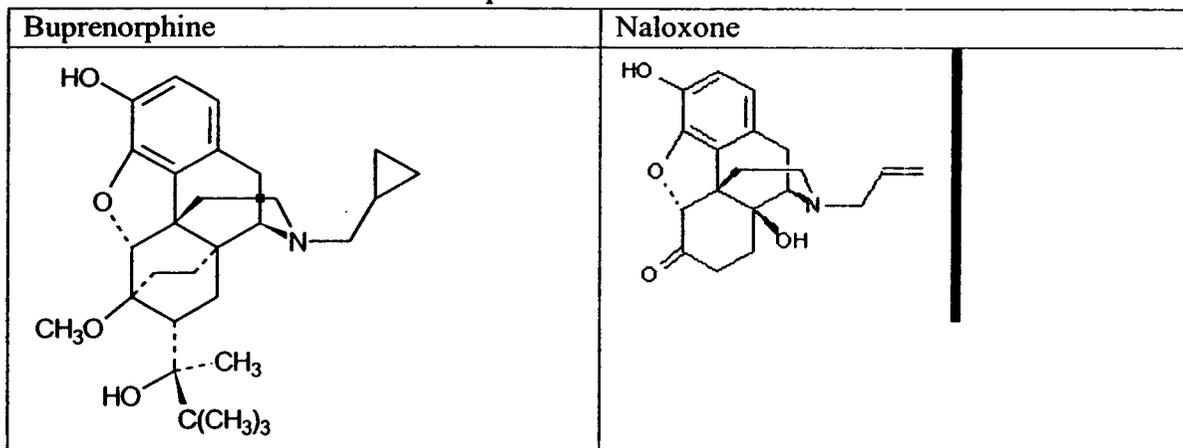
SECTION 3.0 CHEMISTRY

Compound Names: buprenorphine HCl and naloxone HCl dihydrate

Chemical Names: Buprenorphine is 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride.

Naloxone is (-)-17-Allyl-4,5 α -epoxy-3, 14-dihydroymorphinan-6-one hydrochloride.

The structural formula for each compound is:



Buprenorphine hydrochloride is a white powder (Melting Point of about 287 C), weakly acidic with limited solubility in water. Buprenorphine hydrochloride has the molecular formula C₂₉H₄₁NO₄ HCl and the molecular weight is 504.09. Buprenorphine hydrochloride is _____ Buprenorphine's solubilities are about _____ in water and about _____ ml in octanol. There is a USP draft monograph for buprenorphine from NDA 18-401. Release specifications for drug substance quality include, _____

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Naloxone Hydrochloride has the molecular formula $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$ and the molecular weight is 399.87.

Suboxone sublingual tablets are composed of buprenorphine and naloxone at a ratio of 4:1 in two tablet strengths: 8mg/2mg and 2mg/0.5mg. Each tablet also contains lactose, mannitol, corn starch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon / lime flavor. Reckitt & Colman manufacture the tablets in its plant in Hull, England.

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The sponsor has summarized their studies and literature on toxicology data for buprenorphine in Section 3D, Volume 2. The following is a condensation of that summary.

Pharmacologically, buprenorphine behaves as a partial agonist at μ -opiate receptors and an antagonist at κ -opiate receptors. Buprenorphine is subject to a degree of non-clinical abuse. Naloxone, an opiate antagonist currently marketed in injectable form for the complete or partial reversal of opiate effects or for the diagnosis of suspected acute opiate overdose, has been incorporated into formulations to reduce the potential for intravenous abuse.

Pharmacological studies suggest that there is no undesirable pharmacological interaction between buprenorphine and naloxone. Naloxone is an antagonist and at high doses tends to block the agonist actions of buprenorphine.

Metabolic studies demonstrated that the co-administration of naloxone with 3H -buprenorphine or the co-administration of 3H -naloxone with buprenorphine did not alter the disposition, kinetics or metabolism of the tritiated molecule when the compounds were co-administered intravenously, orally, or intramuscularly in the rat or dog.

Extensive acute and subacute toxicity studies by a variety of parenteral and enteral routes are presented in which the toxicity of buprenorphine and naloxone, are compared with the toxicity of mixtures of these components. These studies demonstrate that there is no synergistic enhancement of toxicity when the components of the formulation are co-administered and, indeed, there is some evidence to suggest that the toxicity of buprenorphine be attenuated by the addition of naloxone.

Table 1. Acute Toxicity (LD₅₀) of Buprenorphine Hydrochloride and Naloxone Hydrochloride in the Rat and Mouse.

Test substance	Route of administration					
	i.v.		p.o.		s.c.	
	Rat	Mouse	Rat	Mouse	Rat	Mouse
Bup	119 (101-204)	50.1 (43.5-57.4)	>5000*	2025 (1547-2636)	>1500*	>2500*
Nal	162 (139-189)	106.6 (91.5-123.7)	3395 (2278-5919)	1183 (849-1565)	1450 (1157-1793)	294 (214-401)
Nal: Bup 3:2		180.2 (156.2-210.4)				
Nal +Bup 1000 mg/kg			4732 (3097-9395)		2550 (2054-3171)	447 (325-614)
Nal: Bup 2:3				2362 (1814-3088)		
Nal: Bup 2:3	173 (148-204)					

Data Source: Based on Sponsor's Table 125 in Vol 153, page 239. * Minimum lethal dose

Intramuscular developmental toxicity studies in both the rat and rabbit, fertility studies in the rat by subcutaneous and oral routes and peri- post-natal studies have been conducted. Difficult parturition and high neonatal mortality were observed in these studies, particularly in the high dose groups, but there was no evidence that buprenorphine had adverse effects on pregnancy rates or fertility. A slightly depressed growth rate was observed in pups whose mothers were treated with buprenorphine during lactation but no other adverse effects were observed. Evaluation of the developmental toxicity of co-administered buprenorphine hydrochloride and naloxone hydrochloride in the ratio 1:1 was conducted in oral studies in both the rat and the rabbit. In addition, studies were also conducted in both species by the intramuscular routes using co-administered buprenorphine hydrochloride and naloxone hydrochloride in the ratio 3:2. None of these developmental toxicity studies of buprenorphine or buprenorphine/naloxone combinations by parenteral route of administration produced evidence of teratogenicity.

A peri- and post-natal toxicity study by the oral route was conducted with buprenorphine hydrochloride. The no-effect dose in terms of pre-weaning development from this study was 8 mg/kg/day, which represents a multiple of approximately 30 times the upper limit of the expected human daily dose of Subutex. Data from two studies on buprenorphine by the intramuscular route generally are consistent with those seen following oral administration.

