Table 63. Adverse Events in CR96/013 by Body System and Treatment Group[1] Reported by At Least 2.0% of the Subjects in Any One Treatment Category

Body System / Adverse Event (COSTART Terminology)	N (%)		
	Combination N = 110	Monotherapy N = 106	Placebo N = 110
Body as a Whole	**71 (64.5%)**	**71 (67.0%)**	**75 (68.2%)**
Asthenia	7 (6.4%)	5 (4.7%)	5 (4.5%)
Chills	7 (6.4%)	8 (7.5%)	8 (7.3%)
Fever	3 (2.7%)	3 (2.8%)	5 (4.5%)
Flu syndrome	0	1 (0.9%)	3 (2.7%)
Headache	38 (34.5%)	30 (28.3%)	26 (23.6%)
Infection	7 (6.4%)	13 (12.3%)	8 (7.3%)
Injury accident	3 (2.7%)	5 (4.7%)	5 (4.5%)
Pain	25 (22.7%)	19 (17.9%)	22 (20.0%)
Pain abdomen	14 (12.7%)	13 (12.3%)	11 (10.0%)
Pain back	5 (4.5%)	9 (8.5%)	13 (11.8%)
Withdrawal syndrome	27 (24.5%)	19 (17.9%)	42 (38.2%)
Cardiovascular System	**11 (10.0%)**	**9 (8.5%)**	**8 (7.3%)**
Vasodilation	10 (9.1%)	4 (3.8%)	2 (1.8%)
Digestive System	**35 (31.8%)**	**33 (31.1%)**	**31 (28.2%)**
Constipation	13 (11.8%)	8 (7.5%)	4 (3.6%)
Diarrhea	4 (3.6%)	5 (4.7%)	16 (14.5%)
Dyspepsia	4 (3.6%)	3 (2.8%)	6 (5.5%)
Gastritis	3 (2.7%)	1 (0.9%)	0
Nausea	16 (14.5%)	14 (13.2%)	11 (10.0%)
Nausea/vomiting	0	3 (2.8%)	4 (3.6%)
Vomiting	8 (7.3%)	8 (7.5%)	3 (2.7%)
Nervous System	**38 (34.5%)**	**35 (33.0%)**	**29 (26.4%)**
Anxiety	3 (2.7%)	5 (4.7%)	4 (3.6%)
Dizziness	5 (4.5%)	4 (3.8%)	4 (3.6%)
Drug dependence	0	0	3 (2.7%)
Hyperkinesia	3 (2.7%)	2 (1.9%)	0
Insomnia	16 (14.5%)	23 (21.7%)	18 (16.4%)
Nervousness	7 (6.4%)	6 (5.7%)	4 (3.6%)
Paresthesia	3 (2.7%)	3 (2.8%)	1 (0.9%)
Somnolence	7 (6.4%)	4 (3.8%)	2 (1.8%)
Respiratory System	**11 (10.0%)**	**17 (16.0%)**	**18 (16.4%)**
Asthma	0	1 (0.9%)	3 (2.7%)
Pharyngitis	3 (2.7%)	4 (3.8%)	1 (0.9%)
Rhinitis	6 (5.5%)	9 (8.5%)	15 (13.6%)
Skin and Appendages	**18 (16.4%)**	**17 (16.0%)**	**14 (12.7%)**
Sweat	15 (13.6%)	13 (12.3%)	11 (10.0%)
Special Senses	**4 (3.6%)**	**8 (7.5%)**	**6 (5.5%)**
Lacrimation	0	4 (3.8%)	6 (5.5%)

Data Source: Based on Sponsor's Table 40 and 13.4.1.1: Vol 93, Page 80 and 180.

[1] Multiple reports of the same event in a subject are counted only once and in its greatest treatment relationship.

Treatment-related adverse events that appeared to occur more frequently in buprenorphine-treated subjects when compared to placebo group subjects included headache, abdominal pain, constipation, nausea, vomiting, and insomnia. Placebo-treated subjects appeared to have a greater incidence of withdrawal syndrome, diarrhea, and rhinitis than either buprenorphine treatment group. Frequently reported adverse events

that were judged by the sponsor to have been possibly related to treatment are summarized in Table 63. Only vasodilation appears to have a marked increase in incidence in Suboxone group compared to other two groups.

Table 63 . Adverse Events Possibly Related to Study Drug Reported by At Least 5.0% of the Subjects in Study 1008A

Body System / Adverse Event (COSTART Terminology)	N (%)		
	Combination N = 110	Monotherapy N = 106	Placebo N = 110
Body as a Whole			
Chills	4 (3.6)	6 (5.7)	4 (3.6)
Headache	28 (25.5)	19 (17.9)	15 (13.6)
Pain	9 (8.2)	4 (3.8)	7 (6.4)
Pain Abdominal	7 (6.4)	6 (5.7)	3 (2.7)
Withdraw Syndrome	8 (7.3)	6 (5.7)	19 (17.3)
Cardiovascular System			
Vasodilation	8 (7.3)	2 (1.9)	4 (3.6)
Digestive System			
Constipation	12 (10.9)	7 (6.6)	3 (2.7)
Diarrhea	2 (1.8)	1 (0.9)	6 (5.5)
Nausea	14 (12.7)	9 (8.5)	8 (7.3)
Vomit	7 (6.4)	6 (5.7)	2 (1.8)
Nervous System			
Insomnia	11 (10.0)	18 (17.0)	11 (10.0)
Somnolence	6 (5.5)	4 (3.8)	1 (1.0)
Respiratory System			
Rhinitis	2 (1.8)	4 (3.8)	6 (5.5)
Skin and Appendages			
Sweat	12 (10.9)	10 (9.4)	9 (8.2)

Data Source: Based on Sponsor's Table 40 and 41: Vol 93, Page 80-81

[1] Multiple reports of the same event in a subject are counted only once and in its greatest treatment relationship.

Adverse events in the Open-Label Safety Study (1008B) by dose (Table 64 in next page)

Table 64. Adverse events (≥ 5%) by Body System in the Open-Label Safety Study (1008B)

ADVERSE EVENT (COSTART Coded Term)	Buprenorphine/Naloxone Dose (mg)							All Subjects (N=472)
	Other Doses (N=34)	4/1 (N=131)	8/2 (N=181)	12/3 (N=323)	16/4 (N=394)	20/5 (N=198)	24/6 (N=48)	
Subjects Reporting NO Adverse Events	**11 (32.4%)**	**42 (32.1%)**	**50 (27.6%)**	**45 (13.9%)**	**55 (14.0%)**	**24 (12.1%)**	**2 (4.2%)**	**26 (5.5%)**
Body as a Whole	**19 (55.9%)**	**58 (44.3%)**	**98 (54.1%)**	**237 (73.4%)**	**303 (76.9%)**	**137 (69.2%)**	**39 (81.3%)**	**409 (86.7%)**
Asthenia	1 (2.9%)	6 (4.6%)	4 (2.2%)	12 (3.7%)	23 (5.8%)	17 (8.6%)	3 (6.3%)	48 (10.2%)
Chills	0	1 (0.8%)	1 (0.6%)	5 (1.5%)	34 (8.6%)	8 (4.0%)	2 (4.2%)	44 (9.3%)
Fever	0	0	3 (1.7%)	5 (1.5%)	15 (3.8%)	10 (5.1%)	4 (8.3%)	36 (7.6%)
Flu Syndrome	1 (2.9%)	2 (1.5%)	7 (3.9%)	15 (4.6%)	35 (8.9%)	30 (15.2%)	10 (20.8%)	89 (18.9%)
Headache	6 (17.6%)	17 (13.0%)	27 (14.9%)	68 (21.1%)	111 (28.2%)	46 (23.2%)	13 (27.1%)	202 (42.8%)
Infection	4 (11.8%)	2 (1.5%)	21 (11.6%)	37 (11.5%)	64 (16.2%)	44 (22.2%)	15 (31.3%)	149 (31.6%)
Accidental Injury	0	4 (3.1%)	8 (4.4%)	16 (5.0%)	34 (8.6%)	29 (14.6%)	5 (10.4%)	72 (15.3%)
Pain	3 (8.8%)	21 (16.0%)	34 (18.8%)	70 (21.7%)	119 (30.2%)	62 (31.3%)	21 (43.8%)	197 (41.7%)
Pain, Abdomen	0	1 (0.8%)	4 (2.2%)	25 (7.7%)	37 (9.4%)	23 (11.6%)	4 (8.3%)	77 (16.3%)
Pain, Back	3 (8.8%)	15 (11.5%)	27 (14.9%)	49 (15.2%)	75 (19.0%)	42 (21.2%)	13 (27.1%)	132 (28.0%)
Withdrawal Syndrome	12 (35.3%)	23 (17.6%)	24 (13.3%)	110 (34.1%)	124 (31.5%)	53 (26.8%)	16 (33.3%)	194 (41.1%)
Cardiovascular System	**1 (2.9%)**	**3 (2.3%)**	**12 (6.6%)**	**27 (8.4%)**	**35 (8.9%)**	**14 (7.1%)**	**3 (6.3%)**	**65 (13.8%)**
Vasodilation	0	2 (1.5%)	5 (2.8%)	16 (5.0%)	19 (4.8%)	1 (0.5%)	0	29 (6.1%)
Digestive System	**7 (20.6%)**	**19 (14.5%)**	**36 (19.9%)**	**101 (31.3%)**	**160 (40.6%)**	**78 (39.4%)**	**20 (41.7%)**	**266 (56.4%)**
Abscess, Periodontal	0	1 (0.8%)	3 (1.7%)	2 (0.6%)	5 (1.3%)	3 (1.5%)	3 (6.3%)	10 (2.1%)
Constipation	0	2 (1.5%)	11 (6.1%)	39 (12.1%)	67 (17.0%)	44 (22.2%)	7 (14.6%)	115 (24.4%)
Diarrhea	2 (5.9%)	4 (3.1%)	4 (2.2%)	10 (3.1%)	23 (5.8%)	11 (5.6%)	3 (6.3%)	50 (10.6%)
Dyspepsia	1 (2.9%)	2 (1.5%)	7 (3.9%)	13 (4.0%)	21 (5.3%)	13 (6.6%)	3 (6.3%)	45 (9.5%)
Nausea	1 (2.9%)	6 (4.6%)	5 (2.8%)	19 (5.9%)	41 (10.4%)	10 (5.1%)	6 (12.5%)	76 (16.1%)
Tooth Disorder	1 (2.9%)	1 (0.8%)	6 (3.3%)	11 (3.4%)	14 (3.6%)	5 (2.5%)	5 (10.4%)	37 (7.8%)
Vomiting	0	2 (1.5%)	4 (2.2%)	14 (4.3%)	30 (7.6%)	9 (4.5%)	8 (16.7%)	61 (12.9%)
Endocrine System	**0**	**0**	**0**	**0**	**0**	**1 (0.5%)**	**0**	**1 (0.2%)**
Hemic and Lymphatic System	**1 (2.9%)**	**0**	**4 (2.2%)**	**8 (2.5%)**	**12 (3.0%)**	**9 (4.5%)**	**2 (4.2%)**	**24 (5.1%)**
METABOLIC/NUTRITIONAL DISORDERS	**0**	**5 (3.8%)**	**11 (6.1%)**	**22 (6.8%)**	**27 (6.9%)**	**19 (9.6%)**	**6 (12.5%)**	**56 (11.9%)**
Peripheral Edema	0	2 (1.5%)	3 (1.7%)	9 (2.8%)	15 (3.8%)	11 (5.6%)	4 (8.3%)	24 (5.1%)

