TABLE 13 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
BUN mg/dl (10-25)	2.5 mg	8	13.1	3.09	1.50	3.51
	5.0 mg	8	12.8	2.87	1.75	2.92
	10.0 mg	8	14.5	6.19	0.13	5.25
	15.0 mg	8	11.8	3.28	3.38(*)	4.47
	20.0 mg	8	12.3	3.24	5.88***	1.64
	Placebo	10	11.6	3.10	1.80	4.44
URIC ACID mg/dl (2.5-8.5)	2.5 mg	8	6.0	1.38	-1.01*	0.87
	5.0 mg	8	6.0	1.03	-1.00**	0.61
	10.0 mg	8	6.4	0.86	-0.66 (*)	1.09
	15.0 mg	8	6.2	1.13	-0.86*	0.96
	20.0 mg	8	6.0	1.01	-1.20***	0.58
	Placebo	10	6.3	0.76	-0.60(*)	0.88

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
FAS GLUCOSE mg/dl (70-110)	2.5 mg	8	91.3	6.88	8.25*	6.84
	5.0 mg	8	96.6	4.24	11.63**	6.39
	10.0 mg	8	99.9	14.91	5.50	15.58
	15.0 mg	8	95.1	9.09	8.75**	6.94
	20.0 mg	8	91.8	8.84	6.75(*)	9.69
	Placebo	10	96.8	6.13	4.80*	5.83
TOTAL PROTEIN g/dl (6.0-8.5)	2.5 mg	8	6.9	0.22	0.04	0.33
	5.0 mg	8	7.2	0.57	-0.44**	0.35
	10.0 mg	8	7.2	0.40	-0.29*	0.30
	15.0 mg	8	7.1	0.32	-0.11	0.23
	20.0 mg	8	7.2	0.43	-0.20	0.43
	Placebo	10	7.0	0.34	-0.18	0.42

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
ALBUMIN g/dl (3.2-5.5)	2.5 mg	8	4.5	0.14	0.00	0.19
	5.0 mg	8	4.6	0.31	-0.30**	0.21
	10.0 mg	8	4.6	0.24	-0.20*	0.22
	15.0 mg	8	4.6	0.20	-0.06	0.15
	20.0 mg	8	4.6	0.24	-0.16	0.23
	Placebo	10	4.5	0.16	-0.12	0.25
TOTAL BILIRUBIN mg/dl (0.2-1.1)	2.5 mg	8	0.5	0.22	-0.15(*)	0.20
	5.0 mg	8	0.4	0.11	-0.16*	0.15
	10.0 mg	8	0.6	0.27	-0.30*	0.34
	15.0 mg	8	0.5	0.12	-0.20***	0.08
	20.0 mg	8	0.5	0.19	-0.21*	0.22
	Placebo	10	0.5	0.26	-0.17(*)	0.27

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
CHOLESTEROL mg/dl (140-320)	2.5 mg	8	182.1	24.68	7.88	14.63
	5.0 mg	8	180.0	26.10	-5.50	13.25
	10.0 mg	8	177.8	19.55	0.38	17.63
	15.0 mg	8	187.0	41.62	4.75	16.30
	20.0 mg	8	186.5	17.06	-3.38	24.17
	Placebo	10	180.0	17.08	-1.40	16.30
ALK. PHOSPHATASE U/L (30-115)	2.5 mg	8	78.0	19.36	-1.38	6.70
	5.0 mg	9	78.5	18.86	-5.88*	6.45
	10.0 mg	8	92.1	12.55	-6.13	11.27
	15.0 mg	8	78.4	15.89	5.63**	4.34
	20.0 mg	8	85.3	19.14	-5.88(*)	8.44
	Placebo	10	74.9	10.98	-0.30	7.41

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
LDH U/L (80-225)	2.5 mg	8	155.0	12.98	-5.38	14.32
	5.0 mg	8	168.1	20.36	-20.00*	16.41
	10.0 mg	8	197.8	26.38	2.38	28.64
	15.0 mg	8	207.0	44.91	-43.50*	38.45
	20.0 mg	8	164.8	25.53	-29.75**	21.62
	Placebo	10	164.5	21.73	-2.70	20.14
SGOT U/L (0-41)	2.5 mg	8	17.0	5.50	-0.75	6.41
	5.0 mg	8	15.9	7.61	-1.00	5.71
	10.0 mg	8	19.3	5.68	-1.75	5.50
	15.0 mg	8	17.5	3.63	-1.00	7.41
	20.0 mg	8	18.4	6.00	-4.13*	4.36
	Placebo	10	18.3	3.65	-1.00	4.81

