Table 17. Baseline Drug Use History

	OVERALL TOTAL	COMBINATION	MONOTHERAPY	PLACEBO	P-VALUE[1]
NUMBER SUBJECTS	326	110	106	110	–
DRUG USE HISTORY					
Heroin only	2 (0.6%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	
Heroin, cocaine, alcohol only	2 (0.6%)	1 (0.9%)	1 (1.0%)	0 (0.0%)	
Heroin, cocaine, alcohol & marijuana only	6 (1.9%)	1 (0.9%)	2 (1.9%)	3 (2.8%)	0.72
Heroin, cocaine & other drugs	248 (78.0%)	84 (78.5%)	76 (73.8%)	88 (81.5%)	
Heroin & alcohol	1 (0.3%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	
Heroin & other drugs	59 (18.6%)	20 (18.7%)	23 (22.3%)	16 (14.8%)	
Total	318	107	103	108	
IS THERE HEROIN OR COCAINE USE IN THE HOUSEHOLD WHERE YOU LIVE?					
Yes	154 (47.4%)	45 (40.9%)	51 (48.1%)	58 (53.2%)	
No[2]	170 (52.3%)	65 (59.1%)	54 (50.9%)	51 (46.8%)	0.19
Don't know[2]	1 (0.3%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	
Total	324	110	106	109	
HAVE YOU EVER BEEN ENROLLED IN A METHADONE OR LAAM MAINTENANCE PROGRAM?					
Yes	166 (51.2%)	55 (50.0%)	59 (56.2%)	52 (47.7%)	0.44
No	158 (48.8%)	55 (50.0%)	46 (43.8%)	57 (52.3%)	
Total	325	110	105	109	
HOW MANY TIMES HAVE YOU EVER BEEN ENROLLED IN A METHADONE OR LAAM MAINTENANCE PROGRAM?					
One	80 (48.5%)	29 (52.7%)	29 (50.0%)	22 (42.3%)	
Two	53 (32.1%)	17 (30.9%)	18 (31.0%)	18 (34.6%)	0.96
Three	11 (6.7%)	3 (5.5%)	4 (6.9%)	4 (7.7%)	
Four[2]	11 (6.7%)	3 (5.5%)	5 (8.6%)	3 (5.8%)	
Five or more[2]	10 (6.1%)	3 (5.5%)	2 (3.5%)	5 (9.6%)	
Total	165	55	58	52	
WHY HAVE YOU NEVER ENROLLED IN A METHADONE OR LAAM MAINTENANCE PROGRAM?					
No treatment slots available	16 (10.1%)	6 (10.9%)	4 (8.3%)	6 (10.7%)	
Do not want Methadone or LAAM	83 (52.2%)	31 (56.4%)	23 (47.9%)	29 (51.8%)	0.85
Not eligible[2]	8 (5.0%)	1 (1.8%)	5 (10.4%)	2 (3.6%)	
Other[2]	52 (32.7%)	17 (30.9%)	16 (33.3%)	19 (33.9%)	
Total	159	55	48	56	

Data Source: Based on Sponsor's Table 14: Vol 93, Page 46

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

Baseline Education and Socioeconomic Status

The mean household income was $21,283 and most subjects were employed. Approximately 85% had at least graduated from high school. There was no difference between the treatment groups in any of these socioeconomic factors or other factors evaluated such as employment pattern, type of work, or living arrangement. Overall baseline status is summarized below in Table 18.

Table 18. Baseline Education and Socioeconomic Tabulation

	OVERALL TOTAL	COMBINATION	MONOTHERAPY	PLACEBO	P-VALUE
NUMBER SUBJECTS	326	110	106	110	–
MEAN FAMILY INCOME	$21,283	$21,262	$22,303	$20,330	
(Standard Deviation)	($19,968)	($20,665)	($21,343)	($17,945)	0.77[1]
Total	318	107	103	108	
HIGHEST LEVEL OF EDUCATION ATTAINED (N)	325	110	106	109	
College graduate	47 (14.5%)	15 (13.6%)	12 (11.3%)	20 (18.3%)	
Some college training	124 (38.2%)	33 (30.0%)	47 (44.3%)	44 (40.4%)	0.13[1]
High school graduate	101 (31.1%)	43 (39.1%)	27 (25.5%)	31 (28.4%)	
Under 12 years of schooling	53 (16.3%)	19 (17.3%)	20 (18.9%)	14 (12.8%)	
USUAL EMPLOYMENT PATTERN IN PAST 3 YEARS (N)	324	110	105	109	
Full-time	162 (50.0%)	60 (54.6%)	53 (50.5%)	49 (45.0%)	
Part-time	86 (26.5%)	31 (28.2%)	24 (22.9%)	31 (28.4%)	0.23[3]
Unemployed	60 (18.5%)	14 (12.7%)	20 (19.1%)	26 (23.9%)	
Other	16 (4.9%)	5 (4.6%)	8 (7.6%)	3 (2.8%)	
USUAL KIND OF WORK DURING PAST 3 YEARS (N)	325	110	106	109	
Never gainfully employed	50 (15.4%)	12 (10.9%)	16 (15.1%)	22 (20.2%)	
Unskilled employee	38 (11.7%)	14 (12.7%)	13 (12.3%)	11 (10.1%)	
Semi-skilled employee	49 (15.1%)	17 (15.5%)	21 (19.8%)	11 (10.1%)	0.28[1]
Skilled manual employee	86 (26.5%)	29 (26.4%)	32 (30.2%)	25 (22.9%)	
Clerical/Sales	64 (19.7%)	24 (21.8%)	14 (13.2%)	26 (23.9%)	
Administration[3]	29 (8.9%)	12 (10.9%)	7 (6.6%)	10 (9.2%)	
Business manager[3]	8 (2.5%)	2 (1.8%)	2 (1.9%)	4 (3.7%)	
Higher executive[3]	1 (0.3%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	
USUAL LIVING ARRANGEMENTS IN THE PAST 3 YEARS (N)	325	110	106	109	
With sexual partner and children	73 (22.5%)	29 (26.4%)	22 (20.8%)	22 (20.2%)	
With sexual partner alone	77 (23.7%)	22 (20.0%)	28 (26.4%)	27 (24.8%)	
With parents	23 (7.1%)	6 (5.5%)	8 (7.6%)	9 (8.3%)	0.55[1]
With family	52 (16.0%)	19 (17.3%)	15 (14.2%)	18 (16.5%)	
With friends	32 (9.9%)	16 (14.6%)	9 (8.5%)	7 (6.4%)	
Alone[3]	61 (18.8%)	17 (15.5%)	22 (20.8%)	22 (20.2%)	
Controlled environment[3]	2 (0.6%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	
No stable arrangements[3]	5 (1.5%)	1 (0.9%)	1 (0.9%)	3 (2.8%)	

Data Source: Based on Sponsor's Table 15: Vol 93, Page 48; [1] Comparison of the three treatment groups by Chi-square test, two-tailed p-value; [2] Fisher's exact test, two-tailed [3] Categories combined for chi-square analysis

The three treatment groups were similar with respect to hepatitis B or C serological status and concomitant medication use. These findings are summarized in the following tables.

Table 19. Subjects Positive for Hepatitis B or C at Baseline by Treatment Group in the Efficacy Study

	Combination Therapy		Monotherapy		Placebo		Total	
	Assessed (N)	Positive N (%)	Assessed (N)	Positive N (%)	Assessed (N)	Positive N (%)	Assessed (N)	Positive N (%)
Positive for Hepatitis B	109	52 (47.71)	104	45 (43.27)	108	47 (43.52)	321	144 (44.86)
Positive for Hepatitis C	106	59 (55.66)	100	57 (57.00)	109	58 (53.21)	315	174 (55.24)
Positive for Hepatitis B & C	106	40 (37.74)	100	36 (36.00)	108	37 (34.26)	314	113 (35.99)
Positive for Hepatitis B or C	109	71 (65.14)	104	66 (63.46)	109	68 (62.39)	322	205 (63.66)

Data Source: Based on Sponsor's Table 18: Vol 93, Page 52

Table 20. Concomitant Medications Used by ≥ 5% of Subjects During the Efficacy Study

Drug Class	Buprenorphine/Naloxone Combination Therapy (N=109)	Buprenorphine Monotherapy (N=105)	Placebo (N=109)	Total (N=323)
Non-narcotic Analgesics	33 (30.3%)	29 (27.6%)	27 (24.8%)	89 (27.6%)
Non-Steroidal Anti-inflammatory Agents	23 (21.1%)	25 (23.8%)	24 (22.0%)	72 (22.3%)
Benzodiazepines & Other Tranquilizers	13 (11.9%)	8 (7.6%)	13 (11.9%)	34 (10.5%)
Narcotic Agonists/ Antagonists	9 (8.3%)	9 (8.6%)	13 (11.9%)	31 (9.6%)
Antidepressants	7 (6.4%)	7 (6.7%)	5 (4.6%)	19 (5.9%)
Vitamins & Minerals	10 (9.2%)	5 (4.8%)	4 (3.7%)	19 (5.9%)

Data Source: Based on Sponsor's Table 28: Vol 93, Page 62

Section 7.2.1.6 Sponsor's Efficacy Results

Primary Efficacy Evaluations: Urines Negative for Opiates

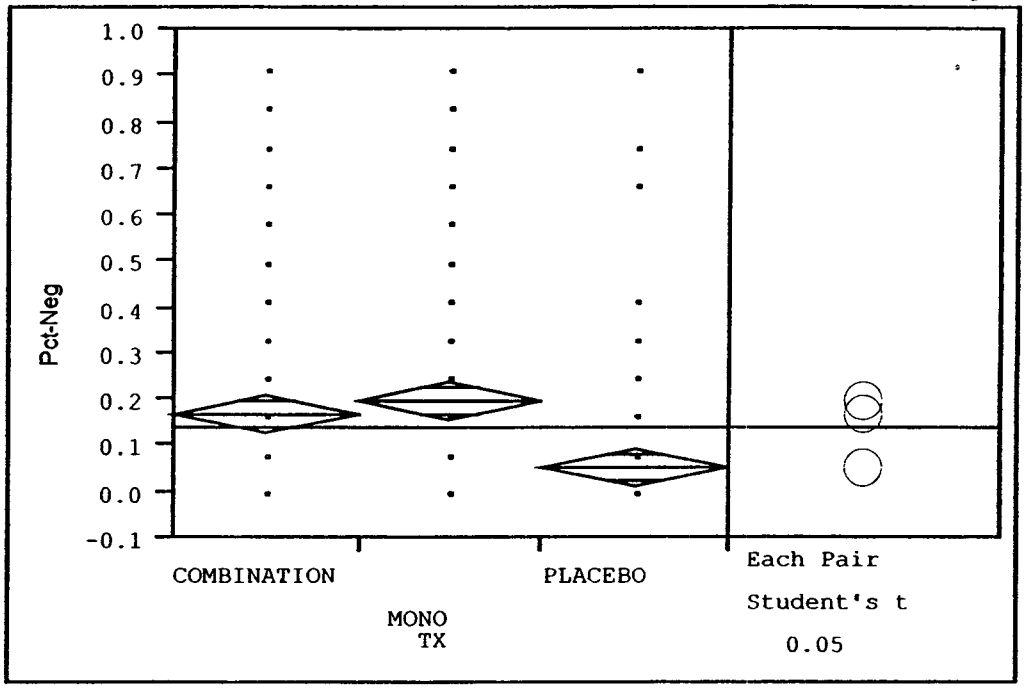
Subjects treated with buprenorphine, whether administered in combination with naloxone or as monotherapy, had a statistically significantly higher percentage of urine samples that were negative for opiates when compared to subjects who were treated with placebo (17.8%, 20.7%, and 5.8% for the combination therapy, monotherapy, and placebo groups, respectively; $p<0.0001$ for the difference between each of the buprenorphine treatment groups and the placebo group). These results are summarized below in Table 21 and Figure 3.

Table 21
Mean Percent Urines Negative for Opiates ("Clean") by Treatment Group

Treatment Group	N	Mean Percent (SE)	P-value *vs.* Placebo[†]
Buprenorphine/naloxone	109	17.8 (2.3)	<0.0001
Buprenorphine	105	20.7 (2.8)	<0.0001
Placebo	109	5.8 (1.7)	-
Total	323	14.7 (1.4)	-

Data Source: Based on Sponsor's Table 31: Vol 93, Page 69; [†]Two-way ANOVA

Figure 3. Plot of Mean Percent (SD) Urine Negative by Treatment Group



When results were analyzed by ANOVA using treatment effect, center effect, and treatment-by-center interaction as terms in the model, there were statistically significant treatment (p=0.0001) and center effects (p=0.0076), but no treatment-by-center interaction (p=0.8856). Results were consistent with each center displaying a higher percentage of clean urine samples for combination therapy and monotherapy than the placebo (Table 22)

Table 22. Urine samples negative for opiates at the 8 Centers

Center	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Boston	16	12.4 (4.4)	15	16.8 (5.5)	16	2.7 (1.7)	47	10.5 (2.5)
Cincinnati	16	32.9 (7.4)	16	36.9 (9.9)	16	18.0 (6.4)	48	29.2 (4.7)
Hines	15	23.9 (7.2)	13	25.3 (8.1)	13	3.4 (1.6)	41	17.9 (3.9)
New York	16	11.5 (4.3)	14	15.2 (5.6)	16	0.0 (0.0)	46	8.6 (2.4)
Philadelphia	12	19.4 (8.9)	13	17.9 (8.2)	12	8.3 (8.3)	37	15.3 (4.8)
San Francisco	13	3.5 (1.9)	12	17.4 (7.5)	14	0.0 (0.0)	39	6.5 (2.6)
West Haven	9	19.1 (8.2)	9	27.5 (11.5)	9	12.0 (10.0)	27	19.5 (5.7)
West LA	12	18.9 (6.5)	13	7.5 (5.1)	13	4.2 (3.0)	38	10.0 (3.0)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

Data Source: Based on Sponsor's Table 13.3.1.1: Vol 93, Page 179

There was no significant effect of age, gender or ethnicity on the percentage of clean urine samples, nor was there a significant interaction between these variables and treatment. Urine samples negative for opiates summarized by gender and ethnicity are shown in the following tables:

Table 23. Urine Samples Negative for Opiates by Gender and Treatment Group

Gender	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Male	68	16.5 (2.8)	70	21.3 (3.5)	71	5.6 (2.1)	209	14.4 (1.7)
Female	41	20.0 (4.0)	35	19.4 (4.6)	38	6.3 (2.8)	114	15.2 (2.3)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

Data Source: Based on Sponsor's Table 13.3.1.2: Vol 93, Page 180

Table 24. Urine Samples Negative for Opiates by Ethnicity and Treatment Group

Ethnicity	Combination Therapy		Monotherapy		Placebo		All Subjects	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
White	65	17.4 (3.1)	62	20.5 (3.5)	70	6.9 (2.4)	197	14.7 (1.8)
Black	32	18.9 (4.2)	35	22.3 (5.5)	25	4.1 (2.4)	92	16.2 (2.7)
Other	12	17.0 (6.4)	8	14.8 (8.9)	14	3.7 (2.6)	34	11.0 (3.3)
All Subjects	109	17.8 (2.3)	105	20.7 (2.8)	109	5.8 (1.7)	323	14.7 (1.4)

Data Source: Based on Sponsor's Table 13.3.1.3: Vol 93, Page 181

Opiate Craving

At study entry, opiate craving on average was moderate (mean scores 60.1 to 62.7), with no difference between treatment groups (p=0.78). There was a steady decline in mean craving scores following treatment with buprenorphine, such that by Week 4 the mean score following combination therapy was 29.4 from the 87 subjects remaining in study and following buprenorphine monotherapy was 33.6 for 84 subjects. These scores were statistically significantly lower than those in the placebo group (p=0.0001, repeated measures ANCOVA). There was little change in opiate craving in the placebo-treated group, with a mean Week 4 craving score of 55.6. These results are summarized in Table 25.

