Figure 1: Paper form

Bowel Function Index (BFI3)

Please answer the following three questions by making a mark on the line between 0 and 100. Please transfer the results to the free squares on the bottom of the page. Add the three results and divide through three.

Question 1 (Q1):
How would you rate the ease of defecation during the last 7 days according to patient assessment?
(0= easy/no difficulty, 100= severe difficulty)

|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
0 50 100

Question 2 (Q2):
Does your patient feel that her/his bowel evacuation has been incomplete during the last 7 days? (0= not at all, 100= very strongly)

|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
0 50 100

Question 3 (Q3):
How would you judge your patients constipation throughout the last 7 days?
(0= no constipation at all, 100= very heavily constipated)

|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
0 50 100

	+			/3 =	
Q1		**Q2**	**Q3**		

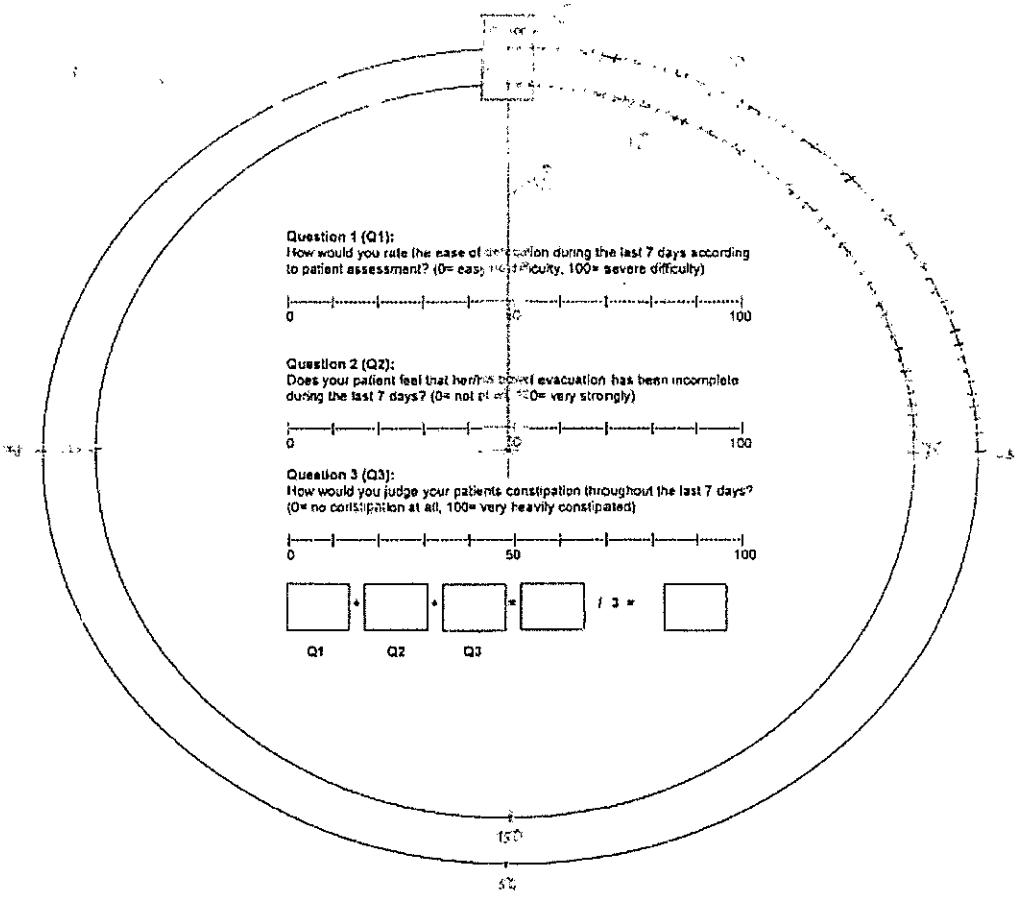

Question 1 (Q1):
How would you rate the ease of defecation during the last 7 days according to patient assessment? (0= easy, 100= severe difficulty)
0
50
100
Question 2 (Q2):
Does your patient feel that her/his bowel evacuation has been incomplete during the last 7 days? (0= not at all, 100= very strongly)
0
50
100
Question 3 (Q3):
How would you judge your patients constipation throughout the last 7 days? (0= no constipation at all, 100= very heavily constipated)
0
50
100
+
+
=
/ 3 =
Q1
Q2
Q3

Figure 2

Figure 3: Patient Demographics and Other Baseline Characteristics by Absolute Dose of Naloxone

	Absolute Dose of Naloxone				
Characteristic	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=51 (100%)	Naloxone 20 mg N=51 (100%)	Naloxone 40 mg N=50 (100%)	Total N=202 (100%)
Sex n (%)					
Male	19 (38.0)	8 (35.3)	17 (33.3)	21 (42.0)	75 (37.1)
Female	31 (62.0)	33 (64.7)	34 (66.7)	29 (58.0)	127 (62.9)
Age [years]					
Mean	53.8	58.4	56.0	57.0	56.3
SD	12.74	12.75	12.65	14.03	13.06
Median	53.0	57.0	56.0	57.5	55.0
Min-Max	29 – 84	28 – 86	33 – 80	27 – 78	27 – 86
Race n (%)					
Caucasian	50 (100.0)	51 (100.0)	51 (100.0)	50 (100.0)	202 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)					
Mean	75.88	77.65	81.76	80.14	78.87
SD	13.43	14.47	13.92	18.11	15.14
Median	75.0	80.0	81.0	81.0	80.0
Min-Max	46 – 107	47 – 105	56 – 115	45 – 110	45 – 115
Height (cm)					
Mean	168.7	169.6	169.4	169.0	169.2
SD	8.29	8.00	7.97	9.12	8.30
Median	168.0	168.0	170.0	168.5	169.0
Min-Max	155 – 190	154 – 191	155 – 185	147 – 189	147 – 191
BMI (kg/m^2)					
Mean	26.70	27.03	28.65	27.93	27.58
SD	4.58	5.11	5.50	5.57	5.22
Median	26.03	25.83	27.78	28.09	26.61
Min-Max	17.1 – 40.3	17.3 – 37.2	18.9 – 42.6	16.8 – 39.8	16.8 – 42.6
Tumor patient n (%)					
Yes	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	5 (2.5)
No	49 (98.0)	50 (98.0)	50 (98.0)	48 (96.0)	197 (97.5)

Figure 4: Patient Demographics and Other Baseline Characteristics by Oxycodone/Naloxone Dose Ratio

	Dose Ratios									
	40 mg/ Placebo	**60 mg/ Placebo**	**80 mg/ Placebo**	**1/1**	**1.5/1**	**2/1**	**3/1**	**4/1**	**6/1**	**8/1**
Characteristic	**N=17 (100%)**	**N=17 (100%)**	**N=16 (100%)**	**N=15 (100%)**	**N=18 (100%)**	**N=34 (100%)**	**N=18 (100%)**	**N=33 (100%)**	**N=12 (100%)**	**N=22 (100%)**
Sex n (%)										
Male	6 (35.3)	6 (35.3)	7 (43.8)	5 (33.3)	8 (44.4)	11 (32.4)	8 (44.4)	10 (30.3)	4 (33.3)	10 (45.5)
Female	11 (64.7)	11 (64.7)	9 (56.3)	10 (66.7)	10 (55.6)	23 (67.6)	10 (55.6)	23 (69.7)	8 (66.7)	12 (54.5)
Age [years]										
Mean	51.8	52.8	56.9	59.9	55.9	56.1	58.3	57.6	57.6	55.9
SD	13.66	12.23	12.51	13.16	12.84	13.89	13.01	14.12	11.74	12.55
Median	52.0	53.0	56.5	61.0	55.5	60.0	60.5	52.0	61.0	55.0
Min-Max	37 – 84	29 – 75	31 – 80	34 – 78	35 – 72	27 – 76	39 – 80	35 – 86	34 – 73	28 - 77
Race n (%)										
Caucasian	17 (100.0)	17 (100.0)	16 (100.0)	15 (100.0)	18(100.0)	34 (100.0)	18 (100.0)	33 (100.0)	12 (100.0)	22 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)										
Mean	78.24	71.82	77.69	79.27	83.50	79.24	85.06	77.79	72.75	80.91
SD	11.00	15.33	13.45	17.71	20.36	15.78	11.93	14.34	14.23	14.26
Median	80.0	70.0	75.0	78.0	85.5	80.5	82.5	78.0	69.0	82.0
Min-Max	60 – 98	46 – 107	57 – 105	53 – 110	45 – 110	50 – 115	66 – 110	47 – 108	50 – 98	56 - 105
Height (cm)										
Mean	168.6	164.8	172.8	165.9	169.4	170.1	169.4	167.6	170.2	172.7
SD	6.56	6.52	9.87	8.62	8.87	7.80	9.19	7.98	9.29	7.22
Median	169.0	164.0	173.0	165.0	169.5	169.5	170.0	165.0	168.0	172.0
Min-Max	158 – 178	155 – 176	158 – 190	147 – 178	148 – 182	158 – 189	155 – 182	154 – 185	155 – 186	160- 191
BMI (kg/m^2)										
Mean	27.51	26.51	26.04	28.74	28.88	27.38	29.97	27.78	25.06	27.13
SD	3.64	5.77	4.18	5.94	5.96	5.19	5.83	5.41	4.36	4.73
Median	26.79	25.65	25.02	28.09	30.47	26.70	28.56	26.64	24.32	26.43
Min-Max	22.6–34.7	17.1–40.3	18.8–34.6	21.2–39.8	16.8–38.6	17.0–38.9	21.7–42.6	17.3–38.3	19.9–36.4	19.5–37.2
Tumor patient n (%)										
Yes	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.9)	1 (5.6)	1 (3.0)	0 (0.0)	0 (0.0)
No	16 (94.1)	17 (100.0)	16 (100.0)	15 (100.0)	17 (94.4)	33 (97.1)	17 (94.4)	32 (97.0)	12 (100.0)	22(100.0)

Figure 5

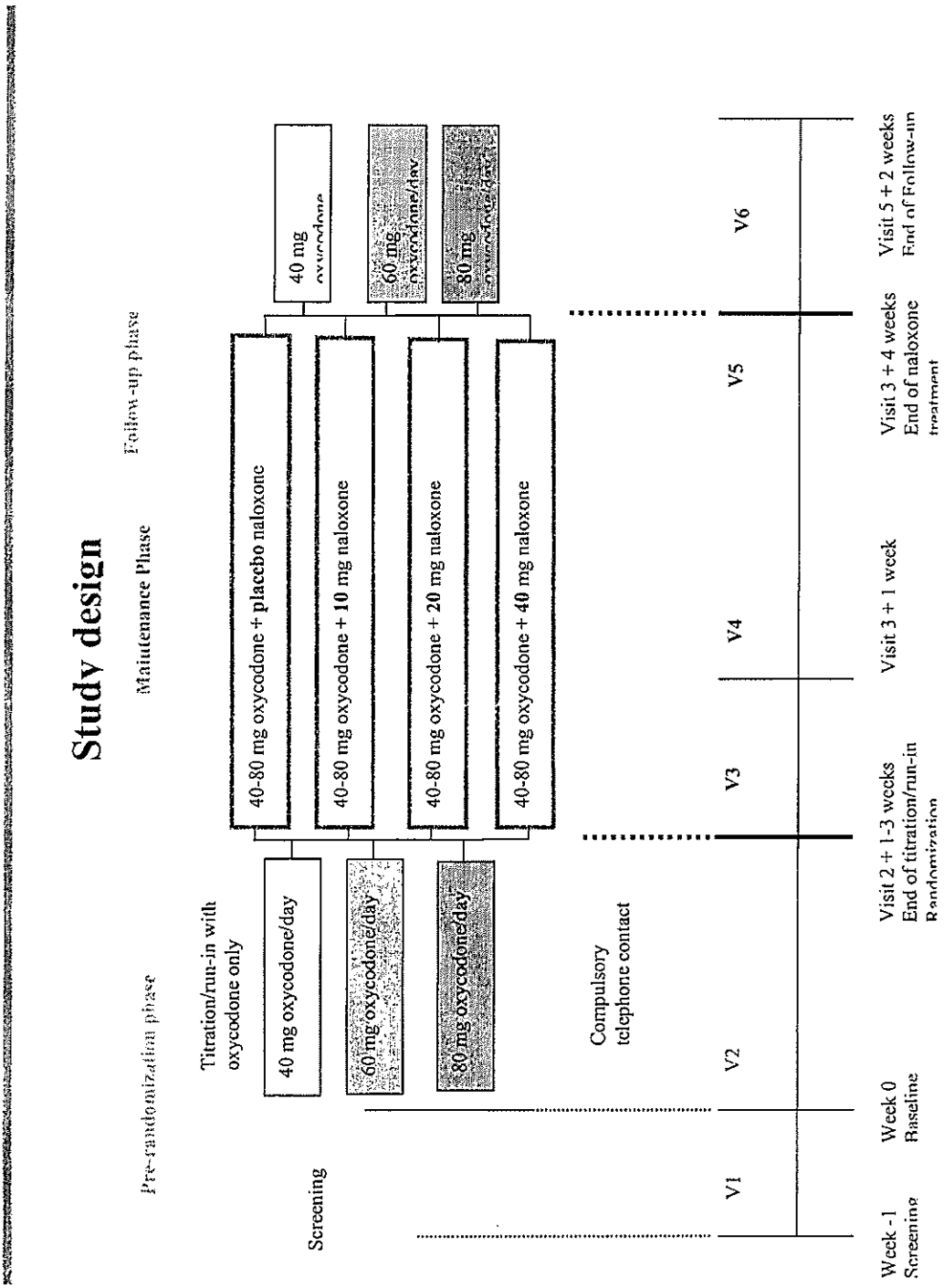

Study design
Pre-randomization phase
Maintenance Phase
Follow-up phase
Screening
Titration/run-in with oxycodone only
40 mg oxycodone/day
60 mg oxycodone/day
80 mg oxycodone/day
40-80 mg oxycodone + placebo naloxone
40-80 mg oxycodone + 10 mg naloxone
40-80 mg oxycodone + 20 mg naloxone
40-80 mg oxycodone + 40 mg naloxone
40 mg
60 mg
80 mg
Compulsory telephone contact
V1
V2
V3
V4
V5
V6
Week -1 Screening
Week 0 Baseline
Visit 2 + 1-3 weeks End of titration/run-in Randomization
Visit 3 + 1 week
Visit 3 + 4 weeks End of naloxone treatment
Visit 5 + 2 weeks End of Follow-up

Figure 6:

Mean Bowel Function at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Average Bowel Function	**40 mg/ Placebo** N=17 (100%)	**60 mg/ Placebo** N=17 (100%)	**80 mg/ Placebo** N=16 (100%)	**1/1** N=15 (100%)	**1.5/1** N=15 (100%)	**2/1** N=32 (100%)	**3/1** N=17 (100%)	**4/1** N=32 (100%)	**6/1** N=11 (100%)	**8/1** N=22 (100%)
Visit 2 (Baseline)										
N	17	17	16	15	17	32	17	32	11	22
Mean	52.2	48.7	59.3	44.7	49.7	51.6	56.2	53.4	56.7	60.3
SD	21.66	28.79	17.93	15.42	18.20	21.54	19.20	22.57	19.94	18.51
Median	53.3	50.0	61.7	40.0	50.0	51.7	53.3	50.8	50.0	66.7
Min-Max	0-83	0-93	29-83	23-77	20-83	0-87	30-93	3-100	30-100	17-87
Visit 3 (Randomization)										
N	17	17	16	15	17	32	17	32	11	22
Mean	44.9	43.0	56.5	41.6	47.9	47.4	41.4	51.4	55.5	59.7
SD	25.77	26.35	17.70	20.03	21.90	20.19	21.28	23.36	23.86	22.16
Median	43.3	36.7	51.7	40.0	46.7	50.0	40.0	56.7	46.7	65.0
Min-Max	0-100	3-87	30-83	17-90	0-87	0-87	0-80	10-100	20-100	17-100
Visit 4 (Maintenance)										
N	15	17	16	15	14	28	16	31	11	21
Mean	41.4	48.3	39.6	20.7	22.3	35.4	25.2	41.6	44.8	45.7
SD	21.83	31.24	25.56	19.24	16.97	25.19	32.79	26.51	27.66	26.86
Median	43.3	50.0	45.0	20.0	20.0	33.3	11.7	40.0	43.3	40.0
Min-Max	0-87	0-93	0-73	0-53	0-53	0-77	0-100	0-100	0-80	0-100
Visit 5 (End of Maintenance)										
N	13	17	15	14	14	27	12	27	10	19
Mean	44.6	43.6	48.2	21.9	21.8	26.7	34.7	39.0	47.8	38.6
SD	22.42	23.75	21.71	22.25	21.35	23.98	26.99	26.24	23.20	24.68
Median	43.3	40.0	53.3	20.0	16.7	23.3	31.7	33.3	51.7	33.3
Min-Max	13-100	0-90	0-80	0-70	0-67	0-90	0-80	0-85	10-70	0-92
Visit 6 (End of Follow-up)										
N	13	17	15	14	13	26	12	28	10	18
Mean	52.1	47.4	48.2	33.2	47.3	42.6	43.9	51.0	49.3	42.9
SD	26.79	24.25	25.82	20.76	24.32	24.37	27.99	24.16	23.92	26.41
Median	50.0	50.0	50.0	35.0	46.7	43.3	41.7	50.0	50.0	45.0
Min-Max	7-100	0-90	0-90	0-80	0-80	0-80	0-90	0-100	10-80	0-80

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 7:

Mean Bowel Function at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Average Bowel Function	**Naloxone Placebo** N=50 (100%)	**Naloxone 10 mg** N=49 (100%)	**Naloxone 20 mg** N=49 (100%)	**Naloxone 40 mg** N=48 (100%)
Visit 2 (Baseline)				
N	50	49	49	48
Mean	53.3	55.8	56.1	47.9
SD	23.28	19.81	20.19	19.65
Median	53.3	53.3	50.0	49.2
Min-Max	0-93	7-100	3-100	0-83
Visit 3 (Randomization)				
N	50	49	49	48
Mean	48.0	52.8	49.4	46.2
SD	23.97	22.86	22.72	20.67
Median	48.3	50.0	50.0	46.7
Min-Max	0-100	10-100	0-100	0-90
Visit 4 (Maintenance)				
N	48	47	47	42
Mean	43.3	42.1	34.2	27.9
SD	26.41	25.53	30.04	22.68
Median	46.7	40.0	30.0	28.3
Min-Max	0-93	0-100	0-100	0-73
Visit 5 (End of Maintenance)				
N	45	41	42	40
Mean	45.4	40.3	31.3	26.1
SD	22.28	23.09	25.82	25.08
Median	43.3	36.7	25.0	20.0
Min-Max	0-100	0-92	0-85	0-90
Visit 6 (End of Follow-up)				
N	45	41	41	39
Mean	49.0	45.1	46.4	42.4
SD	25.01	23.72	26.98	23.19
Median	50.0	50.0	43.3	40.0
Min-Max	0-100	0-80	0-100	0-80

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 8:

Mean Bowel Function at Each Study Visit by Absolute Dose of Naloxone Given the Same Oxycodone/ Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose ratio			
Average Bowel Function	**4/1 10 mg naloxone** N=16 (100%)	**4/1 20 mg naloxone** N=16 (100%)	**2/1 20 mg naloxone** N=16 (100%)	**2/1 40 mg naloxone** N=16 (100%)
Visit 2 (Baseline)				
N	16	16	16	16
Mean	49.0	57.9	54.2	49.0
SD	20.76	24.06	18.04	24.88
Median	50.8	55.0	48.3	56.7
Min-Max	7-80	3-100	33-87	0-77
Visit 3 (Randomization)				
N	16	16	16	16
Mean	41.6	61.3	46.0	48.8
SD	19.90	22.73	20.44	20.51
Median	41.7	63.3	45.0	51.7
Min-Max	10-77	10-100	8-87	0-73
Visit 4 (Maintenance)				
N	15	16	15	13
Mean	35.0	47.8	29.3	42.3
SD	22.01	29.47	23.50	26.19
Median	40.0	43.3	30.0	46.7
Min-Max	0-72	0-100	0-77	0-73
Visit 5 (End of Maintenance)				
N	12	15	15	12
Mean	36.7	40.8	19.2	36.1
SD	20.74	30.54	13.58	30.84
Median	35.0	33.3	20.0	33.3
Min-Max	3-73	0-85	0-50	0-90
Visit 6 (End of Follow-up)				
N	13	15	14	12
Mean	45.0	56.2	38.1	47.8
SD	20.86	26.27	25.34	23.15
Median	50.0	50.0	36.7	55.0
Min-Max	0-70	23-100	0-80	0-77

Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

Figure 9:

Mean Bowel Function: Test for Difference Versus Placebo - ITT Population with Non-missing Values

	Absolute Dose of Naloxone		
Category	Naloxone 10 mg vs Placebo	Naloxone 20 mg vs Placebo	Naloxone 40 mg vs Placebo
Mean bowel function assessing the last 7 days at Visit 4			
N in test group	47	47	42
N in placebo group	48	48	48
Difference in means*	-1.2	-9.0	-15.4
95% CI	(-11.8, 9.4)	(-20.6, 2.5)	(-25.8, -5.0)
P-value**	0.827	0.122	0.004
Mean bowel function assessing the last 7 days at Visit 5 (end of maintenance)			
N in test group	41	42	40
N in placebo group	45	45	45
Difference in means*	-5.1	-14.1	-19.3
95% CI	(-14.9, 4.6)	(-24.4, -3.8)	(-29.5, -9.1)
P-value**	0.296	0.008	<0.001

*Mean in test group minus mean in placebo group; **t-test for difference

Figure 10:

Mean Bowel Function: Response Surface Plot - ITT Population with Non-missing Values

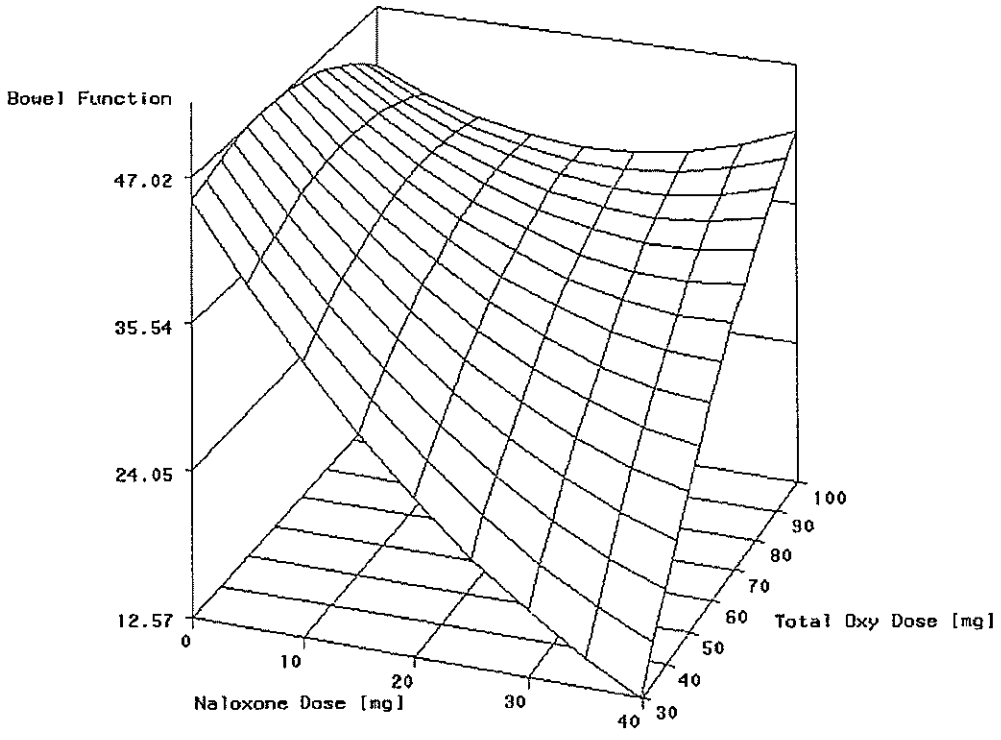


Figure 11:

Mean Bowel Function: Contour Plot with Granulation 10 - ITT Population with Non-missing Values

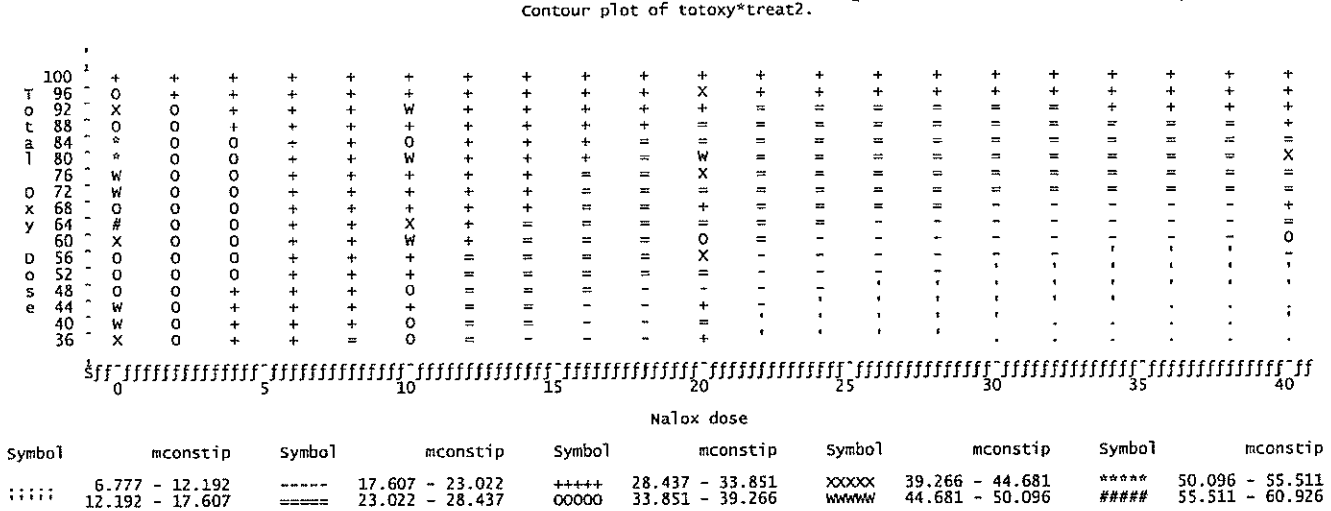


Fig. 12 Global Assessment by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Efficacy (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	2 (11.8)	2 (12.5)	2 (13.3)	3 (17.6)	4 (12.5)	2 (11.8)	5 (15.6)	0 (0.0)	2 (9.1)
Good	8 (47.1)	5 (29.4)	3 (18.8)	9 (60.0)	6 (35.3)	15 (46.9)	8 (47.1)	13 (40.6)	4 (36.4)	7 (31.8)
Fairly good	1 (5.9)	3 (17.6)	3 (18.8)	2 (13.3)	1 (5.9)	5 (15.6)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Moderate	1 (5.9)	2 (11.8)	3 (18.8)	1 (6.7)	2 (11.8)	1 (3.1)	1 (5.9)	3 (9.4)	5 (45.5)	4(18.2)
Slightly poor	1 (5.9)	3 (17.6)	1 (6.3)	0 (0.0)	1 (5.9)	1(3.1)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	2 (12.5)	0 (0.0)	0 (0.0)	1 (3.1)	1(5.9)	5 (15.6)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	1 (5.9)	1 (6.3)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Efficacy (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	1 (5.9)	2 (12.5)	2 (13.3)	4 (23.5)	6 (18.8)	2 (11.8)	3 (9.4)	0 (0.0)	1 (4.5)
Good	7 (41.2)	7 (41.2)	2 (12.5)	8 (53.3)	7 (41.2)	13 (40.6)	9 (52.9)	14 (43.8)	3 (27.3)	7 (31.8)
Fairly good	1 (5.9)	2 (11.8)	3 (18.8)	3 (20.0)	0 (0.0)	3 (9.4)	0 (0.0)	4 (12.5)	2 (18.2)	1 (4.5)
Moderate	3 (17.6)	2 (11.8)	4 (25.0)	1 (6.7)	2 (11.8)	3 (9.4)	1 (5.9)	2 (6.3)	4 (36.4)	5 (22.7)
Slightly poor	0 (0.0)	3 (17.6)	1 (6.3)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Poor	1 (5.9)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	4 (12.5)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	2 (11.8)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	5 (29.4)	2 (12.5)	3 (20.0)	4 (23.5)	9 (28.1)	4 (23.5)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	6 (35.3)	11 (68.8)	10 (66.7)	7 (41.2)	13 (40.6)	7 (41.2)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	1 (5.9)	2 (12.5)	1 (6.7)	2 (11.8)	5 (15.6)	1 (5.9)	4 (12.5)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	4 (23.5)	2 (12.5)	2 (13.3)	3 (17.6)	7 (21.9)	3 (17.6)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	7 (41.2)	9 (56.3)	10 (66.7)	8 (47.1)	15 (46.9)	8 (47.1)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	2 (11.8)	2 (12.5)	2 (13.3)	1 (5.9)	3 (9.4)	1 (5.9)	3 (9.4)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	2 (12.5)	0 (0.0)	2 (11.8)	2 (6.3)	0 (0.0)	2 (6.3)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)

Fig. 12 continued

Global Assessment by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
Assessment at end of maintenance phase (n, (%))	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Preference regarding efficacy (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	6 (37.5)	2 (13.3)	5 (29.4)	4 (12.5)	5 (29.4)	10 (31.3)	1 (9.1)	8 (36.4)
Maintenance phase	5 (29.4)	5 (29.4)	4 (25.0)	10 (66.7)	7 (41.2)	13 (40.6)	5 (29.4)	12 (37.5)	4 (36.4)	7 (31.8)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	2 (13.3)	2 (11.8)	10 (31.3)	2 (11.8)	7 (21.9)	5 (45.5)	4 (18.2)
Preference regarding efficacy (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	8 (47.1)	5 (31.3)	1 (6.7)	5 (29.4)	4 (12.5)	5 (29.4)	9 (28.1)	1 (9.1)	9 (40.9)
Maintenance phase	6 (35.3)	5 (29.4)	5 (31.3)	10 (66.7)	7 (41.2)	14 (43.8)	6 (35.3)	13 (40.6)	4 (36.4)	7 (31.8)
No preference	4 (23.5)	4 (23.5)	5 (31.3)	3 (20.0)	2 (11.8)	9 (28.1)	1 (5.9)	7 (21.9)	5 (45.5)	3 (13.6)
Preference regarding tolerability (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	4 (25.0)	0 (0.0)	5 (29.4)	4 (12.5)	2 (11.8)	9 (28.1)	1 (9.1)	5 (22.7)
Maintenance phase	5 (29.4)	5 (29.4)	6 (37.5)	12 (80.0)	7 (41.2)	15 (46.9)	8 (47.1)	13 (40.6)	5 (45.5)	10 (45.5)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	2 (13.3)	2 (11.8)	8 (25.0)	2 (11.8)	7 (21.9)	4 (36.4)	4 (18.2)
Preference regarding tolerability (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Titration phase	4 (23.5)	7 (41.2)	4 (25.0)	0 (0.0)	5 (29.4)	4 (12.5)	2 (11.8)	8 (25.0)	1 (9.1)	5 (22.7)
Maintenance phase	5 (29.4)	5 (29.4)	6 (37.5)	11 (73.3)	7 (41.2)	15 (46.9)	9 (52.9)	15 (46.9)	5 (45.5)	10 (45.5)
No preference	5 (29.4)	5 (29.4)	5 (31.3)	3 (20.0)	2 (11.8)	8 (25.0)	1 (5.9)	6 (18.8)	4 (36.4)	4 (18.2)