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
SGPT U/L (0-45)	2.5 mg	8	25.0	6.74	-4.50	9.55
	5.0 mg	8	22.8	6.78	-1.88	7.24
	10.0 mg	8	22.4	10.91	0.13	5.92
	15.0 mg	8	23.3	8.16	-8.13*	8.51
	20.0 mg	8	25.3	5.65	-1.00 (*)	4.54
	Placebo	10	20.8	8.09	-0.70	8.81
SODIUM mEq/L (135-145)	2.5 mg	8	140.8	1.28	0.38	1.85
	5.0 mg	8	141.8	1.04	-2.63**	1.51
	10.0 mg	8	141.0	1.20	1.75*	1.56
	15.0 mg	8	141.3	1.39	1.88*	1.96
	20.0 mg	8	143.5	1.31	-0.88(*) ***	1.25
	Placebo	10	142.0	1.94	0.30	3.47

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
POTASSIUM mEq/L (3.5-5.0)	2.5 mg	8	4.3	0.38	-0.01	0.31
	5.0 mg	8	4.3	0.28	0.06	0.40
	10.0 mg	8	4.6	0.52	-0.24	0.48
	15.0 mg	8	4.6	0.56	0.01	0.24
	20.0 mg	8	4.7	0.16	-0.16	0.25
	Placebo	10	4.5	0.45	-0.13	0.37
CHLORIDE mEq/L (95-108)	2.5 mg	8	105.5	1.60	0.38	2.33
	5.0 mg	8	104.0	1.93	1.25(*)	1.75
	10.0 mg	8	104.3	2.87	0.75	2.71
	15.0 mg	8	104.1	1.96	1.50(*)	2.14
	20.0 mg	8	105.4	2.07	0.88	2.48
	Placebo	10	104.4	2.88	0.90	2.92

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 10 (cont'd)

PN 200-110 STUDY #1

LABORATORY DATA - CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. of Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline (Day 2)	S.D.
CO_2 mEq/L (24-32)	2.5 mg	8	25.5	1.51	-0.88	1.89
	5.0 mg	8	27.3	1.04	-1.75*	1.49
	10.0 mg	8	25.5	1.85	0.25	2.44
	15.0 mg	8	25.9	1.81	-0.38	1.85
	20.0 mg	8	26.4	1.41	-0.50	1.41
	Placebo	10	26.7	1.89	-0.50	2.01
CREATININE mg/dl (0.7-1.4)	2.5 mg	8	1.3	0.12	-0.13*	0.15
	5.0 mg	8	1.3	0.23	-0.08	0.16
	10.0 mg	8	1.1	0.12	-0.10*	0.12
	15.0 mg	8	1.1	0.13	-0.03	0.09
	20.0 mg	8	1.1	0.11	0.03	0.10
	Placebo	10	1.2	0.25	-0.13(*)	0.20

(*) $p < .10$, * $p < .05$, ** $p < .01$, *** $p < .001$

TABLE 16

PN 200-110 STUDY #1
SUMMARY OF ADVERSE EFFECTS

Subj.	Adverse Reaction	Hours Post Dose	Duration (Hrs.)	Severity	Due to Drug
		2.5 mg Dose Group			
101	Headache	9	6	Mild	Yes
102	Headache	9	7	Mild	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction: 2/8 = 25%					
		5.0 mg Dose Group			
204	Lightheadedness	3	3	Mild	Yes
206	Headache	5	3	Mild	Yes
207	Headache	1	7	Mild	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction: 3/8 = 38%					
		10.0 mg Dose Group			
301	Lightheadedness	.33	3	Mild	Yes
302	Tiredness		4	Mild	No
304	Headache	3	4	Mild	Yes
305	Headache	1	6	Mild	Yes
309	Headache	6	.02	Mild	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction: 5/8 = 63%					
		15.0 mg Dose Group			
402	Lightheadedness	2	1	Mild	Yes
407	Headache	1	10	Mild	Yes
408	Lightheadedness	1	1	Mild	Yes
408	Sleepiness	1	5	Mild	Unc.
408	Warm Ears	1	1	Mild	Unc.
408	Headache	1	10	Mild	Yes
408	Weakness	1	1	Mild	Unc.
408	Feels Jittery	1	1	Mild	Unc.
408	Cold Body	1	5	Mild	Unc.
409	Pulsating Sens.	1	1	Mild	Unc.
409	Lightheadedness	0.5	1	Mild	Yes
409	Headache	1	1	Mild	Yes
410	Headache	6	4	Mild	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction: 5/8 = 63%					