Table 25. Opiate Craving Score Adjusted Means by Treatment Group and Follow-Up Period

Week of Study	Combination			Monotherapy			Placebo		
	N	Mean	S.E.	N	Mean	S.E.	N	Mean	S.E.
Baseline	108	61.2	2.5	102	60.1	2.6	107	62.7	2.5
Week 1	107	48.0	1.9	101	50.6	2.0	107	61.9	1.9
Week 2	98	33.9	2.4	97	36.4	2.5	100	58.2	2.4
Week 3	96	29.0	2.5	85	34.2	2.7	94	55.3	2.6
Week 4	87	29.4	2.8	84	33.6	2.8	84	55.6	2.8

Data Source: Based on Sponsor's Table 32: Vol 93, Page 70
Combination *vs.* Monotherapy: p-value = 0.1368, repeated measures ANCOVA
Combination *vs.* Placebo: p-value <0.0001, repeated measures ANCOVA
Monotherapy *vs.* Placebo: p-value <0.0001, repeated measures ANCOVA

Secondary Efficacy Evaluations

Subject's global impression or by clinician judgment, buprenorphine-treated subjects, whether treated with buprenorphine as monotherapy or with buprenorphine in combination with naloxone, improved in overall status during the 4-week trial relative to the start of the study. Subjects who received combination therapy or monotherapy had significantly higher scores (better global impression) than those who received placebo. Analysis of urine samples tested for substances of abuse other than opiates (amphetamines, barbiturates, benzodiazepines, cocaine, and methadone) did not suggest an increase in the use of other drugs of abuse.

Section 7.2.1.7 Reviewer's Efficacy Evaluation and Discussion

For this study the sponsor chose two primary efficacy variables. Discussion with Dr. Tom Permutt, statistical reviewer for this NDA, confirmed the sponsor's conclusions regarding the statistical analyses of the primary efficacy variable data.

The medical reviewer performed additional analyses to examine the treatment effects.

7.2.1.7.1 Distribution of Negative Urine Samples

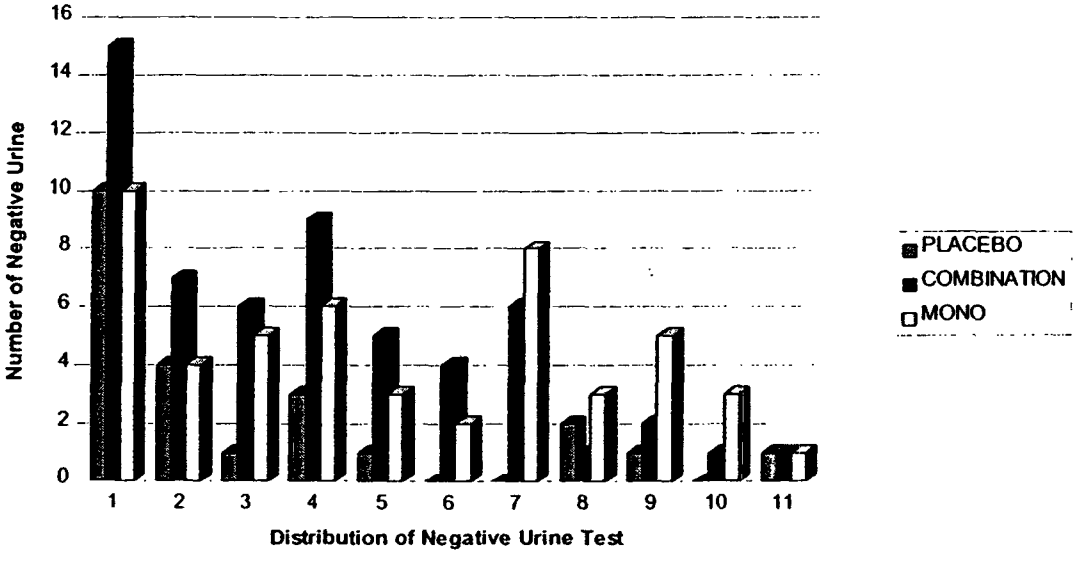
Each subject could provide up to a total of 12 on-treatment urine samples during the 4-week efficacy study. The treatment effect can be then evaluated by examining the distribution of number of negative urine samples, which is presented in Table 26 and Figure 4.

Table 26. Negative Urine By Treatments

Negative Urine Count Total (%)	COMBINATION	MONO	PLACEBO	
0	53 (48.18%)	56 (52.83%)	87 (79.09%)	196
1	15 (13.64%)	10 (9.43%)	10 (9.09%)	35
2	7 (6.36%)	4 (3.77%)	4 (3.64%)	15
3	6 (5.45%)	5 (4.72%)	1 (0.91%)	12
4	9 (8.18%)	6 (5.66%)	3 (2.73%)	18
5	5 (4.55%)	3 (2.83%)	1 (0.91%)	9
6	4 (3.64%)	2 (1.89%)	0 (0.00%)	6
7	6 (5.45%)	8 (7.55%)	0 (0.00%)	14
8	1 (0.91%)	3 (2.83%)	2 (1.82%)	6
9	2 (1.82%)	5 (4.72%)	1 (0.91%)	8
10	1 (0.91%)	3 (2.83%)	0 (0.00%)	4
11	1 (0.91%)	1 (0.94%)	1 (0.91%)	3
Total	**110**	**106**	**110**	**326**

Figure 4

Number of Negative Urine Tests by Treatment Group

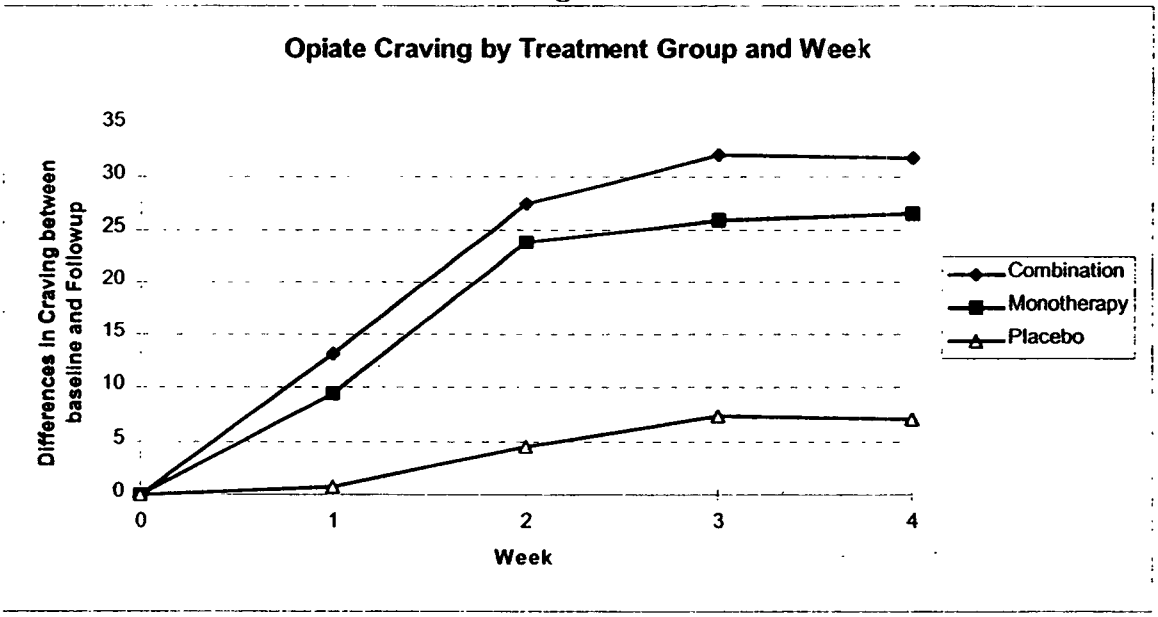


As shown above, the percent of subjects with no change in drug abuse (i.e., zero negative urine) were 48%, 53%, and 79% for Combo, Mono product and placebo group, respectively. The separation of the treatment effect by group (combo, mono and placebo) is clearly shown at three or more negative urine tests: 32%, 34% and 8%. Twenty-one patients had ≥ 8 negative urine tests (out of 12 tests): N=12 for Mono, N=5 for Combo and N=4 for placebo group. The mono product group appears to have a better treatment effect in this regard. No one has a negative result for all 12 urine tests.

7.2.1.7.2 Measures of Opiate Craving

Craving intensity differences (CID) in VAS mean scores were calculated as baseline craving score (time 0 week) minus scores at different follow-up time points. Thus positive differences represent better craving relief (Figure 5).

Figure 5



The severity of VAS craving intensity difference curve show that craving for both combination and mono products groups decreased with time, especially in the first two weeks while craving in placebo group remained relatively unchanged. Craving results could be affected by drop-out and use of off-study medication such as heroin. Drop-out rates were 16%, 15% and 23% for the combination, mono and placebo groups respectively. Those with higher craving scores may drop out, and those with heroin use may report less craving. Therefore, the urine test is a better measure than craving score in this regard.

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SECTION 7.2.2 STUDY CR88/130

SECTION 7.2.2.1. **Protocol Synopsis**

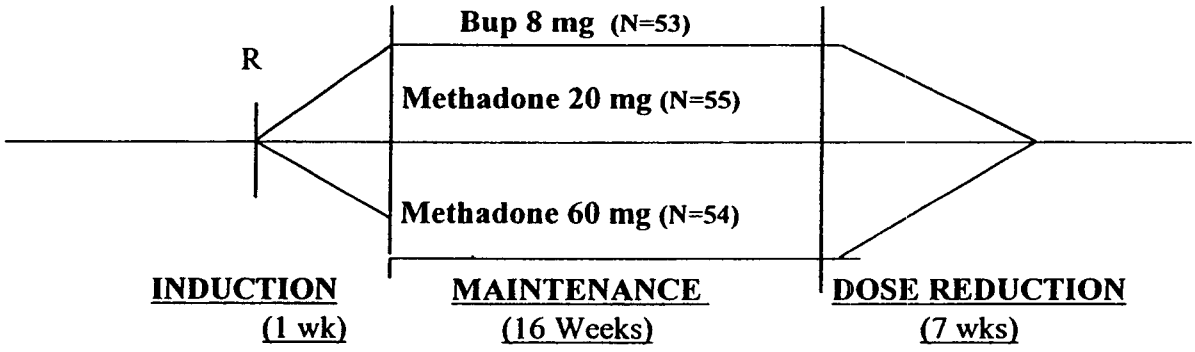
Title: An Assessment of Drug Interactions with Buprenorphine in the Treatment of Opioid Dependence: Phase III study of Buprenorphine sublingual solution versus methadone

Objective: The primary aim of this study was to determine efficacy of buprenorphine 8 mg (as a sublingual solution) in opiate-dependent outpatient maintenance in comparison with the prototype drug, methadone.

Study Design:

This was a double-blind, double-dummy, parallel-group, trial comparing buprenorphine sublingual solution 8 mg/day with oral methadone 20 and 60 mg/day, and consisting of a one- week induction phase, 16-week maintenance phase and a 7-week detoxification phase.

Study Scheme:



Patients who qualified and were enrolled in the study, received daily an oral solution (30 ml, containing designated dose of methadone or placebo) that was swallowed and a liquid (1 ml, containing either buprenorphine or placebo) that was taken sublingually (for 10 minutes under the tongue). Administration of medications was supervised at the clinic, and no takeout doses were allowed. The daily doses in induction and does reduction phases were as follow:

Dosing Schedule in Induction Phase

Drug\Day	Day 1	2	3	4	5	6-9	10
Bup 8 mg	2 mg	4	8	8	8	8	8
Meth 20 mg	20 mg	30	30	30	30	25	20
Meth 60 mg	20 mg	30	40	50	60	60	60

Dosing Schedule in the Dose Reduction Phase

Drug\Week	Week 18	19	20	21	22	23	24
Bup 8 mg	6.7 mg	4.7	3.3	2.7	2.0	1.3	0.65
Meth 20 mg	17 mg	12	8	7	5	4	2
Meth 60 mg	50 mg	35	25	20	15	10	5

Patients with opiate dependence had to meet the following inclusion criteria: age 21 to 50 years, have two opiate-positive urines (only one of which could be methadone), and sign informed consent. Patients were excluded for active cardiovascular or hepatic disease, a psychiatric severity score of at least 7 on the Addiction Severity Index, participation in a structured methadone or buprenorphine maintenance or detoxification program for more than 7 days in the past year, pregnancy or if female with child-bearing potential, inadequate contraception. Randomization included stratification (for balance) to eight (2x2x2) groups based on gender, age (up to or over 35 years), and naloxone challenge test results using the Clinical Institute Narcotic Assessment (CINA) score (up to or over 30).