ADVERSE EVENT (COSTART Coded Term)	Buprenorphine/Naloxone Dose (mg)							All Subjects (N=472)
	Other Doses (N=34)	4/1 (N=131)	8/2 (N=181)	12/3 (N=323)	16/4 (N=394)	20/5 (N=198)	24/6 (N=48)	
Musculoskeletal System	**1 (2.9%)**	**10 (7.6%)**	**9 (5.0%)**	**27 (8.4%)**	**38 (9.6%)**	**24 (12.1%)**	**10 (20.8%)**	**79 (16.7%)**
Myalgia	0	2 (1.5%)	1 (0.6%)	6 (1.9%)	12 (3.0%)	9 (4.5%)	4 (8.3%)	31 (6.6%)
Nervous System	**4 (11.8%)**	**36 (27.5%)**	**64 (35.4%)**	**129 (39.9%)**	**169 (42.9%)**	**84 (42.4%)**	**24 (50.0%)**	**259 (54.9%)**
Anxiety	0	10 (7.6%)	19 (10.5%)	23 (7.1%)	34 (8.6%)	23 (11.6%)	4 (8.3%)	65 (13.8%)
Depression	1 (2.9%)	19 (14.5%)	29 (16.0%)	31 (9.6%)	26 (6.6%)	25 (12.6%)	14 (29.2%)	70 (14.8%)
Insomnia	1 (2.9%)	11 (8.4%)	26 (14.4%)	56 (17.3%)	83 (21.1%)	44 (22.2%)	10 (20.8%)	138 (29.2%)
Nervousness	0	5 (3.8%)	3 (1.7%)	13 (4.0%)	26 (6.6%)	7 (3.5%)	5 (10.4%)	42 (8.9%)
Paresthesia	1 (2.9%)	5 (3.8%)	7 (3.9%)	14 (4.3%)	20 (5.1%)	7 (3.5%)	1 (2.1%)	28 (5.9%)
Somnolence	0	1 (0.8%)	7 (3.9%)	18 (5.6%)	22 (5.6%)	7 (3.5%)	1 (2.1%)	40 (8.5%)
Respiratory System	**2 (5.9%)**	**13 (9.9%)**	**21 (11.6%)**	**62 (19.2%)**	**93 (23.6%)**	**50 (25.3%)**	**14 (29.2%)**	**177 (37.5%)**
Cough Increased	0	2 (1.5%)	5 (2.8%)	10 (3.1%)	17 (4.3%)	7 (3.5%)	3 (6.3%)	36 (7.6%)
Pharyngitis	0	4 (3.1%)	5 (2.8%)	14 (4.3%)	28 (7.1%)	22 (11.1%)	3 (6.3%)	64 (13.6%)
Rhinitis	0	3 (2.3%)	7 (3.9%)	29 (9.0%)	38 (9.6%)	17 (8.6%)	6 (12.5%)	75 (15.9%)
Skin and Appendages	**4 (11.8%)**	**9 (6.9%)**	**15 (8.3%)**	**57 (17.6%)**	**74 (18.8%)**	**35 (17.7%)**	**6 (12.5%)**	**138 (29.2%)**
Rash	2 (5.9%)	1 (0.8%)	5 (2.8%)	14 (4.3%)	8 (2.0%)	6 (3.0%)	0	23 (4.9%)
Sweat	0	1 (0.8%)	4 (2.2%)	28 (8.7%)	47 (11.9%)	16 (8.1%)	5 (10.4%)	74 (15.7%)
Special Senses	**0**	**1 (0.8%)**	**6 (3.3%)**	**15 (4.6%)**	**34 (8.6%)**	**12 (6.1%)**	**3 (6.3%)**	**59 (12.5%)**
Urogenital System	**0**	**11 (8.4%)**	**16 (8.8%)**	**40 (12.4%)**	**39 (9.9%)**	**30 (15.2%)**	**6 (12.5%)**	**97 (20.6%)**

Data Source: Based on Sponsor's Table 13.4.2.1: Vol 93, Page 269-277

The table above shows that many drug related adverse events may have followed a dose response pattern. These events included flu syndrome, headache, pain, withdrawal syndrome, constipation, vomiting, myalgia, insomnia, pharyngitis, rhinitis, peripheral edema and sweat as well as infection and accidental injury. Nineteen specific adverse events were reported by 10% or more of these subjects. In order of decreasing frequency, these were headache (43%), pain (42%), withdrawal syndrome (41%), infections (unspecified) (32%), insomnia (29%), back pain (28%), constipation (24%), flu-like syndrome (19%), abdominal pain (16%), nausea (16%), rhinitis (16%), sweating (16%), accidental injury (15%), depression (15%), anxiety (14%), pharyngitis (14%), vomiting (13%), diarrhea (11%), and asthenia (10%).

To compare to the safety profile of Suboxone, adverse events by body system from the pooled buprenorphine solution studies (CR92/099 and CR92/100), are provided in table below:

Table 65. Adverse events (≥ 5%) by Body System from the Pooled Buprenorphine Solution Studies

ADVERSE EVENT (COSTART Coded Term)	Buprenorphine (mg)							All Subjects
	Dose = 1mg	Dose = 2mg	Dose = 4mg	Dose = 8mg	Dose = 8mg Alternative Day	Dose = 16mg	Dose = 32mg	
All Patients	**227**	**117**	**275**	**347**	**48**	**84**		**1366**
Patients Assessed	**211**	**117**	**259**	**327**	**48**	**84**		**1300**
Subjects Reporting NO Adverse Events	**32 (15.2%)**	**31 (26.5%)**	**36 (13.9%)**	**66 (20.2%)**	**35 (72.9%)**	**23 (9.1%)**	**9 (10.7%)**	**232 (17.9%)**
Body as a Whole	**153 (72.1%)**	**72 (61.5%)**	**185 (71.4%)**	**217 (66.4%)**	**7 (14.6%)**	**190 (74.8%)**	**65 (77.4%)**	**889 (68.4%)**
Asthenia	35 (16.5%)	16 (13.7%)	42 (16.2%)	43 (13.2%)		37 (14.6%)	8 (9.5%)	181 (13.9%)
Chills	17 (8.1%)	5 (4.3%)	21 (8.1%)	18 (5.5%)		16 (6.3%)	6 (7.1%)	83 (6.4%)
Fever	8 (3.8%)	2 (1.7%)	8 (3.1%)	4 (1.2%)		11 (4.3%)	6 (7.2%)	39 (3.0%)
Flu Syndrome	10 (4.7%)	10 (8.6%)	24 (9.3%)	33 (10.1%)		20 (7.9%)	7 (8.3%)	104 (8.0%)
Headache	58 (27.5%)	16 (13.7%)	81 (31.3%)	92 (28.1%)	6 (12.5%)	88 (34.7%)	20 (23.8%)	361 (27.8%)
Infection	44 (20.1%)	19 (16.2%)	63 (24.3%)	75 (22.9%)		74 (29.1%)	21 (25.0%)	296 (22.8%)
Accidental Injury	7 (3.3%)	2 (1.7%)	13(5.0%)	14 (4.3%)		15 (5.9%)	5 (4.8%)	55 (4.3%)
Pain	57 (27.0%)	24 (20.5%)	66 (25.5%)	81 (24.8%)		78 (30.7%)	28 (33.3%)	3347 (25.7%)
Pain, Abdomen	28 (13.3%)	17 (14.5%)	31 (12.0%)	25 (7.7%)	1 (2.1%)	26 (10.3%)	15 (17.9%)	143 (11.0%)
Pain, Back	23 (10.9%)	12 (10.3%)	43 (16.6%)	50 (15.3%)		46 (18.1%)	17 (20.2%)	191 (14.7%)
Withdrawal Syndrome	57 (27.0%)	15 (12.3%)	68 (26.3%)	84 (25.7%)		67 (26.4%)	23 (27.4%)	314 (24.2%)
Cardiovascular System	**13 (6.2%)**	**7 (6.0%)**	**17 (6.6%)**	**16 (4.9%)**		**19 (7.5%)**	**5 (6.0%)**	**77 (5.9%)**
Digestive System	**68 (32.2%)**	**27 (23.1%)**	**91 (35.1%)**	**104 (31.8%)**	**5 (10.4%)**	**98 (38.6%)**	**32 (38.1%)**	**425 (32.7%)**
Constipation	10 (4.7%)	2 (1.7%)	30 (11.6%)	33 (10.1%)	1 (2.1%)	32 (12.6%)	8 (9.5%)	116 (8.9%)
Diarrhea	25 (11.9%)	6 (5.2%)	15 (5.8%)	16 (4.9%)		11 (4.3%)	5 (6.0%)	78 (6.0%)
Dyspepsia	8 (3.8%)	5 (4.3%)	17 (6.6%)	9 (2.8%)	1 (2.1%)	9 (3.5%)	5 (6.0%)	54 (4.2%)
Nausea	22 (10.4%)	7 (6.0%)	32 (12.4%)	38 (11.6%)	2 (4.2%)	28 (11.0%)	11(13.1%)	140 (10.8%)
Vomiting	10 (4.7%)	1 (1.0%)	10 (3.9%)	16 (4.9%)	1 (2.1%)	22 (8.7%)	4 (4.8%)	64 (4.9%)
Endocrine System	**0**	**0**	**0**	**1 (0.3)**		**2 (0.8%)**	**2 (2.4)**	**5 (0.4%)**
Hemic and Lymphatic System	**0**	**1 (0.9)**	**4 (1.5%)**	**6 (1.8%)**		**8 (3.1%)**	**6 (7.1%)**	**25 (1.9%)**