Fig. 13 Global Assessment by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Efficacy (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	6 (12.0)	5 (10.2)	6 (12.2)	7 (14.6)
Good	16 (32.0)	18 (36.7)	23 (46.9)	21 (43.8)
Fairly good	7 (14.0)	6 (12.2)	3 (6.1)	5 (10.4)
Moderate	6 (12.0)	10 (20.4)	4 (8.2)	3 (6.3)
Slightly poor	5 (10.0)	1 (2.0)	1 (2.0)	2 (4.2)
Poor	3 (6.0)	2 (4.1)	6 (12.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Efficacy (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	4 (8.0)	3 (6.1)	5 (10.2)	10 (20.8)
Good	16 (32.0)	18 (36.7)	24 (49.0)	19 (39.6)
Fairly good	6 (12.0)	5 (10.2)	4 (8.2)	4 (8.3)
Moderate	9 (18.0)	10 (20.4)	4 (8.2)	4 (8.3)
Slightly poor	4 (8.0)	4 (8.2)	2 (4.1)	1 (2.1)
Poor	4 (8.0)	2 (4.1)	4 (8.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Tolerability (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	9 (18.0)	8 (16.3)	13 (26.5)	10 (20.8)
Good	27 (54.0)	27 (55.1)	21 (42.9)	24 (50.0)
Fairly good	4 (8.0)	5 (10.2)	6 (12.2)	5 (10.4)
Moderate	2 (4.0)	1 (2.0)	1 (2.0)	1 (2.1)
Slightly poor	3 (6.0)	1 (2.0)	0 (0.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	2 (4.1)	0 (0.0)
very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	7 (14.0)	9 (18.4)	9 (18.4)	8 (16.7)
Good	26 (52.0)	26 (53.1)	25 (51.0)	25 (52.1)
Fairly good	5 (10.0)	5 (10.2)	3 (6.1)	5 (10.4)
Moderate	4 (8.0)	1 (2.0)	4 (8.2)	2 (4.2)
Slightly poor	2 (4.0)	1 (2.0)	1 (2.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
very poor	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)

Fig. 13 continued

Global Assessment by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Assessment at end of maintenance phase (n, (%))	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Preference regarding efficacy (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	17 (34.0)	11 (22.4)	15 (30.6)	9 (18.8)
Maintenance phase	14 (28.0)	19 (38.8)	16 (32.7)	23 (47.9)
No preference	15 (30.0)	12 (24.5)	12 (24.5)	8 (16.7)
Preference regarding efficacy (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	17 (34.0)	12 (24.5)	14 (28.6)	8 (16.7)
Maintenance phase	16 (32.0)	19 (38.8)	19 (38.8)	23 (47.9)
No preference	13 (26.0)	11 (22.4)	10 (20.4)	9 (18.8)
Preference regarding tolerability (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	15 (30.0)	8 (16.3)	10 (20.4)	8 (16.7)
Maintenance phase	16 (32.0)	22 (44.9)	24 (49.0)	24 (50.0)
No preference	15 (30.0)	12 (24.5)	9 (18.4)	8 (16.7)
Preference regarding tolerability (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Titration phase	15 (30.0)	8 (16.3)	9 (18.4)	8 (16.7)
Maintenance phase	16 (32.0)	23 (46.9)	26 (53.1)	23 (47.9)
No preference	15 (30.0)	11 (22.4)	8 (16.3)	9 (18.8)

Figure 14

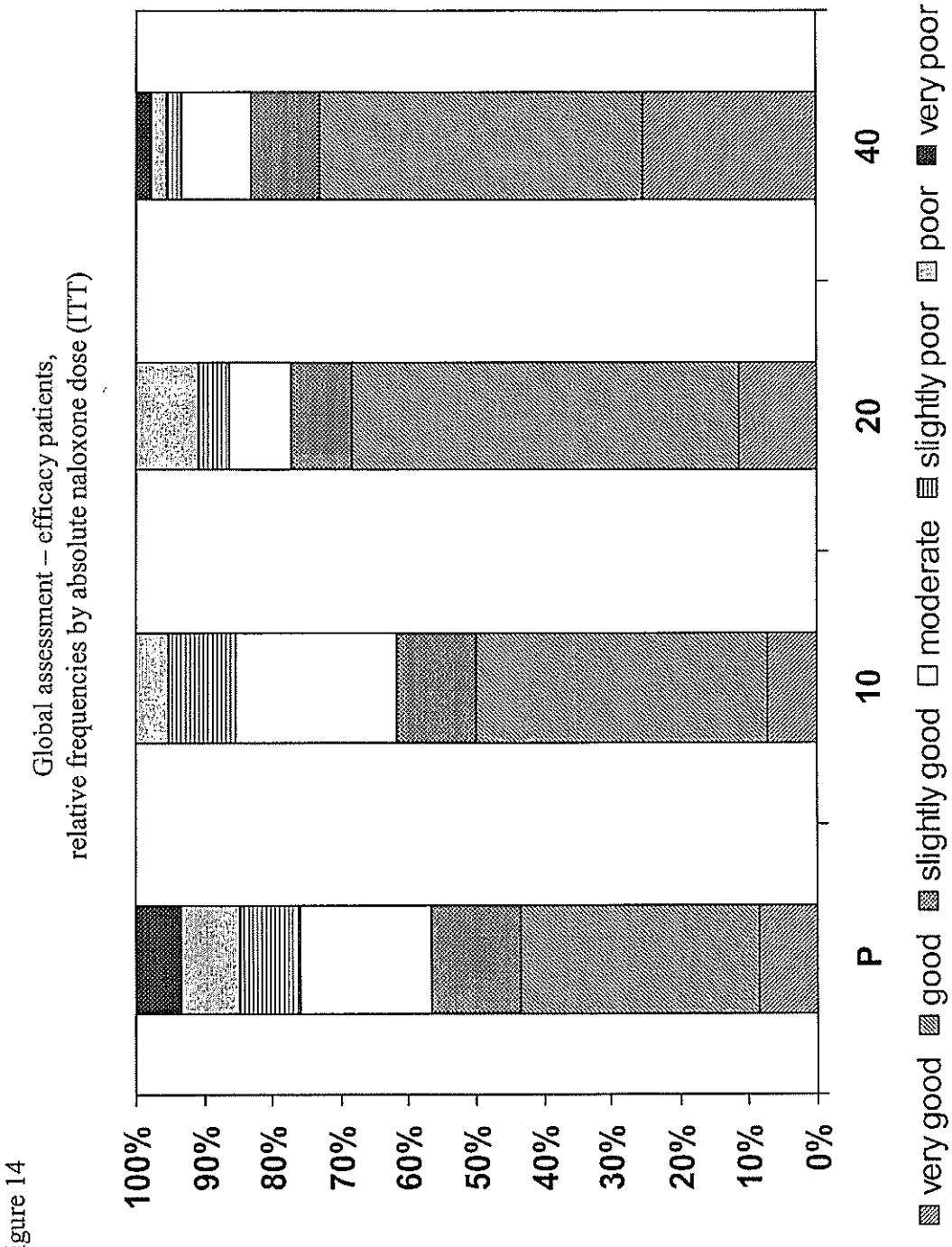

Global assessment – efficacy patients,
relative frequencies by absolute naloxone dose (ITT)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
P
10
20
40
very good
good
slightly good
moderate
slightly poor
poor
very poor

Figure 15

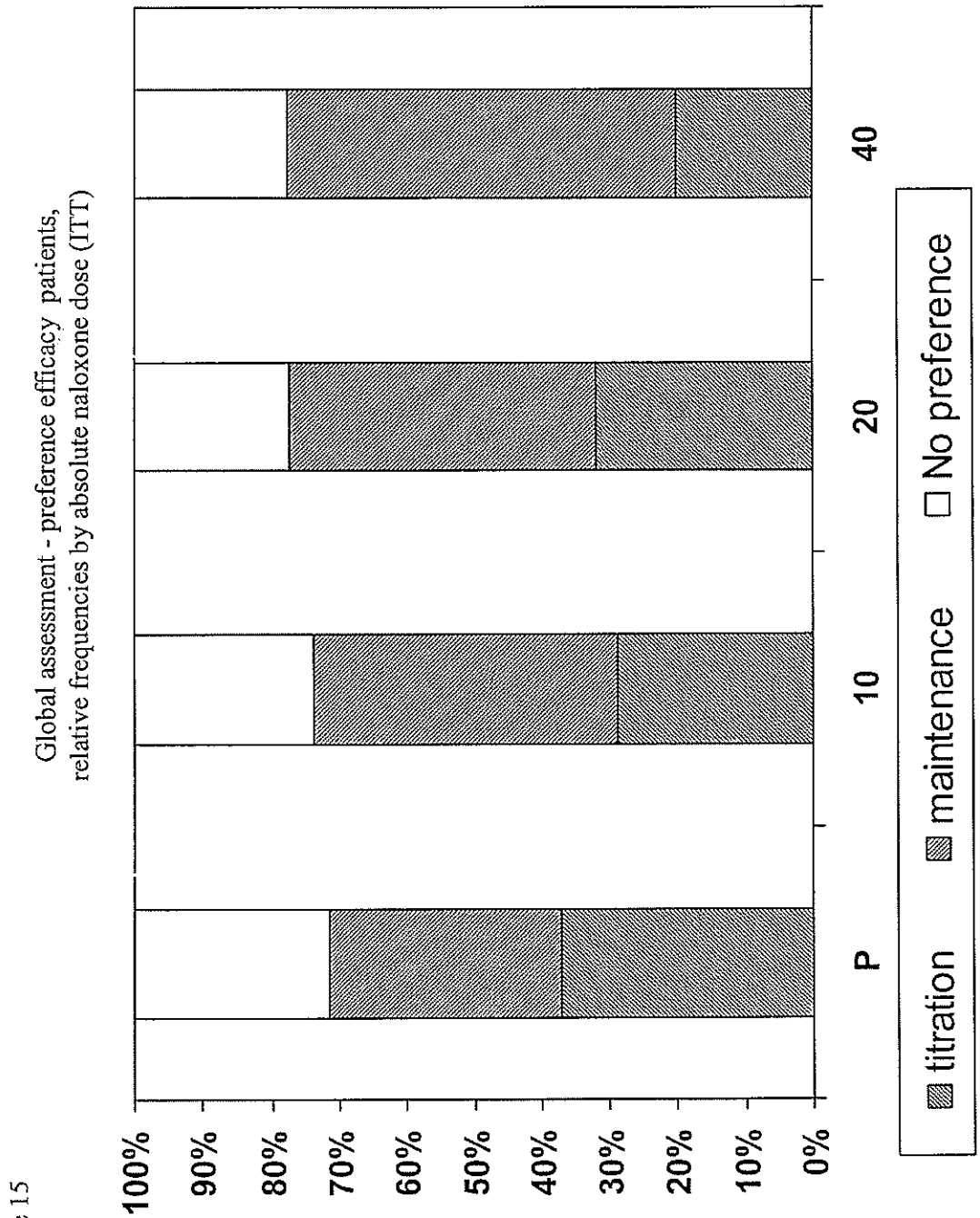

Global assessment - preference efficacy patients,
relative frequencies by absolute naloxone dose (ITT)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
P
10
20
40
titration
maintenance
No preference

Fig. 16 Laxative Intake at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing

	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
Number of days with Laxative Intake	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Visit 3 (Randomization)*										
N ($n^{\dagger}$)	17 (15)	15 (16)	14 (14)	12 (14)	16 (16)	31 (31)	16 (15)	29 (30)	8 (11)	20 (19)
Mean	4.5	4.8	4.6	5.3	5.0	5.2	4.7	4.8	6.3	4.1
SD	3.12	2.54	2.79	2.99	2.88	2.68	2.85	3.10	1.75	3.21
Median	6.0	6.0	6.0	7.0	7.0	7.0	6.0	7.0	7.0	5.5
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	2-7	0-7
Visit 4 (Maintenance)*										
N ($n^{\dagger}$)	15 (8)	16 (13)	15 (10)	15 (9)	14 (6)	26 (16)	16 (4)	31 (21)	9 (9)	20 (12)
Mean	1.8	2.3	2.3	2.3	1.3	1.9	1.0	2.6	3.2	1.3
SD	2.76	2.46	2.79	2.71	2.05	2.58	2.07	2.74	2.39	1.89
Median	0.0	1.0	1.0	1.0	0.0	0.0	0.0	2.0	4.0	0.5
Min-Max	0-7	0-6	0-7	0-7	0-6	0-7	0-6	0-7	0-6	0-6
Visit 5 (End of Maintenance)*										
N ($n^{\dagger}$)	14 (10)	15 (13)	14 (12)	12 (8)	13 (5)	26 (13)	10 (4)	26 (17)	7 (8)	19 (10)
Mean	3.9	3.8	4.1	1.8	1.2	1.9	1.0	3.3	3.1	1.7
SD	3.30	3.55	3.52	3.17	2.61	3.15	2.31	3.53	3.63	2.94
Median	5.0	7.0	7.0	0.0	0.0	0.0	0.0	0.5	1.0	0.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Visit 6 (End of Follow-up)*										
N ($n^{\dagger}$)	13 (10)	15 (14)	14 (13)	12 (11)	11 (11)	24 (21)	11 (8)	24 (19)	6 (8)	13 (14)
Mean	3.8	4.0	4.5	2.8	3.4	4.0	2.3	4.1	3.5	3.9
SD	3.63	3.09	3.35	3.38	3.50	3.36	3.10	3.53	3.83	3.50
Median	7.0	5.0	7.0	0.5	1.0	7.0	1.0	7.0	3.5	7.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Entire Maintenance Phase**										
N ($n^{\dagger}$)	15 (12)	16 (15)	16 (14)	15 (10)	15 (9)	26 (24)	16 (9)	32 (25)	9 (9)	21 (17)
Mean	42.9	44.8	51.2	33.4	21.7	31.1	20.4	43.8	44.2	25.1
SD	44.60	43.84	42.37	42.87	39.71	41.47	39.80	42.57	43.13	33.54
Median	25.0	31.3	60.7	15.8	0.0	7.0	0.0	24.6	39.3	7.7
Min-Max	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100

*Number of days with laxation intake during the last 7 days according to patient diary; **Percentage of days with laxation intake during the maintenance phase according to patient diary $n^{\dagger}$ Number of patients taking laxatives

Fig. 17 Laxative Intake at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Number of days with Laxative Intake	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	46 (45)	44 (44)	45 (47)	43 (45)
Mean	4.6	4.7	4.8	5.3
SD	2.78	2.99	2.91	2.73
Median	6.0	7.0	7.0	7.0
Min-Max	0-7	0-7	0-7	0-7
Visit 4 (Maintenance)*				
N (n†)	46 (31)	44 (31)	47 (24)	40 (22)
Mean	2.1	2.2	1.8	1.8
SD	2.62	2.46	2.52	2.42
Median	1.0	1.0	0.0	0.0
Min-Max	0-7	0-7	0-7	0-7
Visit 5 (End of Maintenance)*				
N (n†)	43 (35)	37 (26)	40 (18)	36 (21)
Mean	3.9	2.6	2.0	1.6
SD	3.38	3.34	3.14	2.93
Median	7.0	0.0	0.0	0.0
Min-Max	0-7	0-7	0-7	0-7
Visit 6 (End of Follow-up)*				
N (n†)	42 (37)	32 (29)	36 (31)	33 (32)
Mean	4.1	3.6	3.9	3.3
SD	3.28	3.51	3.37	3.38
Median	6.5	4.5	7.0	1.0
Min-Max	0-7	0-7	0-7	0-7
Entire Maintenance Phase**				
N (n†)	47 (41)	46 (38)	47 (35)	41 (30)
Mean	46.4	36.5	31.3	27.8
SD	42.78	39.50	41.38	41.25
Median	37.5	15.8	7.1	3.6
Min-Max	0-100	0-100	0-100	0-100

*Number of days with laxation intake during the last 7 days according to patient diary; **Percentage of days with laxation intake during the maintenance phase according to patient diary n† Number of patients taking laxatives

