Back-Up Slides

Source for up to 77% incidence of Flushing with Acurox: Table 12.2.2 from Sponsor's Study 109 final report, page 46

Table 12.2.2 Summary of Adverse Events Occurring in Two or More Subjects by Body System and MedDRA Preferred Term

	Treatment A Acurox (1 × 5 mg/30 mg) (N=26)	Treatment B Acurox (2 × 5 mg/30 mg) (N=26)
Body System/Preferred Term	**Subject**	**Subject**
Gastrointestinal Disorders		
Abdominal pain	0 (0%)	3 (12%)
Constipation	9 (35%)	2 (8%)
Dry mouth	0 (0%)	2 (8%)
Nausea	4 (15%)	15 (58%)
Vomiting	0 (0%)	7 (27%)
General Disorders and Administration Site Condition		
Fatigue	0 (0%)	2 (8%)
Nervous System Disorders		
Confusional state	3 (12%)	0 (0%)
Headache	3 (12%)	8 (31%)
Psychiatric Disorders		
Somnolence	4 (15%)	4 (15%)
Vascular Disorders		
Dizziness	7 (27%)	8 (31%)
Vasodilatation	11 (42%)	20 (77%)

Percentages of subjects (Incidence of AE) are based on the number of subject exposure to each study drug.

Do AEs of "vasodilatation" in this NDA = "flushing"?

- From Sponsor's NDA Section 2.7.4, "Summary of Clinical Safety" pg 33, *Analysis of Adverse Events* (quoting verbatim)*:*
  - "*With Acurox® Tablets, the most frequently reported TEAEs were nausea, vomiting, flushing (or related events such as hot flush, feeling hot, and vasodilatation)…*
  - *…Because of limitations in study design, TEAEs common to both niacin and oxycodone were not always differentiated*."

- *Jungnickel PW et al 1997*: 42 subjects given 500 mg IR niacin

	Mean (SD)					
Symptom	15 Minutes	30 Minutes	60 Minutes	120 Minutes	Peak Intensity*	Intensity-Time Factor†
Flushing						
Placebo (P)	3.00 (3.30)	4.18 (2.92)	3.88 (2.72)	1.77 (2.24)	5.69 (2.87)	12.83 (7.75)
Aspirin 325 mg	2.88 (3.01)	2.36 (2.37)	1.81 (1.61)	1.21 (1.80)	3.88 (2.86)	8.26 (6.97)
Aspirin 650 mg	2.24 (2.39)	2.27 (2.47)	1.83 (2.30)	1.10 (1.88)	3.55 (2.74)	7.75 (6.97)
p Value‡	.314	<.001	<.001	.142	<.001	<.001

Meals in Studies 101 and 107

- 101: low-fat breakfast
  - 1 plain bagel, sliced and toasted
  - 0.5 ounces of blackberry jelly
  - 1.5 ounces of raisins
  - 8 ounces of 2% milk
- 107: standardized high-fat breakfast
  - two fried eggs
  - hash browns
  - two fried bacon strips
  - toast, butter, and whole milk,

Food references in niacin labels

- **Niaspan:**
  - "*NIASPAN should be taken at bedtime with a low-fat snack…Flushing…[is]…greatly reduced by…avoiding administration on an empty stomach*."
- **Niacor:**
  - "*Start with…a single daily dose following the evening meal…Flushing…[is] greatly reduced by…avoiding administration on an empty stomach*."

NSAID references in niacin labels

- **Niaspan:**
  - "*Flushing of the skin may be reduced in frequency or severity by pretreatment with aspirin (up to the recommended dose of 325 mg taken 30 minutes prior to NIASPAN dose).*"
- **Niacor:**
  - "*Flushing of the skin appears frequently and can be minimized by pretreatment by aspirin or NSAIDs*."

http://forum.opiophile.org/showthread.php?t=29589 (accessed 4/20/10)