GLP-compliant data which meet current ICH Guidelines indicate that buprenorphine is not mutagenic. Similarly, ICH-compliant mutagenicity studies of a 4:1 mixture of buprenorphine HCl and naloxone HCl show that this combination is not mutagenic or clastogenic.

A rat carcinogenicity study on buprenorphine hydrochloride and two GLP-compliant dietary mouse carcinogenicity studies provide no convincing evidence that buprenorphine hydrochloride is carcinogenic in either the rat or the mouse following dietary administration.

SECTION 5.0 DESCRIPTION OF CLINICAL DATA SOURCES

Clinical investigations on buprenorphine have been conducted over a 15-year period and much of the data are now published. However, many previous studies may not be conducted according to GCP standards. Most of the studies were funded by the National Institute on Drug Abuse and buprenorphine HCl was provided by Reckitt & Colman and shipped to _____ who act as importers of the drug on behalf of NIDA. The drug was distributed to the investigational sites from RTI at the direction of NIDA where the drug was formulated usually as a solution in 30% aqueous alcohol. For later, large scale studies pre-packed unit dose (1ml) plastic containers of the aqueous alcohol solutions were prepared by _____. More recently, _____ oval sublingual tablets have been prepared by Reckitt & Colman for use in clinical studies.

SECTION 5.1 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

The primary development program can be classified based on the three drug formulations: solution, mono tablets, and combo tablets.

A total of 98 publications or reports are submitted in clinical section of the NDA: 39 publications for PK/PD, 12 published reports for the interactions of buprenorphine and cocaine, 20 published reports or clinical reports lacking CRFs for controlled clinical trials, 11 publications for uncontrolled clinical studies, and 16 publications/reports for other studies and information.

5.1.1 Development Program using the combo tablet formulation

Buprenorphine combo sublingual tablets were studied in about 575 patients in 10 studies in daily doses from 4 mg to 24 mg. However, only one study has CRFs available (See table below). This 4-week double-blind controlled trial (Study 1008A) is designated as pivotal to support the efficacy and safety of both sublingual combo and mono products in the treatment of opioid dependence.

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**Table 2. Clinical Studies Using the Combo Product
Buprenorphine/Naloxone and Buprenorphine Tablet Formulations**

Study No.	Principal Investigator ¹	Country	Dates of Conduct ²	Status	Location in NDA (Vol. / Page)	
					Report	CRFs
Controlled Studies of Buprenorphine / Naloxone Combination Tablets						
CR95/002	Ling	U.S.	1991-1996	Complete	Vol 145/Page 1	
CR96/013 CR96/014 (Study 1008)	Somoza	U.S.	1996-1998	Complete	Vol 93/Page 1	Available
	Malkerneker					
	Casadonte					
	McNicholas					
	Tusel					
	Stine					
	Ling					
	Renner					
	Liberto					
	Douyou					
Fe-Bornstein						
Santos						
Controlled Studies of Buprenorphine Monotherapy Tablets						
CR96/002	Perez	Spain	1996-1998	Complete	Vol 120/Page 175	N/A
CR96/003	Ladewig	Switzerland	1997	Complete	Vol 115/Page 62	N/A
	Petitjean					
	Stohler					
	Deglon					
CR96/004	Gessa	Italy	1996-1998	Complete	Vol 115/Page 1	N/A
Open Label Studies of Buprenorphine Monotherapy Tablets						
CR90/001	Cornier	France	1990	Complete	Vol 146/Page 10	N/A
	Gentilini					
	Lambert					
	Patris					
	Tignal					
CR94/002	Law	U.K.	1997	Complete	Vol 146/Page 293	N/A
CR94/005	Rindom	Denmark	1998	Complete	Vol 146/Page 1	N/A
CR98/001	Lintzeris	Australia	1998	Complete	Vol 146/Page 165	N/A
Bupp2929	Nigam	India	1993	Complete	Vol 146/Page 158	N/A

Data Source: Based on Sponsor's Table 4 in Vol 153, page 15.

¹Please note that if a P.I. name was not available, the primary author of the publication is listed.

²Likewise, if the date of conduct is not available, publication date is listed.

N/A= Not available

5.1.2 Development Program using the mono tablet formulation

Buprenorphine sublingual tablets (mono product) were studied in about 250 patients in 8 studies (4 studies listed Table 3) in daily doses from 4 mg to 24 mg.

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Table 3. Clinical Studies Using the Mono Product Only

PHARMACOKINETIC STUDIES				
Status	Study	Test Product	Subjects	Duration
Completed	CR94/001	Buprenorphine SLT- 8mg SLS- 8mg	6	Single Dose (SD)
Completed	CI90/001	Buprenorphine 0.2mg SLT 4mg/day given as either one, two or four doses	44	5d
20 subjects completed	CR96/009	8 mg SLS 16 mg SLT	24	20d 10d on SLT 10d on SLS
17 subjects completed	CR96/012	4,8,16 and 24 mg SLT	24	SD

Data Source: Based on Sponsor's Table 2 in Vol 153, page 13

5.1.3 Development Program using the solution formulation

Buprenorphine sublingual solution was studied in 1613 patients (1169 men and 444 women) in 33 studies in daily doses from 1 mg to 32 mg. Two 16-week double-blind controlled trials (Studies CR88/130 and CR92/099) that are designated as pivotal to support the efficacy and safety of the sublingual solution in the treatment of opioid dependence. Detailed study reviews for sublingual solution are available in reports written by Dr. Monte L. Scheinbaum under NDA 20-732. Table 4 presents overall study program and database for the solution.