Figure 18 Overall Summary of Adverse Events During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio - Safety Population

	Dose Ratios																			
	40 mg/ Placebo		60 mg/ Placebo		80 mg/ Placebo		1/1		1.5/1		2/1		3/1		4/1		6/1		8/1	
	N=17 (100%)		N=17 (100%)		N=16 (100%)		N=15 (100%)		N=18 (100%)		N=34 (100%)		N=18 (100%)		N=33 (100%)		N=12 (100%)		N=22 (100%)	
Category	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)
Adverse Events	21	8 (47.1)	54	15 (88.2)	36	9 (56.3)	26	8 (53.3)	61	16 (88.9)	84	19 (55.9)	57	11 (61.1)	73	22 (66.7)	18	9 (75.0)	69	17 (77.3)
Causally Related#	12	6 (35.3)	33	11 (64.7)	29	8 (50.0)	23	7 (46.7)	44	12 (66.7)	70	19 (55.9)	40	8 (44.4)	60	18 (54.5)	14	6 (50.0)	51	13 (59.1)
Leading to discontinuation of study drug	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	3	1 (6.7)	14	4 (22.2)	15	5 (14.7)	27	5 (27.8)	2	2 (6.1)	1	1 (8.3)	10	2 (9.1)
Serious Adverse Events	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	0	0 (0.0)	2	2 (11.1)	1	1 (2.9)	1	1 (5.6)	1	1 (3.0)	1	1 (8.3)	3	1 (4.5)
Causally Related#	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (5.6)	1	1 (2.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	1 (4.5)
Leading to discontinuation of study drug	0	0 (0.0)	0	0 (0.0)	1	1 (6.3)	0	0 (0.0)	2	2 (11.1)	1	1 (2.9)	1	1 (5.6)	1	1 (3.0)	1	1 (8.3)	3	1 (4.5)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

E = Number of events

= Related adverse events include all events listed with a definite, probable, possible or unknown/missing relationship to study drug

Figure 19

Overall Summary of Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone - Safety Population

	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
Category	E	N (%)	E	N (%)	E	N (%)	E	N (%)
Adverse Events	111	32 (64.0)	119	35 (68.6)	129	32 (62.7)	140	35 (70.0)
Causally Related#	74	25 (50.0)	93	26 (51.0)	100	27 (52.9)	109	30 (60.0)
Leading to discontinuation of study drug	1	1 (2.0)	13	5 (9.8)	29	6 (11.8)	30	9 (18.0)
Serious Adverse Events	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Causally Related#	0	0 (0.0)	3	1 (2.0)	0	0 (0.0)	2	2 (4.0)
Leading to discontinuation of study drug	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

E = Number of events
# = Related adverse events include all events listed with a definite, probable, possible or unknown/missing relationship to study drug

Fig. 20 Adverse Events During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio (Reported by ≥ 20% of Patients) and System Organ Class - Safety Population

System Organ Class	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=18 (100%)	N=34 (100%)	N=18 (100%)	N=33 (100%)	N=12 (100%)	N=22 (100%)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gastrointestinal Disorders	5 (29.4)	10 (58.8)	4 (25.0)	7 (46.7)	11 (61.1)	16 (47.1)	8 (44.4)	16 (48.5)	6 (50.0)	9 (40.9)
Skin and Subcutaneous Tissue Disorders	4 (23.5)	6 (35.3)	6 (37.5)	4 (26.7)	8 (44.4)	8 (23.5)	8 (44.4)	9 (27.3)	1 (8.3)	11 (50.0)
Nervous System Disorders	3 (17.6)	8 (47.1)	6 (37.5)	1 (6.7)	8 (44.4)	9 (26.5)	5 (27.8)	5 (15.2)	1 (8.3)	5 (22.7)
Musculoskeletal and Connective Tissue Disorders	3 (17.6)	3 (17.6)	1 (6.3)	3 (20.0)	3 (16.7)	7 (20.6)	4 (22.2)	9 (27.3)	2 (16.7)	5 (22.7)
Psychiatric Disorders	3 (17.6)	5 (29.4)	3 (18.8)	2 (13.3)	4 (22.2)	6 (17.6)	4 (22.2)	6 (18.2)	2 (16.7)	5 (22.7)
Ear and Labyrinth Disorders	0 (0.0)	6 (35.3)	2 (12.5)	1 (6.7)	3 (16.7)	4 (11.8)	2 (11.1)	2 (6.1)	1 (8.3)	3 (13.6)

Fig. 21 Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone (Reported by ≥ 10% of Patients) and System Organ Class - Safety Population

System Organ Class	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
	N	(%)	N	(%)	N	(%)	N	(%)
Gastrointestinal Disorders	19	(38.0)	22	(43.1)	24	(47.1)	27	(54.0)
Skin and Subcutaneous Tissue Disorders	16	(32.0)	17	(33.3)	16	(31.4)	16	(32.0)
Nervous System Disorders	17	(34.0)	9	(17.6)	11	(21.6)	14	(28.0)
Musculoskeletal and Connective Tissue Disorders	7	(14.0)	8	(15.7)	13	(25.5)	12	(24.0)
Psychiatric Disorders	11	(22.0)	10	(19.6)	8	(15.7)	11	(22.0)
Ear and Labyrinth Disorders	8	(16.0)	6	(11.8)	4	(7.8)	6	(12.0)
General disorders and administration site conditions	0	(0.0)	5	(9.8)	4	(7.8)	5	(10.0)

Figure 22. Mean Plasma Concentration - Time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Phamacokinetics

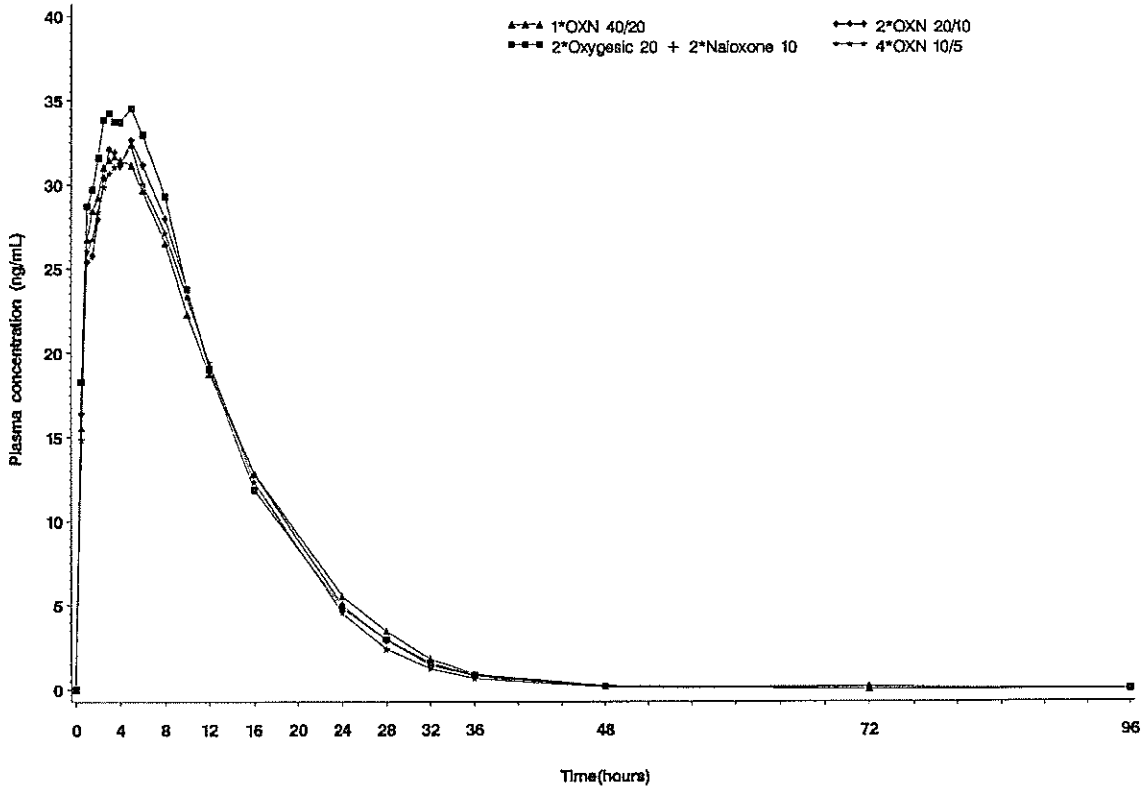


Figure 23. Mean Plasma Concentration - Time Curves for Naloxone-3-Glucuronide Over Time by Treatment - Full Analysis Population for Phamacokinetics

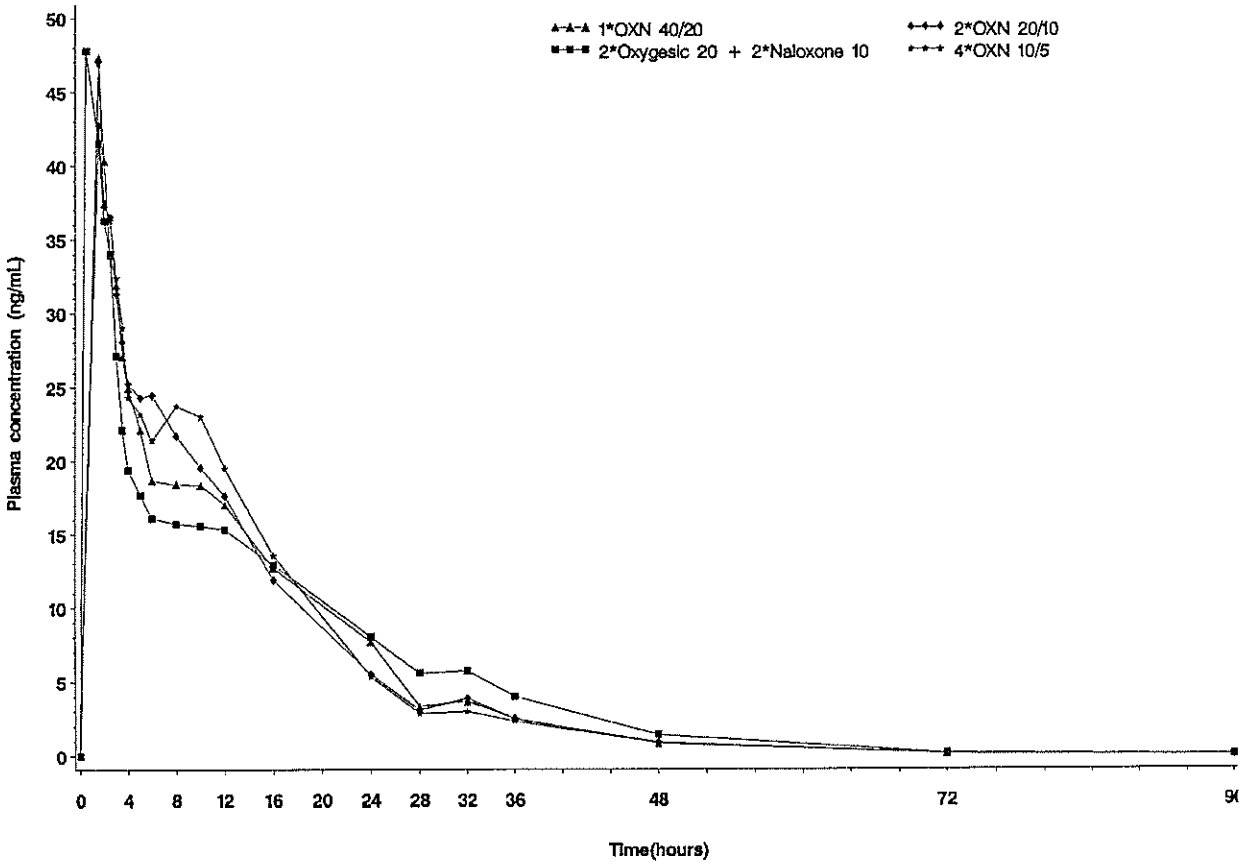


Figure 24. Mean Plasma Concentration - Time Curves for Naloxone Over Time by Treatment - Full Analysis Population for Phamacokinetics

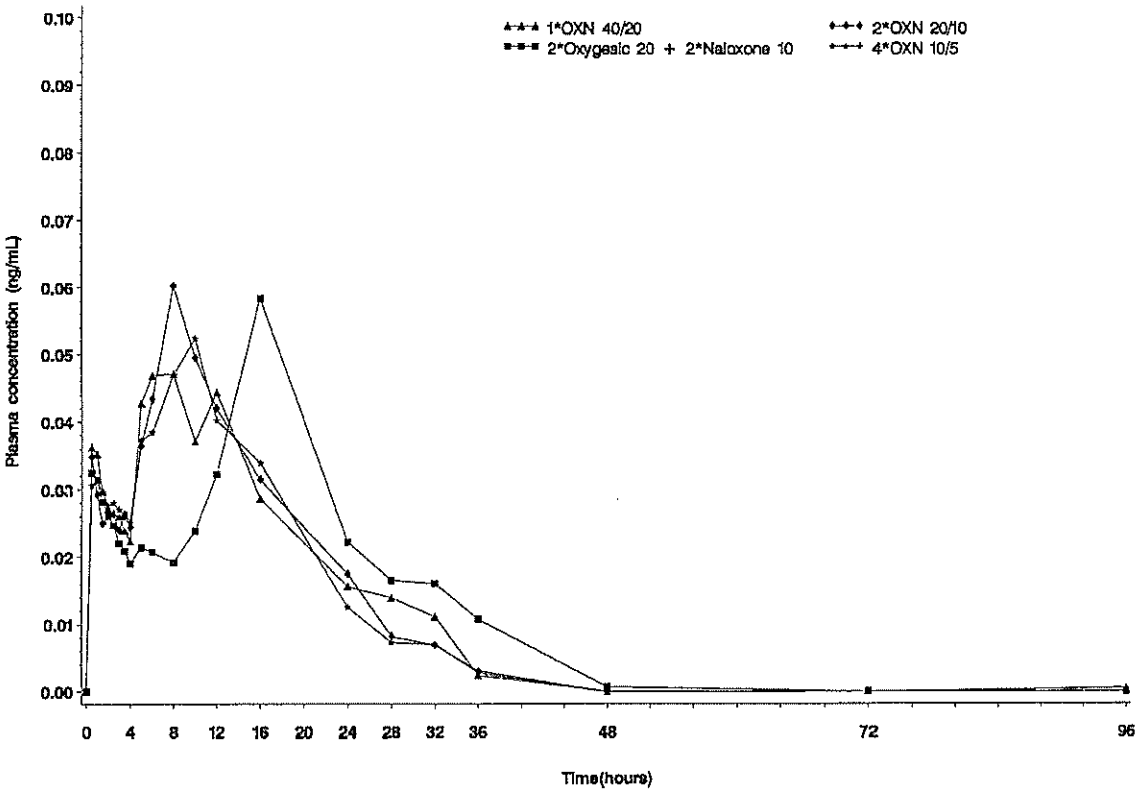


Figure 25. Mean Plasma Concentration - Time Curves for Noroxycodone Over Time by Treatment - Full Analysis Population for Phamacokinetics