- *In fact alot of people on here reckon a fatty meal before…makes it come on better etc.*
- *yeah any good fatty meal will make roxies work better in my experience*
- *Peanut butter and jelly with opiates used to be my trademark…Usually, I prefer to take opiates with food or on a full stomach. My stomach becomes upset if I don't.*
- *most of the people agree that after having a nice fatty meal your dose feels stronger*
- *in my experience a fatty meal about 10 minutes after i take oxycodone helps potentiate tremendously.*
- *the high fat content in peanut butter and peanut oil would potentiate your dose or increase the levels of Oxycodone in your bloodstream. When given with a high fat meal, peak plasma levels increased by 25%*

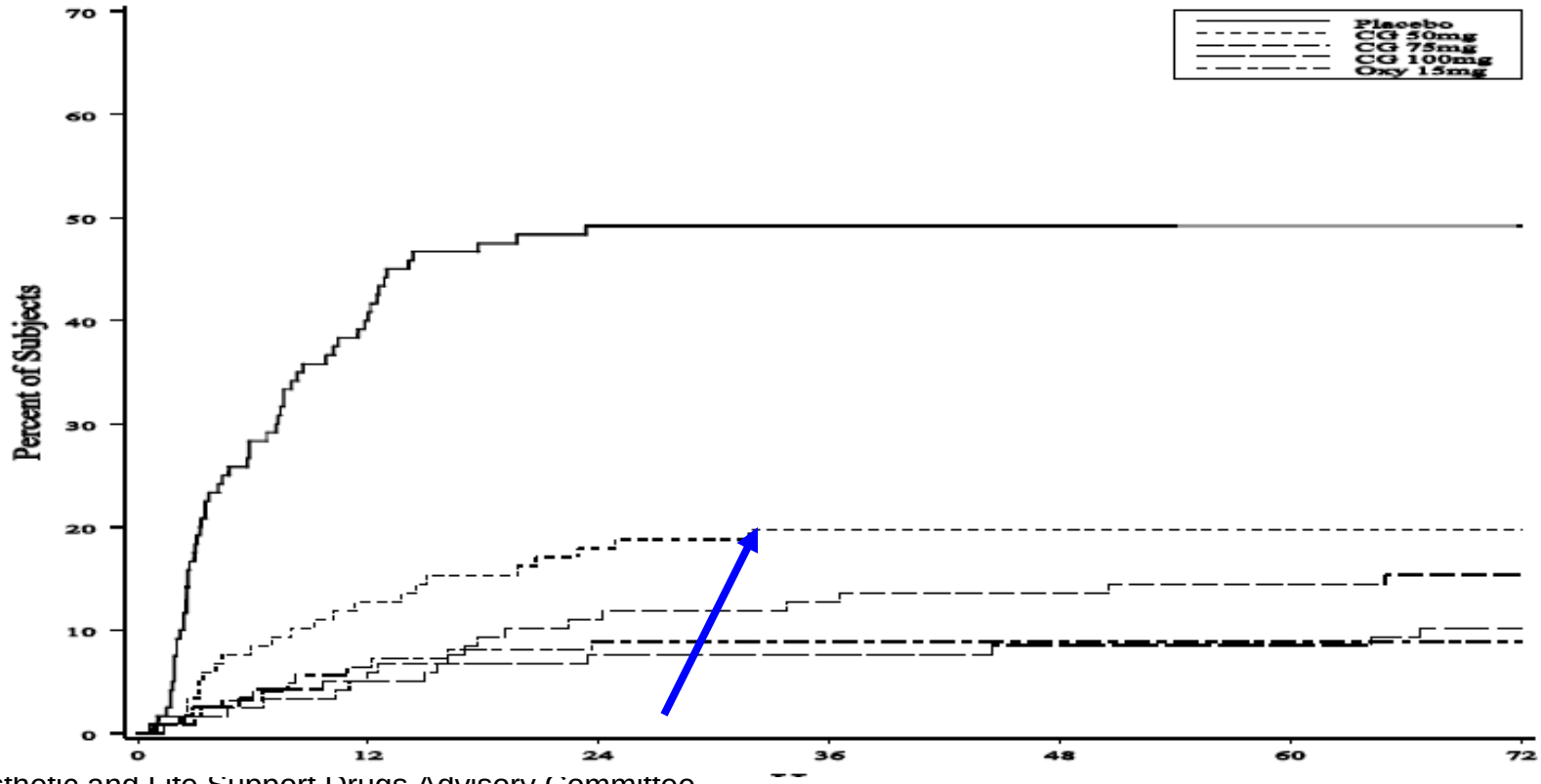
Rescue in Study 105

Secondary Endpoint	Placebo (N=136)	Acurox 2 x 5/30mg (N=135)	P-value: Acurox 2 x 5/30mg vs placebo	Acurox 2 x 7.5/30mg (N=135)	P-value: Acurox 2 x 7.5/30mg vs placebo
Number and % Patients Requiring Rescue Medication	132 (97.1%)	119 (88.1%)	0.0038	111 (82.8%)	<0.0001

Recent NDA – rate of rescue

(bunionectomy study – mostly females)

Figure 3: Time to Rescue Medication
(Study R331333-PAI-3003; KF5503/32)



Oxycontin Label				Niaspan Label				
	Placebo (n=45) (%)	OxyContin (n=227) (%)	IR oxycodone (n=225) (%)	Placebo (n = 157 (%)	500 mg (n=87) (%)	1000 mg (n = 110) (%)	1500 mg (n = 136) (%)	2000 mg (n = 95) (%)
Constipation	7	23	26					
Nausea	11	23	27	7	5	6	4	11
Somnolence	4	23	24					
Dizziness	9	23	16					
Pruritus	2	13	12	2	8	0	3	0
Vomiting	7	12	14	4	0	2	4	9
Headache	7	7	8					
Dry Mouth	2	6	7					
Asthenia	0	6	7					
Sweating	2	5	6					
Flushing				19	68	69	63	55
Cough, Incr				6	3	2	< 2	8
Rash				0	5	5	5	0
Diarrhea				13	7	10	10	14

Phase 2/3 Studies

Adverse Events Occurring in ?1% of Subjects						
System Organ Class Preferred Term	Number of Subjects, n (%)					
	105 -Bunionectomy			103 - normals		
	Placebo (N=136)	Acurox® 10/60 mg (N=135)	Acurox® 15/60 mg (N=134)	Acurox® 5/0 mg (N=22)	Acurox® 5/30 mg (N=22)	Acurox® 5/60 mg (N=22)