ADVERSE EVENT (COSTART Coded Term)	Buprenorphine (mg)							All Subjects
	Dose = 1mg	Dose = 2mg	Dose = 4mg	Dose = 8mg	Dose = 8mg Alternative Day	Dose = 16mg	Dose = 32mg	
METABOLIC/NUTRITIONAL DISORDERS	7 (3.3%)	5 (4.3%)	9 (3.5%)	11 (3.4%)		14 (5.5%)	6 (7.1%)	52 (4.0%)
Musculoskeletal System	**27 (12.8%)**	**8 (6.8%)**	**25 (9.7%)**	**33 (10.1%)**		**28 (11.2%)**	**15 (17.9%)**	**136 (10.5%)**
Cramps Leg	7 (3.3%)	0	3 (1.2%)	5 (1.5%)		8 (3.2%)	5 (6.0%)	28 (2.2%)
Nervous System	**109 (51.7%)**	**48 (41.0%)**	**134 (51.7%)**	**149 (45.6%)**	**4 (8.3%)**	**145 (57.1%)**	**45 (53.6%)**	**634 (48.8%)**
Anxiety	28 (13.3%)	14 (12.0%)	41 (15.8%)	46 (14.1%)		44 (17.3%)	18 (21.4%)	191 (14.7%)
Depression	31 (14.7%)	15 (12.3%)	31 (12.0%)	37 (11.3%)		46 (18.1%)	15 (17.9%)	175 (13.5%)
Dizziness	5 (2.4%)	5 (4.3%)	9 (3.5%)	9 (2.8%)		14 (5.5%)	1 (1.2%)	43 (3.3%)
Insomnia	56 (26.5%)	23 (19.7%)	79 (30.5%)	75 (22.9%)	2 (4.2%)	82 (32.3%)	24 (28.6%)	341 (26.3%)
Nervousness	19 ((.0%)	5 (4.3%)	15 (5.8%)	18 (5.5%)		18 (7.1%)	3 (3.6%)	78 (6.0%)
Somnolence	9 (4.3%)	4 (3.4%)	16 (6.2%)	18 (5.5%)		14 (5.5%)	5 (6.0%)	66 (5.1%)
Respiratory System	**52 (24.6%)**	**20 (17.1%)**	**54 (20.9%)**	**72 (22.0%)**		**72 (28.4%)**	**18 (21.4%)**	**288 (22.2%)**
Pharyngitis	9 (4.3%)	2 (1.7%)	11 (4.3%)	15 (4.6%)		16 (6.3%)	3 (3.6%)	56 (4.3%)
Rhinitis	35 (16.6)	13 (11.1%)	30 (11.6%)	36 (11.0%)		37 (14.6%)	9 (10.7%)	160 (12.3%)
Skin and Appendages	**46 (21.8%)**	**17 (15.5%)**	**53 (20.5%)**	**57 (17.4%)**		**53 (20.9%)**	**16 (19.1%)**	**242 (18.6%)**
Sweat	34 (16.1%)	13 (11.1%)	43 (16.6%)	36 (11.1%)		38 (15.0%)	11 (13.1%)	175 (13.5%)
Special Senses	**28 (13.3%)**	**8 (6.8%)**	**29 (11.2%)**	**21 (6.4%)**		**28 (11.0%)**	**5 (6.0%)**	**119 (9.2%)**
Lacrimation Disorder	15 (7.1%)	6 (5.1%)	17 (6.6%)	13 (4.0%)		12 (4.7%)	3 (3.6%)	66 (5.1%)
Urogenital System	**18 (8.5%)**	**3 (2.3%)**	**25 (9.7%)**	**27 (8.3%)**	**1 (2.1%)**	**26 (10.2%)**	**13 (15.5%)**	**113 (8.7%)**
Dysmenorrhea	8 (3.8%)	2 (1.7%)	9 (3.5%)	8 (2.5%)		6 (2.4%)	6 (7.2%)	39 (3.0%)

Data Source: Based on Sponsor's Table 1.4.29: Vol 154, Page 201-212

Common adverse events (≥ 5%) are almost identical between the two formulations with few exceptions. However, dose response pattern in the solution is not as clear as the combo tablet. In the solution studies, many dose-related adverse events show differences between 4 mg above and below, but no clear separations between 4, 8, 16 and 32 mg. For example, constipation in the combo tablet groups are 2% (4/1 tablet), 6% (8/2), 12% (12/3), 17% (16/4), 22% (20/5) and 15% (24/6) while the rates in the pooled solution data set are 5% (1 mg), 2% (2 mg), 12% (4 mg), 10% (8 mg), 13% (16 mg) and 10 % (32 mg). The differences between the two formulations may be explained by two factors: data pooling effect and naloxone effect.

To further examine the possible data pooling effect, adverse events from the single largest (N=731) solution study (CR92/099) are provided below:

Table 66. Common Adverse Events (≥5%) in CR92/099 According to Treatment Dose Group

EVENT	DOSE 1mg	DOSE 4mg	DOSE 8mg	DOSE 16mg	TOTAL
	N=184	N=180	N=186	N=181	N=731
"NONE"	18	11	7	12	48
ALLERG REACT	10	3	6	6	24
ASTHENIA	31	41	38	35	145
CHILLS	17	18	17	16	68
FEVER	12	4	8	14	38
FLU SYND	18	31	29	17	95
HEADACHE	55 (30%)	70 (39%)	69 (37%)	67 (37%)	261
INFECT	45 (24%)	60 (33%)	62 (33%)	59 (33%)	226
INJURY ACCID	9	16	15	14	54
PAIN	54	57	69	61	241
PAIN ABDO	32	24	23	27	106
PAIN BACK	19 (5%)	44 (24%)	38 (20%)	37 (20%)	138 (19%)
PAIN CHEST	7	6	9	10	32
WITHDRAW SYND	53 (29%)	61 (34%)	64 (34%)	55 (30%)	233 (32%)
VASODILAT	11	5	3	10	29
ANOREXIA	4	7	11	4	26
CONSTIP	11 (6%)	25 (14%)	27 (15%)	30 (17%)	93 (13%)
DIARRHEA	24	15	18	10	67
DYSPEPSIA	9	16	6	11	42
LIVER FUNC ABNORM	8	11	6	8	33
NAUSEA	23	28	42	26	119
VOMIT	9 (5%)	11 (6%)	16 (9%)	20 (11%)	56 (8%)
COUGH INC	8	12	9	7	36
PHARYNGITIS	10	12	16	14	52
RHINITIS	38	27	29	32	126
SWEAT	31	30	37	34	132
LACRIMATION DIS	22	12	10	9	53
DYSMENORRHEA	7	9	6	5	27
INFECT URIN TRACT	4	5	9	4	22

Data Source: Based on Dr. Scheinbaum's review Table 20, Page 48 and sponsor's table 1.4.33 Vol 154;page 215

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The table shows the common (at least 5% incidence in any group) adverse events according to dosage group in CR92/099. The dose response pattern is similar to the

pooled data set, which suggests that naloxone may be responsible for many dose-related effects especially withdrawal symptoms in the combo tablet. However, there are a number of confounding factors such as study design and study population that makes a quantitative comparison difficult between the Suboxone study and the buprenorphine solution study. Differences in adverse event profiles will be discussed in details in Section 8.10.

Adverse events from Study CR88/130 are not included in the pooled table. Therefore, common events (>10%) are presented here. The higher dose of methadone was associated with a higher incidence of adverse events (mostly constipation, dizziness, nausea and vomiting) than for the lower methadone dose group (Table 67). Neither methadone dose group differed significantly from buprenorphine in frequency of adverse events.

Table 67. Percentage Incidence of adverse events in the three dose groups of study CR88/130 arranged by rank order of events in the buprenorphine group.

	% of Patients (N=53)	% of Patients (N=55)	% of Patients (N=54)
Event	Bup 8mg	Meth 20mg	Meth 60mg
Constipation	**50%**	**38%**	**60%**
Decreased Libido	**40%**	**22%**	**31%**
Insomnia	**37%**	**44%**	**45%**
Headache	**37%**	**33%**	**43%**
Anxiety	**30%**	**24%**	**31%**
Dry Mouth	**30%**	**27%**	**31%**
Sedation	**28.%**	**36%**	**36%**
Nausea	**28%**	**18%**	**43%**
Decreased Appetite	**28%**	**31%**	**45%**
Dizzy	**22%**	**13%**	**31%**
Vomiting	**20%**	**9%**	**29%**
Ringing in Ears	**15%**	**16%**	**19%**
Itching	**15%**	**22%**	**29%**
Difficulty Urinating	**13%**	**22%**	**29%**

Data Source: Based on Dr. Scheinbaum's review Table 17, Page 43 and sponsor's table 1.4.32 Vol 154;page 213

SECTION 8.4.2 ADVERSE EVENTS BY GENDER

Adverse events by gender are analyzed based on data from Study 1008, in which the to-be-marketed drug was evaluated in double-blind phase and open-label phase.

Section 8.4.2.1 Study 1008A - Double-Blind Phase

Approximately two-thirds of the subjects were male and one-third was female. In general, adverse events were reported with greater incidence by female subjects, which is often the case. When adverse events were compared for male subjects *versus* female

subjects, female subjects treated with buprenorphine (whether combination or monotherapy sublingual tablets) reported more sweating and abdominal pain than did males, with female buprenorphine naloxone combination-treated subjects possibly experiencing more withdrawal syndrome than did male subjects (but still in lower numbers than in the placebo-treated group). These events were reported approximately twice as frequently for female subjects than for male subjects. There was little difference between males and females in the placebo group for these events. Headache, nausea, and constipation appeared to be reported more frequently by women for all three treatment groups, including placebo. There were no apparent trends for pain.

Adverse events are summarized by gender in Table below. This represents the subset of events that occurred with an overall incidence of 5% or greater.