Section 7.2.2.2 Efficacy and Statistical Analysis:

The primary efficacy parameters were retention in treatment (days of continuing to receive study medication from the first day of treatment) and maintenance of abstinence. The latter was based upon clean urine sampling for opiates, i.e., the amount of opiate or opiate metabolite was less than 300 ng/ml in at least two of three assays. Urine samples were collected under observation on Monday, Wednesday and Friday for each patient; however, if the patient was unable to provide a sample on the scheduled sampling day, then samples on the following day were also considered valid. Otherwise samples were recorded as missing. Urine toxicology was assessed as the number of clean (for opiates other than buprenorphine or methadone) urine samples recorded by each patient expressed as a percentage of the total number of samples which should have been provided during the time that the patient remained in the maintenance phase (PCC Method), the number of clean urine samples recorded by each patient expressed as a percentage of the total number of samples which should have been provided during the full 17 week maintenance phase (TEC Method) and the number and percent of patients with 13 consecutive clean urines. Secondary efficacy assessments included cocaine detection in urine samples, clinic attendance and missed doses, a daily opiate withdrawal symptom questionnaire, and every two weeks opiate craving score (10 cm visual analog scale) and a Beck Depression Inventory.

Continuous variables were compared between treatment groups using ANOVA, applied to either the raw data or the ranks of the raw data, as appropriate. Unordered categorical data were compared between treatment groups using the Pearson chi-square test of association and ordered categorical data were compared between treatment groups using the Cochran-Mantel-Haenszel ANOVA statistic. Retention in treatment was analyzed using time to termination and a binary variable indicating whether the patient completed the maintenance phase or terminated early. The time to termination was compared

between treatment groups using log-rank analysis. The completion/termination indicator was compared between treatment groups using binomial logistic regression. Urine toxicology was analyzed by the PCC and TEC methods defined above. Clean urine data was compared between treatment groups using analysis of covariance (ANCOVA). The 13 consecutive clean urine variable was compared between treatment groups using binomial logistic regression. Treatment, age, gender and age by gender interaction were included in the statistical models.

Section 7.2.2.3. Protocol Amendments:

No protocol amendment can be found in the original IND 35,877, in this NDA submission and in the previous medical review.

Section 7.2.2.4 Conduct of Study

Patient Distribution/Disposition: There were 162 of 200 planned patients who were randomized and received at least one dose of study medication. The study compared buprenorphine sublingual solution 8 mg/day with methadone 20 mg/day and methadone 60 mg/day in 162 patients. Patient disposition is tabulated in Table 27. Only 50 patients completed the maintenance phase. Most discontinuations were termed "No Show".

Table 27. Patient Disposition

	Buprenorphine	Methadone 20	Methadone 60	TOTAL
TOTAL PATIENTS	53	55	54	162
Completing maintenance phase (17 weeks)	22	11	17	50
Terminating prior to 17 weeks	31	44	37	112
Terminating for poor response	4	10	3	17
Terminating for No show	21	26	24	71
Terminating during detox	5	7	4	16
Completing detox	17	4	13	34

Data Source: Based on Sponsor's Table I-2B: Vol 117, Page 35

The most common reason for early termination was "No Show", accounting for 66% of early terminators. Twenty-three patients (17% of early terminators) terminated for reasons unrelated to the study and only four patients (3% of early terminators) terminated because of "Adverse Effects" (Table 28). More patients in the low dose (20 mg) methadone group terminated than in the other two groups because of "Poor response." Three patients were terminated because of protocol violation. One (#2536) had his dose code inadvertently broken while incarcerated over the weekend, another patient (#2582)

failed to report a recent prior involvement in a methadone treatment program and the third patient (#2840) became pregnant.

Table 28. Termination by Treatment Group during the Maintenance Phase

CR88/130	Buprenorphine (8mg)	Methadone (20mg)	Methadone (60mg)	TOTAL
TOTAL PATIENTS	**53**	**55**	**54**	**162**
Poor response (Patient)	4	10	3	17
Adverse effects	1	0	3	4
No show	21	26	24	71
TOTAL - Treatment/study related reasons	**26**	**36**	**30**	**92**
Incarceration	2	2	2	6
Medical - Unrelated to study	0	1	1	2
Attendance difficulties	1	0	2	3
Administrative	1	1	2	4
Protocol violation	0	3	0	3
Death	0	1	0	1
Other	1	0	0	1
TOTAL - Non-treatment/study related reasons	**5**	**8**	**7**	**20**
TOTAL - Patients completing the maintenance phase	**22**	**11**	**17**	**50**

Data Source: Based on Sponsor's Table I-2A: Vol 117, Page 34

Demographics:

Demographic information is listed in Table 29. Treatment groups appeared very similar except that the buprenorphine may have had less months history of addiction.

Table 29. Demographic Characteristics by Treatment Group

	Buprenorphine	Methadone 20	Methadone 60	TOTAL
TOTAL PATIENTS	53	55	54	162
Gender (M:F)	38:15	38:17	37:17	113:49
Mean Age	33.4	32.7	33.1	33.1
Race (W:B:H)	33:18:2	31:23:1	30:24:0	94:65:3
Mean Height (in)	68.5	69.1	69.0	68.9
Mean Weight (lb)	154.6	156.6	155.9	155.7
Mean CINA Score	31.2	31.6	30.3	31.1
Mean Months addicted	13	24	24	19
Median Opioid Usage ($/d)	90	100	100	90
Median Cocaine Usage (days/2wk)	1	1	2	1
Mean Baseline Withdrawal Score A	46.5	35.2	46.3	42.6
Mean Baseline Beck	17.3	19.2	18.2	18.2

Data Source: Based on Sponsor's Table II-1-5: Vol 117, Page 36-41

Section 7.2.2.5 Sponsor's Efficacy Results:

The two primary efficacy parameters were retention in treatment and maintenance of abstinence, as assessed by absence of opiates in urine samples. The number of patients who were retained in treatment and the clean urine data are shown in Table 30.

The percentage of clean urines where the denominator was the number of urines that should have been collected over the 16-week maintenance period (TEC Method) was significantly higher for buprenorphine 8 mg/day (34.5% vs. 15.3%) than for methadone 20 mg/day. It was not significantly different from methadone 60 mg/day (27.4%); the latter showed borderline superiority to methadone 20 mg/day. When the percent of clean urines for patients while active in the trial was considered (PCC Method), the values were naturally higher: 47.7% for buprenorphine 8 mg/day, 42.1% for methadone 60 mg/day, and 30.8% for methadone 20 mg/day. The difference between buprenorphine 8 mg and methadone 20 mg was again significant. The number of patients with 13 consecutive clean urines over any time period was also highest for buprenorphine 8 mg/day. There was only one such patient in the methadone 20 mg/day and seven in the methadone 60 mg/day group. Buprenorphine 8 mg was deemed more effective than methadone 20 mg/day, but not significantly different from methadone 60 mg/day (Figure 6). Methadone 60 mg had borderline superiority to methadone 20 mg. Older patients were more likely than younger ones to provide 13 consecutive clean urines.

Table 30. Primary efficacy parameter results

	TREATMENT GROUP		
	Buprenorphine (8mg)	Methadone (20mg)	Methadone (60mg)
TOTAL PATIENTS	**53**	**55**	**54**
RETENTION Number of Patients	22	11	17
PCC SCORE (%) Mean	47.7*	30.8	42.1
TEC SCORE (%) Mean	34.5**	15.3	27.4
13 CONSECUTIVE OPIATE CLEAN URINES Number of Patients	14	1	7

Data Source: Based on Sponsor's Table III-1: Vol 117, Page 42
* $P < 0.02$ and ** $P < 0.01$ when compared to Methadone 20 mg group.

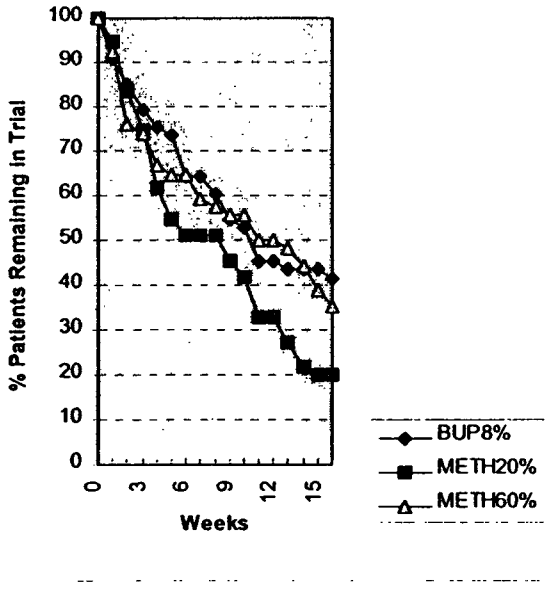
Clinic Attendance, Withdrawal Scores and Level of Depression: There was no difference between treatment groups for these parameters.

Opiate Craving Scores: There was no difference between treatment groups for these parameters except that methadone 60 patients had significantly less craving than those on methadone 20.

Section 7.2.2.6 Reviewer's Efficacy Evaluation and Discussion:

Retention in Treatment: Patients on buprenorphine 8 mg remained in the study significantly ($p<.05$) longer than those on methadone 20 mg. There were no significant differences between methadone 60 mg patients and those on the buprenorphine treatments. The survival curve is shown in Figure 6. Interestingly, older patients tended to remain in the study longer than younger ones, but other demographic parameters had no statistically significant effects.

Figure 6. CR88/130 Survival Curve



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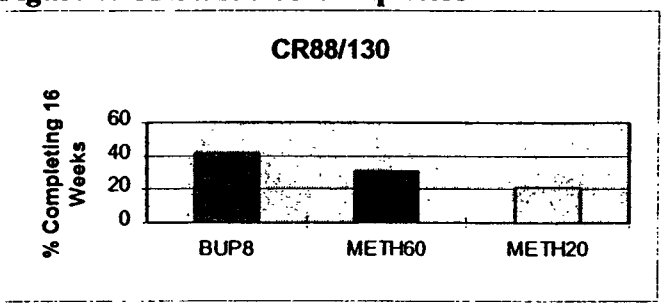
When viewed as the percentage of patients in each treatment group who completed maintenance, the values are 21% for methadone 20 mg, 31% for methadone 60 mg and 42% for buprenorphine 8 mg (Figure 7).

Figure 7. CR88/130 % Completers



Abstinence: Three ways of assessing the urine data were used: PCC (the number of clean urines expressed as a percentage of the number which should have been provided during the time the patient spent in the study), TEC (the number of clean urines expressed as a percentage of the number which should have been provided during the full 16 weeks of the study), and the number of patients having 13 consecutive clean urine samples. PCC gives a more favaoural score to those patients who remain "opiate free" but terminate the study early while TEC takes into account how long patients remain in the study and, hence, is less favorable to patients who terminate early. Thus, TEC appears to represent an approach close to "intent-to-treat" analysis.

Statistical analyses of these three variables showed that 8mg sublingual buprenorphine was clearly more effective than 20mg oral methadone and there was an indication that 60mg methadone was more effective than 20mg methadone. There was no evidence that 8mg sublingual buprenorphine differed from 60mg oral methadone.

Conclusion: Based on measures of retention in treatment and abstinence as described above buprenorphine 8 mg/day sublingual solution was superior to methadone 20 mg/day and appeared to be similar to methadone 60 mg/day in efficacy.

Section 7.2.3 Study CR92/099

Section 7.2.3.1 Protocol Synopsis

Title: A Multicenter Clinical Trial of Buprenorphine in Treatment of Opiate Dependence: Phase III dose ranging study of buprenorphine sublingual solutions.

Objective: The primary aim of this study was to determine the safety and effectiveness of 8 mg buprenorphine sublingual (solution) per day as compared to 1 mg per day in decreasing illicit opiate use. A secondary purpose was to gather safety experience with 4 mg and 16 mg daily dosing.

Study Design:

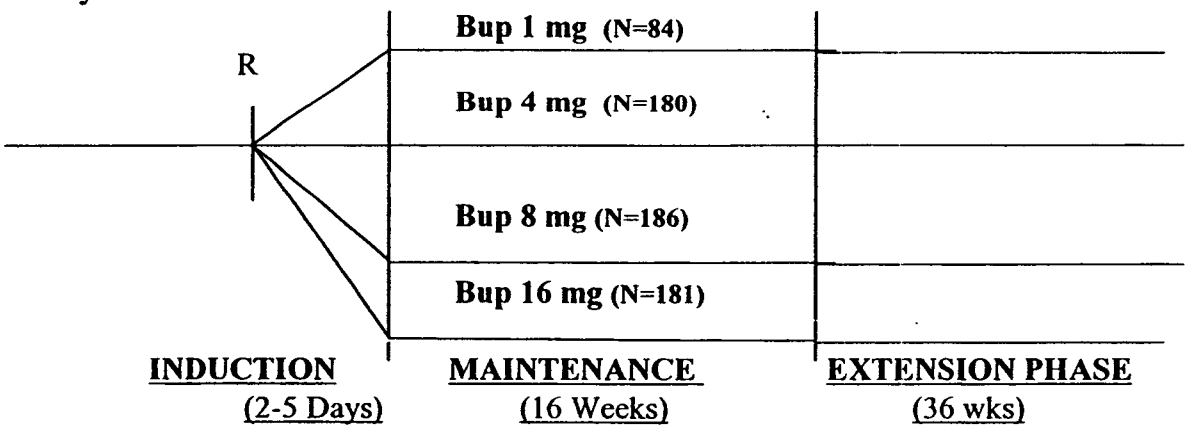
This was a randomized, double-blind, parallel-group, 12-center, trial comparing four daily doses of buprenorphine sublingual solutions in outpatients with opioid dependence.

Following an induction period of up to five days, patients were maintained on single daily doses of 1 mg, 4 mg, 8 mg or 16 mg for up to 16 weeks. Dosing schedule in induction phase was as follow:

Treatment	Day 1	2	3	4	5
Bup 1 mg	1 mg	1	1	1	1
Bup 4 mg	2 mg	4	4	4	4
Bup 8 mg	2 mg	4	8	8	8
Bup 16 mg	2 mg	4	8	16	16

Patients who missed 4 to 6 days dosing could be reinduced up to three times. All study drugs was taken sublingually, holding for 5 minutes under the tongue in the presence of staff personnel. No takeout doses were allowed. Patients who completed the study could enter a 36-week extension protocol (CR92/100) which allowed double-blind dose changes up to a maximum of 32 mg/day.