Gastrointestinal Disorders						
Nausea	14 (10.3)	68 (50.4)	83 (61.9)	8 (36.4)	4 (18.2)	5 (22.7)
Vomiting	5 (3.7)	46 (34.1)	67 (50.0)	1 (4.5)	0 (0.0)	2 (9.1)
Constipation	1 (0.7)	4 (3.0)	6 (4.5)	1 (4.5)	1 (4.5)	1 (4.5)
Dry mouth	0 (0.0)	1 (0.7)	4 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.7)	2 (1.5)	0 (0.0)	1 (4.5)	1 (4.5)
Diarrhea	5 (3.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)	2 (9.1)
Nervous System Disorders						
Dizziness	6 (4.4)	22 (16.3)	32 (23.9)	5 (22.7)	3 (13.6)	0 (0.0)
Headache	3 (2.2)	13 (9.6)	11 (8.2)	7 (31.8)	6 (27.3)	4 (18.2)
Somnolence	2 (1.5)	8 (5.9)	6 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	4 (3.0)	3 (2.2)	1 (4.5)	6 (27.3)	5 (22.7)
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)	9 (40.9)	5 (22.7)
Syncope	0 (0.0)	1 (0.7)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Burning sensation	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders						
Flushing	2 (1.5)	22 (16.3)	15 (11.2)	3 (13.6)	7 (31.8)	9 (40.9)
Hypotension	1 (0.7)	2 (1.5)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders						
Pruritus	1 (0.7)	17 (12.6)	13 (9.7)	6 (27.3)	5 (22.7)	9 (40.9)
Pruritus generalised	1 (0.7)	9 (6.7)	10 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperhidrosis	0 (0.0)	4 (3.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	2 (1.5)	2 (1.5)	3 (2.2)	0 (0.0)	1 (4.5)	1 (4.5)
General Disorders and Administration Site Conditions						
Adverse drug reaction	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	7 (31.8)	5 (22.7)
Feeling hot	1 (0.7)	6 (4.4)	5 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza like illness	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (1.5)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and Infestations						
Cellulitis	2 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Postop wound infection	3 (2.2)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders						
Palpitations	0 (0.0)	2 (1.5)	2 (1.5)	0 (0.0)	0 (0.0)	1 (4.5)
Tachycardia	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Pooled Group 1 AEs