**Table 68. Adverse Events by Gender:
Subset of Adverse Events Reported by at Least 5% of Subjects Overall
in the Efficacy Study (1008A)**

Adverse Event (COSTART Coded Term)	Gender	Combination Therapy (N = 107)	Monotherapy (N = 103)	Placebo (N = 107)	All Subjects (N = 317)
Number of Subjects at Baseline	Male	68	70	71	209
	Female	41	35	38	114
Headache	Male	21 (31.3%)	17 (24.6%)	10 (14.3%)	48 (23.3%)
	Female	18 (45.0%)	13 (38.2%)	14 (37.8%)	45 (40.5%)
Withdrawal Syndrome	Male	15 (22.4%)	14 (20.3%)	26 (37.1%)	55 (26.7%)
	Female	12 (30.0%)	5 (14.7%)	14 (37.8%)	31 (27.9%)
Pain	Male	15 (22.4%)	13 (18.8%)	12 (17.1%)	40 (19.4%)
	Female	9 (22.5%)	6 (17.6%)	8 (21.6%)	23 (20.7%)
Insomnia	Male	9 (13.4%)	14 (20.3%)	7 (10.0%)	30 (14.6%)
	Female	6 (15.0%)	8 (23.5%)	10 (27.0%)	24 (21.6%)
Nausea	Male	8 (11.9%)	8 (11.6%)	6 (8.6%)	22 (10.7%)
	Female	8 (20.0%)	6 (17.6%)	6 (16.2%)	20 (18.0%)
Sweating	Male	8 (11.9%)	6 (8.7%)	7 (10.0%)	21 (10.2%)
	Female	7 (17.5%)	7 (20.6%)	4 (10.8%)	18 (16.2%)
Pain Abdomen	Male	6 (9.0%)	7 (10.1%)	4 (5.7%)	17 (8.3%)
	Female	6 (15.0%)	5 (14.7%)	3 (8.1%)	14 (12.6%)
Rhinitis	Male	1 (1.5%)	3 (4.3%)	5 (7.1%)	9 (4.4%)
	Female	4 (10.0%)	7 (20.6%)	9 (24.3%)	20 (18.0%)
Infection	Male	4 (6.0%)	8 (11.6%)	4 (5.7%)	16 (7.8%)
	Female	2 (5.0%)	4 (11.8%)	3 (8.1%)	9 (8.1%)
Diarrhea	Male	3 (4.5%)	3 (4.3%)	5 (7.1%)	11 (5.3%)
	Female	1 (2.5%)	2 (5.9%)	11 (29.7%)	14 (12.6%)
Chills	Male	4 (6.0%)	6 (8.7%)	2 (2.9%)	12 (5.8%)
	Female	4 (10.0%)	2 (5.9%)	6 (16.2%)	12 (10.8%)
Pain Back	Male	1 (1.5%)	2 (2.9%)	6 (8.6%)	9 (4.4%)
	Female	3 (7.5%)	6 (17.6%)	6 (16.2%)	15 (13.5%)
Constipation	Male	4 (6.0%)	5 (7.2%)	1 (1.4%)	10 (4.9%)
	Female	9 (22.5%)	3 (8.8%)	2 (5.4%)	14 (12.6%)
Vasodilation	Male	5 (7.5%)	4 (5.8%)	2 (2.9%)	11 (5.3%)
	Female	5 (12.5%)	0	5 (13.5%)	10 (9.0%)
Vomiting	Male	5 (7.5%)	6 (8.7%)	2 (2.9%)	13 (6.3%)
	Female	3 (7.5%)	2 (5.9%)	3 (8.1%)	8 (7.2%)
Asthenia	Male	3 (4.5%)	4 (5.8%)	4 (5.7%)	11 (5.3%)
	Female	4 (10.0%)	1 (2.9%)	3 (8.1%)	8 (7.2%)

Data Source: Based on Sponsor's table 116 Vol 153; page 203

Section 8.4.2.2 Study 1008B – Open Label Phase

Sixty nine percent (69%) of the subjects in the safety study were male and 31% were female. As expected, a number of adverse events were reported more frequently in women than in men, including vomiting [30 women (20.7%) compared to 31 men (9.5%)], increased cough [16 women (11.0%) compared to 20 men (6.1%)], and vasodilation [15 women (10.3%) compared to 14 men (4.3%)]. Accidental injuries

appeared to occur more frequently amongst men [58 men (17.7%) compared to 14 women (9.7%)]. For subjects who were exposed to combination therapy for at least 6 months a similar trend was noted in that a number of adverse events were reported more frequently by women, namely withdrawal syndrome, infection, constipation, nausea, pharyngitis, vomiting, somnolence, dizziness, and vasodilation. Accidental injury, depression, and myalgia were reported more frequently by men than women. There were no obvious differences in person-days of exposure to the various dose levels that might account for these differences.

Adverse events reported by at least 5% of all subjects in the safety study are summarized by gender in table below.

Table 69. Number (%) of Adverse Events Reported by at Least 5% of Subjects by Gender in the Safety Study (1008B)

Adverse Event	Male (N=327)	Female (N=145)	All Subjects (N=472)
Headache	136 (41.6%)	66 (45.5%)	202 (42.8%)
Pain	143 (43.7%)	54 (37.2%)	197 (41.7%)
Withdrawal Syndrome	126 (38.5%)	68 (46.9%)	194 (41.1%)
Infection	98 (30.0%)	51 (35.2%)	149 (31.6%)
Insomnia	104 (31.8%)	34 (23.4%)	138 (29.2%)
Pain, Back	98 (30.0%)	34 (23.4%)	132 (28.0%)
Constipation	72 (22.0%)	43 (29.7%)	115 (24.4%)
Flu Syndrome	65 (19.9%)	24 (16.6%)	89 (18.9%)
Pain Abdomen	49 (15.0%)	28 (19.3%)	77 (16.3%)
Nausea	46 (14.1%)	30 (20.7%)	76 (16.1%)
Rhinitis	52 (15.9%)	23 (15.9%)	75 (15.9%)
Sweating	48 (14.7%)	26 (17.9%)	74 (15.7%)
Accidental Injury	58 (17.7%)	14 (9.7%)	72 (15.3%)
Depression	52 (15.9%)	18 (12.4%)	70 (14.8%)
Anxiety	48 (14.7%)	17 (11.7%)	65 (13.8%)
Pharyngitis	43 (13.1%)	21 (14.5%)	64 (13.6%)
Vomiting	31 (9.5%)	30 (20.7%)	61 (12.9%)
Diarrhea	35 (10.7%)	15 (10.3%)	50 (10.6%)
Asthenia	34 (10.4%)	14 (9.7%)	48 (10.2%)
Dyspepsia	29 (8.9%)	16 (11.0%)	45 (9.5%)
Chills	28 (8.6%)	16 (11.0%)	44 (9.3%)
Nervousness	27 (8.3%)	15 (10.3%)	42 (8.9%)
Somnolence	24 (7.3%)	16 (11.0%)	40 (8.5%)
Tooth Disorder	24 (7.3%)	13 (9.0%)	37 (7.8%)
Fever	25 (7.6%)	11 (7.6%)	36 (7.6%)
Cough Increased	20 (6.1%)	16 (11.0%)	36 (7.6%)
Dizziness	22 (6.7%)	11 (7.6%)	33 (7.0%)
Myalgia	25 (7.6%)	6 (4.1%)	31 (6.6%)
Vasodilation	14 (4.3%)	15 (10.3%)	29 (6.1%)
Paresthesia	19 (5.8%)	9 (6.2%)	28 (5.9%)
Peripheral Edema	15 (4.6%)	9 (6.2%)	24 (5.1%)

Data Source: Based on Sponsor's table 117 Vol 153;page 204

SECTION 8.4.3 ADVERSE EVENTS BY AGE

Analyses of adverse events by age are not performed as subjects aged over 65 years old were excluded from Study 1008, in which the to-be-marketed drug was evaluated in double-blind phase and open-label phase.

SECTION 8.4.4 ADVERSE EVENTS BY RACE

Adverse events by gender are analyzed based on data from Study 1008, in which the to-be-marketed drug was evaluated in double-blind phase and open-label phase.

Section 8.4.4.1 Study 1008A – Double-Blind Phase
The majority of subjects were non-Hispanic Whites (61.0% overall), with 28.5% of the subjects Black. Approximately 10% of the subjects were of other ethnicities. There was no evidence that suggested a difference between ethnicities in the adverse events profile of buprenorphine. Where there were differences between the ethnicities, they were consistent across all three treatment groups. The most striking observations are high incidences of headache and withdrawal syndrome in subjects of ethnic groups other than White or Black. These, however, reflect an imbalance resulting from the small numbers of subjects included.

Adverse events are summarized by ethnicity in Table 70. The table below reflects the subset of events that occurred with an overall incidence of 5% or more.

**Table 70. Adverse Events by Ethnicity:
Subset of Adverse Events Reported by at Least 5% of Subjects Overall
in the Efficacy Study**

Adverse Event (COSTART Coded Term)	Race	Combination Therapy (N = 107)	Monotherapy (N = 103)	Placebo (N = 107)	All Subjects (N = 317)
Number of Subjects at Baseline	**White**	**65**	**62**	**70**	**197**
	Black	**32**	**35**	**25**	**92**
	Other	**12**	**8**	**14**	**34**
Headache	White	24 (37.5%)	15 (25.0%)	12 (17.6%)	51 (26.6%)
	Black	9 (28.1%)	11 (31.4%)	6 (24.0%)	26 (28.3%)
	Other	6 (54.5%)	4 (50.0%)	6 (42.9%)	16 (48.5%)
Withdrawal Syndrome	White	16 (25.0%)	13 (21.7%)	27 (39.7%)	56 (29.2%)
	Black	6 (18.8%)	4 (11.4%)	7 (28.0%)	17 (18.5%)
	Other	5 (45.5%)	2 (25.0%)	6 (42.9%)	13 (39.4%)
Pain	White	16 (25.0%)	15 (25.0%)	15 (22.1%)	46 (24.0%)
	Black	5 (15.6%)	3 (8.6%)	2 (8.0%)	10 (10.9%)
	Other	3 (27.3%)	1 (12.5%)	3 (21.4%)	7 (21.2%)
Insomnia	White	9 (14.1%)	18 (30.0%)	11 (16.2%)	38 (19.8%)
	Black	4 (12.5%)	2 (5.7%)	3 (12.0%)	9 (9.8%)
	Other	2 (18.2%)	2 (25.0%)	3 (21.4%)	7 (21.2%)
Nausea	White	11 (17.2%)	9 (15.0%)	6 (8.8%)	26 (13.5%)
	Black	3 (9.4%)	4 (11.4%)	3 (12.0%)	10 (10.9%)
	Other	2 (18.2%)	1 (12.5%)	3 (21.4%)	6 (18.2%)
Sweating	White	9 (14.1%)	8 (13.3%)	7 (10.3%)	24 (12.5%)
	Black	5 (15.6%)	4 (11.4%)	1 (4.0%)	10 (10.9%)
	Other	1 (9.1%)	1 (12.5%)	3 (21.4%)	5 (15.2%)
Pain Abdomen	White	6 (9.4%)	10 (16.7%)	2 (2.9%)	18 (9.4%)
	Black	5 (15.6%)	1 (2.9%)	3 (12.0%)	9 (9.8%)
	Other	1 (9.1%)	1 (12.5%)	2 (14.3%)	4 (12.1%)
Rhinitis	White	1 (1.6%)	7 (11.7%)	6 (8.8%)	14 (7.3%)
	Black	3 (9.4%)	2 (5.7%)	5 (20.0%)	10 (10.9%)
	Other	1 (9.1%)	1 (12.5%)	3 (21.4%)	5 (15.2%)
Infection	White	3 (4.7%)	5 (8.3%)	5 (7.4%)	13 (6.8%)
	Black	3 (9.4%)	6 (17.1%)	1 (4.0%)	10 (10.9%)
	Other	0	1 (12.5%)	1 (7.1%)	2 (6.1%)

Data Source: Based on Sponsor's table 119 Vol 153;page 206

Section 8.4.4.2 Study 1008B – Open Label Phase

Approximately one-half of the subjects were White, with 30% Black and approximately 20% of other ethnicities (primarily Hispanic). Differences between ethnic groups were detected for a number of adverse events (Table 71), though there were no consistent trends in difference between a single ethnic group and the other ethnic groups. Nausea, sweating, accidental injury, depression, anxiety, chills, and fever varied two- to four-fold in incidence among ethnic groups. Summaries of the incidence of frequently reported adverse events (reported by at least 5% of subjects), by ethnicity, are provided for all subjects who participated in the safety study in Table below.