TABLE 4. Clinical Studies of Buprenorphine Sublingual Solution

Study Type	Study	Total patients	Bup patients (F)	Duration	Bup dose range (mg)
Single dose clinical p/col	CR80/071	10	10 (0)	SD	1-4
	CR90/061	16	8 (0)	SD	1-32
	CR91/071	25	17 (0)	SD	0.5-32
	CR90/062	13	13 (0)	SD	2-8
	CR92/095	6	6 (0)	SD	6
Multiple dose clinical p/col	CR85/045	5	5 (0)	14d	2-16
	CR91/073	6	6 (1)	5d	2-12
	CR91/072	66	47 (6)	17d	2-16
	Bupp 3712	8	8 (2)	9w	2-8
Pharmacokinetic	CR91/080	12	12 (3)	SD	2
	CR92/180	6	6 (1)	SD	2
	CR87/027	24	24 (0)	SD	0.2-0.8
	CR94/001	6	6 (0)	SD	8
	CR95/001	8	8 (0)	SD	4-16

TABLE 1 Clinical Studies Of Buprenorphine Sublingual Solution (cont.)	CR92/111	9	9 (1)	18d	4-8
Non-controlled pilot	CR81/075	21	21 (0)	28d	2
	CR84/004	32	32 (8)	5w	2-4
	CR86/075	41	41 (10)	35d	2-8
	CI90/001	44	44 (10)	5d	4
	CR90/068	30	30 (13)	21d	2-16
Maintenance with reference	CR88/130*	162	53 (15)	180d	8
	CR90/066	164	84 (27)	26w	2-16
	CR89/095	140	56 (18)	26w	2-6
	CR90/069	225	75 (21)	52w	8.00
	CR91/076	132	60 (18)	26w	4-12
	CR91/076	51	24 (5)	26w	8-16
Dose ranging maintenance	CR92/099*	731	731 (237)	16w	1-16
(extension of CR92/099)	CR92/100*	332	332 (95)	36w	1-32
	CR92/102*	150	108 (38)	13w	2-8
	CR87/087	24	24 (0)	52d	8
	CR92/107	13	13 (5)	97d	2-16
Detoxification	CR84/040	45	22 (0)	13w	0.17-2
	CR90/065	25	10 (5)	17d	1-6
TOTAL	33.00	2582	1613 (444)		

Data Source: Based on Sponsor's Table 5 in Vol 153, page 16 and Dr. Scheinbaum's review on NDA 20-732.

This review will focus on studies with CRFs for efficacy and all relevant data for safety.

Figure 1. Overview of Sources of 3172 Subjects Exposed to Buprenorphine/Naloxone and Buprenorphine Monotherapy Include for Which Safety Data are Available

	Buprenorphine/Naloxone Sublingual Tablet	Buprenorphine Sublingual Tablet	Buprenorphine Sublingual Solution
Clinical Studies with CRFs	472 Subjects (1008)	105 Subjects ^{1,2} (1008)	813 Subjects (CR88/130, CR92/099 and CR92/100, CR92/102)
Clinical Studies without CRFs	25 Subjects	248 Subjects	422 Subjects
Post-Marketing	-	1042 Subjects ³	-

Data Source: Based on Sponsor's Figure 1 in Vol 153, page 50

¹ 103 subjects in the safety sample; ² 83 subjects also received combination tablets ³ From 2 post-marketing surveys. Estimated total exposure in France is -

SECTION 5.2. DEMOGRAPHICS

Demographics of efficacy studies are shown in Section 7.2. This section presents summaries of baseline demographics in the studies of the three formulations for safety analyses.

Table 5. Summary of Baseline Demographics for 1305¹ Subjects Receiving Buprenorphine/Naloxone or Buprenorphine (Tablet or Solution) in Four Studies* for which CRFs are Available

	Combination Tablet (N = 497)	Monotherapy Tablet (N = 105)	Monotherapy Solution (N = 813)
Gender			
Male	343 (69.0%)	70	563
Female	154 (31.0%)	35	250
Age (years)			
Mean	38.5	-	-
Range	19 - 62	19 - 57	18 - 67
Ethnicity			
Caucasian	257 (51.7%)	62	402
Black	142 (28.6%)	35	214
Hispanic	85 (17.1%)	0	0
Other	13 (2.6%)	8	197

Data Source: Based on Sponsor's Table 24 in Vol 153, page 50.

* CR96/013 and CR96/014, CR88/130, CR92/099 and CR92/100, CR92/102

Table 6. Summary of Baseline Demographics for Subjects Receiving Buprenorphine/Naloxone Combination Tablets

	Study		Overall (N = 497)
	CR96/013 (CR96/014) (N = 472)	CR95/002 (N = 25)	
Gender			
Male	327 (69.3%)	16 (64.0%)	343 (69.0%)
Female	145 (30.7%)	9 (36.0%)	154 (31.0%)
Age (years)			
Mean	38.9	30.7	38.5
Range	19 - 60	23 - 62	19 - 62
Ethnicity			
Caucasian	238 (50.4%)	19 (76.0%)	257 (51.7%)
Black	142 (30.1%)	0	142 (28.6%)
Hispanic	79 (16.7%)	6 (24.0%)	85 (17.1%)
Other	13 (2.7%)	0	13 (2.6%)

Data Source: Based on Sponsor's Table 27 in Vol 153, page 53

Table 7. Summary of Baseline Demographics for Subjects Receiving Buprenorphine Tablets (Data used for Safety Sample)

	Source		TOTAL (N = 351)
	CR96/013/ CR96014 (N = 105 ¹)	Other (N = 248)	
Gender			
Male	70	168 ²	238
Female	35	42 ²	77
Age (years)			
Mean	36.6	--	--
Range	19 - 57	18 - 45	18-57
Ethnicity			
Caucasian	62	103 ³	165
Black	35	-	35
Other	8	2	10

Data Source: Based on Sponsor's Table 31 in Vol 153, page 59

¹ Safety sample = 103 subjects ²Based on seven studies (N = 210) ³Ethnicity data available for three studies (N = 105)

Table 8. Summary of Baseline Demographics for Subjects Receiving Buprenorphine Sublingual Solution (Data used for Safety Sample)

	Source		TOTAL (N = 1235)
	Pooled Data (CR88/130, CR92/099/100, CR92/102) (N = 813)	Publications (N = 422)	
Gender			
Male	563 (69.2%)	302 ¹ (75.9%)	865 (71.4%)
Female	250 (30.8%)	96 (24.1%)	346 (28.6%)
Age (years)			
Mean (SD)	35.7 (0.3)	-	-
Range	18 - 67	19 - 66	18 - 67
Ethnicity			
Caucasian	402 (49.4%)	116 ² (41.1%)	518 (47.3%)
Black	214 (26.3%)	62 (122.0%)	276 (25.2%)
Other	197 (24.2%)	104 (36.9%)	301 (27.5%)

Data Source: Based on Sponsor's Table 34 in Vol 153, page 63

¹Gender data based on 9 studies (No data for CR87/087 N=24)

² Ethnicity data based on 6 studies (N=241) and partial data from 1 study, CR90/066 (N=41)

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SECTION 5.3 EXTENT OF EXPOSURE

See Section 8.3.1 of this review.