Study Scheme:



Outpatients with opioid dependence had to meet the following criteria: DSM-III-R diagnosis of opiate dependence with daily use for at least one month, at least 18 years old, and able to give informed consent. Females of child-bearing potential were excluded if pregnant, nursing or with inadequate contraception. Patients were excluded if urine was positive for methadone or had enrolled in a methadone program in the past month, or had acute hepatitis (elevations of LFT's greater than 5 times normal) or other serious medical illnesses (AIDS excluded but not HIV positive patients), DSM-III-R diagnosis of alcohol or sedative-hypnotic dependence, current use of anticonvulsants, Antabuse or neuroleptics, unable to attend to attend clinic regularly, previously participated in a buprenorphine study or currently enrolled in another research project. The protocol allowed each of the 12 sites to enroll up to 60 patients; however, an amendment permitted sites to enroll additional 10 females if possible. The minimum originally planned enrollment was 480 patients. The actual population receiving at least one dose of study drug was 731.

Section 7.2.3.2 Efficacy and Statistical Analysis:

Primary efficacy measurements for the study were retention in the trial and absence of urinary opiates. Urine samples were collected under observation three times weekly (Monday, Wednesday and Friday). Positive urines for opiates or cocaine were those equivalent to 300 ng/ml morphine or cocaine or their metabolites. A sample was recorded as missing when there was failure to give a sample. Efficacy assessments also included days of retention in treatment, opiate and cocaine craving scores (assessed weekly) and global rating scores completed by both patient and staff at 4-week intervals (using 0 to 100 scales for current status and 5-point scales for comparisons with the previous ratings).

Assessment of completion vs. termination as a measure of retention was analyzed by Chi square test. Urine toxicology was assessed as the number of clean urine samples recorded by each patient expressed as a percentage of the total number of samples which should have been provided during the time that the patient remained in the maintenance phase (PCC Method), the number of clean urine samples recorded by each patient expressed as a percentage of the total number of samples which should have been provided during the full 17 week maintenance phase (TEC Method) and the number and percent of patients with 13 consecutive clean urines for opiates.

Section 7.2.3.3 Protocol Amendments

Amendment 1:

This amendment was dated 8/01/92, and it permitted up to 16 weeks of additional dosing with the study drug, until a formal extension protocol is finalized.

Amendment 2:

Dr. Scheinbaum had documented another amendment that permitted sites to enroll additional 10 females if possible. The minimum originally planned enrollment was 480 patients. The actual population receiving at least one dose of study drug was 731. Date of the amendment is unknown.

Amendment 3:

This amendment was dated 3/02/93, and it was for the extension study. The amendment allowed investigator to dose subjects, as necessary, on a 6-day/week schedule while the original protocol calls for a 5-day dosing schedule. The amendment was trigged by a concern regarding the Friday buprenorphine dose no holding subjects adequately until the clinics doses again on Monday morning. A number of subjects experienced a level of discomfort that they were unwilling to tolerate and were either "using" (evidenced by either dirty urines or self-report, or both) or were requesting to drop from the study.

Section 7.2.3.4. Conduct of Study

Patient Distribution/Disposition

The study compared four doses of buprenorphine sublingual solution in 731 patients. The 12 sites had similar numbers of patients in each treatment group with total patient populations ranging from 53 at the Philadelphia VA to 70 at West LA. Table 30 shows patient disposition according to dosage group. Roughly half the patients completed the trial, and most of these went on to the extension study. "No show" was the major reason for early discontinuation. The number and percents of patients terminating for poor response was inversely related to dose. The "Poor response (Investigator)" classification represents patients who would have required a fourth reinduction. Twenty five patients terminated due to "Adverse effects."

TABLE 30. Patient Disposition by Dosage Group Study CR92/099

		Treatment	Group		
	1 mg	4 mg	8 mg	16 mg	TOTAL
TOTAL PATIENTS	184	180	186	181	731
PATIENTS COMPLETING	74 (40%)	93 (52%)	98 (53%)	110 (61%)	375 (51%)
PATIENTS ENTERING EXTENSION STUDY	67	82	91	92	332

Data Source: Based on Sponsor's Table I-1: Vol 121, Page 39

Table 31. Reasons for termination in 16 week efficacy phase

CR92/099	1mg	4mg	8mg	16mg	TOTAL
TOTAL PATIENTS	**184**	**180**	**186**	**181**	**731**
Poor response (Investigator)	2	3	5	4	14
Poor response (Patient)	40	18	11	11	80
Adverse effects	2	7	9	7	25
No show	48	33	39	32	152
TOTAL - Treatment/study related reasons	**92**	**61**	**64**	**54**	**271**
Incarceration	1	9	7	4	21
Medical - Unrelated to study	3	3	4	2	12
Attendance difficulties	6	12	9	6	33
Administrative	2	0	0	0	2
Other	6	2	4	5	17
TOTAL - Non-treatment/study related reasons	**18**	**26**	**24**	**17**	**85**
TOTAL - Patients completing study	**74**	**93**	**98**	**110**	**375**

Data Source: Based on Sponsor's Table I-3/ C: Vol 121, Page 43,45

Demographics: Demographic information is listed in Table 32. No differences between treatment groups appeared were noted. The only demographic difference detected was that male patients tended to be older than females.

Table 32. Demographic Characteristics by Treatment Group

	Treatment	Group	(Buprenorphine	mg/day)	
	1 mg	4 mg	8 mg	16 mg	TOTAL
TOTAL PATIENTS	184	180	186	181	731
Gender (M:F)	116:68	123:57	120:66	135:46	494:237
Mean Age (yrs)	36.3	35.4	35.7	36.5	36.0
Race (W:B:H:O)	87:44:51:2	94:34:50:2	91:39:53:3	83:44:52:2	355:161:206:9
Mean Height (in)	67.4	67.6	67.6	68.1	67.7
Mean Weight (lb)	155.6	156.0	159.5	163.0	158.5
Median Yrs Heroin Use	10.0	8.0	10.0	11.3	10.0
Mean Staff Global Rating at Screen	82.3	82.4	83.6	81.3	82.4
Mean Patient Global Rating at Screen	83.6	84.6	87.7	82.1	83.7
Pts Al so using Cocaine	159	149	155	147	600
Mean Heroin Craving at Screen	79.3	80.5	80.7	80.6	80.3
Mean Cocaine/Alcohol Craving at Screen	14.8/5.9	17.5/6.6	17.0/5.6	16.8/4.0	16.5/5.5

Data Source: Based on Sponsor's Table II-1-13: Vol 121, Page 48-61

Concomitant Medication

Table 33. Concomitant Medications

DOSAGE GROUP	1 mg	4 mg	8 mg	16 mg	Total
TOTAL PATIENTS	184	180	186	181	731
PATIENTS WHO USED CONCOMITANT MEDICATIONS	119	125	128	125	497
PATIENTS WHO USED GI MEDICATIONS	12	21	16	24	73
PATIENTS WHO USED CV MEDICATIONS	13	8	16	11	48
PATIENTS WHO USED CNS DRUGS (e.g. benzodiazepines and antidepressants)	40	55	44	38	177
PATIENTS WHO USED PAIN MEDICATION	69	74	79	64	286
PATIENTS WHO USED ENDOCRINE MEDICATION	1	8	0	1	10
PATIENTS WHO USED ANTIINFECTIVE MEDICATION	45	32	37	44	158
PATIENTS WHO USED RESPIRATORY MEDICATION	13	20	22	21	76
PATIENTS WHO USED ENT MEDICATION	16	11	21	20	68
PATIENTS WHO USED SKIN MEDICATION	5	2	6	10	31
PATIENTS WHO USED ORAL CONTRACEPTIVES	7	5	8	5	8

Data Source: Based on Dr. Sheinbaum's review Table 9 in NDA 20-732 Page 23

Most patients used concomitant medications. Table 33 lists types of concomitant medication usage according to dosage group. Usage generally appears quite similar for

treatment groups. A minor exception was for endocrine medication which appeared more common with the 4 mg group (6 of these 8 patients had used corticosteroids). Urine toxicology was able to identify a range of illicit substance usage, but only opiates and cocaine were considered relevant for the analyses.

Section 7.2.3.5 Sponsor's Efficacy Results

Abstinence: The percentages of clean urines, whether the denominator was the number of urines that should have been collected either over the 16-week study (TEC) or was collected while patients were active in the trial (PCC), were significantly higher for buprenorphine 8 mg/day ($p<.001$) than for buprenorphine 1 mg/day (Table 34). There were significantly ($p<.05$) more patients with 13 consecutive clean urines with 8 mg than with 1 mg daily doses There were significant differences between centers, but there were no significant center-dosage interactions.

Retention in Treatment: The percentage of patients who remained in the study in each treatment group were 40% for 1 mg/day, 52% for 4 mg/day, 53% for 8 mg/day and 61% for buprenorphine 16 mg/day (Figure 8). Patients on buprenorphine 8 mg remained in the study significantly ($p=.02$) longer than those on buprenorphine 1 mg/day. There were no significant differences between 4, 8 and 16 mg doses.

Table 34. Summary of main efficacy results of 16 week phase.

CR92/099	TREATMENT GROUP			
	1mg	4mg	8mg	16mg
TOTAL PATIENTS	**184**	**180**	**186**	**181**
RETENTION				
Number of Patients	74	93	98	110
(%)	40.2	51.7	52.7	60.8
PCC SCORE (%)				
Mean	15.2	24.8	27.0*	32.6
TEC SCORE (%)				
Mean	11.6	20.2	21.7**	28.8
13 CONSECUTIVE OPIATE CLEAN URINES				
Number of Patients	7	21	17***	34
			***P < 0.001, ** P < 0.001, *** P < 0.05 compared to 1-mg group.**	

Data Source: Based on Sponsor's Table III-1: Vol 121, Page 68

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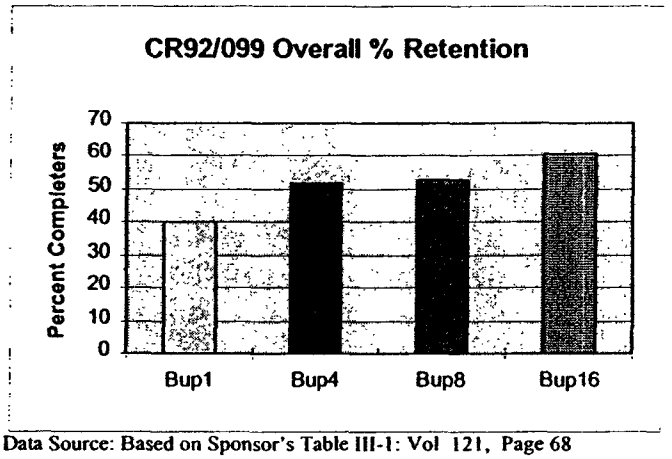
Figure 8. CR92/099 Percent Retention



Data Source: Based on Sponsor's Table III-1: Vol 121, Page 68

Secondary Efficacy Variables:

Secondary efficacy parameters included cocaine clean urines. There were significantly more cocaine-clean urines for the buprenorphine 8 mg group relative to 1 mg (22% vs 12% from TEC data and 7 vs. 16 patients with 13-consecutive clean urines for cocaine), and there was little difference between the 1 mg group and the 4 mg and 16 mg groups. In addition, there was little effect on cocaine use throughout the study, suggesting that the observed differences between the 1 mg and the 8 mg group may reflect a "random" effect rather than a specific effect on cocaine use.

Reasons for Termination, Craving Scores and Global Rating Scores: Analysis of these parameters showed significant superiority of the 8 mg/day dose relative to 1 mg/day. The staff global rating showed significant support for continued dose response, while the others failed to show significant dose trends.

Section 7.2.3.6 **Reviewer's Efficacy Evaluation and Discussion**:

Based on the primary efficacy parameters of absence of opiates in urine samples, ie "Clean Opiate Urines" and retention in treatment, 4mg, 8mg and 16 mg per day sublingual buprenorphine were shown to be clearly more effective than 1mg per day sublingual buprenorphine. There were no significant differences between 4, 8 and 16 mg doses, except for all dose comparisons in the TEC analysis, in which the 16 mg showed significant superiority relative to 4 mg/day (Figure 9 and 10).

Figure 9. PCC By DOSE

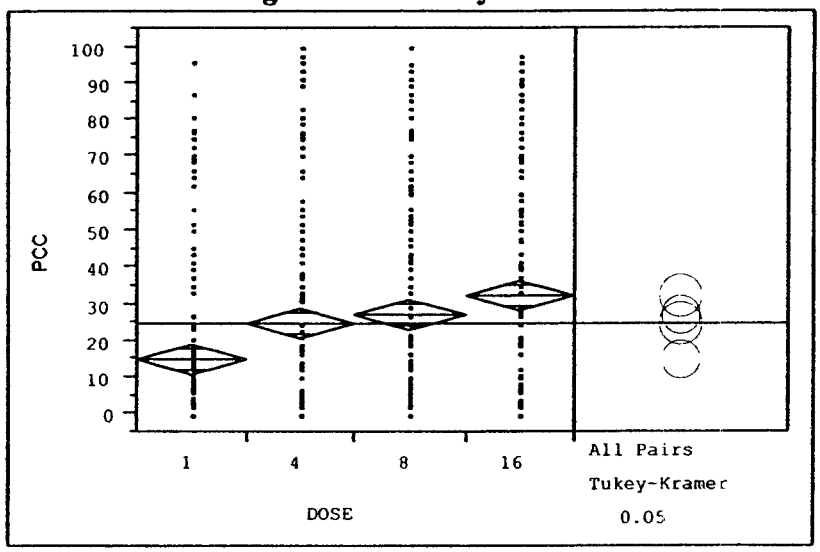
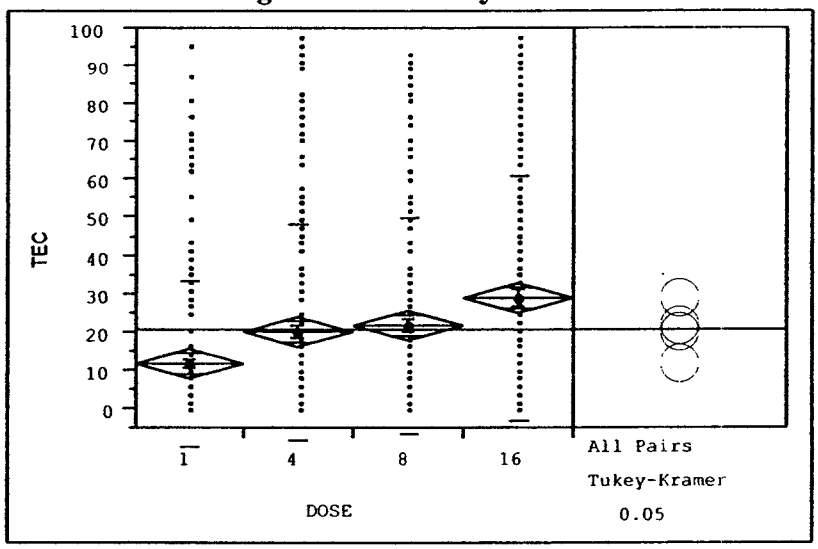


Figure 10. TEC By DOSE



Retention: The survival curve for patients on 16 mg is suggestive of a continued dose response (Figure 11). The 1 mg dose was probably not a no-effect dose since 40% of these patients remained throughout the 16-week study. There were no gender differences in retention, but dose effect was more pronounced for nonwhite patients than white patients.