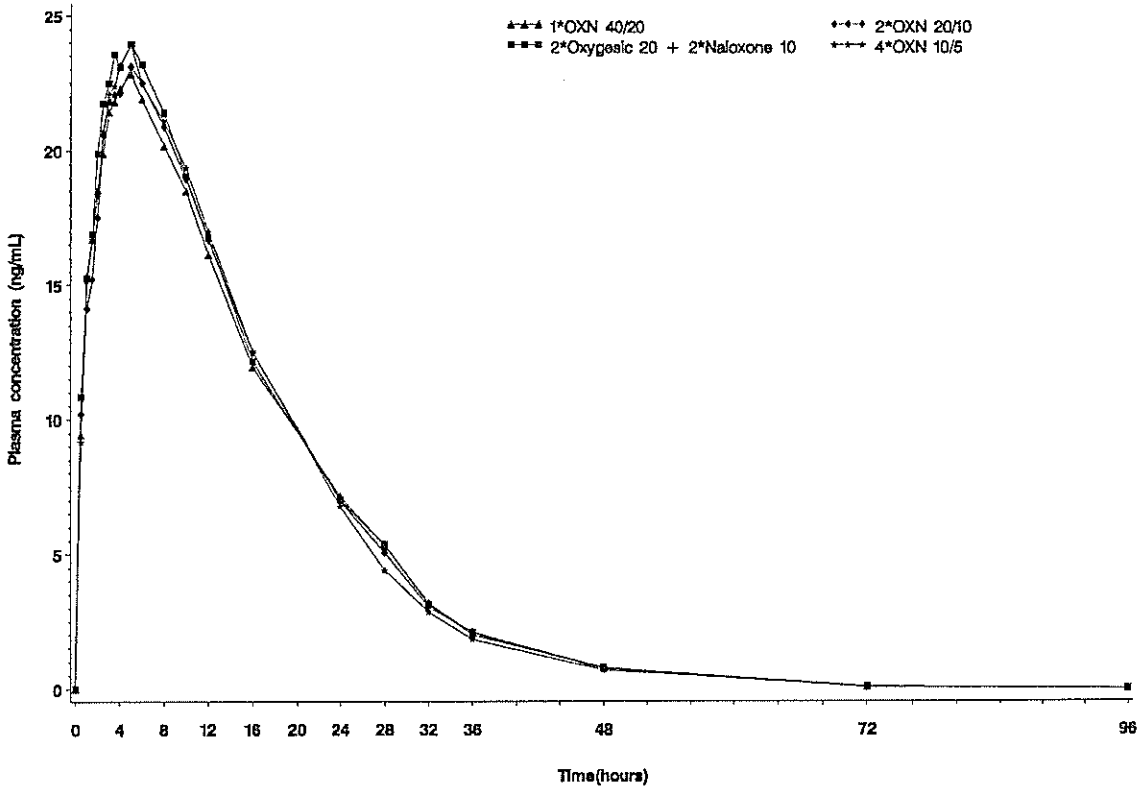


Figure 26. Mean Plasma Concentration - Time Curves for Oxymorphone Over Time by Treatment - Full Analysis Population for Phamacokinetics

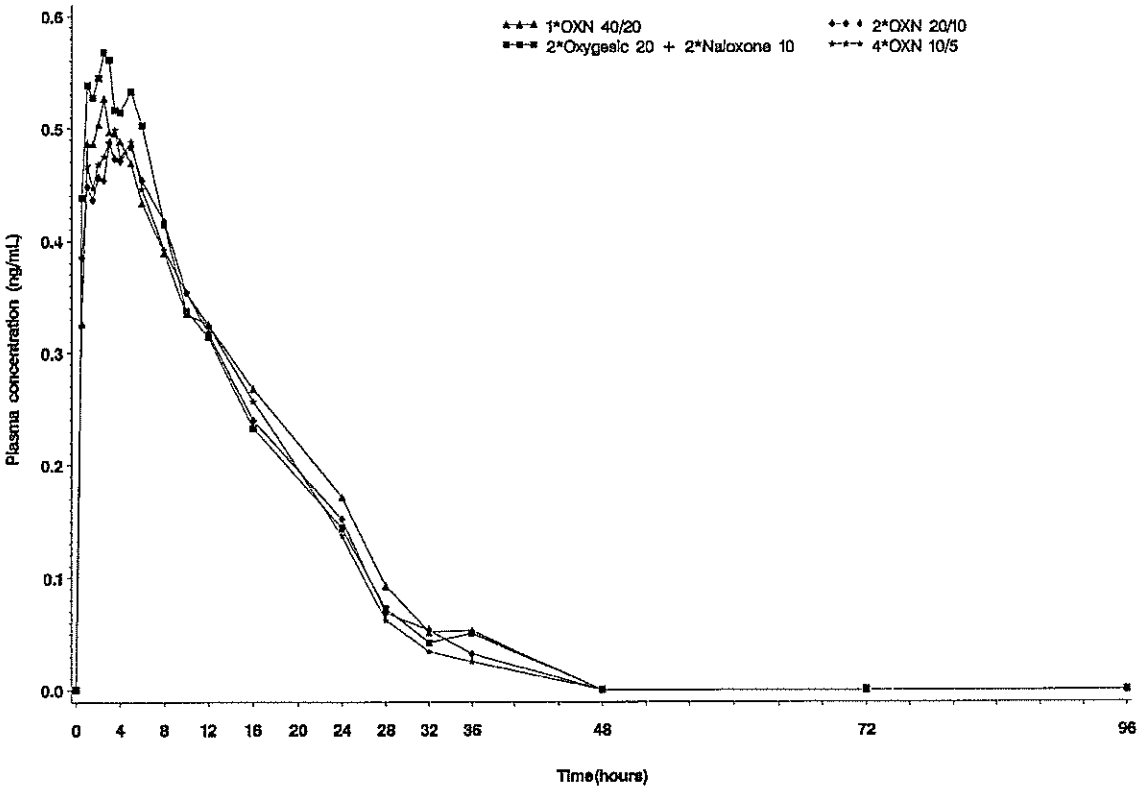


Figure 27. Mean Plasma Concentration - Time Curves for Noroxymorphone Over Time by Treatment - Full Analysis Population for Phamacokinetics

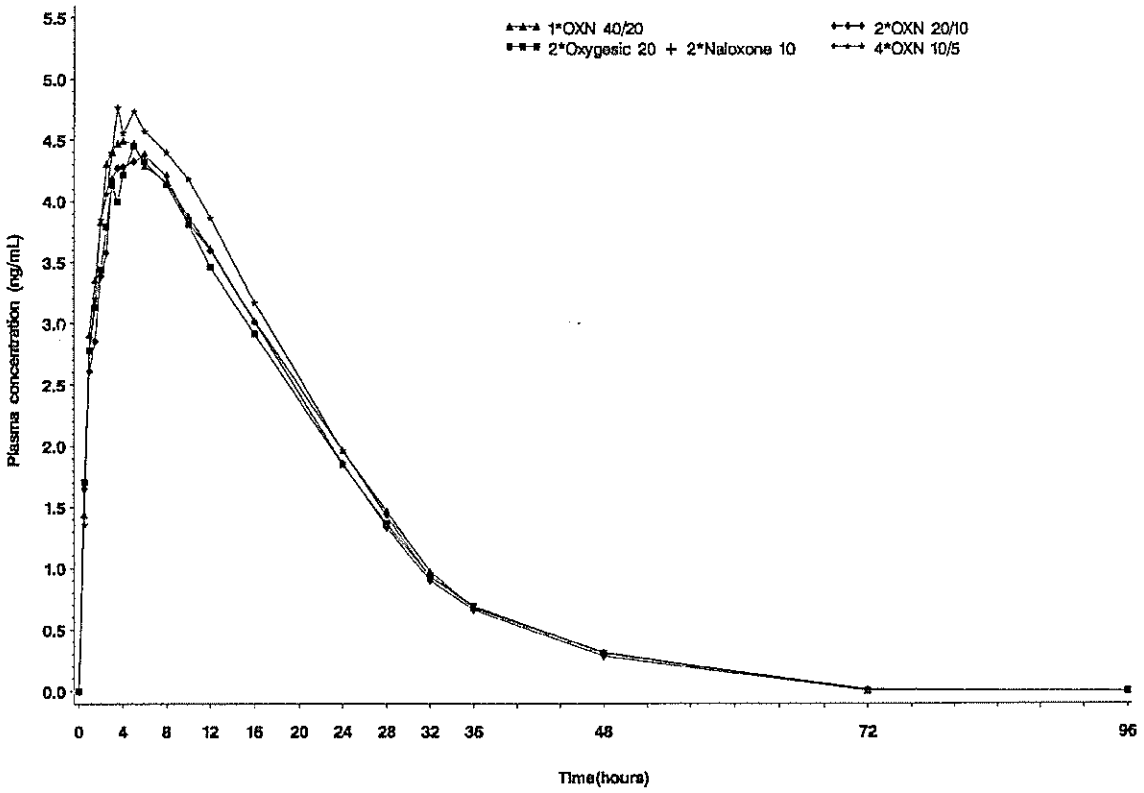
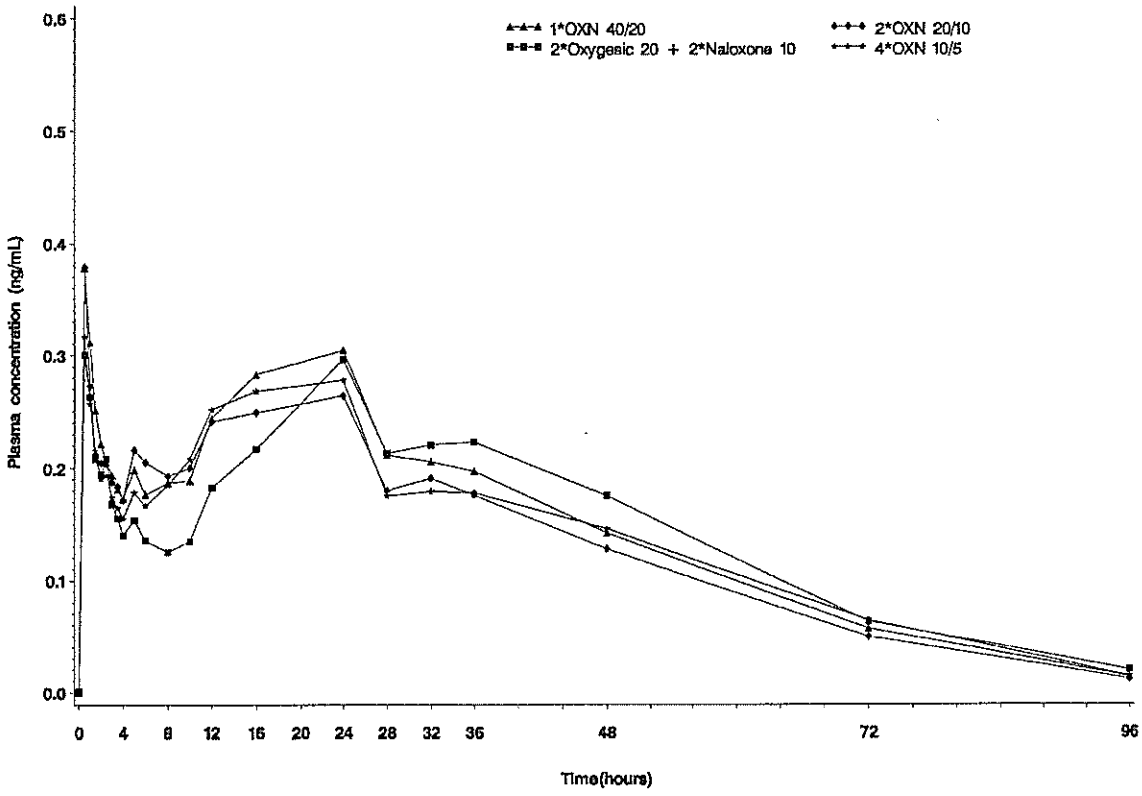
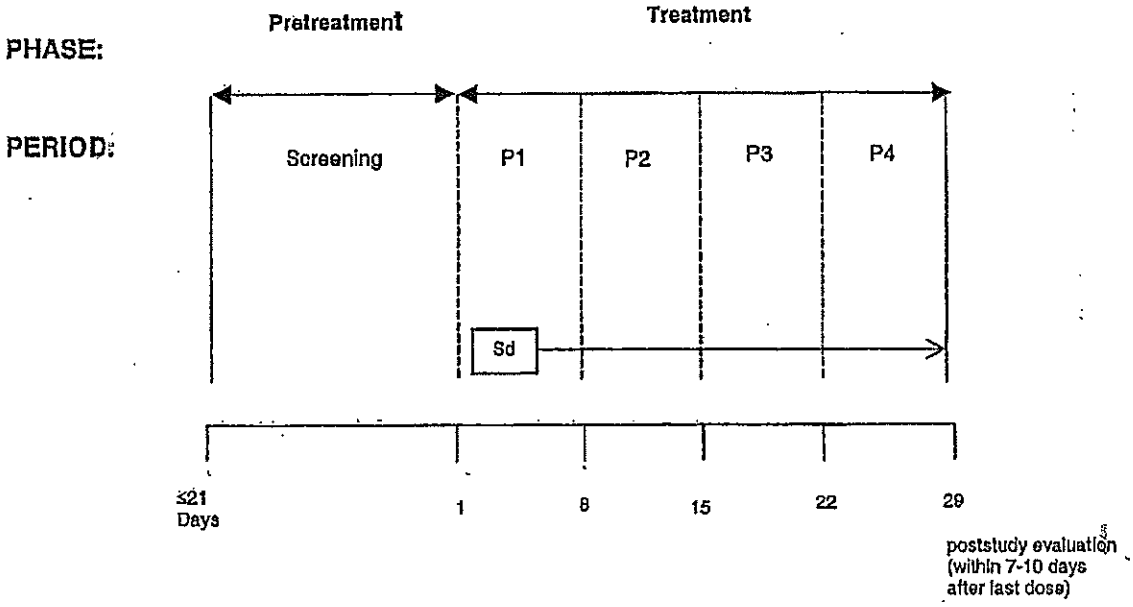


Figure 28. Mean Plasma Concentration - Time Curves for 6-β-Naloxol Over Time by Treatment - Full Analysis Population for Phamacokinetics



Study Design



Sd = Study drug according to the RAS
P1-P4= Study Periods 1-4 each with a single dose of study drug according to a RAS, followed by at least a 7-day washout between doses (periods 1-3 only)