Table 71. Adverse Events by Ethnicity: Subset of Adverse Events Reported by at Least 5% of Subjects Overall in the Efficacy Study

Adverse Event (COSTART Coded Term)	Race	Combination Therapy (N = 107)	Monotherapy (N = 103)	Placebo (N = 107)	All Subjects (N = 317)
Number of Subjects at Baseline	**White**	**65**	**62**	**70**	**197**
	Black	**32**	**35**	**25**	**92**
	Other	**12**	**8**	**14**	**34**
Diarrhea	White	2 (3.1%)	5 (8.3%)	7 (10.3%)	14 (7.3%)
	Black	1 (3.1%)	0	6 (24.0%)	7 (7.6%)
	Other	1 (9.1%)	0	3 (21.4%)	4 (12.1%)
Chills	White	5 (7.8%)	7 (11.7%)	4 (5.9%)	16 (8.3%)
	Black	2 (6.3%)	0	2 (8.0%)	4 (4.3%)
	Other	1 (9.1%)	1 (12.5%)	2 (14.3%)	4 (12.1%)
Pain Back	White	3 (4.7%)	4 (6.7%)	4 (5.9%)	11 (5.7%)
	Black	0	4 (11.4%)	5 (20.0%)	9 (9.8%)
	Other	1 (9.1%)	0	3 (21.4%)	4 (12.1%)
Constipation	White	7 (10.9%)	6 (10.0%)	2 (2.9%)	15 (7.8%)
	Black	6 (18.8%)	2 (5.7%)	1 (4.0%)	9 (9.8%)
	Other	0	0	0	0
Vasodilation	White	7 (10.9%)	4 (6.7%)	4 (5.9%)	15 (7.8%)
	Black	3 (9.4%)	0	2 (8.0%)	5 (5.4%)
	Other	0	0	1 (7.1%)	1 (3.0%)
Vomiting	White	4 (6.3%)	5 (8.3%)	2 (2.9%)	11 (5.7%)
	Black	2 (6.3%)	3 (8.6%)	2 (8.0%)	7 (7.6%)
	Other	2 (18.2%)	0	1 (7.1%)	3 (9.1%)
Asthenia	White	4 (6.3%)	4 (6.7%)	6 (8.8%)	14 (7.3%)
	Black	3 (9.4%)	1 (2.9%)	1 (4.0%)	5 (5.4%)
	Other	0	0	0	0

Data Source: Based on Sponsor's table 119 Vol 153;page 207

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Table 72. Number (%) of Adverse Events Reported by at Least 5% of Subjects by Ethnic Group in the Open-Label Study (1008B)

Adverse Event	White (N=238)	Black (N=142)	Other (N=92)	All Subjects (N=472)
Headache	111 (46.6%)	50 (35.2%)	41 (44.6%)	202 (42.8%)
Pain	100 (42.0%)	54 (38.0%)	43 (46.7%)	197 (41.7%)
Withdrawal Syndrome	101 (42.4%)	71 (50.0%)	22 (23.9%)	194 (41.1%)
Infection	79 (33.2%)	54 (38.0%)	16 (17.4%)	149 (31.6%)
Insomnia	80 (33.6%)	21 (14.8%)	37 (40.2%)	138 (29.2%)
Pain, Back	72 (30.3%)	32 (22.5%)	28 (30.4%)	132 (28.0%)
Constipation	43 (18.1%)	45 (31.7%)	27 (29.3%)	115 (24.4%)
Flu Syndrome	56 (23.5%)	17 (12.0%)	16 (17.4%)	89 (18.9%)
Pain Abdomen	37 (15.5%)	21 (14.8%)	19 (20.7%)	77 (16.3%)
Nausea	47 (19.7%)	12 (8.5%)	17 (18.5%)	76 (16.1%)
Rhinitis	36 (15.1%)	23 (16.2%)	16 (17.4%)	75 (15.9%)
Sweating	43 (18.1%)	23 (16.2%)	8 (8.7%)	74 (15.7%)
Accidental Injury	53 (22.3%)	15 (10.6%)	4 (4.3%)	72 (15.3%)
Depression	22 (9.2%)	7 (4.9%)	41 (44.6%)	70 (14.8%)
Anxiety	38 (16.0%)	0	27 (29.3%)	65 (13.8%)
Pharyngitis	34 (14.3%)	23 (16.2%)	7 (7.6%)	64 (13.6%)
Vomiting	40 (16.8%)	11 (7.7%)	10 (10.9%)	61 (12.9%)
Diarrhea	28 (11.8%)	12 (8.5%)	10 (10.9%)	50 (10.6%)
Asthenia	27 (11.3%)	10 (7.0%)	11 (12.0%)	48 (10.2%)
Dyspepsia	29 (12.2%)	11 (7.7%)	5 (5.4%)	45 (9.5%)
Chills	19 (8.0%)	4 (2.8%)	21 (22.8%)	44 (9.3%)
Nervousness	17 (7.1%)	11 (7.7%)	14 (15.2%)	42 (8.9%)
Somnolence	26 (10.9%)	10 (7.0%)	4 (4.3%)	40 (8.5%)
Tooth Disorder	24 (10.1%)	6 (4.2%)	7 (7.6%)	37 (7.8%)
Fever	21 (8.8%)	4 (2.8%)	11 (12.0%)	36 (7.6%)
Cough Increased	16 (6.7%)	10 (7.0%)	10 (10.9%)	36 (7.6%)
Dizziness	18 (7.6%)	8 (5.6%)	7 (7.6%)	33 (7.0%)
Myalgia	20 (8.4%)	6 (4.2%)	5 (5.4%)	31 (6.6%)
Vasodilation	17 (7.1%)	9 (6.3%)	3 (3.3%)	29 (6.1%)
Paresthesia	17 (7.1%)	8 (5.6%)	3 (3.3%)	28 (5.9%)
Edema Peripheral	12 (5.0%)	9 (6.3%)	3 (3.3%)	24 (5.1%)

Data Source: Based on Sponsor's table 120 Vol 153;page 208

The same general observation (i.e., adverse event profiles by race) is true for subjects exposed to combination therapy for at least 6 months. Since there is no consistent trend, these differences are considered reflective of normal variation. There were no obvious trends between the races with respect to dose or duration of exposure.

SECTION 8.4.5 ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY

Section 8.4.5.1 Data from Study CR96/013 and CR96/014 (1008)

There were no patients with hepatic insufficiency included in Study 1008. Descriptive comparisons of adverse events by baseline liver function are described in this section.

4-week, Double Blind, Placebo Controlled Study. Overall, 232 subjects in the efficacy study had normal baseline liver function and 85 had abnormal baseline liver function. Differences in baseline liver function (as measured by SGPT) did not appear to be associated with any consistent trend in the incidence of adverse events.

Open Label Treatment. As was done for the efficacy study, subjects were categorized on the basis of baseline SGPT into those whose baseline value was within normal range and those who were "abnormal" (that is, above normal range). The notable differences were observed in subjects treated with combination therapy for at least 6 months. In that subgroup, subjects with normal baseline liver function reported the following adverse events with notably higher frequency: infection (50.5% of subjects with normal SGPT and 36.1% of subjects with abnormal SGPT), back pain (44.4% of subjects with normal SGPT and 32.8% of subjects with abnormal SGPT), sweating (16.8% of subjects with normal SGPT and 8.2% of subjects with abnormal SGPT), anxiety (21.2% of subjects with normal SGPT and 14.8% of subjects with abnormal SGPT), pharyngitis (22.3% of subjects with normal SGPT and 16.4% of subjects with abnormal SGPT), diarrhea (15.8% of subjects with normal SGPT and 4.9% of subjects with abnormal SGPT), nervousness (11.4% of subjects with normal SGPT and 6.6% of subjects with abnormal SGPT), and tooth disorder (12.5% of subjects with normal SGPT and 6.6% of subjects with abnormal SGPT).

When all participants in the safety study were considered, differences were of lesser magnitude than those observed for 6 month completers and occurred in fewer adverse events (withdrawal syndrome, infection, constipation, rhinitis, sweating, and anxiety). Table 73 provides summaries of frequently reported adverse events by baseline liver function for all subjects.

Table 73. Number (%) of Adverse Events Reported by at Least 5% of Subjects by Baseline Liver Function in the Safety Study CR96/013 (CR96/014)

Adverse Event	Normal (N=329)	Abnormal (N=113)	All Subjects (N=442)
Headache	145 (44.1%)	46 (40.7%)	191 (43.2%)
Pain	141 (42.9%)	45 (39.8%)	186 (42.1%)
Withdraw Syndrome	145 (44.1%)	42 (37.2%)	187 (42.3%)
Infection	110 (33.4%)	28 (24.8%)	138 (31.2%)
Insomnia	97 (29.5%)	38 (33.6%)	135 (30.5%)
Pain, Back	99 (30.1%)	29 (25.7%)	128 (29.0%)
Constipation	88 (26.7%)	23 (20.4%)	111 (25.1%)
Flu Syndrome	62 (18.8%)	23 (20.4%)	85 (19.2%)
Pain Abdomen	58 (17.6%)	16 (14.2%)	74 (16.7%)
Nausea	53 (16.1%)	20 (17.7%)	73 (16.5%)
Rhinitis	58 (17.6%)	13 (11.5%)	71 (16.1%)
Sweating	59 (17.9%)	13 (11.5%)	72 (16.3%)
Accidental Injury	53 (16.1%)	15 (13.3%)	68 (15.4%)
Depression	51 (15.5%)	17 (15.0%)	68 (15.4%)
Anxiety	52 (15.8%)	12 (10.6%)	64 (14.5%)
Pharyngitis	50 (15.2%)	12 (10.6%)	62 (14.0%)
Vomiting	42 (12.8%)	18 (15.9%)	60 (13.6%)
Diarrhea	40 (12.2%)	9 (8.0%)	49 (11.1%)
Asthenia	37 (11.2%)	9 (8.0%)	46 (10.4%)
Dyspepsia	30 (9.1%)	11 (9.7%)	41 (9.3%)
Chills	30 (9.1%)	14 (12.4%)	44 (10.0%)
Nervousness	33 (10.0%)	9 (8.0%)	42 (9.5%)
Somnolence	30 (9.1%)	9 (8.0%)	39 (8.8%)
Tooth Disorder	29 (8.8%)	6 (5.3%)	35 (7.9%)
Fever	23 (7.0%)	11 (9.7%)	34 (7.7%)
Cough Increased	23 (7.0%)	10 (8.8%)	33 (7.5%)
Dizziness	26 (7.9%)	7 (6.2%)	33 (7.5%)
Myalgia	20 (6.1%)	9 (8.0%)	29 (6.6%)
Vasodilation	23 (7.0%)	5 (4.4%)	28 (6.3%)
Paresthesia	19 (5.8%)	4 (3.5%)	23 (5.2%)
Peripheral Edema	17 (5.2%)	5 (4.4%)	22 (5.0%)

Data Source: Based on Sponsor's table 123 Vol 153;page 213

SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH RENAL INSUFFICIENCY

Suboxone has not been evaluated in patients with renal insufficiency.