SECTION 6.0 HUMAN PHARMACOKINETICS

Overview: Buprenorphine is readily absorbed by most routes except orally due to extensive metabolism in the liver and intestine. When given sublingually as an alcoholic solution, buprenorphine has an absolute bioavailability of approximately 35%; sublingual tablets are approximately 50 to 70% bioequivalent relative to the solution. Onset of effect is rapid, within 30 minutes of administration, and depending on the dose, the duration of effect following a single dose may last up to 72 hours. Peak concentrations appear within 1 hour when administered as Suboxone or Subutex. The pharmacokinetic half-life of buprenorphine at steady state is approximately 32 to 35 hours. Circulating drug is approximately 96% protein bound. Following administration most of the drug is excreted unchanged in the feces; lower amounts of N-dealkylated and conjugated metabolites are detected in the urine.

Absorption:

Buprenorphine is rapidly absorbed following sublingual administration as tablets containing buprenorphine/naloxone or buprenorphine alone. Measurable levels are present at the first sampling time point (15 minutes post-dose), with peak levels observed within 1 hour of dosing. Plasma levels are best described by a mono-exponential rising phase, with a bi-exponential decay. Detectable levels (≥ 1 ng/mL) persist for at least 72 hours following a single dose. Steady state levels are reached in approximately 8 days.

The extent of sublingual absorption is incomplete. The absolute bioavailability of sublingual tablets is approximately 35% when the extent of absorption of a sublingual tablet (0.4 and 0.8 mg doses) is compared to an intravenous dose. The buprenorphine sublingual tablets have a relative bioequivalence of approximately 50% to 70% compared to sublingual solution.

Extent of absorption as reflected by both peak concentration (C_{max}) and area under the plasma-concentration curve (AUC) increased linearly but not proportionally with dose, absorption of the 24 mg dose of buprenorphine was more variable than at lower doses.

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Table 9. Mean Buprenorphine and Naloxone Pharmacokinetic Parameter Values when Administered as a Single Dose of Suboxone in Study CR97/007 (N = 14 Opioid-experienced Volunteers)

Parameter (unit)	Buprenorphine Dose			
	4 mg	8 mg	16 mg	24 mg
C _{max} (ng/mL)	2.33	3.53	5.83	6.44
T _{max} (hours)	0.95	1.04	1.08	0.96
AUC (hr × ng/mL)	13.4	23.4	39.5	47.6
	Naloxone Dose			
	4 mg	8 mg	16 mg	24 mg
C _{max} (ng/mL)	0.12	0.25	0.44	0.47
T _{max} (hours)	0.52	0.57	0.40	0.52
AUC (hr × ng/mL)	0.12	0.30	0.53	0.60

Data Source: Based on Sponsor's Table 17 in Vol 153, page 39

Table 10. Mean Buprenorphine and Naloxone Pharmacokinetic Parameter Values when Administered as a Single Dose in Study CR95/001 (N = 8 Opioid-experienced Volunteers)

Parameter (unit)	Buprenorphine + (4:1 Naloxone)			Buprenorphine
	4 mg	8 mg	16 mg	16 mg
C _{max} (ng/mL)	1.84	3.00	5.95	5.47
T _{max} (hours)	1.06	0.57	0.79	1.04
AUC (hr × ng/mL)	8.14	9.82	34.89	32.63
	Naloxone (dose)			
	1 mg	2 mg	4 mg	--
C _{max} (ng/mL)	0.11	0.18	0.28	--
T _{max} (hours)	0.59	0.65	0.72	--

Data Source: Based on Sponsor's Table 18 in Vol 153, page 39

The effects of different holding times in the mouth and of salivary pH have been evaluated and found to have no clinically meaningful impact on extent of absorption of buprenorphine. For the sublingual solution, there was no difference in buprenorphine plasma concentration 60 minutes post-dose when an alcoholic solution was held for 2, 4, or 10 minutes nor did absolute bioavailability differ between holding times of 3 and 5 minutes. In Study CR91/080, a slight increase of absorption was seen as salivary pH increased, as would be expected with a weak base (pKa = 8.4).

The time necessary for *in vivo* dissolution of buprenorphine/naloxone sublingual tablets and buprenorphine monotherapy sublingual tablets increases with dose. Complete tablet dissolution of 16 mg dose generally occurs in less than 10 minutes for both formulations. The sponsor has not evaluated the PK profiles when more than two tablets are given simultaneously.

Distribution

No tissue distribution data are available in humans.

Volume of distribution during the terminal elimination phase (V_{dp}) was estimated following multiple dosing of buprenorphine sublingual solution in doses of 8 mg alone and with naloxone in 1:1 and 1:2 ratios (CR92/111). Mean V_{dp} was 2828 liters, indicating significant distribution in deep compartments relative to the low plasma concentration.

Metabolism

Studies in animals demonstrate that the metabolism of buprenorphine is *via* N-dealkylation to norbuprenorphine and conjugation of buprenorphine and norbuprenorphine with glucuronic acid.

The metabolic pathways and excretion of buprenorphine in humans are the same as those in animals, as demonstrated by the intravenous infusion of 200 μ Ci 3 H-buprenorphine 1 mg in saline, administered as a single dose to 6 opiate-experienced, non-opiate-dependent men.

Studies using cytochrome P450 have shown that N-dealkylation is exclusively by the CYP3A4 isoform.

Elimination and Excretion

Studies show that the terminal elimination half-life of buprenorphine is around 35 hours following multiple dosing.

Studies in rats indicate that glucuronate conjugates of buprenorphine are excreted in bile (approximately 75%), hydrolyzed in the gut, and reabsorbed un-conjugated to undergo further entero-hepatic cycling. Free and unconjugated buprenorphine and norbuprenorphine are also excreted in the urine (approximately 25%).

Following a single intravenous dose of radiolabeled buprenorphine in humans, a total of 99 \pm 13% (69 \pm 11% in feces *versus* 30 \pm 7% in urine) of the radioactivity was recovered in a 9-day post-dose urine and feces collection (CR94/006). Most of the radioactivity was attributed to free and conjugated buprenorphine and norbuprenorphine.

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 Overview of Efficacy

This NDA submission contains one "adequate, well-controlled" study (CR96/013 - 1008) for the to-be-marketed buprenorphine sublingual combo tablet, Suboxone. In addition, sponsor submits three double-blind controlled trials of buprenorphine sublingual solution (CR88/130, CR92/099 and CR92/102) to support the efficacy of Suboxone in the treatment of opioid dependence. PK linkage between Suboxone and buprenorphine

sublingual solution has been studied. PK analyses of the dose-proportionality data suggest that the relative bioavailability of Suboxone to the solution is about 70% in the 4-16 mg dose range of Suboxone tablets (see PK review for details). Therefore, studies on the solution formulation provide supporting evidence on the effective dose range of Suboxone. Bioequivalency of the two buprenorphine sublingual tablets (mono product - Subutex and combo product - Suboxone) has not been established.