Figure 29

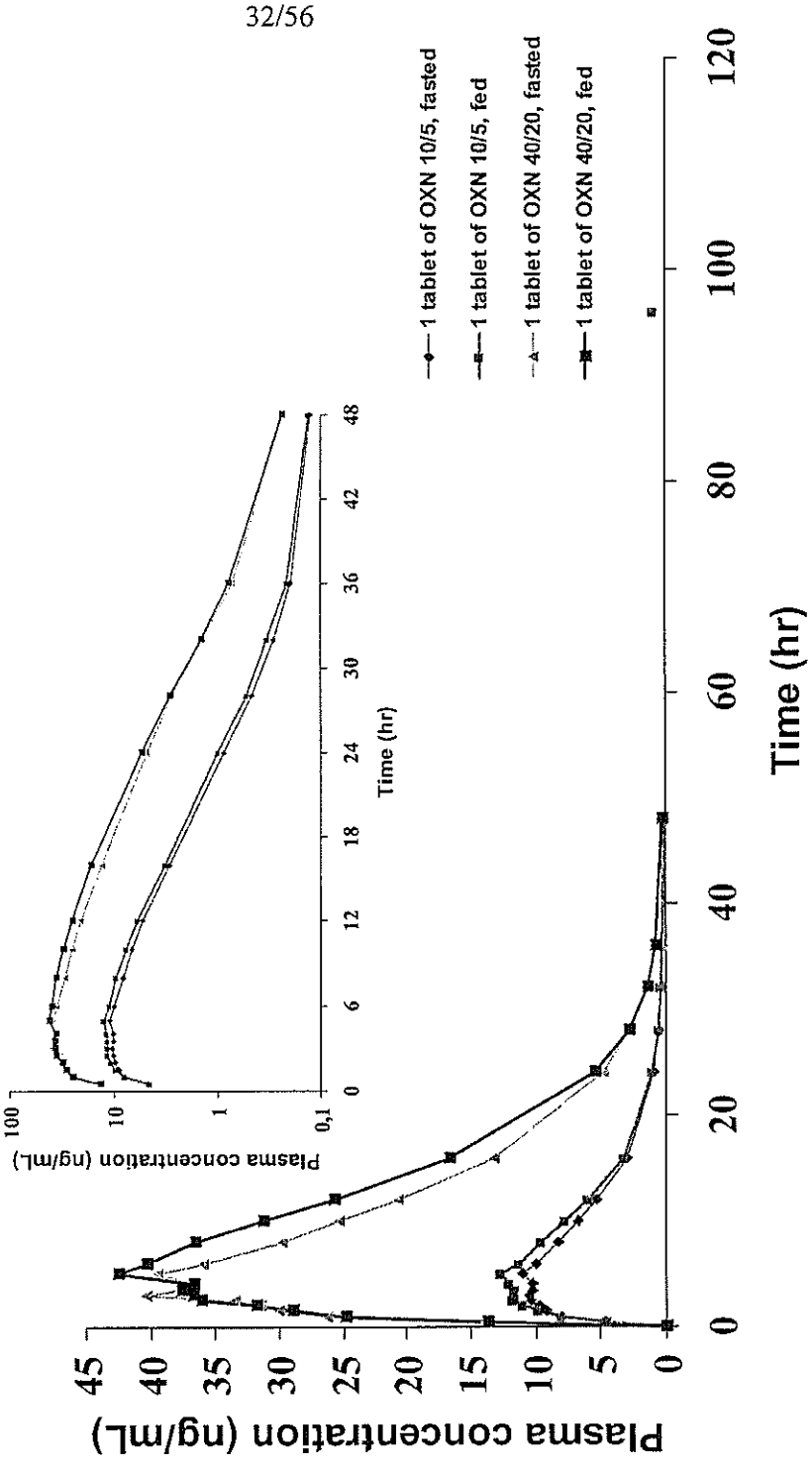


Fig. 30: Mean plasma oxycodone profiles

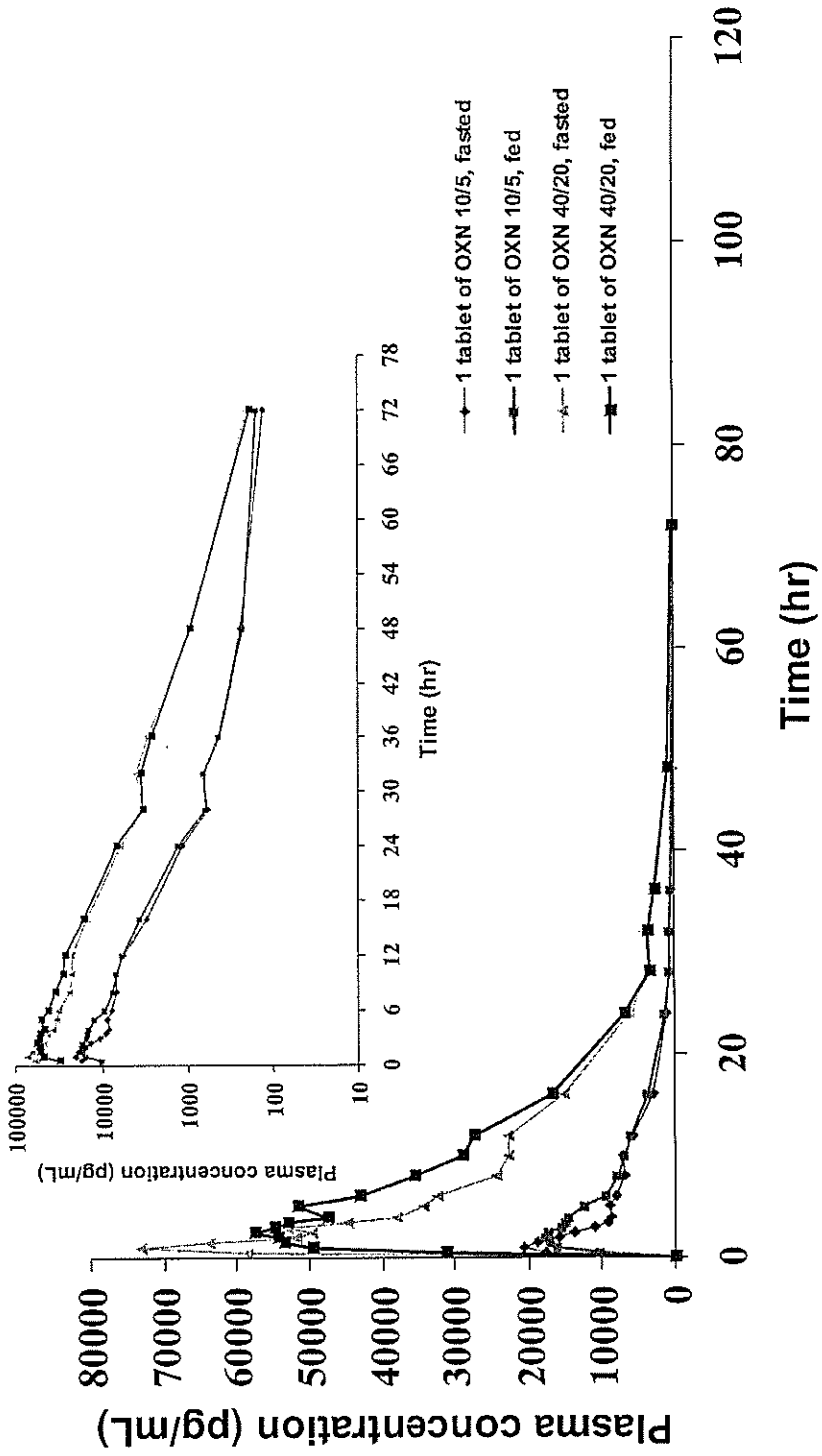


Fig. 31: mean plasma naloxone-3-glucuronide profiles

Fig.32 Summary of Oxycodone Pharmacokinetic Parameters by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics

PK Metrics	Statistics	OXN 40/20 Fast	OXN 40/20 Fed	OXN 10/5 Fast	OXN 10/5 Fed
AUC [0-t] (ng.h/mL)	N	21	23	27	24
	Mean (SD)	517.81 (176.87)	604.34 (198.84)	136.82 (41.04)	153.26 (50.97)
	Median	453.96	543.65	141.87	144.00
	Min, Max	261.26, 840.69	296.70, 1021.06	65.07, 216.93	76.39, 298.17
	Geometric Mean	489.46	574.33	130.43	145.62
	Exponentiated LS Mean	506.70	594.03	130.22	148.55
AUC [0-Inf] (ng.h/mL)	N	21	23	26	23
	Mean (SD)	519.67 (177.55)	606.16 (199.48)	136.11 (40.96)	155.37 (52.01)
	Median	455.95	544.48	137.06	149.50
	Min, Max	262.18, 842.79	297.35, 1025.03	65.71, 217.80	77.07, 299.48
	Geometric Mean	491.20	576.06	129.81	147.45
	Exponentiated LS Mean	507.78	595.06	132.15	149.72
Cmax (ng/mL)	N	21	23	27	24
	Mean (SD)	40.16 (10.42)	50.29 (12.92)	12.16 (3.54)	14.54 (3.27)
	Median	37.60	45.10	12.50	13.80
	Min, Max	23.90, 61.60	31.00, 77.50	6.06, 19.20	9.37, 23.00
	Geometric Mean	38.90	48.81	11.65	14.21
	Exponentiated LS Mean	40.75	50.48	11.62	14.46
Tmax (h)	N	21	23	27	24
	Mean (SD)	3.07 (1.519)	4.35 (3.109)	3.13 (1.370)	3.35 (1.463)
	Median	2.50	3.00	3.00	3.50
	Min, Max	1, 6	1, 12	1, 5	0.5, 5
	LS Mean	3.05	4.31	3.13	3.35
t1/2 (h)	N	21	23	26	23
	Mean (SD)	5.10 (1.275)	4.85 (1.083)	4.40 (0.692)	4.12 (0.763)
	Median	5.36	5.04	4.39	3.93
	Min, Max	2.88, 7.81	2.65, 6.81	3.37, 5.94	2.84, 6.93
	LS Mean	5.15	4.89	4.43	4.18
LambdaZ (1/h)	N	21	23	26	23
	Mean (SD)	0.146 (0.0423)	0.151 (0.0388)	0.161 (0.0251)	0.173 (0.0278)
	Median	0.129	0.138	0.158	0.177
	Min, Max	0.089, 0.241	0.102, 0.262	0.117, 0.206	0.100, 0.244

Fig.33 **Statistics for Oxycodone Pharmacokinetic Metrics by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics**

PK Metrics	Treatment Comparison	Exponentiated LS Means Ratio (%)	LS Means Difference	90% CI - Lower -	90% CI - Upper -
AUC [0-t]	OXN 40/20 Fed vs. OXN 40/20 Fast	117.23		112.78	121.86
	OXN 10/5 Fed vs. OXN 10/5 Fast	114.07		109.97	118.34
AUC [0-inf]	OXN 40/20 Fed vs. OXN 40/20 Fast	117.19		112.85	121.70
	OXN 10/5 Fed vs. OXN 10/5 Fast	113.30		109.20	117.54
Cmax	OXN 40/20 Fed vs. OXN 40/20 Fast	123.87		116.16	132.10
	OXN 10/5 Fed vs. OXN 10/5 Fast	124.45		117.12	132.24
Tmax (h)	OXN 40/20 Fed vs. OXN 40/20 Fast		1.26	0.37	2.15
	OXN 10/5 Fed vs. OXN 10/5 Fast		0.21	-0.62	1.04
t1/2 (h)	OXN 40/20 Fed vs. OXN 40/20 Fast		-0.26	-0.65	0.14
	OXN 10/5 Fed vs. OXN 10/5 Fast		-0.25	-0.63	0.13

Fig.34 **Summary Statistics for Naloxone-3-Glucuronide Pharmacokinetic Parameters by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics**

PK Metrics	Statistics	OXN 40/20 Fast	OXN 40/20 Fed	OXN 10/5 Fast	OXN 10/5 Fed
AUC [0-t] (ng.h/mL)	n	21	23	27	24
	Mean (SD)	638.86 (196.83)	728.89 (234.65)	161.18 (55.65)	176.11 (71.59)
	Median	587.93	664.48	150.94	158.04
	Min, Max	388.51, 1180.68	361.44, 1327.86	77.59, 299.63	88.38, 394.25
	Geometric Mean	613.20	695.95	152.00	164.60
	Exponentiated LS Mean	641.76	712.62	152.45	162.90
AUC [0-inf] (ng.h/mL)	n	17	19	19	12
	Mean (SD)	671.14 (203.28)	703.06 (156.64)	164.33 (53.42)	201.64 (72.25)
	Median	607.96	673.36	153.79	176.87
	Min, Max	410.39, 1181.54	485.06, 1049.87	80.21, 301.98	132.91, 396.40
	Geometric Mean	645.00	687.07	156.41	192.51
	Exponentiated LS Mean	653.82	718.21	156.10	169.75
Cmax (ng/mL)	n	21	23	27	24
	Mean (SD)	86.05 (24.39)	84.68 (23.60)	23.65 (7.01)	24.30 (9.03)
	Median	84.21	86.56	23.06	24.93
	Min, Max	49.00, 159.26	45.37, 139.09	12.08, 43.04	10.28, 48.73
	Geometric Mean	83.08	81.48	22.65	22.74
	Exponentiated LS Mean	84.54	82.31	22.67	22.41
Tmax (h)	n	21	23	27	24
	Mean (SD)	1.07 (1.228)	3.04 (2.788)	1.13 (0.957)	2.50 (1.399)
	Median	0.50	2.50	1.00	2.25
	Min, Max	0.5, 6	0.5, 12	0.5, 5	0.5, 5
	LS Mean	1.10	3.01	1.14	2.48
t1/2 (h)	n	17	19	19	12
	Mean (SD)	7.73 (1.728)	7.44 (2.041)	9.16 (3.865)	7.70 (1.407)
	Median	7.88	7.59	8.10	7.64
	Min, Max	5.47, 11.19	3.52, 11.19	4.12, 21.60	5.60, 9.68
	LS Mean	7.96	7.30	8.84	7.24
LambdaZ (1/h)	n	17	19	19	12
	Mean (SD)	0.094 (0.0208)	0.101 (0.0325)	0.086 (0.0310)	0.093 (0.0179)
	Median	0.088	0.091	0.086	0.091
	Min, Max	0.062, 0.127	0.062, 0.197	0.032, 0.168	0.072, 0.124

Fig. 35 **Statistics for Naloxone-3-Glucuronide Pharmacokinetic Parameters by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics**

PK Metrics	Treatment Comparison	Exponentiated LS Means Ratio (%)	LS Means Difference	90% CI - Lower -	90% CI - Upper -
AUC [0-t]	OXN 40/20 Fed vs. OXN 40/20 Fast	111.04		105.79	116.56
	OXN 10/5 Fed vs. OXN 10/5 Fast	106.85		102.05	111.87
AUC [0-Inf]	OXN 40/20 Fed vs. OXN 40/20 Fast	109.85		102.59	117.62
	OXN 10/5 Fed vs. OXN 10/5 Fast	108.74		100.72	117.39
Cmax	OXN 40/20 Fed vs. OXN 40/20 Fast	97.36		88.46	107.16
	OXN 10/5 Fed vs. OXN 10/5 Fast	98.85		90.33	108.18
Tmax (h)	OXN 40/20 Fed vs. OXN 40/20 Fast		1.91	1.12	2.71
	OXN 10/5 Fed vs. OXN 10/5 Fast		1.34	0.60	2.08
t1/2 (h)	OXN 40/20 Fed vs. OXN 40/20 Fast		-0.66	-1.99	0.66
	OXN 10/5 Fed vs. OXN 10/5 Fast		-1.59	-3.07	-0.12

Fig.36 **Summary Statistics for Naloxone Pharmacokinetic Parameters by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics**

PK Metrics	Statistics	OXN 40/20 Fast	OXN 40/20 Fed	OXN 10/5 Fast	OXN 10/5 Fed
AUC [0-t] (pg.h/mL)	n	21	23	27	24
	Mean (SD)	953.14 (652.46)	1089.05 (813.25)	116.12 (163.04)	192.26 (266.68)
	Median	800.75	870.45	45.10	99.64
	Min, Max	184.75, 2737.35	320.08, 3350.23	0.00, 600.55	16.43, 1221.58
	Geometric Mean	772.36	910.17	65.59	102.37
	Exponentiated LS Mean	737.78	916.77	59.48	98.34
AUC [0-inf] (pg.h/mL)	n	3	6		
	Mean (SD)	1851.24 (638.07)	1389.93 (1035.49)		
	Median	1974.87	1091.79		
	Min, Max	1160.41, 2418.45	720.58, 3473.73		
	Geometric Mean	1769.68	1186.12		
	Exponentiated LS Mean		1109.63		
Cmax (pg/mL)	n	21	23	27	24
	Mean (SD)	73.73 (45.14)	151.90 (202.07)	24.65 (24.30)	50.02 (46.88)
	Median	54.10	88.80	16.20	32.20
	Min, Max	30.30, 177.00	50.20, 1034.00	0.00, 103.00	15.70, 205.00
	Geometric Mean	62.82	108.40	23.09	37.47
	Exponentiated LS Mean	63.87	111.88	21.66	37.04
Tmax (h)	n	21	23	23	24
	Mean (SD)	5.17 (4.613)	2.00 (2.174)	5.00 (3.286)	2.35 (3.184)
	Median	5.00	1.00	5.00	1.00
	Min, Max	0.5, 16	0.5, 8	0.5, 12	0.5, 12
	LS Mean	5.06	1.93	4.77	2.32
t1/2 (h)	n	9	7		
	Mean (SD)	13.90 (5.379)	9.88 (5.397)		
	Median	13.08	8.39		
	Min, Max	6.39, 21.79	5.10, 21.54		
	LS Mean		9.32		
LambdaZ (1/h)	n	9	7		
	Mean (SD)	0.059 (0.0290)	0.083 (0.0315)		
	Median	0.053	0.083		
	Min, Max	0.032, 0.108	0.032, 0.136		

Fig. 37 **Statistics for Naloxone Pharmacokinetic Parameters by Treatment: Full Analysis Population for Plasma Pharmacokinetic Metrics**