SECTION 8.4.7 ADVERSE EVENTS RELATED PREGNANCY, NURSING, LABOR AND DELIVERY

Section 8.4.7.1 Data from Study CR96/013 (CR96/014)

Five subjects became pregnant during Study CR96/013 (CR96/014). Four of these subjects received combination therapy and one received monotherapy. Three of the

pregnancies were reported to have been aborted, one ended in miscarriage at 4 to 6 weeks of gestation, and one was carried to term. The child was born "drug addicted" and with respiratory difficulties but without other health problems. Upon follow-up, the baby was reportedly doing well.

Section 8.4.7.2 Data from Published Studies

Six published reports of open label studies (and case reports) in pregnant, opioid-dependent women are submitted, and results are summarized in table below. It is clear from the reported studies that neonates experience some withdrawal effects that are usually mild but in some cases severe.

Table 74. Treatment of Pregnant Addicts with Buprenorphine Tablets.

Study	Patients	Bup max dose	Outcome
CR97/001	9	10mg/day	Normal births, no withdrawal
CR96/010	3	12mg/day	Normal births, mild withdrawal
Bupp 3988	4	1.5mg/day	Normal births, mild withdrawal
Bupp 4217	1	4mg/day	Normal births, mild withdrawal
Bupp 4282	6	8mg/day	Normal births, mild withdrawal
Bupp 4283	6	16mg/day	Normal births, withdrawal

Data Source: Based on Sponsor's table 124 Vol 153;page 214

CR97/001, Fischer (Clinical Supply Subutex Tablets, Austria)

Study CR97/001 was an open label study in 9 opioid-dependent, pregnant women who were transferred from their current oral maintenance therapy with slow-release morphine or methadone, to buprenorphine in an inpatient setting over a period of 3 days. Buprenorphine was then continued as part of the standard maintenance treatment program adopted at the study center. This required subjects to visit the clinic 2 to 3 times a week for group psychotherapy and for the supervised collection of weekly urine samples. Induction onto maintenance buprenorphine in 6 subjects who were receiving methadone and in 3 who were receiving slow-release morphine during pregnancy was achieved with transient dysphoric mood states presented for the first 2 days of the transition. No withdrawal symptoms were reported during the course of pregnancy and negative urine tests confirmed the absence of illicit drug use. Ultrasound and/or cardiotocogram investigations showed that no untoward effect was suffered by the fetus during the transition.

In 6 women the baby was delivered vaginally without the need for analgesic products. Three subjects required Caesarean section (1 was HIV positive) and 2 experienced abnormally prolonged labor. The average duration of gestation was 39.5 weeks (36 to 42 weeks). All 9 children had a normal birth weight Apgar scores were 9 at 1 minute and 10 at 5 and 10 minutes. No neonates showed indication of neonatal abstinence syndrome, but the duration of follow-up was not reported.

CR96/010, Johnson (Clinical Supply Subutex Tablets, US)

Study CR96/010 was a pilot study in 3 pregnant women treated with up to 8 mg to 12 mg Subutex for 18 weeks (Weeks 24 to 42 of gestation). No clinically significant abnormalities were observed in maternal and neonatal safety outcome measures during the ante-partum, labor/delivery, and post-partum periods. Onset, peak, and duration of neonatal withdrawal symptoms were 4–36, 16–72, and 115–120 hours, respectively. The two withdrawal symptoms most often observed were tremors and hyperactive moro. Peak neonatal abstinence scores ranged from 6–13 (maximum possible = 48). No neonate required medical intervention. Days of hospitalization were 2, 2, 2 and 5, 4, 4 for mother and neonate, respectively.

Bupp 3988, Reisinger (Low Dose Buprenorphine Tablets, Belgium)

Another study was conducted in 4 pregnant addicts who received 1 to 1.5mg per day of sublingual buprenorphine throughout their pregnancy. All pregnancies and deliveries were normal, occurring between the 39th and 41st weeks. The babies weighed between 2.9 and 3.5 kg and had Apgar scores of 9/10/10 in all 4 cases. One baby exhibited agitation at 13 days, thought attributable to buprenorphine withdrawal. The children all developed normally.

Bupp 4217, Marquet (Subutex Tablets, France)

A case report (Bupp 4217) describes 4 mg/day Subutex given to a 4-month pregnant woman after it was discovered that she had been a heroin addict for several years. While receiving buprenorphine she rapidly withdrew from heroin. Repeated urine assays showed that she remained abstinent from illegal drugs. At Week 39 the subject gave birth under good conditions to a normal female baby (Apgar score 10 at 1 and 10 minutes). A weak withdrawal syndrome occurred in the baby approximately 48 hours after birth with agitation, sleep disturbance, tremor, yawning, noisy breathing and mild fever. The adapted Finnegan score used to assess the severity of withdrawal symptoms was 12 (maximum score = 40). The newborn was discharged from the intensive care unit on Day 6 with a normal score. The buprenorphine concentration at 20 hours was six-times higher in the newborn's serum (1.9 ng/mL) than in the mother's serum (0.3 ng/mL). The levels in the child did not, however, exceed the therapeutic levels achieved in adults receiving maintenance therapy. Only low levels of buprenorphine (total of 3.28 μg) were ingested *via* the mothers milk during each 24-hour period.

Bupp 4282, Marquet (Subutex Tablets, France): Another report by the same group (Bupp 4282) was of 6 pregnant addicts treated with 4 mg to 8 mg/day buprenorphine sublingual tablets. All neonates presented with no abnormalities and normal Apgar

scores at birth. Concentrations of buprenorphine and its metabolite were similar in mother and child. Drugs of abuse were detected in 2 children (1 codeine and cocaine; the other morphine and codeine or heroin): both presented with severe withdrawal. 2 of the 4 children who had only buprenorphine detected had no withdrawal; the other 2 had slight to mild signs.

Bupp 4283, Jernite (Subutex Tablets, France): Another report describes the treatment of 6 pregnant addicts. In 3 cases the mother was taking sublingual maintenance (2, 4, and 16 mg/day); of the other 3, 1 was an IV abuser (8 mg/injection), 1 took strong benzodiazepines and cocaine, and the other was not an opioid addict. Weaning of 5 of the babies was similar to that for other opioids, with withdrawal symptoms. The other also received clorazepate, and also showed hypotonia and somnolence. Treatment with a paregoric elixir or barbiturates led to favorable outcomes.

There is another case report of a terminated pregnancy (Bupp 4050). The case report describes premature rupture of the membranes at 24 weeks gestation, followed by fetal death and cervical spasm, in a women receiving buprenorphine for heroin addiction.

Other Information, including 3 Publications in the Safety Update
Two other studies are presented: one of these describes the effects of buprenorphine infusion in premature neonates (Bupp 2997), and another (Bupp 3179) is a review of the use of methadone during pregnancy.

The pharmacokinetics of buprenorphine were studied in 12 premature neonates in intensive care therapy (Bupp 2997). Their mean gestational age was 30 weeks (range 27 to 32 weeks) postnatal age from 1 to 27 days, and mean birth weight 1.47 kg (range 0.92 to 2.4 kg). The mean (± SD) steady state buprenorphine concentration for all patients was 4.3 ± 2.6 ng/ mL; for patients receiving 0.72 μg/kg/h it was 3.6 ± 1.8 ng/mL. A 1-compartment model was fitted to the concentration-time data (fit was not improved by a 2-compartment model). Mean plasma clearance of buprenorphine was 0.23 ± 0.07 L/h/kg, mean elimination half-life was 20 ± 8 hours, and mean V_D was 6.2 ± 2.1 L/kg. There were significant falls in heart rate at 1, 6, and 12 hours, and in systolic blood pressure at 6 hours. No significant changes were seen in other physiological parameters.

The sponsor provides three new publications relating to the use of buprenorphine in pregnant addicts in the Safety Update.

STUDY #1: BUPP 4268. **CUTRONE ET AL. BUPRENORPHINE NEONATAL WITHDRAWAL SYNDROME, WHICH THERAPY? PED. MED. CHIR. MED. SURG. PREG., 1998;20:67-69**

This case report from Italy describes Temgesic 4 tablets/day (0.2 mg/tablet) given to a pregnant woman until the 3rd month of pregnancy, at which time, knowing she was pregnant, she halved the dose (0.4 mg/day). She had been a heroin addict for 3 years. At

Week 35 the subject had a cesarean section due to the threat of a premature birth with a cardiotachographic trace showing late deceleration in heart rate. A male baby was born with a birth weight of 2600 g, Apgar score 3 at 1 minutes and 7 at 5 minute. A withdrawal syndrome occurred in the baby on the second day after birth, with hypothermia (39.2^0 C), spontaneous tremors, muscular hypertony, continuous acute crying, polypnea, and feeding difficulties. An initial dose of 1 ml/kg of methadone 3 times per day was used. Subsequently, given the persistence of marked withdrawal signs, the dose was gradually increased up to 1.3 ml/kg three times per day. A serious episode of apnea and bradycardia occurred on the 3rd day, and naloxone (unknown dose) was used for the possible methadone's toxic effect. _Phenobarbital then was used for the treatment of withdrawal syndrome for a total of 41 days. The infant showed a severe delay of neuromoter development at 3 and 5 months. This case is marked by two aspects: a withdrawal syndrome with a particularly severe and prolonged course and severe delay in growth with marked neurological and behavioral changes, with subsequent development into tetraparesis and epilepsy which was difficult to control pharmacologically. The author indicates that there is little doubt that the withdrawal symptoms are attributed to the buprenorphine, however, the severe deficit in neural maturation cannot with certainty be attributed solely to the drug. The author suggests that the use of methadone should be avoided in the case of neonatal buprenorphine withdrawal syndrome.

Study #2 - Bupp 4543 Auriacombe et al. Pregnancy, abortion and delivery in a group of heroin addict subjects undergoing replacement treatment (methadone and buprenorphine) in Aquitaine.