This review section includes summary of studies pertinent to efficacy. The following tables present an overview for studies to be reviewed under Section 7.2.1 to 7.2.4. The sponsor's claims for induction, effective dose range, and maintenance will be reviewed under Section 7.2.5 to 7.2.7.

Table 11. Efficacy Studies for Supporting NDA 20-733 (Suboxone)

Study	Type/Drug	Design	# of Patients	CRF	NDA Submission
CR96/013 CR96/014	Phase III clinical comparison of Suboxone (16 mg), Subutex (16 mg) and Placebo tablets	1) Multicenter, double blind, placebo-controlled, parallel group study; 2) open label extended treatment	472	Yes	Section 8.D.2.1.1, Vol 93, Page 1
CR88/130	Efficacy of buprenorphine 8 mg in opiate-dependent outpatient maintenance in comparison with methadone. Bup Solution: 8 mg/day	Double blind, methadone-controlled, parallel group	53 (buprenorphine) 109 (Methadone)	Yes	Section 8.D.3.1.1, Vol 117 - 119
CR92/099 CR92/100	Safety and effectiveness of 8-mg buprenorphine sublingual (solution) per day as compared to 1 mg per day in decreasing illicit opiate use. 1) 1, 4, 8, or 16 mg x 16 wks 2) ≤ 32 mg/day to max. 52 wks	1) Double-blind, parallel group multicenter, dose comparison study 2) Extended double blind, flexible dose treatment	731 (CR92/099) 332 (CR92/100)	Yes	Section 8.D.4.4.1, Vol 121 – 128 and Vol 129 – 135
CR92/102	A placebo controlled trial: daily versus alternative-day dosing. Bup. Solution: 2 or 8 mg/day x 14 days or 8 mg on alt. days	Double blind, placebo-controlled, parallel group	Part A: 150 • 60 for BS 2 mg • 30 for BS 8 mg • 60 for Placebo Part B: 128	Yes	Section 8.D.2.2.1, Vol 113 – 114

Finally, in Section 8.10, data concerning the activity of the naloxone component in the Suboxone tablet are described and reviewed. In order to make use of efficacy data on buprenorphine-only formulations, it is necessary to regard the naloxone in Suboxone as inactive when the product is used as directed (i.e. sublingual administration to patients maintained on buprenorphine).

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 STUDY CR96/013 (1008A)

SECTION 7.2.1.1. Protocol Synopsis

Title: A MULTICENTER EFFICACY/SAFETY TRIAL OF BUPRENORPHINE/NALOXONE FOR THE TREATMENT OF OPIATE DEPENDENCE

Objectives:

To demonstrate the safety and efficacy of 4-week treatment with sublingual buprenorphine/naloxone for opiate-dependence in primary care clinics (Study CR96/013), referred to as “the efficacy study”; and to demonstrate the safety of long-term treatment (up to 52 weeks) (Study CR96/014), referred to as “the safety study”.

The second phase of the study (Study CR96/014) conducted at four additional sites) was a 48- to 52-week open label safety assessment of the buprenorphine/naloxone arm only, in doses up to 24 mg/6 mg per day. Only Study CR96/013 is reviewed in this section, and Study CR96/014 will be reviewed in the safety section.

Investigators/Location:

The study was conducted in eight Veterans Affairs Medical Centers in the United States that have specialty clinics serving substance-abusing or substance-dependent subjects. The Principal Investigators of the study were Peter Bridge, M.D. [National Institute on Drug Abuse (NIDA)] and Paul J. Fudala, Ph.D. [Department of Veterans Affairs (DVA), Philadelphia].

Table 12. Listing of Site Investigators and Their Affiliations

Site No.	Site Investigators	Affiliation	
630	Paul Casadonte, MD	VAMC	New York, NY
691	Walter Ling, MD	VAMC	West Los Angeles, CA
578	Usha Malkerneker, MD	VAMC	Hines, IL
642	Laura McNicholas, MD, PhD	VAMC	Philadelphia, PA
750	John A. Renner, Jr., MD	VAMC	Boston, MA
539	Eugene Somoza, MD	VAMC	Cincinnati, OH
689	Susan Stine, MD, PhD	VAMC	West Haven, CT
662	Donald J. Tusel, MD	VAMC	San Francisco, CA

Data Source: Based on Sponsor's Table 1: Vol 93, Page 3

Population:

The sponsor planned to enroll up to 384 subjects (48 per site or 16 per treatment group per site).

Subjects were eligible for enrollment in the study if they meet all of the following inclusion criteria:

- Males or non-pregnant, non-nursing females, 18 to 59 years of age (inclusive);
- DSM-IV (Diagnostic and Statistical Manual of the American Psychiatric Association) diagnosis of current opiate dependence;
- Seeking opiate-substitution pharmacotherapy for opiate dependence;
- Able to give informed consent and were willing to comply with all study procedures (e.g., providing of urine samples under observation, completing questionnaires).

Major exclusion criteria were:

- Acute or chronic condition that would make participation in the study medically hazardous (e.g., acute hepatitis, unstable cardiovascular, hepatic, or renal disease, unstable diabetes; symptomatic AIDS, not HIV-seropositive alone);
- Presence of aspartate or alanine aminotransferase (AST or ALT, respectively) levels greater than three times the upper limit of normal;
- Current dependence (by DSM-IV criteria) on any psychoactive substance other than opiates, caffeine, or nicotine dependence;
- Enrollment in an opiate-substitution [*i.e.*, methadone, levo-alpha-acetylmethadol (LAAM)] treatment program within 45 days of enrolling in the present study.

Study Design:

The study was a multicenter, randomized, placebo controlled, double blind clinical trial conducted at eight sites.