PK Metrics	Treatment Comparison	Exponentiated LS Means Ratio (%)	LS Means Difference	90% CI - Lower -	90% CI - Upper -
AUC [0-t]	OXN 40/20 Fed vs. OXN 40/20 Fast	124.26		92.88	166.25
	OXN 10/5 Fed vs. OXN 10/5 Fast	166.34		123.83	221.12
AUC [0-inf]	OXN 40/20 Fed vs. OXN 40/20 Fast				
Cmax	OXN 40/20 Fed vs. OXN 40/20 Fast	175.13		137.24	223.47
	OXN 10/5 Fed vs. OXN 10/5 Fast	171.03		134.36	217.72
Tmax (h)	OXN 40/20 Fed vs. OXN 40/20 Fast		-3.13	-4.63	-1.72
	OXN 10/5 Fed vs. OXN 10/5 Fast		-2.46	-3.84	-1.08
t1/2 (h)	OXN 40/20 Fed vs. OXN 40/20 Fast				

Fig. 38 **Study Diagram**

SD = Study drug according to random allocation schedule
P1-P5 = Periods 1-5 each identical with a single dose of study drug according to random allocation schedule, followed by a ≥ 7 day washout (Periods 1, 2, 3 and 4 only)

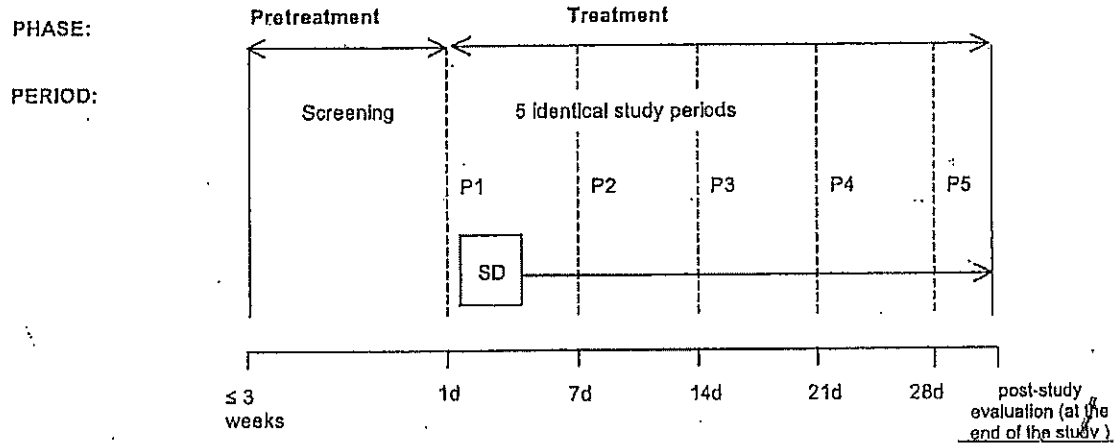
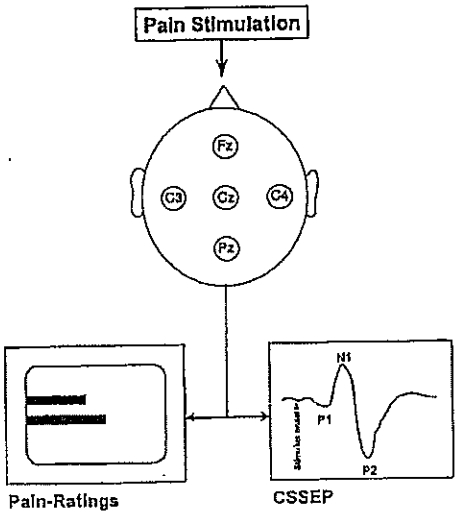


Figure 39

The Experimental Pain Model



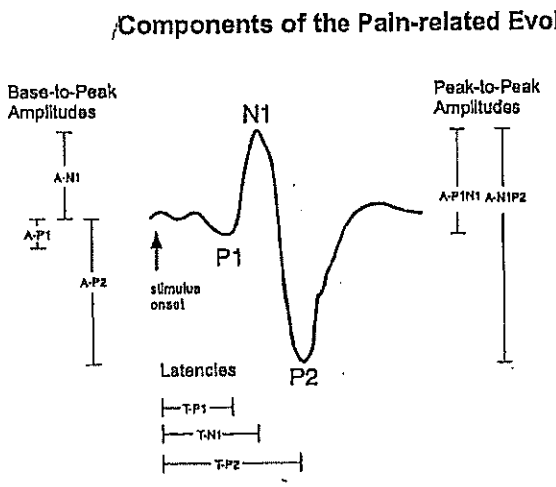

Components of the Pain-related Evoked Potential
Base-to-Peak Amplitudes
A-N1
A-P1
A-P2
N1
P1
P2
stimulus onset
Latencies
T-P1
T-N1
T-P2
Peak-to-Peak Amplitudes
A-P1N1
A-N1P2

Figure 40

Fig.41 **Pain-related Evoked Potentials, Statistically Significant Total Changes from Baseline in Amplitude P1, Amplitude P1N1, Latency P1, and Latency P2 after Stimulation with 60 and 70% CO_2: Safety Population**

	Overall Treatment	Oxycodone PR	Oxy nal 20/5	Oxy nal 20/15	Oxy nal 20/45	Placebo
Amplitude P1 (in µV)						
Cz 70% CO_2						
Mean	–	-2.25	-2.51	-0.31	-2.58	9.27
SD	–	8.302	15.054	11.527	13.276	13.493
p-value Placebo	0.0460	0.0101	0.0090	0.0326	0.0167	–
p-value Oxy PR	–	–	0.9811	0.6414	0.8996	–
Amplitude P1N1 (in µV)						
C4 60% CO_2						
Mean	–	-15.25	-9.93	-6.43	-2.25	-1.31
SD	–	16.643	15.333	11.578	10.076	8.875
p-value Placebo	0.0125	0.0040	0.0841	0.3345	0.8294	–
p-value Oxy PR	–	–	0.2184	0.0463	0.0024	–
Latency P1 (in ms)						
Cz 60% CO_2						
Mean	–	97.6	83.4	50.4	36.6	-16.8
SD	–	55.02	59.81	84.22	80.26	55.22
p-value Placebo	<0.0001	<0.0001	<0.0001	0.0035	0.0313	–
p-value Oxy PR	–	–	0.5354	0.0307	0.0049	–
Cz 70% CO_2						
Mean	–	85.0	101.0	32.2	41.2	8.6
SD	–	61.84	74.97	85.16	77.73	73.51
p-value Placebo	0.0006	0.0010	0.0001	0.2431	0.0543	–
p-value Oxy PR	–	–	0.5087	0.0261	0.1684	–
C3 60% CO_2						
Mean	–	96.8	72.2	56.2	31.6	-25.6
SD	–	57.01	67.58	76.25	105.42	71.74
p-value Placebo	0.0001	<0.0001	0.0003	0.0024	0.0408	–
p-value Oxy PR	–	–	0.3701	0.1170	0.0133	–

Fig. 41 continued

Pain-related Evoked Potentials, Statistically Significant Total Change from Baseline in Amplitude P1, Amplitude P1N1, Latency P1, and Latency P2 after Stimulation with 60 and 70% CO_2: Safety Population (continued)

	Overall Treatment	Oxycodone PR	Oxy nal 20/5	Oxy nal 20/15	Oxy nal 20/45	Placebo
C3 70% CO_2						
Mean	–	76.0	96.0	31.6	39.4	-6.4
SD	–	68.49	73.62	101.19	91.30	82.10
p-value Placebo	0.0012	0.0018	0.0001	0.1167	0.0207	–
p-value Oxy PR	–	–	0.3982	0.0966	0.4196	–
C4 60% CO_2						
Mean	–	95.0	68.6	35.0	39.4	-17.2
SD	–	55.58	78.79	74.69	96.89	82.37
p-value Placebo	0.0011	0.0001	0.0017	0.0542	0.0585	–
p-value Oxy PR	–	–	0.3209	0.0242	0.0294	–
C4 70% CO_2						
Mean	–	86.6	88.4	40.4	38.0	-17.2
SD	–	66.79	69.03	104.42	91.37	78.24
p-value Placebo	0.0004	0.0001	0.0001	0.0265	0.0111	–
p-value Oxy PR	–	–	0.8705	0.0773	0.1849	–
Fz 60% CO_2						
Mean	–	88.4	86.6	27.6	32.2	-20.2
SD	–	59.67	68.49	86.39	57.84	72.95
p-value Placebo	<0.0001	<0.0001	<0.0001	0.0328	0.0291	–
p-value Oxy PR	–	–	0.9806	0.0040	0.0069	–
Fz 70% CO_2						
Mean	–	56.4	82.4	27.0	28.8	-23.2
SD	–	82.34	86.69	91.18	104.66	97.31
p-value Placebo	0.0061	0.0077	0.0003	0.0925	0.0406	–
p-value Oxy PR	–	–	0.3089	0.2961	0.5532	–
Pz 60% CO_2						
Mean	–	81.8	66.0	24.2	24.8	-2.2
SD	–	59.19	87.53	100.34	91.52	69.40
p-value Placebo	0.0144	0.0027	0.0099	0.3523	0.2873	–
p-value Oxy PR	–	–	0.6298	0.0308	0.0516	–

Fig. 41 continued

Pain-related Evoked Potentials, Statistically Significant Total Change from Baseline in Amplitude P1, Amplitude P1N1, Latency P1, and Latency P2 after Stimulation with 60 and 70% CO_2: Safety Population (continued)

	Overall Treatment	Oxycodone PR	Oxy nal 20/5	Oxy nal 20/15	Oxy nal 20/45	Placebo
Pz 70% CO_2						
Mean	–	75.0	80.2	38.8	26.2	-1.0
SD	–	87.62	89.76	82.47	74.80	94.46
p-value Placebo	**0.0135**	**0.0041**	**0.0018**	0.1130	0.1271	–
p-value Oxy PR	–	–	0.7939	0.1732	0.1788	–
Latency P2 (in ms)						
Cz 70% CO_2						
Mean	–	92.8	144.8	122.4	42.2	-48.0
SD	–	165.79	173.28	259.11	143.96	261.14
p-value Placebo	**0.0293**	**0.0288**	**0.0037**	**0.0073**	0.1088	–
p-value Oxy PR	–	–	0.4558	0.5928	0.5800	–
Fz 60% CO_2						
Mean	–	97.8	118.2	154.8	-8.6	-32.4
SD	–	177.66	228.17	200.21	95.89	260.44
p-value Placebo	**0.0175**	0.0550	**0.0176**	**0.0054**	0.7140	–
p-value Oxy PR	–	–	0.6440	0.3564	0.1260	–
Pz 70% CO_2						
Mean	–	76.2	106.4	153.6	47.4	-63.8
SD	–	151.19	177.11	256.77	123.53	246.66
p-value Placebo	**0.0117**	**0.0280**	**0.0088**	**0.0006**	0.0586	–
p-value Oxy PR	–	–	0.6673	0.1813	0.7899	–

Cross-reference Tables 14.2.1.1-14.2.1.10

Significant changes from baseline in latency P1 over time of treatment could be observed at recording position Cz after stimulation with 60% CO_2 and are graphically presented in Figure 5.

Pain-related Evoked Potentials: Mean Changes from Baseline in Latency P1 at Recording Position Cz after Stimulation with 60% CO_2: Full Analysis for Pharmacokinetics Population

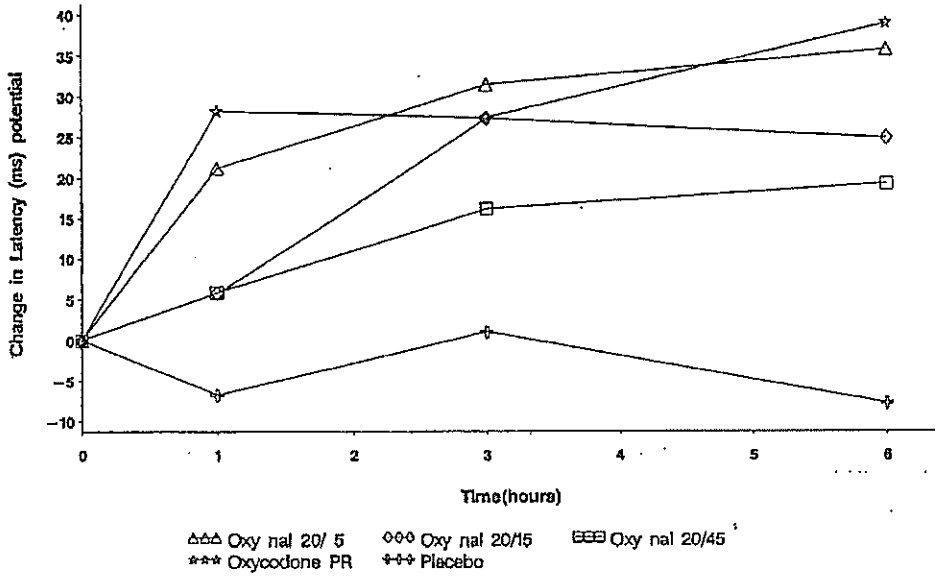


Figure 42

Fig.43 Mean Tonic Pain Scores in the 2nd Half of the Treatment Period, Change from Baseline over Time of Treatment: Full Analysis for Pharmacokinetics Population

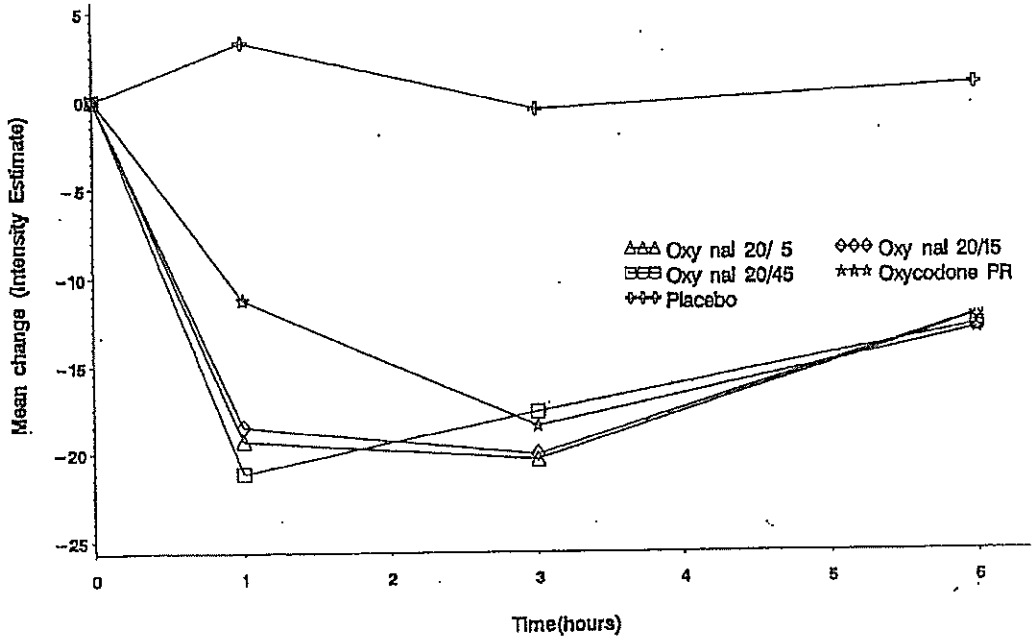
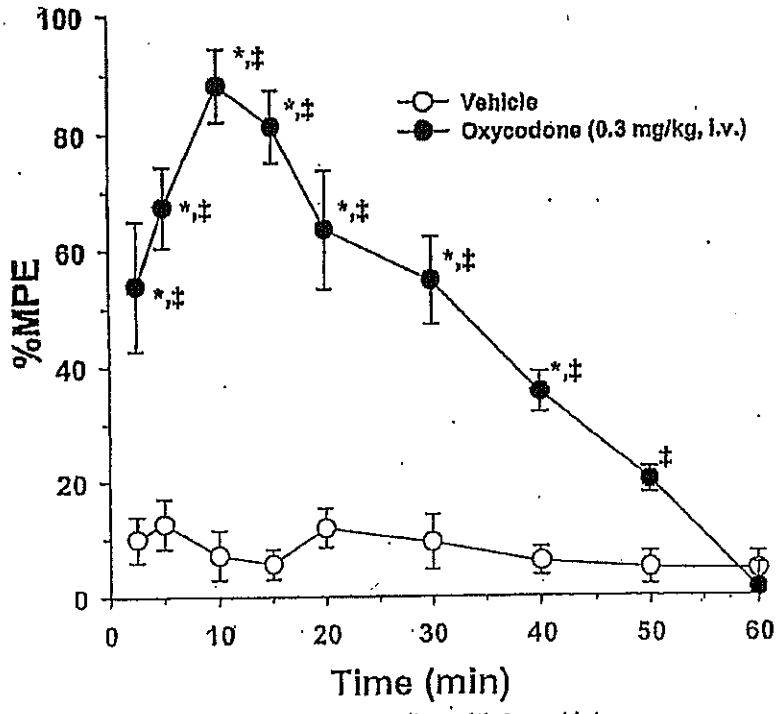