The investigators monitored a group of opiate-dependent subjects who undergone treatment with methadone and buprenorphine in France. Sixteen out of the 245 subjects (male=165 and female=80) were pregnant women. Pregnancy outcomes include 3 intentional abortions, 1 miscarriage, 2 premature births at 37 weeks (with no negative repercussions) and 10 births at term. Eleven out of 16 pregnant women had replacement treatment (meth=7; bup=4) when they became pregnant, and average daily doses were 63 mg for meth and 5 mg at the time of delivery. Pregnancy was the reason for setting up methadone treatment for other five women, and average daily dose was 90 mg on delivery. Of the 10 children while mother was still taking the treatment, 7 had withdrawal syndrome and 6 required pharmacological treatment (opium and diazepam). In all cases, withdrawal syndrome appeared before Day 5, and its mean duration was 33 days for meth and 9 days for bup. The study didn't report the percentage of infant who experienced withdrawal with a history of exposure to buprenorphine. The authors suggest that the pregnancies in the buprenorphine cases, for which very limited data are available, raised fewer problems than those using methadone, essentially due to the shorter withdrawal syndrome in the newborn.

Study #3 – Bupp 4556 Quenum FH. Buprenorphine (Subutex) and neonatal withdrawal syndrome. Arch Pediatr 1998;5:206.

This report describes a neonatal withdrawal case whose mother was given Subutex during pregnancy at a dose of three time 2mg/day. The baby was born at term with a birthweight of 3,680 g. No signs of respiratory depression were observed during the birth. Initially, the baby received no treatment. She was fed exclusively on baby milk. At 6 days, she was admitted to NCU due to a withdrawal symptom combining diarrhea, tremors, hyper-excitability, hypertonia and disturbed sleep. There were sings of dehydration. The baby was treated with Elixir Paregorique (six times 4 drops a day) for 6 weeks. At 3 months, the infant had adequate weight increase.

Section 8.4.7.3 Data from Post-Marketing Experience

Nine fetal deaths were reported in mothers receiving Subutex during the first 41 months following Subutex marketing in France (through July 31 1999). These cases have been reviewed in Section 8.2.1.

Forty-two cases of neonatal withdrawal syndrome were reported during the first 27 months following marketing of Subutex, through June 1998 in France. Daily dose and length of therapy were not reported for 14 cases. For the remaining 28 reports, the daily dose taken by the mother ranged from 2 mg/day to 16 mg/day. The duration of treatment of the mother with Subutex ranged from 1 day to 3 years. Length of gestation is known in only 7 cases and ranged from 34 to 40 weeks. Of the 42 reports, gender of the neonate was unknown in 13 cases. Of the others, 17 neonates were male and 12 were female. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1 (69%). Approximately half of the reports gave no details of the withdrawal symptoms. For the others the withdrawal symptoms are given in Table 75.

In the safety update, additional 24 new cases of neonatal withdrawal syndrome are reported. Most of the cases were similar to ones reported during the previous period. Other symptoms reported for neonates, whose mothers were treated with Subutex, are also given in Table 75.

Table 75. Neonatal Withdrawal Symptoms

Neonatal Withdrawal Syndrome	
Body as a Whole - General	
Appetite decreased	1
Crying abnormal	7
Fever	1
CNS Disorders	
Coma	1
Convulsions	6
Hyperkinesia	3
Hypertonia	6
Hypokinesia	1
Hypotonia	1
Myoclonus	2
Somnolence	2
Tremor	7
Eye Disorders	
Miosis	1
Heart Rate and Rhythm	
Bradycardia	2
Tachycardia	1
Fetal Disorders	
Fetal distress	1
GI System	
Diarrhea	2
Vomiting	4
Metabolic and Nutritional	
Acidosis	3
Hypoglycemia	1
Psychiatric	
Agitation	9
Insomnia	1
Nervousness	1
Respiratory	
Respiratory Arrest	1
Respiratory Depression	1
Dyspnea	3
Tachypnea	1
Skin and Subcutaneous	
Sweating	2

Data Source: Based on Sponsor's table 127 Vol 153;page 255 and Table 20 in the Safety Update, Vol 1;page 37

SECTION 8.5 OTHER SAFETY FINDINGS

SECTION 8.5.1 CLINICAL LABORATORY EVALUATIONS

The laboratory database consists of results from Study CR96/013, CR96/014 and the pooled solution studies.

A physical examination including measurement of vital signs, clinical laboratory studies including clinical chemistry, hematology, and pregnancy testing for women of childbearing potential were to be performed at Screening, at Week 4, and then monthly throughout participation in the safety study. ECGs were performed at screening and at Weeks 4, 12, 24, 36, and 52 in Study CR96/013 (CR96/014). Ninety subjects in Suboxone group had baseline and on-treatment laboratory data compared to 85 subjects in Subutex group, and 84 subjects in placebo group.

Criteria for individual "possibly clinically significant" laboratory values, consistent with those recommended by the FDA Division of Neuropharmacological Drug Products, are provided in table below:

Table 76. Definitions of FDA-Specified Criteria for "Possibly Clinically Significant" Laboratory Values

Laboratory Test	Criterion Values
Chemistry	
SGOT	≥3 × ULN
SGPT	≥3 × ULN
Alkaline phosphatase	≥3 × ULN
Lactate dehydrogenase (LDH)	≥3 × ULN
BUN	≥30 mg/dL
Creatinine	≥2.0 mg/dL
Total bilirubin	≥2.0 mg/dL
Hematology	
Hematocrit	
Male	≤37%
Female	≤32%
Hemoglobin	
Male	≤11.8 g/dL
Female	≤9.5 g/dL
WBC count	≤2.8 × 10^3/μL or ≥16 × 10^3/μL
Eosinophils	≥10%
Neutrophils	≤15%
Platelet count	≤75 × 10^3/μL or ≥700 × 10^3/μL
Urinalysis	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥2 units

Section 8.5.1.1 Clinical Chemistry

Section 8.5.1.1.1 Results for Suboxone

A small proportion of subjects had "possibly clinically significant" elevations in SGOT (1.3%) or SGPT (1.3%) at baseline (Table 77). It appears that there was an increase in the proportion (3%) of patients with elevated values of SGOT and SGPT from baseline to

Week 4 while there was no marked increase in this proportion over time during the 52-week study period (Table 78). The on-treatment proportions were always higher than baseline (range: SGOT 2.1% to 4.6%; SGPT 2.1% to 4.6%). There were very few instances of "possibly clinically significant" elevations in alkaline phosphatase or total bilirubin, and none for LDH.

Table 77. Liver Function Parameters: Number of Subjects with "Possibly Clinically Significantly" Elevated Values by Treatment Group(Study CR96/013 – 1008A)

Parameter	Analysis Visit	Treatment Group					
		Combination Therapy		Monotherapy		Placebo	
		N Assessed	N (%)	N Assessed	N (%)	N Assessed	N (%)
SGOT	Baseline†	90	1 (1.1)	85	0	84	0
	4 Weeks	90	2 (2.2)	85	3 (3.5)	84	3 (3.6)
SGPT	Baseline†	90	0	85	2 (2.4)	84	0
	4 Weeks	90	2 (2.2)	85	2 (2.4)	84	2 (2.4)
Total Bilirubin	Baseline†	88	0	85	0	82	0
	4 Weeks	90	1 (1.1)	85	0	82	0

Data Source: Based on Sponsor's Table 1.5.3 Vol 155;page 243-244
†Subjects with a baseline and an on-treatment value are represented

Table 78. Liver Function Parameters: Numbers of Subjects with "Possibly Clinically Significantly" Elevated Values by Analysis Visit Window (CR96/014 – 1008B)

Analysis Visit	SGOT		SGPT		Alkaline Phosphatase		Total Bilirubin	
	N Assessed	N(%)	N Assessed	N(%)	N Assessed	N(%)	N Assessed	N(%)
Baseline†	391	5 (1.3)	389	5 (1.3)	391	0	386	1 (0.3)
4	402	16 (4.0)	401	16 (4.0)	402	1 (0.2)	401	1 (0.2)
8	349	16 (4.6)	349	16 (4.6)	349	1 (0.3)	349	2 (0.6)
12	321	11 (3.4)	320	9 (2.8)	321	0	320	0
16	295	11 (3.7)	295	12 (4.1)	295	0	294	1 (0.3)
20	268	8 (3.0)	266	10 (3.8)	268	0	267	1 (0.4)
24	246	9 (3.7)	246	6 (2.4)	248	0	248	2 (0.8)
28	241	7 (2.9)	241	5 (2.1)	241	0	241	0
32	221	8 (3.6)	220	8 (3.6)	221	0	220	0
36	205	6 (2.9)	205	6 (2.9)	206	0	204	0
40	195	4 (2.1)	194	4 (2.1)	194	1 (0.5)	194	0
44	182	7 (3.8)	181	7 (3.9)	182	0	180	0
48	175	6 (3.4)	172	4 (2.3)	175	0	175	0
52	87	2 (2.3)	87	2 (2.3)	87	0	87	0

†Number of subjects with baseline and on-treatment values
Data Source: Based on Sponsor's Table 13.4.2.21 Vol 94; page 434

Section 8.5.1.1.2 Results from the Pooled Solution Data

Liver Function Tests (SGOT, SGPT, GGT, LDH, Total Bilirubin). The mean SGOT level increased from 37.4 IU/L at baseline to 44.4 IU/L at 2 weeks, the first sampling time following initiation of buprenorphine treatment. The percent of clinically abnormal

SGOT values nearly doubled during this time period, from 2.3% at baseline to 4.5% at 2 weeks (Table below). Similarly, the mean SGPT level increased from 43.1 IU/L to 48.2 IU/L from baseline to the 2-week visit, and the percent of clinically abnormal SGPT values increased from 4.6% to 7.8% over this time. The pooled data suggest that the abnormalities in SGOT and SGPT appear to be not time-dependent. The results from the pooled data set is consistent with the findings from Study 1008, which found that, after the initial increase from the baseline values, there was no trend towards further SGOT or SGPT increase at later time points. Interpretation of these data for evidence of a time-dependent effect of buprenorphine on liver function tests must be done with caution, however, in light of the marked reduction in numbers of subjects that occurred over time.