System Organ Class Preferred Term	Number of Dose Exposures, n (%)					
	Acurox® 5/30 mg Fed (N=27)	Acurox® 5/30 mg Fasted (N=51)	Acurox® 10/60 mg Fasted (N=50)	Acurox® 15/90 mg Fasted (N=63)	Roxicodone® 15 mg Fasted (N=40)	Total Dose Exposures (N=231)
Any TEAE	**6 (22.2)**	**22 (43.1)**	**33 (66.0)**	**32 (50.8)**	**18 (45.0)**	**111 (48.1)**
Nervous System Disorders						
Confusional state	0 (0.0)	3 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)
Dizziness	3 (11.1)	8 (15.7)	12 (24.0)	16 (25.4)	10 (25.0)	49 (21.2)
Headache	3 (11.1)	3 (5.9)	8 (16.0)	2 (3.2)	1 (2.5)	17 (7.4)
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	2 (5.0)	3 (1.3)
Somnolence	0 (0.0)	4 (7.8)	4 (8.0)	0 (0.0)	0 (0.0)	8 (3.5)
Syncope vasovagal	0 (0.0)	1 (2.0)	0 (0.0)	9 (14.3)	5 (12.5)	15 (6.5)
Gastrointestinal Disorders						
Abdominal pain	1 (3.7)	1 (2.0)	3 (6.0)	0 (0.0)	0 (0.0)	5 (2.2)
Constipation	1 (3.7)	9 (17.6)	2 (4.0)	0 (0.0)	0 (0.0)	12 (5.2)
Dry mouth	0 (0.0)	1 (2.0)	2 (4.0)	0 (0.0)	0 (0.0)	3 (1.3)
Nausea	2 (7.4)	4 (7.8)	17 (34.0)	10 (15.9)	7 (17.5)	40 (17.3)
Vomiting	0 (0.0)	0 (0.0)	8 (16.0)	9 (14.3)	6 (15.0)	23 (10.0)
Vascular Disorders						
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	1 (2.5)	4 (1.7)
Vasodilatation	0 (0.0)	11 (21.6)	25 (50.0)	4 (6.3)	0 (0.0)	40 (17.3)
Skin and Subcutaneous Tissue Disorders						
Pruritus	0 (0.0)	1 (2.0)	1 (2.0)	3 (4.8)	2 (5.0)	7 (3.0)
Vasodilatation	0 (0.0)	0 (0.0)	1 (2.0)	6 (9.5)	0 (0.0)	7 (3.0)
General Disorders and Administration Site Conditions						
Fatigue	0 (0.0)	1 (2.0)	2 (4.0)	1 (1.6)	0 (0.0)	4 (1.7)

Study 105 ALT/ASTs

	placebo (N=136)	Any Acurox (N=269)
# of patients >3xULN for both ALT & AST	0	2
# of patients >3xULN for only ALT	0	2

- recall no bilirubins drawn
- studies 103 (N=66) or 109 (N=26) no LFT Δs

Glucose: from Niaspan label

- "*Niacin treatment can increase fasting blood glucose.*
- *Frequent monitoring of blood glucose should be performed to ascertain that the drug is producing no adverse effects.*
- *Diabetic patients may experience a dose-related increase in glucose intolerance*."

Glucose

- In Study 111 , increase in mean blood glucose noted on Day 11 (102.73 mg/dL) as compared with Baseline (91.43 mg/dL)
- Subject 028 had blood glucose of 124 mg/dL at Baseline, and 285 mg/dL at Day 11.
  - Urinalysis showed negative glucose and ketones.
  - Subject had no known pervious history of diabetes and no evidence of a protocol violation otherwise.