Fig.44 Determination of the Peak Time of Intravenous Oxycodone Antinociception in Male Sprague Dawley Rats in the 51°C Warm Water Withdrawal test



* p < 0.05, compared to baseline withdrawal latency
‡ p < 0.05, compared to respective vehicle time-point

Fig. 45 Dose Response of Intravenous Oxycodone Antinociception in Male Sprague Dawley Rats In the 51°C Warm Water Withdrawal Test

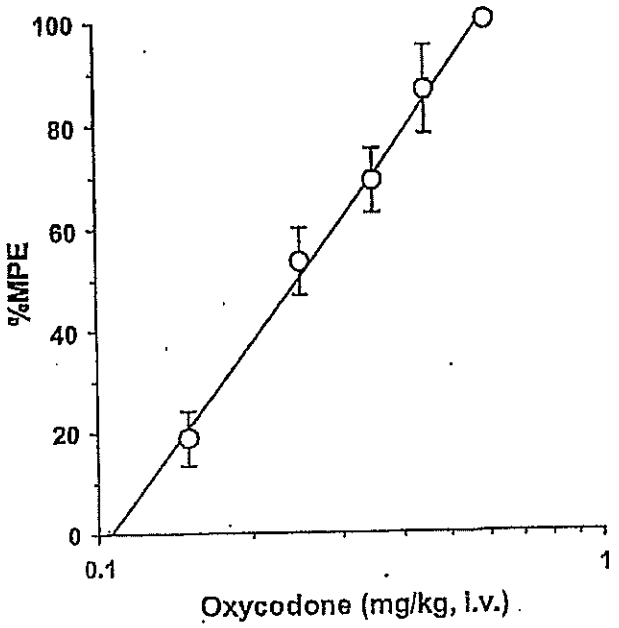
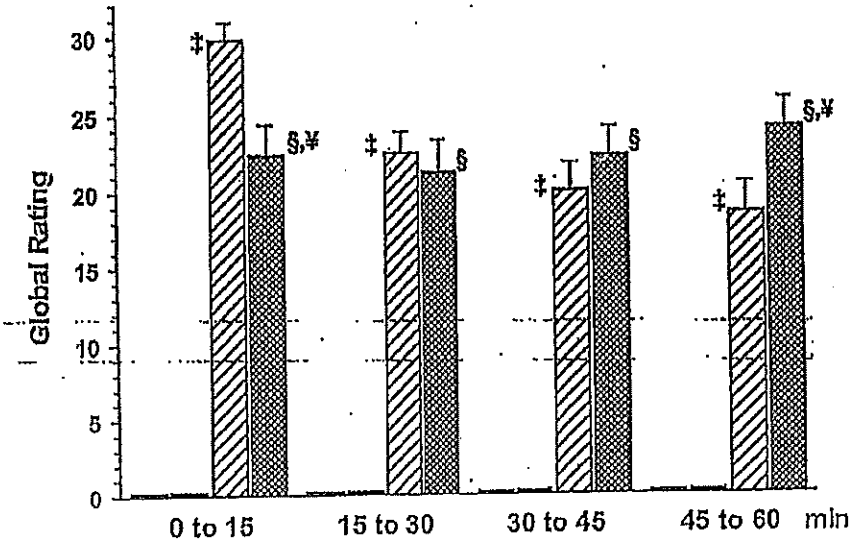
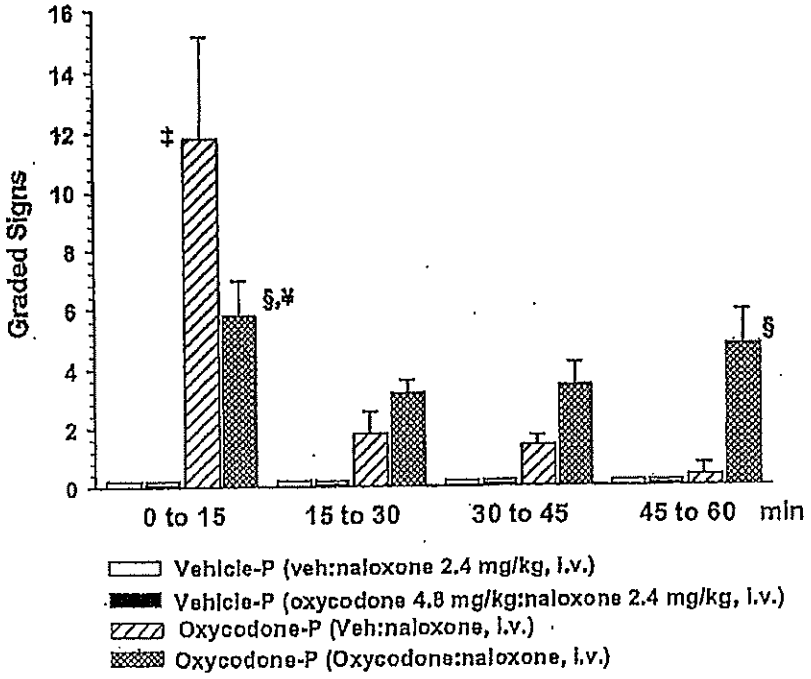


Fig. 46 Global Rating of Withdrawal Precipitation in Oxycodone-Dependent Rats following Intravenous Administration of 2:1 Oxycodone:Naloxone or Vehicle:Naloxone in Oxycodone-Dependent Rats (Oxycodone-P) - A Comparison with Naïve animals (Vehicle-P)



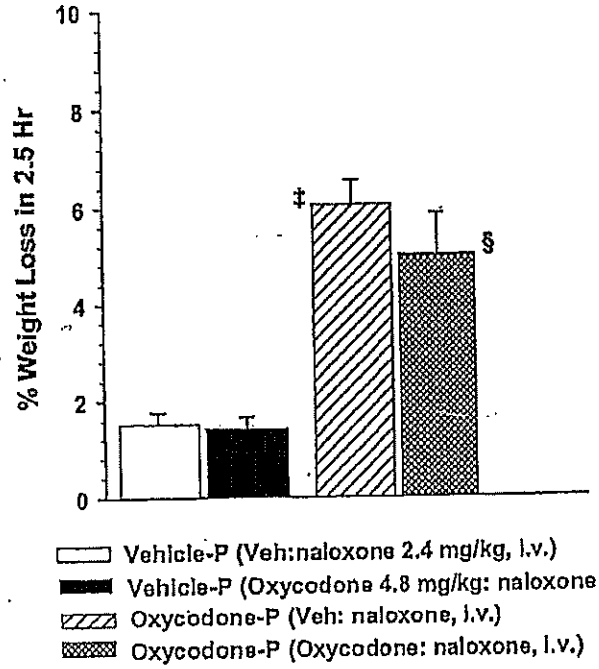
‡ $p < 0.05$, compared to vehicle-P (veh:naloxone 2.4 mg/kg, i.v.)
§ $p < 0.05$, compared to vehicle-P (oxycodone 4.8 mg/kg:naloxone 2.4 mg/kg, i.v.)
¥ $p < 0.05$, compared to oxycodone-P (veh:naloxone, i.v.)

Fig.47 **Precipitation of Graded Withdrawal Signs of Wet-Dog Shakes and Escape Attempts with Intravenous Oxycodone:Naloxone 2:1 or Vehicle:Naloxone in Oxycodone-Dependent Rats(Oxycodone-P) - A Comparison with Naïve animals (Vehicle-P)**



‡ $p < 0.05$, compared to vehicle-P (veh:naloxone 2.4 mg/kg, i.v.)
§ $p < 0.05$, compared to vehicle-P (oxycodone 4.8 mg/kg:naloxone 2.4 mg/kg, i.v.)
¥ $p < 0.05$, compared to oxycodone-P (veh:naloxone, i.v.)

Fig. 48 · **Weight Loss Following 2.5 h of Withdrawal Precipitated by Administration of Intravenous Oxycodone:Naloxone 2:1 or Vehicle:Naloxone In Oxycodone-Dependent Rats(Oxycodone-P) - A Comparison with Naïve animals (Vehicle-P)**



‡ $p < 0.05$, compared to vehicle-P (veh:naloxone 2.4 mg/kg, i.v.)
§ $p < 0.05$, compared to vehicle-P (oxycodone 4.8 mg/kg:naloxone 2.4 mg/kg, i.v.)

Fig. 49 Sumscores for Elicited Naloxone Typical Adverse events at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Sumscores	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 4 (Maintenance)*										
N (n†)	15 (1)	17 (5)	16 (0)	15 (3)	15 (6)	28 (6)	16 (5)	31 (8)	11 (2)	21 (2)
Mean	0.1	0.4	0.0	0.7	1.1	0.7	0.8	0.6	0.4	0.4
SD	0.26	0.71	0.0	1.71	2.12	1.44	1.47	1.38	0.81	1.43
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-0	0-6	0-8	0-4	0-4	0-6	0-2	0-6
Visit 5 (End of Maintenance)*										
N (n†)	14 (1)	17 (4)	15 (1)	14 (0)	14 (4)	28 (4)	12 (0)	29 (3)	10 (1)	19 (1)
Mean	0.1	0.3	0.1	0.0	0.4	0.4	0.0	0.1	0.2	0.1
SD	0.27	0.59	0.26	0.0	0.85	0.98	0.0	0.31	0.63	0.23
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-1	0-0	0-3	0-4	0-0	0-1	0-2	0-1
Entire Maintenance Phase**										
N (n†)	15 (3)	17 (9)	16 (3)	15 (5)	15 (9)	29 (10)	16 (6)	31 (12)	11 (4)	21 (9)
Mean	0.4	0.9	0.3	1.1	1.5	1.2	1.1	1.3	0.8	1.0
SD	1.06	1.11	0.58	1.96	2.20	1.93	1.81	1.88	1.33	1.66
Median	0.0	1.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-4	0-4	0-2	0-6	0-8	0-6	0-6	0-6	0-4	0-7

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited naloxone typical side effect

Fig. 50 Sumscores for Elicited Naloxone Typical Adverse events at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Sumscores	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 4 (Maintenance)*				
N (n†)	48 (6)	47 (6)	47 (14)	43 (12)
Mean	0.2	0.3	0.8	0.9
SD	0.48	1.07	1.47	1.84
Median	0.0	0.0	0.0	0.0
Min-Max	0-2	0-6	0-6	0-8
Visit 5 (End of Maintenance)*				
N (n†)	46 (6)	42 (4)	43 (4)	41 (5)
Mean	0.2	0.1	0.2	0.2
SD	0.42	0.40	0.57	0.80
Median	0.0	0.0	0.0	0.0
Min-Max	0-2	0-2	0-3	0-4
Entire Maintenance Phase**				
N (n†)	48 (15)	47 (17)	47 (18)	44 (20)
Mean	0.5	0.8	1.2	1.4
SD	0.97	1.43	1.94	2.06
Median	0.0	0.0	0.0	0.0
Min-Max	0-4	0-7	0-6	0-8

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited naloxone typical side effect

Fig. 51 Sumscores for Elicited Opioid Typical Adverse events at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Sumscores	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 3 (Randomization)*										
N (n†)	17 (2)	17 (5)	16 (3)	15 (3)	17 (6)	32 (3)	17 (10)	32 (10)	11 (1)	22 (8)
Mean	0.4	1.0	0.4	0.2	0.7	0.3	1.5	1.0	0.5	0.9
SD	1.22	1.77	1.02	0.41	1.10	0.95	1.66	1.82	1.51	1.36
Median	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-4	0-1	0-3	0-5	0-5	0-7	0-5	0-4
Visit 4 (Maintenance)*										
N (n†)	15 (4)	17 (10)	16 (4)	15 (5)	15 (7)	28 (6)	16 (8)	31 (10)	11 (1)	21(10)
Mean	0.7	1.0	0.5	0.5	1.7	0.5	1.4	0.6	0.4	0.9
SD	1.40	1.27	1.03	0.83	2.96	1.29	2.22	1.09	1.21	1.18
Median	0.0	1.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0
Min-Max	0-5	0-5	0-3	0-2	0-10	0-5	0-8	0-5	0-4	0-4
Visit 5 (End of Maintenance)*										
N (n†)	14 (2)	17 (7)	15 (2)	14 (0)	14 (2)	28 (0)	12 (1)	29 (4)	10 (1)	19(4)
Mean	0.6	1.1	0.3	0.0	0.3	0.0	0.1	0.3	0.2	0.3
SD	1.50	1.56	0.70	0.0	0.83	0.0	0.29	0.75	0.63	0.56
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-2	0-0	0-3	0-0	0-1	0-3	0-2	0-2
Visit 6 (End of Follow-up)*										
N (n†)	13 (1)	17 (5)	15 (0)	14 (1)	13 (4)	26 (0)	12 (0)	28 (2)	10 (0)	18 (2)
Mean	0.1	0.5	0.0	0.1	0.5	0.0	0.0	0.1	0.0	0.1
SD	0.28	1.07	0.0	0.27	0.78	0.0	0.0	0.59	0.0	0.32
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-4	0-0	0-1	0-2	0-0	0-0	0-3	0-0	0-1
Entire Maintenance Phase**										
N (n†)	15 (5)	17 (13)	16 (7)	15 (7)	15 (9)	29 (11)	16 (10)	31 (14)	11 (4)	21 (11)
Mean	1.0	2.1	0.9	0.8	2.2	1.1	1.9	1.0	0.8	1.3
SD	1.69	1.82	1.26	0.94	2.91	2.01	2.42	1.43	1.33	1.83
Median	0.0	2.0	0.0	0.0	2.0	0.0	1.0	0.0	0.0	1.0
Min-Max	0-5	0-6	0-4	0-2	0-10	0-8	0-8	0-5	0-4	0-6

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited opioid typical side effect

Fig. 52 Sumscores for Elicited Opioid Typical Adverse events at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Sumscores	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	50 (10)	49 (15)	49 (16)	48 (10)
Mean	0.6	0.9	0.9	0.3
SD	1.39	1.67	1.53	0.75
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-7	0-5	0-3
Visit 4 (Maintenance)*				
N (n†)	48 (16)	47 (16)	47 (17)	43 (14)
Mean	0.7	0.7	0.8	0.9
SD	1.23	1.26	1.63	1.94
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-8	0-10
Visit 5 (End of Maintenance)*				
N (n†)	46 (11)	42 (7)	43 (3)	41 (2)
Mean	0.7	0.3	0.1	0.1
SD	1.34	0.63	0.50	0.49
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-2	0-3	0-3
Visit 6 (End of Follow-up)*				
N (n†)	45 (6)	41 (2)	41 (2)	39 (5)
Mean	0.2	0.0	0.1	0.2
SD	0.70	0.22	0.49	0.51
Median	0.0	0.0	0.0	0.0
Min-Max	0-4	0-1	0-3	0-2
Entire Maintenance Phase**				
N (n†)	48 (25)	47 (23)	47 (23)	44 (20)
Mean	1.3	1.2	1.2	1.4
SD	1.67	1.61	1.88	2.27
Median	1.0	0.0	0.0	0.0
Min-Max	0-6	0-6	0-8	0-10

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited opioid typical side effect