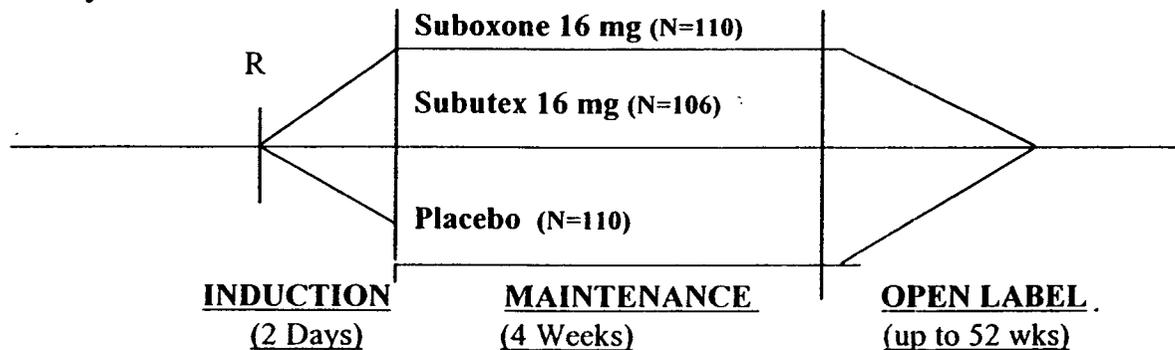
Subjects were to be randomly assigned to one of three treatment groups:

Group I: placebo

Group II: buprenorphine 16 mg per day

Group III: buprenorphine 16 mg/naloxone 4 mg per day.

Study Scheme:



Two strengths of buprenorphine and two strengths of buprenorphine/naloxone combination tablets were to be used in this study. Each monotherapy tablet contained buprenorphine 2 or 8 mg; each combination tablet contained either buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 8 mg/naloxone 2 mg. Placebo tablets were matched for appearance and taste.

At the screen visit, patients were to undergo physical examination, laboratory studies, EKG, urine toxicology, and pregnancy test, and to complete a Craving Scale and Risk Assessment Battery.

Subjects were to be seen daily in the clinic (Monday through Friday) during the first 4 weeks of Study 1008A for dosing and efficacy assessments. Patients were to receive their medication on-site Monday through Friday with take-home Saturday and Sunday doses are dispensed on Fridays. The total dose was to be taken once daily, sublingually. The subject was to be instructed to hold the medication under the tongue for approximately 5-10 minutes until completely dissolved.

The initial induction dosing schedule is described in Table 13 below.

Table 13. Subject Drug Therapy Kits

Card Type (number of cards)	Day of Study	Combination	Monotherapy	Placebo
Induction/ Reinduction (1)	1	One B - 8 mg	One B - 8 mg	One placebo
	2	Two B - 8 mg	Two B - 8 mg	Two placebos
Maintenance (4)*	3-28	Two B/N - 8/2 mg per day	Two B - 8 mg per day	Two placebos per day
Take-home (4)	weekends	Two B/N - 8/2 mg per day	Two B - 8 mg per day	Two placebos per day
Holidays	holidays	Two B/N - 8/2 mg	Two B - 8 mg	Two placebos
Induction/ Reinduction (3)	when needed	One B - 8 mg	One B - 8 mg	One placebo
		Two B - 8 mg	Two B - 8 mg	Two placebos

Data Source: Based on Sponsor's Table 3: Vol 93, Page 14

B = buprenorphine; B/N = buprenorphine/naloxone

- There are four Maintenance Cards to be used on weekdays. When one card is completely used, another card is begun. Each Maintenance Card has a 5-day supply.

Following induction, medication was to be dispensed using drug therapy kits for each subject. Each subject drug therapy kit contained 13 dosage cards for weekday and weekend use as described in Table 14.

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Table 14
Phase 1: Induction Onto Therapy¹

Treatment Group	Day 1	Day 2	Day 3-28
Placebo	0	0	0
Buprenorphine monotherapy	Buprenorphine 8 mg	Buprenorphine 16 mg	Buprenorphine 16 mg
Buprenorphine/Naloxone	Buprenorphine 8 mg	Buprenorphine 16 mg	Buprenorphine 16 mg Naloxone 4 mg

Data Source: Based on Sponsor's Table 6: Vol 93, Page 19

¹ Re-induction by same schedule to occur in the event three consecutive doses missed

Subjects who missed three consecutive doses of medication (unless medication was held due to an adverse event) were re-induced according to the original induction schedule. Thus, subjects who failed to receive a Friday dose and do not receive that weekends' Saturday and Sunday doses were to be re-induced onto the study medication. Subjects who missed one or two consecutive doses, were to continue on their assigned dosage, *i.e.*, no re-induction procedure was to be utilized.

Assessments included Patient Global Impression Rating (three times weekly M/W/F), Clinician Global Impression Rating (three times weekly M/W/F), and Patient Recorded Craving Scale (five times weekly Monday through Friday). The subject was to be instructed to record the peak craving that occurred over the previous 24 hours. Subjects were to record their estimate on a 100-mm line designated "no" craving on one end and "maximum craving ever experienced" on the other. Urine samples for drugs of abuse were to be collected three times per week under observation, on Mondays, Wednesdays and Fridays. If a subject failed to give a sample on the day it was due, it was to be recorded as missing. Urine samples were to be sent to a central laboratory for analysis for morphine and corresponding metabolites. All Monday samples (or the first sample collected in a week) were to be additionally analyzed for amphetamines, barbiturates, benzodiazepines, cocaine, and methadone. Data on concomitant medications and adverse events was to be collected weekly.

All subjects were to receive one, 1-hour session of individualized counseling per week, in addition to initial HIV counseling. Patients were compensated at a rate of \$10 per day for each day they attended the clinic.

Patients leaving the study were to have a Termination Visit including, examination, laboratory studies, EKG and pregnancy test, Craving Scale, Risk Assessment Battery, concomitant medications and adverse events.

Patients completing the first study phase were given the opportunity to continue in the second, 48-week phase of safety study. Additional patients were also recruited directly into the safety study. The first dose (buprenorphine 8 mg) in the open-label phase was to be given on Monday through Wednesdays only. The second dose (8 or 12 mg, depending on the clinician determined, targeted dosage level) was also given as the buprenorphine mono-component product. All succeeding dosages, except those used for re-induction,

were to be given as the buprenorphine/naloxone combination. Daily dosages could be increased (to a maximum of 24 mg/6 mg) or decreased, based on clinical judgement, in 4 mg/1 mg increments throughout the duration of the study.

Section 7.2.1.2 Efficacy and Statistical Analysis

Two primary endpoints were specified: mean percent urine negative for opiates and opiate craving score.

Percentage of urine samples negative for opiates was defined as: a urine sample would be considered negative if the amount of opiate or opiate metabolites in the sample was less than 300 ng/mL. Missing urine samples were considered positive. The number of clean urine samples recorded by each subject was to be expressed as a percentage based on the total number of samples which should have been provided during the time that the subject remained in the study (PCC) and based on the total number of samples that should have been provided during the full 4-week study period (*i.e.*, 12 samples).