Unbalance in Sequence

	Seq	# of Subjests		Seq	# of Subjests
Study 102	1	6	Study 111	11	8
	2	4		12	9
	3	4		13	8
	4	5		21	13
				22	12

Summary Statistics on Emax for Three Measures of Interest (Study 102, N=19)

Abuse Potential Measure	TRT	Mean	Std Err	Min	Q1	Med	Q3	Max
Like Effect VAS	N0	12.63	2.07	2	4	10	22	29
	N240	10.26	1.87	1	3	10	15	29
	N480	9.84	1.92	1	2	8	15	29
	N600	8.68	1.78	1	2	5	15	29
	N600*	10.37	2.20	1	2	5	20	29
Dislike Effect VAS	N0	5.63	1.88	1	1	1	8	29
	N240	9.05	2.23	1	1	4	16	29
	N480	11.26	2.34	1	2	9	17	29
	N600	13.84	2.89	1	1	10	29	29
	N600*	5.47	1.72	1	1	1	10	28
ARCI MBG	N0	5.53	1.32	0	0	2	12	14
	N240	4.05	1.04	0	0	2	10	12
	N480	4.68	1.19	0	0	2	11	14
	N600	4.47	1.23	0	0	3	10	15
	N600*	4.53	1.14	0	0	3	10	14

Summary Statistics on Emax (or Emin) for Three Measures of Interest (Study 111, N=25)

Abuse Potential Measure	TRT	Mean	Std Err	Min	Q1	Med	Q3	Max
Emax of Like/Dislike Effect VAS	N240	16.96	0.81	15	15	15	16	28
	N240+O40	19.12	0.90	15	15	18	22	29
	P	15.12	0.09	15	15	15	15	17
	N240+O40*	20.4	0.97	15	15.5	19	23.5	29
	O40*	20.6	0.81	15	18	20	22.5	29
Emin of Like/Dislike Effect VAS	N240	8.44	1.24	1	1.5	7	15	15
	N240+O40	10.24	1.33	1	3.5	13	15	25
	P	13.92	0.75	1	15	15	15	15
	N240+O40*	12.04	1.17	1	7.5	15	15	20
	O40*	14.28	0.55	4	15	15	15	17
ARCI MBG	N240	2.72	0.76	0	0	1	4.5	13
	N240+O40	4.84	1.05	0	0	4	10.5	14
	P	0.32	0.25	0	0	0	0	6
	N240+O40*	6.52	1.05	0	1	6	11.5	15
	O40*	5.76	1.03	0	0.5	4	11	14

Analysis Results on Emax (or Emin) during 2 Hours after Dosing (Part 1 of Study 111)

Treatment	Emax of Like		Emin of Dislike		Emax of MBG	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
N240	15.10	0.87	7.93	0.93	2.70	0.65
N240+O40	17.30	0.87	10.30	0.93	4.50	0.65
P	15.00	0.87	14.17	0.93	0.30	0.65
Comparison	**Emax of Like**		**Emin of Dislike**		**Emax of MBG**	
	LSm Diff	StdErr	LSm Diff	StdErr	LSm Diff	StdErr
N240 vs. N240+O40	-2.20 (*)	1.05	-2.37	1.2002	-1.80	0.80
N240 vs. P	0.10	1.05	-6.23 (*)	1.2002	2.4 (*)	0.80
N240+O40 vs. P	2.30 (*)	1.05	-3.87 (*)	1.2002	4.2 (*)	0.80

Analysis Results on Emax (or Emin) during 2 Hours after Dosing (Part 2 in Study 111)

Treatment	Emax of Like		Emin of Dislike		Emax of MBG	
	LSmean	StdErr	LSmean	StdErr	LSmean	StdErr
N240+O40	17.97	0.82	11.70	0.85	5	0.87
O40	18.73	0.82	15.53	0.85	4.13	0.87
Comparison	Emax of Like		Emin of Dislike		Emax of MBG	
	LSm Diff	StdErr	LSm Diff	StdErr	LSm Diff	StdErr
N240+O40 vs. O40	-0.77	0.82	-2.83	1.20	0.87	0.73