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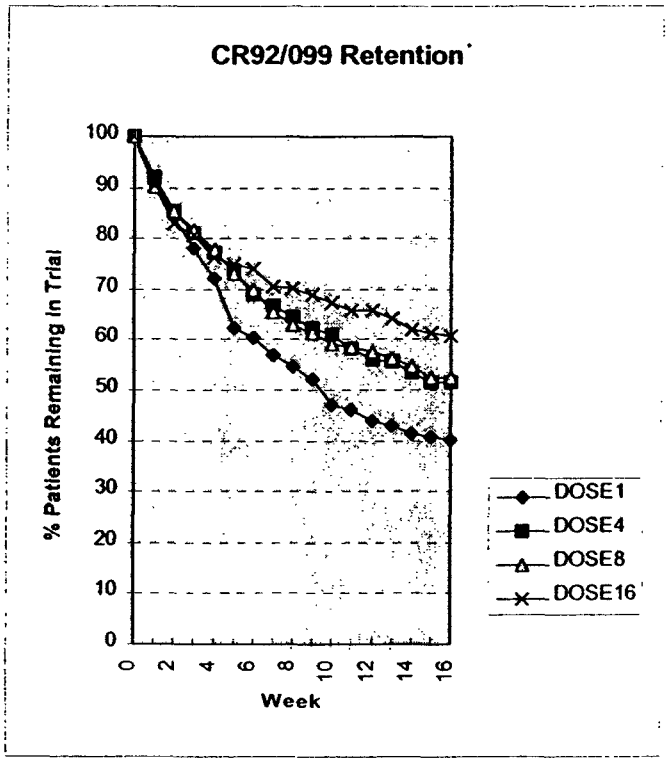
Figure 11. Retention



Conclusion: Buprenorphine 4 mg, 8 mg and 16 mg/day sublingual solution were more efficacious than buprenorphine 1 mg/day both by measures of retention in the study and abstinence in the dose range study.

Section 7.2.4 Study 92/102

Again, buprenorphine sublingual solution was the study drug, and the to-be-marketed Suboxone was not evaluated in this study. The study contains a 2-week placebo phase, in which the efficacy of the solution formulation was compared to placebo. This information is not available in studies reviewed in the previous sections. Therefore, this review will focus on the placebo controlled part of the study.

SECTION 7.2.4.1 Protocal Synopsis

Study Title: Part 1: A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence; **Part 2:** Buprenorphine treatment of opioid dependence: daily versus alternate day dosing

Objectives:

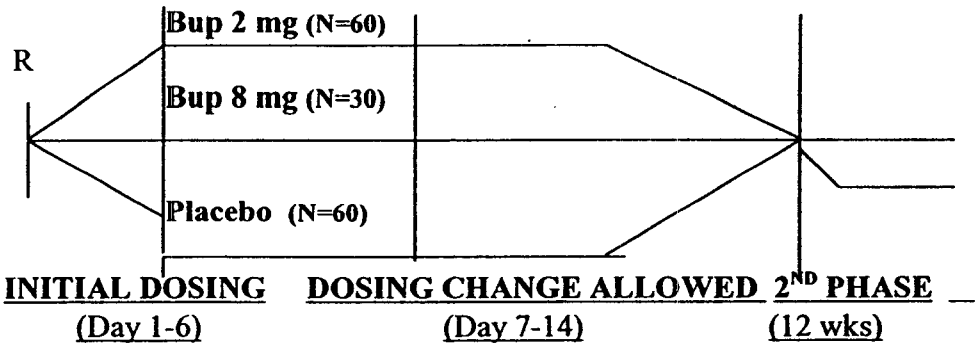
Part 1: To compare the clinical efficacy of buprenorphine versus a concurrent placebo control on early treatment outcomes in an opioid dependent population

Part 2: To assess treatment outcomes during daily versus alternate day dosing with a single uniform dose of 8mg buprenorphine

Study Design (Placebo Controlled Part of the Study):

A double-blind, multiple dose, parallel group comparison of sublingual buprenorphine (2 and 8mg/day) and placebo. Subjects were randomly assigned to either placebo or the 2mg or 8mg buprenorphine dose groups in a 2:2:1 ratio. All subjects remained on their allocated dose through to day 6. On days 6-13 they could request a dose-change knowing that this would be randomly assigned from one of the other two treatments. The second dose was also blind, and patients understood that if they were receiving an active dose, they might be assigned to a placebo dose should they choose an alternative medication. Subjects continued on the second dose through to day 14.

Study Scheme:



Inclusion Criteria: Subjects meeting DSM-III criteria for opioid dependence

Number of Subjects: 150 patients

- Buprenorphine 2mg: 60 (45 male, 15 female) mean age = 33.7y
- Buprenorphine 8mg: 30 (15 male, 15 female) mean age = 31.7y
- Placebo: 60 (43 male, 17 female) mean age = 35.0y

Duration of Treatment was14 days (followed by induction onto 8mg buprenorphine during week 3).

Evaluation Criteria: The primary outcome measures were "days on initial dose" (until leaving the study or changing dose) and percentage of patients requesting a dose change.

Secondary efficacy parameters include urine toxicology data. Two or three samples were collected during the first 7 days of the study.

SECTION 7.2.4.2 Conduct of Study

Patient Deposition: Of the 150 patients who participated in the study 52 dropped out prior to the Phase II study and there were no significant differences between the groups.

Table 35. Patient Deposition

CR92/102	Placebo	2mg	8mg	TOTAL
TOTAL PATIENTS	60	60	30	150
Poor response (Patient)	8	3	3	14
No show	12	10	6	28
TOTAL - Treatment/study related reasons	20	13	9	42
Incarceration	1	1	0	2
Medical - Unrelated to study	1	0	0	1
Attendance difficulties	1	1	2	4
Other	1	2	0	3
TOTAL - Non-treatment/study related reasons	4	4	2	10
TOTAL - Patients entering Phase II	36 (60%)	43 (72%)	19 (63%)	98

Data Source: Based on Sponsor's Table I-2A: Vol 113, Page 29

SECTION 7.2.4.3 Results

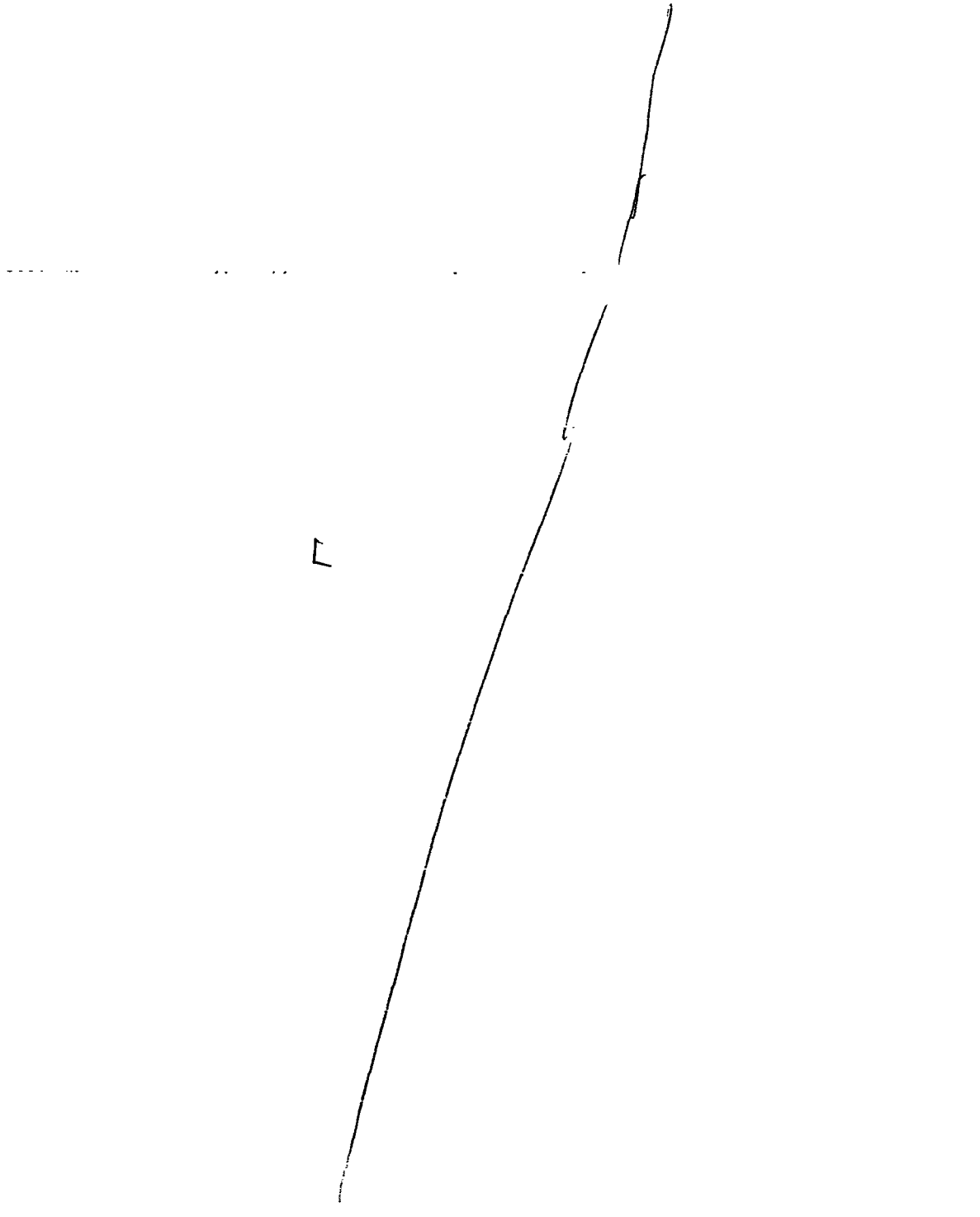
Efficacy Results:
For days on initial dose (N=150) there were more for the two buprenorphine doses (mean of 10-11 days) compared to placebo (mean of 8 days) ($P < 0.02$). For dose change requests (N=110) 65% of the placebo patients compared with 27% and 32% in the 2mg and 8mg buprenorphine groups changed doses ($P < 0.02$). There were no statistically significant differences between the 2 mg and the 8 mg groups in both primary outcome measures.

A similar pattern was observed for secondary treatment outcomes: percentage of opiate positive urines were 97% for placebo and 78% and 76% for the buprenorphine 2mg and 8mg groups, and both buprenorphine groups had higher mean scores for dose adequacy VAS and a greater mean days of clinic attendance than the placebo group.

Discussion and Conclusions: The results provide some evidence of the efficacy of sublingual buprenorphine solution as compared to placebo during the 2-week of treatment of opioid dependence. However, it is interest to observe that here is no evidence suggesting any efficacy differences between the 2 mg and 8 mg treatment groups. The investigators originally anticipated that only a small percentage (e.g. 20% or less) of those initially assigned to 8 mg buprenorphine would request a change. Nearly all patients assigned to placebo would request alternative medication, while some intermediate percentage (e.g. 65 – 75%) of 2 mg subjects would request a change in medication. In fact, 25-30% of subjects in both active treatment groups requested a dose

change. There were no differences in dropout rates (30-40%) between the groups in this 2-week study. These results provide useful information to design a short-term induction study.

Section 7.2.5



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Efficacy Evaluation:
There were no significant differences across conditions in rates of illicit drug use, with 45% of urine samples positive for opioids across the entire treatment period.

Conclusion: Although the results suggest that a 3-day/week dosing schedule might improve compliance and increase client satisfaction without impacting illicit drug use, the number of patients completing the study is too low to allow for interpretation of the efficacy findings.

Section 7.2.7 Effective Dose Range

The sponsor provides the study CR96/014 to support — (Table 48). The study is an open label safety rather than efficacy study. It provides information on how much the medication was used, but not necessary to show how effective of each dose is. The dosing information in the study will be presented in the safety section this review.

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SECTION 8.0 SAFETY FINDINGS

Section 8.1 Methods

The safety of buprenorphine in the treatment of opiate dependency has been evaluated in over 100 clinical studies. The sponsor submits a total of 158 clinical studies in this NDA application either as clinical reports or publications. In these studies 5134 subjects (3115 male, 1270 female, and 749 with gender not specified) have been treated with buprenorphine, of which 575 subjects were treated with Suboxone tablets and 1834 with Subutex tablets. However, safety data are not available from all of these studies. The safety database (Figure 14) includes safety data for 3127 subjects receiving buprenorphine sublingually (alone or in combination with naloxone).

Figure 14. 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	105 Subjects[1,2]	813 Subjects
Clinical Studies without CRFs	25 Subjects	248 Subjects	422 Subjects
Post-Marketing	-	1042 Subjects[3]	-

Data Source: See Figure 1 in Section 5.1.3.
[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 —

- The primary source of **safety data for the buprenorphine/naloxone combination tablet** is one multicenter study, designated by the two protocols used as Study CR96/013 and CR96/014. (This study is also referred to in the NDA as Study 1008.) During the initial 4-week double blind phase (#1008A phase 1, CR96/013) of this year-long trial, the study includes a comparison to placebo and buprenorphine monotherapy tablet groups. For the remaining period, up to 52 weeks in total, only Suboxone tablets were administered (#1008A phase 2 and #1008B, CR96/014). Safety data are available from one additional, small pilot trial conducted with the combination tablet and are summarized separately. In total, safety data are available from 497 subjects who have been exposed to the combination tablet in these studies.