Subject-reported craving for opiates was to be assessed at study entry and at each daily clinic visit. For analysis, Subject-reported craving for opiates was expressed as a weekly average for each of the 4 weeks.

Secondary Efficacy Variables

Secondary outcome measures included urine samples negative for assayed substances other than opiates (amphetamines, barbiturates, benzodiazepines, cocaine, and methadone), subject clinical global impression, clinician global impression, retention in the trial based on the last clinic visit date, and the amount of psychosocial treatment services provided (TSR). One additional secondary outcome measure was the RAB that pertains to clinically significant, ancillary effects of drug abuse.

All statistical tests were performed as two-sided tests using the 5% level of significance. The baseline characteristics and primary efficacy variables were to be analyzed using “intent to treat” methodology (*i.e.*, all randomized subjects were to be included in the analyses). The protocol-specified analyses are described below.

Only one of the three possible pairwise treatment comparisons, buprenorphine/naloxone *versus* placebo, was considered as primary in the protocol. Therefore, no adjustment of the Type I error level was planned for the analyses of these measures. However, result of another pairwise comparison, buprenorphine (mono product) *versus* placebo, was of interest as well. Therefore, two analysis results (of urine tests) using both the 5% and 2.5% levels of significance were reported.

The mean percentages of “clean” urine samples for all three treatment groups were compared by pairwise normal (approximation to the binomial) Z-tests and Tukey-Kramer HSD. For the opiate craving score, where at most five observations per week were

obtained, the four-weekly average scores were calculated. Repeated-measures ANOVA or covariance (ANCOVA) procedures, with the single baseline score as covariate, and with terms for follow-up time and follow-up time/treatment interactions, were used to analyze opiate craving.

Determination of Sample Size

The sponsor estimated that in order to detect a difference of 10% clean urines between the buprenorphine/naloxone and placebo groups, with a Type I error of 0.05 and a power of 0.90, 84 subjects per treatment group (252 subjects total) would be required. Taking into consideration a potential 33% attrition rate, a target sample size of 128 subjects per treatment group (or 384 subjects in total) was chosen.

Section 7.2.1.3. Protocol Amendment

No amendments to the protocol were filed to IND 35,877 or described in the NDA submission. However, enrollment was terminated prematurely by the Data Monitoring Board (details see in the patient disposition section below).

Section 7.2.1.4 Conduct of Study

Patient Distribution and Disposition: ___

A total of 326 subjects were enrolled: 110 subjects randomized to receive the combination therapy (buprenorphine/naloxone), 106 subjects to receive monotherapy (buprenorphine), and 110 subjects to receive placebo. The proposed number of subjects expected to enter the efficacy study was 384, however the Data Monitoring Board recommended that enrollment into phase 1 be closed. All 326 subjects comprise the intent-to-treat efficacy sample and all contribute safety data. The Intent-to-Treat efficacy sample is comprised of only 323 subjects because 3 subjects, one in each treatment group, were randomized but were never dosed (Subjects 691-1075 [combination therapy], 630-1019 [monotherapy], and 691-1039 [placebo]) and were therefore excluded from analyses. The disposition of subjects in the efficacy study, including reasons for discontinuation based on the termination form is provided in the following table.

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Table 15
Summary of Subject Disposition by Treatment Group and
Reason for Discontinuation in the Efficacy Study

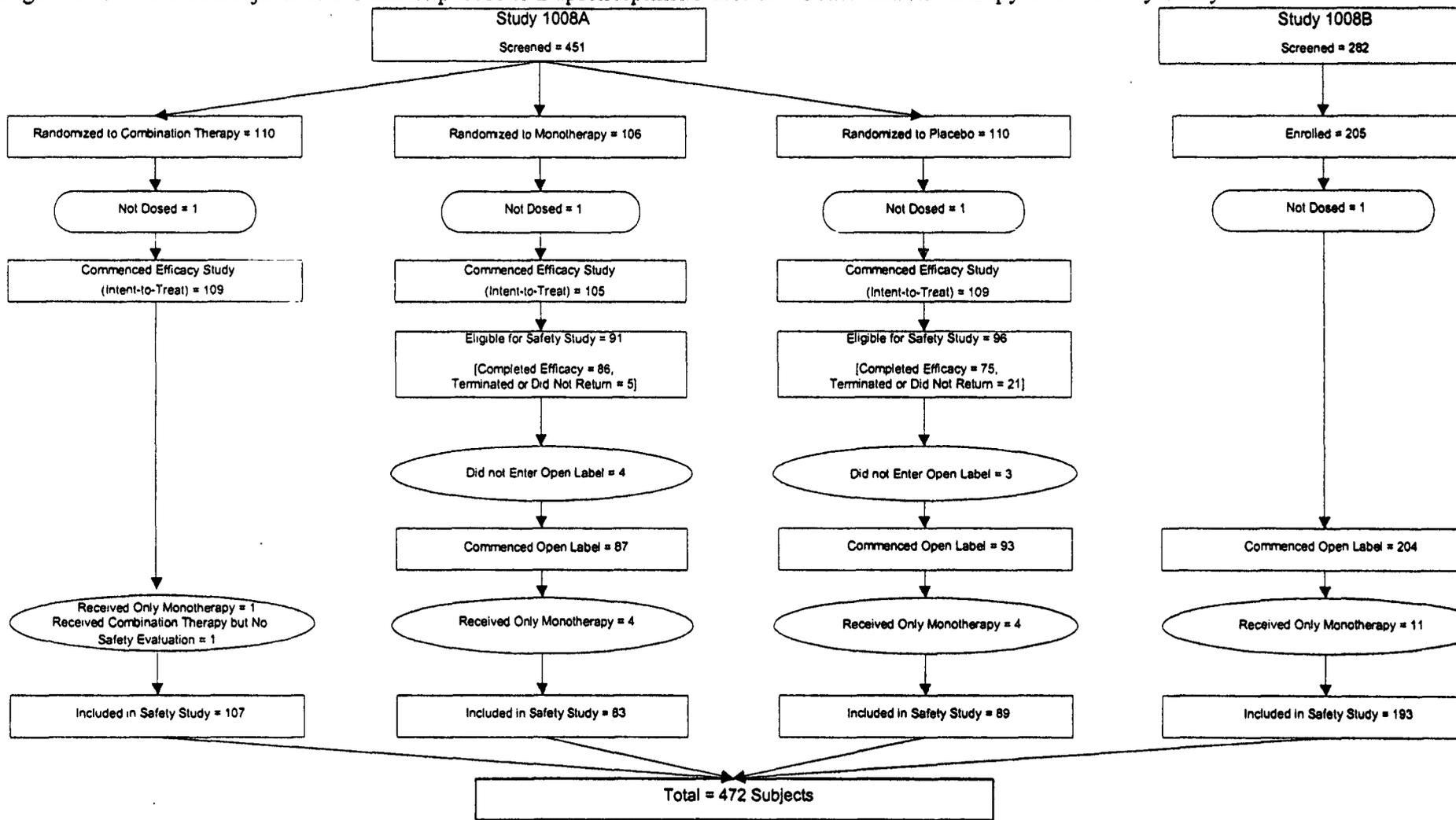
	Number of Subjects (N=326)			
	Combination Therapy	Monotherapy	Placebo	Total
Subject Disposition				
Screened				451
Randomized to treatment	110	106	110	326
Not dosed	1	1	1	3
Intent-to-Treat (Efficacy)	109	105	109	323
Enrolled at time of study closure (Unable to complete because efficacy study ended)	11	4	12	27
Full efficacy population	98	101	97	296
Completed	82 (84%)	86 (85%)	75 (77%)	243 (82%)
Discontinued	16 (16%)	15 (15%)	22 (23%)	53 (18%)
Reason for Discontinuation				
Poor Response	0	0	1	1
Adverse event	3	2	0	5
Failure to return to clinic	7	4	5	16
Failure to return to clinic (Greater than last 7 days)*	4	1	8	13
Incarceration	2	0	1	3
Attendance difficulties (e.g., moved)	0	1	3	4
Administrative discharge	0	2	2	4
Other (including Subject's choice)	0	5	2	7