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Table 79. Mean Values and the Proportion of Subjects by Study Visit with Liver Function Test Values Outside Normal Range[1] (N=576 Subjects in Studies CR99/099 and CR92/100)

Visit	SGOT (IU/L)				SGPT (IU/L)				GGT (IU/L)[2]	
	Mean (S.E.)	N	No. Abnormal	% Abnormal	Mean (S.E.)	N	No. Abnormal	% Abnormal	Mean (S.E.)	N
Baseline	37.4 (1.0)	706	16	2.27	43.1 (1.9)	702	32	4.56	59.8 (4.4)	576
Week 2	44.4 (1.9)	619	28	4.52	48.2 (2.4)	612	48	7.84	56.7 (4.1)	521
Week 4	44.7 (2.4)	519	29	5.59	49.4 (2.8)	517	43	8.32	54.4 (3.6)	501
Week 8	44.9 (1.8)	503	28	5.57	51.1 (2.5)	501	38	7.58	56.6 (4.2)	416
Week 12	45.3 (2.6)	421	21	4.99	51.9 (4.2)	424	27	6.37	59.3 (4.8)	378
Week 16	44.8 (2.0)	369	19	5.15	48.8 (2.7)	368	22	5.98	58.6 (4.5)	349
Week 24	52.1 (5.6)	110	6	5.45	66.6 (10.2)	111	13	11.71	70.0 (10.5)	112
Week 32	44.1 (3.8)	73	2	2.74	51.5 (6.1)	79	7	8.86	65.4 (9.3)	78
Week 40	43.0 (3.4)	131	5	3.82	51.2 (4.3)	133	13	9.77	65.8 (7.4)	130
Week 48	44.9 (4.8)	43	1	2.33	47.7 (5.9)	43	2	4.65	81.8 (18.5)	41
Week 52	40.0 (2.8)	123	5	4.07	44.7 (3.8)	125	8	6.40	74.5 (9.3)	117

Data Source: Based on Sponsor's 90 Vol 153;page 150
[1] Abnormal Values defined as values 3 times greater than the upper limit of normal
[2] GGT values available only from Studies CR92/099 and CR92/100

Table 80. Mean SGOT (IU/L)by Visit Categorized by Randomized Dose (N=706 Subjects in Pooled Studies CR88/130, CR92/099, CR92/100, and CR92/102)

Visit	Statistic	Buprenorphine Daily Dose					
		1 mg	4 mg	8 mg	8 mg q.o.d [1]	16 mg	All buprenorphine recipients
Baseline	N	141	149	229	43	144	706
	Mean	40.9	39.7	36.3	35.2	34.0	37.4
	S.E.	3.1	2.8	2.1	3.6	1.5	1.2
2 weeks	N	130	132	184	42	131	619
	Mean	43.0	42.1	44.5	47.6	46.8	44.4
	S.E.	3.2	2.9	3.6	8.8	5.5	1.9
4 weeks	N	117	128	137	3	134	519
	Mean	40.8	42.4	53.8	35.3	41.2	44.7
	S.E.	2.7	3.0	8.3	4.6	2.1	2.4
8 weeks	N	87	110	163	22	121	503
	Mean	43.8	45.5	45.1	54.1	43.2	44.9
	S.E.	3.1	4.9	3.1	12.2	2.8	1.8
16 weeks	N	67	87	114	N/A	101	369
	Mean	43.5	45.3	45.4		44.8	44.8
	S.E.	3.6	4.6	4.1		3.6	2.0
24 weeks	N	18	26	30	N/A	36	110
	Mean	55.9	68.7	42.5		46.3	52.1
	S.E.	15.3	19.0	5.5		5.3	5.6
32 weeks	N	16	18	15	N/A	24	73
	Mean	40.9	41.3	41.9		49.7	44.1
	S.E.	5.0	5.6	4.7		10.0	3.8
40 weeks	N	22	31	47	N/A	31	131
	Mean	45.4	44.3	38.0		47.6	43.0
	S.E.	5.9	6.1	4.1		10.8	3.4
48 weeks	N	3	12	12	N/A	16	43
	Mean	28.3	48.8	40.8		48.1	44.9
	S.E.	1.3	9.8	11.8		6.2	4.8
52 weeks	N	18	28	40	N/A	37	123
	Mean	39.8	49.4	34.0		39.4	40.0
	S.E.	6.9	7.3	3.1		5.6	2.8

Data Source: Based on Sponsor's 92 Vol 153;page 152; [1] 8 mg q.o.d. dose administered in Study CR92/102 only

Results from the table above did demonstrate a possible positive dose response for SGOT at Week 2. A similar trend to a positive dose response for SGPT, but not for GGT, with greater positive changes from baseline at higher buprenorphine doses was observed (results in the table).

Elevations of liver enzymes often are observed in opioid-dependent subjects, frequently due to viral hepatitis and concomitant alcohol abuse. Injection of drugs of unknown purity, often with dirty injection equipment, may contribute to these pre-existing conditions. To further examine effect of buprenorphine on liver function parameters, subjects with elevated liver function tests ≥ 8 times the upper limit of normal in solution studies (CR92/099 and CR92/100) are presented in table below.

Table 81. Subjects with Elevated Liver Function Tests (LFTs) ≥ 8 times the upper limit of normal in CR92/099 and CR92/100

Patient No.		Gender	Age	Bup Dose (mg/day)	Severity	Study Drug Relationship	Suspected Etiology (if known); Comments
055/067*		F	41	13.7[1] mg	Severe	No	Alcohol
056/020		M	31	8 mg	Severe	No	Hepatitis B
057/015		M	62	8 mg	Moderate	No	INH and rifampin
058/037*		M	45	16 mg	Moderate	No	Alcohol
059/033		M	43	4 mg	Moderate	No	Alcohol; baseline GGT elevated, withdrew at 20 days
059/073		M	33	8 mg	Moderate	No	Alcohol; LFTs increase at baseline
059/77		M	39	16 mg	Moderate	No	Alcohol; LFTs increase at baseline, wk 12
578/048		M	61	8 mg	Moderate	No	Possible alcohol
578/061		F	50	4 mg	Moderate	No	Alcohol
642/014		M	37	1 mg	Moderate	No	Alcohol; GGT increased at baseline and afterwards
642/015		M	25	16 mg	Severe	No	LFTs increased at wks 2-4; normalized hepatitis B
642/026*		M	51	13.7[1] mg	Moderate	No	INH; possible alcohol
662/051*		M	26	16 mg	Severe	No	Chronic hepatitis C
662/056*		M	40	5.7[1] mg	Moderate	No	Isolated LFTs increased at 22 wks
662/075*		M	47	4 mg	Severe	No	Isolated LFTs wks 8-16
672/012		F	37	8 mg	Severe	No	Alcohol; LFTs increased at 4 wks; lost to follow-up (56 days)
672/080		M	30	2 mg	Severe	No	Acute hepatitis B, LFTs normalized at 28 wks
750/028		M	22	8 mg	Moderate	No	History of LFTs, hepatitis B &C, LFTs increase at 2 wks, then normalized
750/041*		M	45	1.7[1] mg	Severe	No	Viral hepatitis; bup temporarily withheld
750/071		M	36	1 mg	Moderate	No	Chronic hepatitis C; LFTs normalized with interferon Rx
056/016		M	40	4 mg	Moderate	No / ?	Unknown; possible viral
056/067		F	29	1 mg	Severe	No / ?	Unknown
059/008		M	38	4 mg	Moderate	No / ?	Unknown
059/037		F	30	1 mg	Moderate	No / ?	Elevated LFTs at baseline
059/051		M	43	1 mg	Moderate	No / ?	Unknown; LFTs increase at baseline
578/063		M	46	8 mg	Moderate	No / ?	Elevated GGT at baseline and afterwards
630/020		M	41	16 mg	Moderate	No / ?	Elevated GGT at baseline and afterwards
059/018*		M	36	2.9[1] mg	Moderate	Possible	Isolated GGT increase at 24 wks
059/056*		M	36	13.7[1] mg	Severe	Possible	Isolated LFTs increase at 24 wks
578/062		M	46	1 mg	Severe	Possible	Elevated GGT; possible alcohol, terminated study (53 days)
630/061*		M	50	6.9[1] mg	Moderate	Possible	Isolated LFTs increase at 16 wks
630/074*		M	45	3.4[1] mg	Moderate	Possible	Isolated LFTs increase at 24 wks
750/025		M	29	4 mg	Moderate	Possible	Possible alcohol; history of hepatitis
750/027		M	42	4 mg	Moderate	Possible	Possible alcohol; LFTs normalized
750/067*		M	39	6.9[1] mg	Severe	Possible	Bup dose decreased: LFTs normalized

Data Source: Based on Sponsor's Table 60, vol 153; page 106

CR92/100 only; [1] Doses were not administered daily, ranged from 3x week to 6x week. Average daily dose = Dose x #days administered/ 7 days

Liver function test elevations ≥ 8 times the upper limit of normal were recorded in 35 subjects (30 men and 5 women) participating in these studies (N=731). No subjects were withdrawn from the studies because of elevated liver enzyme values alone. Only 1 subject (#056/003) treated with buprenorphine was withdrawn from the study because of

a serious adverse event related to liver function; the patient was found to have a positive hepatitis antigen upon hospital admission, and the event was considered to be unrelated to study drug. In 19 cases, the abnormality could be accurately ascribed to alcohol intake, hepatitis, or the use of prescribed drugs for a condition other than substance abuse. Eight of these events (occurring in 7 men and 1 woman) occurred at the baseline assessment prior to treatment with buprenorphine, but their baseline elevations were less than ≤ 3 times the upper limit of normal. It cannot be ruled out that buprenorphine exacerbates hepatic dysfunction and disease. In the remaining 8 cases (23%=8/35), no identifiable cause could be determined, and buprenorphine is very likely to be a contributing factor.

Similarly, 10 subjects with increased liver function tests (LFTs ≥ 8 times) were reported in Study CR96/014. Again, buprenorphine is very likely to be a contributing factor to 2-3 cases (20-30%).

Subjects with Elevated Liver Function Tests (LFTs) ≥ 8 times the upper limit of normal in CR96/014

Patient No.	Gender	Age	Suboxone Dose (mg/day)	Study Drug Relationship	Suspected Etiology (if known); Comments
546-2021	M	46	16 mg	No	Hepatitis B
546-2030	M	45	12 mg	No	Alcohol Hepatitis
662-2039	M	27	20 mg	No	Hepatitis C
662-2051	M	47	12 mg	No	Hepatitis B & C
672-2066	M	35	16 mg	No	Hepatitis C
689-1018	M	42	12 mg	No	Hepatitis B
750-1040	M	38	20 mg	No	Hepatitis C
750-1063	M	43	20 mg	Possible	Exacerbation of Hepatitis B
750-1054	M	35	20 mg	Possible	Elevated LFTs at Week 48
630-1031	F	46	16 mg	Possible	Elevated ALT at Week 12

Conclusions on effects of buprenorphine on liver function

1. There is consistent evidence that buprenorphine is associated with elevations of liver function tests especially in SGOT and SGPT. The impairment of liver function may occur up to 6% of subjects who receive Suboxone for more than 6-month (data source: Sponsor's Table 13.4.2.2, vol 93;p280). The elevations are most likely to happen within 2-4 week of treatment, and it appears to be a dose-related effect during this period. Buprenorphine may exacerbate hepatic dysfunction and disease. However, longer treatment with buprenorphine does not appear to increase the frequency of abnormal liver function tests.

Other Clinical Chemistry Tests:

There were no treatment emergent, clinically significant changes in mean kidney function and electrolyte parameters. For example, mean kidney function test values were within normal range at baseline (BUN 12.4 mg/dL; creatinine 0.88 mg/dL), and there were no consistent upward or downward trends in mean change in values over the 52-week study