- **Safety data for the buprenorphine tablet (monotherapy)** formulation derive from 351 patients participating in four studies: the monotherapy arm of Study CR96/013 (identified above), three additional controlled studies for which there are no case report forms, and five open label studies. Since only one of these studies has source documentation, results are discussed separately. In addition, safety data available in two French post-marketing reports are summarized (1042 subjects).

- **Eight hundred thirteen (safety sample)** patients have received buprenorphine oral solution in three earlier controlled studies (CR88/130, CR92/099/100 and CR92-102). The data for these studies have been pooled for analysis. These are supported by safety observations reported in ten publications (from 422 subjects), also identified.

The sponsor used the COSTART classification system for coding the actual AE's as written on the CRF to the preferred terms.

This review of safety of buprenorphine tablets/solution in the exposed population focuses on the information provided by the sponsor in the Integrated Summary of Safety and study summaries for the noted trials. In addition, narrative summaries of deaths, serious adverse events and discontinuations were reviewed. Finally, many of the original tabular summaries were examined in their entirety.

SECTION 8.2 SERIOUS ADVERSE EVENTS

Section 8.2.1 Deaths

Section 8.2.1.1. Deaths from Clinical Trials

There were no death or overdose cases in Suboxone or Subutex studies. There were six deaths reported in the solution studies (Table 50): two in the 332-patient multicenter extension study (CR92/100), two in the 162-patient study CR88/130, one of whom was on methadone, and two in the 225-patient study (CR90/069), one of whom was on methadone. The four deaths on buprenorphine were not thought by the investigators to be related to buprenorphine treatment. The reviewer agrees (the same statement applies to all safety review sections unless the reviewer specifies). The cases are discussed below by study.

In the multicenter study (CR92/100) 1 of the subjects was a 47-year-old male taking 8 mg of buprenorphine sublingual solution who had been in the study for 147 days and died of a coronary thrombosis. The other was a 37-year-old male taking 32 mg of buprenorphine sublingual solution who had been in the study for 265 days. This subject was HIV positive and was hospitalized secondary to dehydration and sepsis. The subject died within 24 hours of hospitalization. Toxicology studies indicated use of cocaine within 24 to 48 hours prior to death. There was no suggestion of morphine or heroin abuse and the buprenorphine blood concentration was consistent with chronic administration as part of the clinical trial. The subject had been in the study for approximately 9 months and was seen at clinic the day prior to illness onset with no symptoms of acute medical illness.

In Study CR88/130, one death was a 38-year-old male receiving 8 mg buprenorphine sublingual solution who had been in the study for 37 days. The subject was found dead by the police 4 days after his last dose of 8 mg buprenorphine. He had attended clinic everyday for the 37 days that he was in the study. The manner and exact time of his death were unknown and autopsy revealed no significant abnormalities. Toxicology revealed the presence in the blood of cocaine and buprenorphine, at a level consistent with the study dosage. Cocaine, buprenorphine, and opiates were found in the urine. The cause of death was recorded as acute narcotic (cocaine) intoxication.

There was one death reported in Study (CR90/069). This was a male who died of cancer after a brief hospitalisation.

Table 50. Deaths Occurring Amongst Subjects on Buprenorphine in CR92/099, CR92/100, CR92/102, and CR88/130

ID#	Gender	Age (yrs)	Buprenorphine Dose	Time on Drug	Cause	Comment
CR92/100						
642/075	M	47 male	8 mg/day	5 months	Coronary thrombosis	Autopsy confirmed; Blood positive for buprenorphine, cocaine. Bup. non-contributory to death.
672/013	M	37 female	32 mg 5 days/wk	9 months	Sepsis	HIV positive, Blood positive for buprenorphine, cocaine. Bup non-contributory to death.
CR88/130						
2328	M	38 male	8 mg/day	37 days	Drug overdose	Died > 4 days after last buprenorphine dose. Cause recorded as "acute narcotic (cocaine) intoxication".
CR90/069						
N/A	M	N/A	N/A	N/A	Cancer	The case was reported in a publication. No CRF available.

Data Source: Based on Sponsor's Table 68: Vol 153, Page 108

Section 8.2.1.2 Deaths during the Marketing of Subutex in France

As of July 31, 1999, a total of 66 deaths from Subutex in France were reported (Table 51). The most frequent cause of death was asphyxia (27 subjects), followed by "cause unknown" (22 subjects), and fetal disorder (9 cases). The deaths during marketed use in France are summarized below.

Table 51. Deaths during the Marketing of Subutex in France

Body System	Number of Patients	Most Frequent Events
Body as a whole	22	Most reports are "cause unknown"
Cardiovascular	1	Patient misused Subutex by IV route (cardiac failure, hypertension pulmonary, pleural effusion, tachycardia supraventricular, vasospasm, cyanosis, bradycardia, dyspnea)
Fetal disorders	9	Congenital anomaly (n=6)
Infection / infestation	1	Patient misused Subutex by IV route (septic shock)
Injury / poisoning	2	Moving vehicle accident (n=2)
Liver and Biliary	3	One patient misused Subutex by IV route (hepatocellular damage, asthenia, jaundice, and hepatitis aggravated); one patient HIV, Hep B and Hep C positive (hepatic cirrhosis); one patient HIV and Hep C positive (hepatic cirrhosis aggravated)
Psychiatric	1	Suicide (accomplished)
Respiratory	27	Asphyxia (n=21) One patient misused Subutex by smoking and sniffing (pulmonary edema, coma)

Data Source: Based on Sponsor's Table 129: Vol 153, Page 257 and Safety Update Table 19 on Vol 1; page 32

During the reported post-marketing period, 38 (57.6%) of 66 deaths occurred in subjects whose laboratory or clinical history was available to indicate that they had overdosed with more than one drug, usually a benzodiazepine, either intentionally or by accident. For the other 22 (38.6%) cases, no buprenorphine or other drug blood level data were available or relevant to ascertain other drug involvement. The data summarizing buprenorphine-related death reporting is shown in Table 52 (the data presented in the table are from reports provided to Schering France and contain information that cannot be confirmed in all cases).

Table 52. Buprenorphine-Related Death Reports for Post-Marketing of Subutex

Reported drug use at time of death	Probable Overdose due to Benzodiazepine	Not Specified	Overdose Unlikely	Totals
CNS Depressants	31	1	2	31
No other drug use reported	7	4	15	26
Totals	38	5	17	57

Data Source: Based on Sponsor's Table 130: Vol 153, Page 258 and Text in the Safety Update, Vol 1; page 33

One of the unknowns in the above cases is the route of administration of buprenorphine and/or other drugs. However, it is clear from some of the other reported French adverse events relating to necrosis and inflammation of the injection site that some subjects were misusing buprenorphine by injection. It is known from reports of the misuse of Temgesic (Buprex) that addicts will inject buprenorphine extracts along with benzodiazepines, notably temazepam.

The sponsor attributes many of these 66 deaths to the use of parenterally administered respiratory depressant drugs at the same time as buprenorphine. In France, the warning concerning the use of Subutex with other drugs, particularly benzodiazepines, has been strengthened to reflect this potential drug interaction.

The sponsor describes a publication of a subset of the post-marketing adverse events which described acute poisoning with high-dose buprenorphine among 49 patients, 20 of whom died, in France between February 1996 and October 1997. (Tracqui A, *et al.* La Presse Medicale 1998;12:557-561) All 20 deceased subjects in this study were subject to autopsy. One (5%) out of the 20 deaths was attributed solely to buprenorphine poisoning. In 17 (85%) forensic cases, the deaths were associated with evidence of concomitant use of benzodiazepines. Eight (40%) of the 20 autopsied subjects showed evidence of recent intravenous injection which could have included buprenorphine.

Three (4.5%) of the 66 deaths were due to liver failure. All 3 subjects were male, were HIV-positive, and had hepatitis C. Two of the deaths occurred in subjects with hepatic cirrhosis. The third subject presented with hepatocellular damage and aggravated hepatitis, and died of hepatocellular damage-related causes. As of July 31 1999 (38 months post-marketing of Subutex in France), a total of 34 serious liver/biliary system-related adverse events were reported, most of subjects had hepatitis.

Nine fetal deaths were reported in mothers receiving Subutex during the first 41 months following Subutex marketing in France (through July 31, 1999). These included three therapeutic abortions (one for trisomy 18; one for trisomy 21; one for myelomeningocele and talipes), a 21-week miscarriage (fetus had a ventricular septal defect), and four stillbirths (mother #1 seropositive for rubella; toxoplasmosis and hepatitis C, and used heroin and alcohol; mother #2 was a heroin addict, fetus found to have Fallot's tetralogy at autopsy; mother #3 seropositive for hepatitis C and hepatitis A and used tobacco and hashish; mother #4 misused 14 mg Subutex by injection).

Section 8.2.1.3 Deaths from Low Dose Buprenorphine Analgesic Products: Postmarketing Experience (1978- July 1999)

Low-dose buprenorphine products have been marketed in a number of countries for the treatment of moderate to severe pain since 1978. Deaths were reported in 143 subjects receiving low-dose buprenorphine (table below). Many of these were subjects who had serious medical conditions, particularly cancer, for which they were receiving low-dose buprenorphine for relief of their pain. The sponsor indicated that among the 143 deaths, buprenorphine was considered the probable or possible causative or contributory factor in 18 cases by reporting health professionals.

Deaths and causes reported the sponsor by in low-dose buprenorphine

Death Category	Number
Deaths due to underlying medical diseases:	
Cancer	64
Cardiac problems	12
Others	24
Deaths Possible due to buprenorphine	18
Deaths due to non-medical causes	11
Deaths with no sufficient data to make a judgement by the sponsor	8
Deaths due to adverse drug reaction to another drug	6
Total	143

Data Source: Based on Sponsor's Text: Vol 153, Page 113-116 and Text in the Safety Update, page 41.

Eighteen deaths ascribed to buprenorphine are listed below.

- **Subject JP/970312/1276** (New Zealand). A female (62 years of age) was given Temgesic Sublingual 0.4 mg as a single dose for unknown indication. She developed cardiovascular collapse, followed by left ventricular failure and mild renal impairment. No evidence of primary cardiac cause. No concomitant medications were reported.

- **Subject JP/970211/822** (UK). A female patient (unknown age) was given Temgesic Injection 0.3 mg for unknown indication. She developed pulmonary edema. No concomitant medications were reported.

- **Subject JP/970305/1177** (UK). A female (27 years of age) was prescribed Temgesic Sublingual for abdominal pain. She took 2.6 mg in 1 day. She died suddenly. No concomitant medications were reported.

- **Subject JP/970508/2239** (Ireland). A female (unknown age) was given Temgesic (unspecified) for post-operative analgesia. She experienced respiratory depression proceeding to respiratory arrest and subsequent cardiac arrest. Concomitant medication was diazepam 20 mg.

- **Subject JP/970205/705** (Peru). A male (72 years of age) was given Temgesic Injection 0.3 mg intravenous for pain. The patient became confused and starting hallucinating and became cold and pale. No resuscitation was attempted at the family's request. No concomitant medications were reported.

- **Subject JP/970211/814** (UK). A female (59 years of age) was given Temgesic Injection, unknown dose for an unknown indication. She experienced respiratory depression. No concomitant medications were reported.

- **Subject JP/970204/685** (Thailand). A male (70 years of age) was given Temgesic Injection, unknown dosage for post-operative pain (bladder tumor). The patient experienced respiratory arrest and prolonged unconsciousness. No concomitant medications were reported.

- **Subject JP/970205/704** (Peru). A male (unknown age) was given Temgesic Injection 0.3 mg intravenous for sedation. The patient became cyanotic and developed pulmonary edema. No concomitant medications were reported.

- **Subject JP/970218/911** (UK). A male (45 years of age) was given Temgesic Sublingual 1 tablet bid for unknown indication. The patient developed vomiting and circulatory failure and died. Concomitant medications were glyceryl trinitrate 0.5 mg oral and benoral 1 bid oral.

- **Subject ADRS/970106/300** (USA). A patient (gender unspecified, 50 years of age) was given Temgesic Injection 600μg for Tonsillectomy. The patient suffered from cardiac arrest, coma, and somnolence. No concomitant medications were reported.

- **Subject JP/970506/2190** (Japan). A male (71 years of age) with lung cancer was given Lepetan (Buprenorphine) Suppositories (1.6 mg) rectally for cancer pain. The patient developed anaphylactic shock 1 minute after the medication. His general condition was getting worse. Concomitant medications were [redacted] an investigational new drug for cancer treatment [redacted], and furosemide; Triparen, Amiparen, and Intralipid, were part of parenteral nutrition.

- **Subject ADRS/961021/20** (Japan). A female (70 years of age) was given Temgesic Injection 1 ampule epidurally for post-operative analgesia. Concomitant medications were lidocaine epidural and bupivacaine hydrochloride epidural. The patient developed paraplegia, which was subsequently diagnosed as spinal cord infarct by MRI. The case was reported in literature.

- **Subject JP/970211/820** (UK). A male (unknown age) was given Temgesic Injection 0.3 mg for unknown indication. He died of cardiac arrest. Concomitant medications were Omnopon, Hyoscine, and hydrocortisone.

- **Subject JP/970207/743** (Germany). A female (70 years of age) was given Temgesic Injection 0.1 mg intravenous for infarction (unspecified). Concomitant medications were morphine intravenous, Pantopon intravenous and Fortral intravenous. The patient had protracted respiratory insufficiency.

- **Subject JP970225/1000** (Finland). A male (82 years of age) was given Temgesic Sublingual 0.2 mg for unknown indication. He developed lethargy, weakness, and agranulocytosis. Concomitant medications were Ibumetin, verapamil, Furomex, Digoxin, and Hipeksal. Ibumetin and buprenorphine were thought to have caused the adverse reaction.

- **Subject ADRS/970117/523** (El Salvador). A female (unknown age) was given Temgesic Injection for unknown indication. Concomitant medication was Dipyrone. The patient experienced hypotension.

- **Subject JP/970131/623** (Norway). A male (14 years of age) with mental retardation was given Temgesic Injection of 0.3mg intramuscular for dental treatment under anesthesia. Concomitant medications were phenergan subcutaneously, atropine subcutaneously and Leptanal intravenously. The patient developed respiratory depression.