Data Source: Based on Sponsor's Table 11: Vol 93, Page 36

* These subjects subsequently returned to the clinic and received treatment during the open label safety phase of the study.

Due to a demonstration of efficacy based on a planned interim data analysis, the Data Monitoring Board (DMB) recommended that the efficacy study be closed. At that time, there were 27 subjects who were enrolled but unable to complete the full 4 week efficacy study period. For the 296 subjects who were not affected by the early closure of the study, retention in the study was 82%; 243 subjects completed and 53 (18%) discontinued. Five of these subjects discontinued due to adverse events. Three of them were receiving buprenorphine/naloxone combination therapy; their adverse events included nausea, vomiting, and withdrawal symptoms (Subject 630-1064); withdrawal symptoms alone (Subject 662-1022); and irritability, headache, and decreased appetite (Subject 662-1040). The remaining 2 subjects received buprenorphine monotherapy and experienced nausea (Subject 689-1063) and sedation and dizziness (Subject 750-1082).

Figure 2. Sources of Subjects and Total Exposure to Buprenorphine/Naloxone Combination Therapy in the Safety Study



Data Source: Based on Sponsor's Figure 1: Vol 93, Page 38

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Protocol Deviations

Nine subjects were enrolled who did not meet the inclusion/exclusion criteria. Six of these subjects were randomized to treatment, but were subsequently determined to have had alcohol, cocaine or amphetamine dependence concurrently with opiate dependence. Three of these subjects were randomized to monotherapy, 2 subjects were randomized to combination therapy, and the remaining subject was randomized to placebo. Subject 539-1031 was randomized to monotherapy with an AST value that was at least four times above the upper limit of normal; he completed phase 1 of the study. Subject 689-1083 was 1 month too old for the study. Subject 691-1075 had been randomized to combination therapy, but was not expected to remain available to attend clinic for duration of study, and was therefore immediately terminated from the study. These protocol violations do not seem to have significantly affected the interpretation of the results.

Demographic and Baseline Characteristics

All the subjects enrolled in Study 1008A were opiate-abusing or –dependent. The majority of subjects were Caucasian males in their mid-thirties, who had a history of abusing heroin, cocaine and other drugs. Approximately one-half of the subjects ever had enrolled in a methadone or LAAM maintenance program. Use of illicit drugs (heroin or cocaine) by others in the household was reported for about one-half of the subjects. At entry into Study 1008A, the mean age was 37.8 years. Of the subjects, 35.3% were female, while 60.4% of the subjects were white, 28.5% were black and 7.7% were Hispanic. None of the females were pregnant at study entry. Baseline demographics and drug use history are summarized overall and by treatment group in Tables 16 and 17, respectively. There were no statistically significant baseline differences between treatment groups in any of these factors.

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Table 16. Baseline Demographics

	OVERALL TOTAL	COMBINATION	MONOTHERAPY	PLACEBO	P- VALUE ¹
NUMBER SUBJECTS	326	110	106	110	-
MEAN AGE (Standard Deviation)	37.8 (9.5)	38.1 (8.3)	37.1 (10.9)	38.1 (9.2)	0.68
GENDER					
Male	211 (64.7%)	69 (62.7%)	70 (66.0%)	72 (65.5%)	0.86
Female	115 (35.3%)	41 (37.3%)	36 (34.0%)	38 (34.5%)	
Total	326	110	106	110	
RACE					
Black, not of Hispanic origin	93 (28.5%)	32 (29.1%)	35 (33.0%)	26 (23.6%)	0.57
Hispanic	25 (7.7%)	9 (8.2%)	7 (6.6%)	9 (8.2%)	
White, not of Hispanic origin	197 (60.4%)	65 (59.1%)	62 (58.5%)	70 (63.6%)	
Native American ²	4 (1.2%)	2 (1.8%)	0 (0.0%)	2 (1.8%)	
Asian or Pacific Islander ²	7 (2.2%)	2 (1.8%)	2 (1.9%)	3 (2.7%)	
Total	326	110	106	110	
CURRENT MARITAL STATUS					
Married	71 (21.9%)	21 (19.3%)	29 (27.4%)	21 (19.3%)	0.28
Widowed ²	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	
Separated ²	31 (9.6%)	15 (13.8%)	8 (7.5%)	8 (7.3%)	
Divorced	74 (22.8%)	29 (26.6%)	19 (17.9%)	26 (23.9%)	
Never married	147 (45.4%)	44 (40.4%)	50 (47.2%)	53 (48.6%)	
Total	324	109	106	109	

Data Source: Based on Sponsor's Table 13-15: Vol 93, Page 44-49

¹ Comparison of the three treatment groups by Chi-square test, two-tailed p-value; ² Categories combined for chi-square analysis

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