- **Subject ADR S/970117/526** (Pakistan). A male (60 years of age) was given Temgesic Injection 0.3 mg for post-operative pain. He developed hypotensive shock four hours later. Concomitant medications were Ampiclox 2 gm, Indocid R 1,200 mg, and vitamin tablets.

SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS

The International Conference on Harmonization (ICH) defines a serious adverse (medical) event as one that was life-threatening, resulted in hospitalization or prolongation of hospitalization, or was severe and unexpected. For buprenorphine studies (e.g., 1008A&B, CR92/099/100), an additional definition has been used for subjects who had liver enzymes greater than eight times the upper limit of normal because the event was often reported in the previous studies.

Section 8.2.2.1 Serious AE from Study CR96/013 and CR96/014 (1008A&B)
During double-blind phase of Study 1008A, 13 serious and unexpected adverse events were reported. Three subjects were receiving buprenorphine monotherapy, 3 subjects were receiving combination therapy, and 7 subjects were receiving placebo. The most common serious adverse events were reported as a result of hospitalization for detoxofication at patient request (Table 53).

Table 53
Listing of Serious Unexpected Adverse Events by Treatment Group

Subject Number	Coded Term	Week	Severity	Treatment Relationship	Termination
BUPRENORPHINE/NALOXONE					
630-1082	Seizure	4	Moderate	Possibly	No
691-1064	Vomit, diarrhea	3	Severe	Unrelated	No
750-1068	Detoxification request	2	Mild	Unrelated	No
BUPRENORPHINE (Mono)					
539-1055	Suicide ideation	2	Moderate	Unrelated	Yes
642-1046	Suicide ideation	1	Moderate	Possibly	No
750-1091	Endocarditis	4	Severe	Unrelated	No
PLACEBO					
642-1029	Kidney cancer	4	Severe	Unrelated	No
662-1078	Infection	4	Moderate	Unrelated	No
750-1037	Detoxification request	3	Moderate	Possibly	Yes
750-1040	Elevated LFTS	4	Severe	Unrelated	No
750-1053	Detoxification request	1	Moderate.	Possibly	No
750-1056	Detoxification request	1	Moderate	Possibly	No
750-1092	Detoxification request	1	Moderate	Unrelated	Yes

Data Source: Based on Sponsor's Table 46: Vol 153, Page 86

Open Label Treatment (1008B). A total of 91 serious adverse events were reported in the safety study by 57 subjects receiving buprenorphine/naloxone combination therapy. The most common was elevation in liver function tests, occurring in 10 subjects, pneumonia in 7 subjects, chest pain in 6 subjects, and detoxification, drug or alcohol overdose, suicide ideation/attempt or depression reported for 5 subjects each. Serious adverse events that occurred in 2 or more subjects are summarized in Table 54, in decreasing order of incidence.

Table 54. Serious Adverse Events Occurring in at Least 2 Subjects in the Open-Label Study (1008B)

Serious Adverse Event	Number of Subjects (%)
Increased Liver Function Tests	10 (2.1%)
Pneumonia	7 (1.5%)
Chest Pain	6 (1.3%)
Depression	5 (1.1%)
Detoxification	5 (1.1%)
Drug/Alcohol Overdose	5 (1.1%)
Suicide Attempt/Ideation	5 (1.1%)
Asthma	4 (0.8%)
Accident	3 (0.6%)
Anxiety	3 (0.6%)
Cyst	2 (0.4%)
Cellulitis	2 (0.4%)
Myocardial Infarction	2 (0.4%)
Abscess	2 (0.4%)
Infection	2 (0.4%)

Data Source: Based on Sponsor's Table 74: Vol 93, Page 132

Single events reported were vomiting, hypertension, psychiatric hospitalization, shortness of breath, cholecystitis, seizure, dehydration, panic attack, anal cancer, dizziness, deep venous thrombosis, abdominal pain, gastrointestinal bleeding, congestive heart failure, disassociated reaction, congestive obstructive pulmonary disease, and diarrhea.

Section 8.2.2.2. Serious Non-Fatal Medical Events from the Solution Studies:
As seen in Table 55, the most commonly occurring serious adverse events were elevated liver function tests, depression and/or suicide, infection, abscess, accidents, chest pain, and gastrointestinal problems.

Table 54. Most Frequently Reported Serious Non-Fatal Medical Events (N = 813 Subjects) (≥ 4 Events)

Nonfatal Serious Medical Events	CR92/099 CR92/100	CR88/130	CR92/102	Total
Elevated Liver Function Tests	35	1	-	36
Depression/Suicide Thoughts or Attempts	20	1	-	21
Infection	8	1	-	9
Accident	8	-	-	8
Abscess	7	-	2	9
Chest Pain	5	2	-	7
Gastrointestinal Problems	4	2	-	6

Data Source: Based on Sponsor's Table 59: Vol 153, Page 104

Liver function test elevations qualifying as serious adverse events will be discussed in Section 8.5.1.1 of this review.

The next most frequent serious adverse event reported in the multicenter studies of sublingual buprenorphine solution (CR92/099 and CR92/100) were depression (16), attempted suicide (2), or thoughts of suicide (2). The reports were not equally distributed among the study centers as 15 events were reported at one center. None of these events were judged to be related to the study medication.

Of the remaining reports of serious adverse events in Studies CR92/099 and CR92/100, 3 were judged to be possibly related to the study medication: a subject with moderate pedal edema, a subject with severe abuse of cocaine and benzodiazepines, and a subject admitted to the hospital with severe asthma and bronchitis. The last subject (#055/034) also suffered the only serious adverse event where the relationship to receipt of the study drug was designated probable: an accidental overdose, where she was administered 32 mg of buprenorphine instead of 2 mg. The subject did not require hospitalization but was followed closely in clinic, reporting vomiting and activation followed by fatigue and headache. The study drug was withheld for 5 days, and the subject was then restarted on the protocol for 2 days, but then failed to return to clinic. At follow-up 3 months later, the subject did not report any problems.

In Study CR88/130, a total of 13 serious adverse events were reported for 10 subjects. Eight of these subjects were among the 87 methadone recipients in the CR88/130 safety sample. Among the 46 subjects who received buprenorphine and were in the safety sample, only 2 (4%) developed a serious medical event. None of the events experienced by these 2 subjects (a hernia requiring surgery; chest pain and allergic bronchospasm requiring overnight observation in hospital) were considered to be related to receipt of buprenorphine. Both subjects remained on study.

Three (3%) of 96 subjects included in the safety sample of Study CR92/102 developed serious medical events (2 subjects with abscesses at drug injection sites and 1 subject with acute obstructive lung disease) and required hospitalization. In no case was the adverse event judged to be associated with receipt of buprenorphine. Two of the subjects were discontinued from the study.

Section 8.2.2.3. Serious Non-Fatal Medical Events from in the Ongoing Study CR96/015 (Safety Update)

This is an ongoing double-blind, double dummy study comparing two methods of short--term detoxification in opioid dependent subjects. The study is in three phases. In Phase 1 the addict is stabilized on either Suboxone or methadone over a period of 2-6 weeks. In Phase 2, patients in the Suboxone group have their dose reduced to zero over a period of 2 weeks, and patients in the methadone group have their dose is reduced to zero over the first 3 days. In the latter group the dose of lofexidine (to suppress withdrawal symptoms) is increased, then decreased over the next 11 days. Phase 3 is a 2-day follow-up period.

A total of 77 of a target of 80 subjects have entered the study. Of these 14 have

completed the all three phases and 13 are ongoing. Thirty-four patients have discontinued 30 in the stabilization phase and 4 in the withdrawal phase.

There have been 7 serious medical events in seven patients. Five of these cases were overdose or overdose attempts on opiates or other non-study medication. Two were infections that required treatment. None of these events are attributed to the study drug by investigator. These cases are described below. CRFs for these cases are provided in the safety update submission. Study randomization code has not been broken.

- PR/98 1109/32. This was a 26 year-old female who attempted suicide by taking an overdose (cocktail of metronidazole, Phenergan, Buscopan and ibuprofen), and lacerating her left forearm with a knife. She had also drank 7-10 pints of cider (alcoholic apple drink). The patient was not on study medication at the time of the event. The patient was hospitalized and recovered.

- PR/98 1126/42. This was a 20 year old male who presented feeling physically unwell with pyrexia of 39.6^{0}C, chest infection, drowsiness, high systolic blood pressure (164/72 sitting, 144/76 lying down), tachycardia >110bpm, difficulty walking and completing simple tasks. The subject used 10mg diazepam the previous night. The probable cause of illness was chest infection. The patient was hospitalized and recovered.

- PR/9902 15/84. This was a 21 year-old male who unintentionally overdosed on heroin after breaking-up from girlfriend. Patient awoke 2 hours later on the floor. He was not hospitalized and recovered.

- PR/990215/85. This was a 33 year-old male who drank a bottle of whisky, and took 1/2 to 3/4 gram of heroin intravenously. Patient awoke several hours later on the floor. He was not hospitalized and recovered.

- PR/9902 *15/86.* This was a 33 year-old female who unintentionally overdosed on heroin and crack at the same time as taking study medication (30mg methadone or 4mg Suboxone). The study randomization code was not broken. She was not hospitalized and recovered.

- PR/990506/129. This was a 42 year old male who took an overdose of soluble paracetamol (15 x 500mg) and ibuprofen (10 x 400mg). Induced emesis 30min later with salt water. Emergency blood tests ruled out danger to life and the need for an antidote. He was not hospitalized.

- PR/990825/74. This was a 31 year old male who at the second week of the withdrawal phase when withdrawal symptoms were almost resolved, started to feel weak, began to vomit and have abdominal pain. He was admitted to hospital with mild pyrexia (37.6^{0}C), right-sided abdominal tenderness, increasing chest tightness over the last 2 weeks with non-productive cough. Symptoms were consistent with gastroenteritis.

SECTION 8.2.3 OVERDOSE EXPERIENCES

There have been no cases of overdose with Suboxone sublingual tablets. There is some overdose experience from the marketing of the Subutex (mono buprenorphine) sublingual tablets in France and from clinical studies with buprenorphine sublingual solutions. Some summary information on deaths related to overdose has been discussed in the section above.

Section 8.2.3.1 Overdose Reports from the Marketing of Subutex in France

Case 1: A 33-year old patient presented with hepatocellular damage, jaundice, asthenia, and aggravated hepatitis. Prior to death, the patient was treated with Subutex for 6 days and was known to have injected Subutex intravenously at a daily dose of 64 mg/day.

Reviewer's Comment: This case suggests that very high intravenous doses of 64 mg per day may be toxic to the liver, but do not produce fatal respiratory depression. This intravenous dose is equivalent to a sublingual dose of about 200 mg per day. The maximum recommended sublingual dose of Suboxone for the treatment of opioid dependence is 24 mg per day and the likely dose is 16 mg per day.

Cases 2 to 50: The interaction of benzodiazepines and Subutex is reported in Bupp 4295. All subjects were opiate addicts and most were taking other drugs concomitantly with Subutex. The first series included 20 males and 9 females, aged 20 to 35 with non-fatal poisoning. These subjects were also taking ethanol, cannabis, imidazopyridines, LSD, barbiturates, clorazepate, lorazepam, antidepressants, heroin, and benzodiazepines. The second series included 19 males and 1 female, aged 14 to 48 with fatal outcomes (a subset of deaths described in Section 8.2.1. These patients were also taking clorazepate, oxazepam, flunitrazepam, ethanol, morphine, codeine, propoxyphene, cyamemezine, clobazam, meprobamate, bromazepam, paroxetine, alimemazine, amitriptylene, and diazepam. In all cases, blood concentrations of buprenorphine were found to remain at a low level [— ng/ml, (mean = 1.4 ng/ml), and — ng/ml, (mean = 8.4 ng/ml), in non-fatal and fatal cases, respectively]. Almost all cases involved concomitant intake of psychotropic medications, especially benzodiazepines. Intravenous injection of crushed tablets also appears to be a risk factor.

Reviewer's Comment: Experience with Subutex sublingual tablets in France suggests that buprenorphine and benzodiazepines interact to increase the risk of respiratory depression. In some of the cases, asphyxia was the cause of death, due to inhalation of vomit. The route of administration of the product marketed in France (Subutex tablets) is sublingual. However, it is probable that addicts had misused the product intravenously yielding contamination/reaction to excipients and high intravenous doses of buprenorphine.

Section 8.2.3.2 Overdose Experience from Clinical Trials

Case 51: A female patient (in Study CR92/099, Section 8.2.2) was given the wrong dosage of study drug (32 mg sublingually instead of 2 mg). She was observed in clinic for toxicity and advised to seek hospital treatment if symptoms developed. She experienced vomiting and activation, followed by fatigue and headache. Study drug was withheld for five days, and the patient was re-inducted for two days, but then failed to return to clinic. At follow-up three months later, the patient reported no further problems.

Reviewer's Comment: This overdose showed that acute administration of 32 mg sublingual buprenorphine (approximately equivalent to 10 mg intravenously) did not cause serious or prolonged adverse effects.

SECTION 8.3 ASSESSMENT OF DROPOUTS

SECTION 8.3.1 BUPRENORPHINE EXPOSURE

Dosing information was evaluated based on safety data for 1390 subjects with CRFs: 472 subjects for buprenorphine/naloxone combination tablets, 105 for buprenorphine tablets and 813 for buprenorphine solution.

Section 8.3.1.1 Dosing and Duration of Exposure - Buprenorphine/Naloxone Tablets

A majority of the subjects received buprenorphine/naloxone combination tablets, 404 of 497 subjects, received 16 mg/day (naloxone 4 mg/day). The range of doses was from 4 mg/day (naloxone 1 mg/day) to 24 mg/day (naloxone 6 mg/day). The overall duration of treatment was up to 52 weeks; 261 subjects were treated for 6 months or more.

When the overall exposure to buprenorphine/naloxone in 472 subjects participating in the double blind and open label studies is taken into consideration, the 16/4 mg/day and the 20/5 mg/day doses of buprenorphine/naloxone combination therapy were the most frequently administered. The minimum and maximum buprenorphine/naloxone doses used for maintenance treatment were 4/1 mg/day and 24/6 mg/day, respectively (Figure 15).

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Figure 15. Frequency of Buprenorphine Modal Dose in the Safety Study CR96/013 (CR96/014) (Based on Prescribed Dose of Buprenorphine/Naloxone Combination Tablets, Sponsor's Figure 3, Vol 93, page 64)

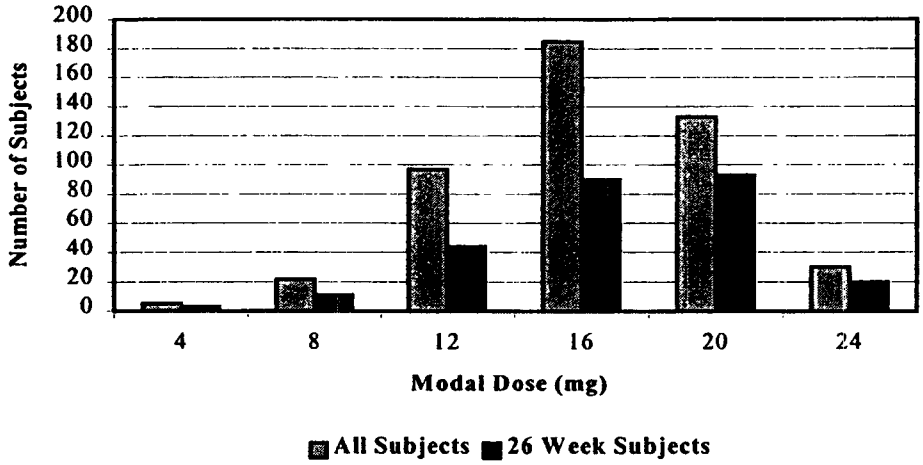

Table 56. Summary of Person-Days Exposure to Combination Therapy by Dose in the Safety Study (All Subjects)

Dose	N	Actual	
		Person-Days	Average Person-Days
Other†	34	556	16.4
4	131	2506	19.1
8	181	6742	37.2
12	323	18601	57.6
16	394	32448	82.4
20	198	25832	130.5
24	48	6245	130.1
All	**472**	**92930**	**196.9**
Dose (mg)	**Number of Subjects Exposed ≥ 6 Months**	**Actual**	
		Person-Days	**Average Person-Days**
Other	31	542	17.5
4	118	2393	20.3
8	152	6032	39.7
12	199	15032	75.5
16	230	27176	118.2
20	138	22885	165.8
24	34	5414	159.2
All	**261**	**79474**	**304.5**

Data Source: Based on Sponsor's Table 13.2.4: Vol 93, Page 172 and Vol. 153, page 54.

† "Other" doses (buprenorphine 2 mg/naloxone 0.5 mg and buprenorphine 6 mg/naloxone 1.5 mg) were only used when subjects were being tapered off the study medication.

Reviewer's Note: Person-time measure is often used when a change in denominator (such as number of people on a specific dose, drop-out) occurs over time. In order to utilize fully the period of observation for each individual, and to weigh properly each person's contribution to the study, a person-time unit, e.g., person-days, is created

Section 8.3.1.2 Dosing and Duration of Exposure - Buprenorphine Tablets

The sponsor submits information for the buprenorphine tablet formulation derived from 351 subjects participating in nine studies. However, only one of these studies (Study CR96/013 - 1008A) has source documentation. In Study CR96/013, 105 subjects were randomized to receive buprenorphine 16 mg/day for 4 weeks. Two subjects received at least one dose of study medication but no follow up safety data were recorded.

Doses for the three controlled studies and the five open label studies ranged from 0.6 mg/day to 16 mg/day, with a range of planned duration from 3 days to 26 weeks. Reports did not provide descriptive statistics for dose or duration.

Section 8.3.1.3 Dosing and Duration of Exposure - Buprenorphine Sublingual Solution

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. However, only half of them have document sources (CRFs). Of the 813 subjects who comprised the safety sample in the controlled clinical trials of sublingual buprenorphine solution for which there are CRFs, 765 subjects (94%) received buprenorphine on a daily basis (q.d.) while 48 subjects (6%) received the drug on alternate days (q.o.d). The duration of exposure to buprenorphine sublingual solution by dose is illustrated in table below. Duration of exposure ranged from ≤ 2 weeks [66 subjects (8%)] to >52 weeks [96 subjects (12%)]; 294 subjects (36%) received 26 or more weeks of this drug.

Table 57. Dose and Duration Based on Initial Dose of Exposure for Subjects Receiving Buprenorphine Sublingual Solution (813 Subjects with Safety Data in Pooled Studies)

	DOSE (mg)	ALL	≤ 2 Weeks	>2≤ 4 Weeks	>4≤ 8 Weeks	>8≤ 13 Weeks	>13≤ 26 Weeks	>26≤ 52 Weeks	>52 Weeks
		N	N	N	N	N	N	N	N
Overall		813	66	74	113	139	127	198	96
Dose (mg/day)	1	168	16	21	31	21	20	44	15
	4	164	12	13	24	16	28	45	26
	8	266	18	24	40	56	44	58	26
	8 Alt. Day	48	2	5	7	34	0	0	0
	16	167	18	11	11	12	35	51	29

Data Source: Based on Sponsor's Table 36: Vol 153, Page 65

Overall, there was a total of 98,679 person days buprenorphine exposure (average of 121.4 person days per subject) among the 813 subjects in the study. The 8 mg/day buprenorphine dose had the highest exposure (28,357 person days), with an average of 75.2 person days per subject.

Table 58. Pooled Solution Studies- Actual Person Days per Dose

Dose	N	Actual	
		Person Days	Average Person Days
Bup 1mg	211	13200	62.56
Bup 2mg	117	3307	28.26
Bup 4mg	259	19250	74.32
Bup 8mg	377	28357	75.22
Bup 8mg (Alt Day)	48	2382	49.63
Bup 16mg	254	24605	96.87
Bup 32mg	84	7578	90.21
All Bup Subjects	813	98679	121.38
Met 20mg	47	2743	58.36
Met 60mg	43	3342	77.72
ALL SUBJECTS	903	104764	116.02

Data Source: Based on Sponsor's Table 37: Vol 153, Page 65

Modal dose for the pooled solution data is presented in Table below. The most common dose was 8 mg/day.

Table 59. Modal Dose of Buprenorphine Solution - Pooled Data for Safety Sample

Modal Dose	No. of Subjects
Bup 1mg	153
Bup 2mg	9
Bup 4mg	157
Bup 8mg	259
Bup 8mg (Alternate Day)	48
Bup 16mg	158
Bup 32mg	29
Met 20mg	47
Met 60mg	43

Data Source: Based on Sponsor's Table 38: Vol 153, Page 66

SECTION 8.3.2 ADVERSE EVENTS

Section 8.3.2.1 Discontinuation from Studies

A summary table on discontinuation from treatments (combo, mono and solution) is provided below. Rates of discontinuation are similar across treatments. Study terminations due to adverse events are listed.

Table 60. Overview of Classification and Enumeration of Discontinuation from Treatment: for 1305[1] Subjects Receiving Buprenorphine/Naloxone or Buprenorphine (Tablet or Solution) in Four Studies (1008, CR92/099, CR92/100 and CR88/130) **for which CRFs are Available**

Status/ Reason for Discontinuation	Combination Tablet	Monotherapy Tablet	Monotherapy Solution
Exposed	497	105[1]	813
Completed	174 (35.0%)	86 (81.9%)	303 (37.3%)
Discontinued	323 (65.0%)	19 (18.1%)	510 (62.7%)
Reason for Discontinuation			
Adverse event	16 (3.2%)	2 (1.9%)	30 (3.7%)
Death	0	0	2[2] (0.2%)
Failure to return to clinic	130 (26.2%)	6 (5.7%)	250 (30.8%)
Poor response	7 (1.4%)	0	122 (15.0%)
Administrative discharge	44 (8.9%)	2 (1.9%)	13 (1.6%)
Pregnancy	4 (0.8%)	0	0
Unrelated medical problem	10 (2.0%)	0	22 (2.7%)
Other	112 (22.5%)	9 (8.6%)	80 (9.8%)

Data Source: Based on Sponsor's Table 29,32, and 39: Vol 153, Page 59, 60, and 67

[1] Safety sample is 103 subjects who had only 4-week treatment vs 52-week treatments in other two groups.

[2] In total there were 3 deaths for the pooled buprenorphine sample, however one subject died (in CR88/130) four days post dose and was therefore not captured as a discontinuation.

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Table 61. Adverse events in patients who terminated (N=20) from 1008

Patient	Gender	Bup/ Nal (mg)	Bup (mg)	ADR	Related
546-2013	M	16/4		Hypertension	Unlikely
546-2027	M	12/3		Hypertension	Unlikely
546-2038	F	12/3		Detoxification symptoms	Poss
629-2001	F	12/3		Scalp hair loss	No
629-2068	M	16/4		Sweating and weight loss	Poss
630-1003	F	12/3		Vomiting	Yes
630-1064	M	16/4		Nausea, vomiting, diarrhea, chills, abdominal cramps	Yes
630-1086	F		16	Dizziness and sleepiness	Poss
662-1022	M	16/4		Withdrawal symptoms	Yes
662-1034	F	16/4		Withdrawal symptoms	Yes
662-1040	F	16/4		Withdrawal symptoms	Yes
662-1058	M	4/1		Withdrawal symptoms and nausea	Poss
689-1083	M	24/6		Edema of the legs	Poss
691-2024	M	20/5		"Upset stomach" and "abdominal cramping."	Poss
546-2032	M		8	Elevated blood pressure	Unlikely
546-2065	F		16	"Runny nose, eyes teary, skin crawly."	Poss
620-2017	M		8	Abdominal pain	Poss
629-2028	M		8	Anxiety, dizziness	Poss
629-2024	M		8	Abdominal pain	Unlikely
662-1050	F		16	Withdrawal symptoms	Poss

Data Source: Based on Sponsor's report: Vol 93, Page 90, 125-130

Table 62. Adverse events in patients who terminated (N=30 for Bup. and N=6 for Methadone) from CR92/099, CR92/100 and CR88/130

Study	Gender	Bup (mg)	Meth (mg)	ADR	Severity	Related
CR88/130	M		60	Alcohol Intol	Sev	No
CR88/130	F		60	Diarrhea	Sev	No
CR88/130	F		60	Headache Nausea Vomit	Sev	Prob / poss
CR88/130	F		20	Hepatitis Sepsis	Sev	No
CR88/130	F		60	Nausea Vomit	Sev	Prob
CR88/130	M		60	Overdose	Sev	Prob
CR92/099	F	1		Back pain	Sev	No
CR92/099	F	1		Headache	Sev	Prob
CR92/099	M	1		Suicide attempt	Sev	No
CR92/099	F	1		Various	Unk	Poss
CR92/099	M	4		Accident	Sev	No
CR92/099	M	4		Anorexia Asthenia Myalgia Nausea Sweat Vasodil	Sev	Poss
CR92/099	F	4		Anorexia Diarrhea Nausea Abdom Pain	Sev	Poss
CR92/099	M	4		Anxiety Depression Withdrawal Syndrome	Mod	No
CR92/100	M	4		Back pain	Mod	No
CR92/099	M	4		Decreased libido	Mod	Poss
CR92/099	M	4		Dizziness Headache	Mod	Prob
CR92/099	M	4		Nervousness	Mod	Poss
CR92/100	M	4		Suicide attempt	Mod	No
CR92/099	F	4		Vomit	Mod	Poss
CR92/099	M	4		Withdrawal Syndrome	Sev	Poss
CR92/099	F	8		Agitation Diarrhea Sweat	Sev	Poss
CR92/099	F	8		Anxiety Chills Nausea Sweat	Mod	Poss
CR92/099	M	8		Asthenia Somnolence	Mod	Yes / prob
CR92/099	M	8		Chest pain	Unk	No
CR92/099	M	8		Depression	Sev	No
CR92/100	M	8		Depression	Mod	No
CR92/099	M	8		Dizziness Syncope	Unk	Prob / poss
CR92/099	M	8		Hepatiitis	Sev	No
CR88/130	F	8		Insomnia NauseaVomit	Mod to sev	Prob / poss
CR92/099	M	8		Nausea	Mod	Poss
CR92/099	F	8		Nausea Abdom Pain Vomit	Mod to sev	Prob
CR92/099	M	8		Nausea Vomit	Mod	Yes
CR92/099	F	8		Withdrawal Syndrome	Sev	Prob
CR92/099	M	8		Withdrawal Syndrome	Mod	Poss
CR92/100	M	16		Alcohol Intol	Sev	No
CR92/099	M	16		Anxiety Asthma	Mod	Poss / No
CR92/099	F	16		Confusion Overdose Nausea	Mod	Prob
CR92/099	M	16		Depression	Mod	No
CR92/099	F	16		Dizziness Somnolence	Mod	Poss
CR92/099	M	16		Intestinal Obst	Sev	No
CR92/099	F	16		Leg cramps	Sev	Poss
CR92/099	F	16		Rash	Sev	Prob
CR92/099	M	16		Withdrawal Syndrome	Sev	Prob
CR92/099	M	16		Withdrawal Syndrome	Sev	Poss

Data Source: Based on Dr. Scheinbuam's review: Table 36, Page 42

SECTION 8.4 OTHER ADVERSE EVENTS

SECTION 8.4.1 ADVERSE EVENTS OVERALL

The buprenorphine/naloxone combination sublingual tablet is the primary focus of this New Drug Application (NDA). The adverse event information is derived primarily from one large, multicenter trial in 472 opiate-dependent subjects, including the subset of 261 subjects treated for more than 6 months. In addition, 106 subjects who had received 4-week buprenorphine monotherapy tablets, and 110 subjects in placebo are also evaluated for comparison.

Supplemental adverse event information is available from controlled clinical trials of buprenorphine sublingual solution that have been monitored and have CRFs. A total of 813 subjects have adverse events information. The data have been pooled for analysis.

Overall, the type and incidence of adverse events reported among recipients of sublingual buprenorphine solution do not appear to differ from the adverse event experience among recipients of buprenorphine tablet formulations.

Section 8.4.1.1 Adverse Events From Buprenorphine/Naloxone Tablets

The most frequently reported adverse events by subjects treated with Suboxone were headache, withdrawal syndrome, pain, insomnia, nausea , sweating, and abdominal pain (12.5% of subjects). There appear to be some differences in adverse events when buprenorphine is administered as monotherapy compared to it is administered in combination with naloxone (more discussions in sections below and 8.10). Placebo subjects reported a higher incidence of back pain, withdrawal syndrome, diarrhea, and rhinitis than buprenorphine-treated subjects did.