TABLE 16 (cont'd)

PN 200-110 STUDY #1
SUMMARY OF ADVERSE REACTIONS

Subj.	Adverse Reaction	Hours Post Dose	Duration (Hrs.)	Severity	Due to Drug
		20.0 mg Dose Group			
501	Headache	3	7	Mild	Yes
502	Headache	3	1	Mild	Yes
504	Inc.Heartbeat	1	6	Mild	Unc.
504	Headache	3	6	Mild	Yes
505	Headache	3	8	Mild	Yes
505	Drowsiness	4	1	Mild	Unc.
506	Lightheadedness	1	1	Mild	Yes
506	Headache	3	4	Mild	Yes
508	Headache	1	11	Mild	Yes
508	Nausea	1	8	Mild	Yes
508	Lightheadedness	1	6	Mild	Yes
508	Emesis	2	.02	Mild	Yes
508	Emesis	3	.02	Mild	Yes
508	Emesis	4	.06	Mild	Yes
508	Emesis	9	.08	Mild	Yes
508	Hot Flash	6	.03	Mild	Yes
509	Headache	3	4	Mild	Yes
510	Lightheadedness	1	1	Mild	Yes
510	Headache	2	3	Mild	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction: 8/8 = 100%					
		Placebo Group			
209	Headache	1	2	Mild	Yes
209	Eyes Burn/Ache	1	2	Mild	Unc.
303	Headache	9	3	Mild	Yes
307	Lightheadedness	1	5	Mild	Yes
406	Sleepiness	-	8	Mild	No
Ratio of Subjects Reporting at Least One Adverse Reaction: 4/10 = 40%					

TABLE 17

PH 200-110 STUDY #1

COMPARATIVE FREQUENCY OF SUBJECTS [illegible]NG AN ADVERSE REACTIONS

Adverse Reaction	PH 200-110 Treatment Groups					Placebo
	2.5 mg (N=8)	5 mg (N=8)	10 mg (N=8)	15 mg (N=8)	20 mg (N=8)	(N=10)
Miscellaneous:						
Eyes Burning	0	0	0	0	0	1
Eye Discomfort	0	0	0	0	0	1
Cardiovascular:						
Tachycardia	0	0	0	0	1	0
Gastro-Intestinal:						
Nausea	0	0	0	0	1	0
Vomiting	0	0	0	0	1	0
Central Nervous System:						
Chills	0	0	0	1	0	0
Dizziness	0	1	1	3	3	1
Drowsy	0	0	0	1	1	1
Fatigue	0	0	1	1	0	0
Headache	2	2	3	4	8	2
Nervousness	0	0	0	1	0	0
Excessive Stimulation	0	0	0	1	0	0
Autonomic Nervous System:						
Hot Flashes	0	0	0	0	1	0
Warm Feeling	0	0	0	1	0	0

TABLE 18

PN 200-110 STUDY #1

COMPARATIVE FREQUENCY OF SUBJECTS REPORTING AT LEAST ONE ADVERSE REACTION

Treatment Group	N	Number of Subjects With at Least One Adverse Reaction	Number of Subjects With No Adverse Reactions
2.5 mg	8	2	6
5.0 mg	8	3	5
10.0 mg	8	5	3
15.0 mg	8	5	3
20.0 mg	8	8	0
Placebo	10	4	6

(*)p<.10, *p<.05, **p<.01, ***p<.001

Study 2

Title:

The Evaluation of the Safety and Multiple Dose Toleration of Orally Administered PN 200-110 in Healthy Male Volunteers Compared to Placebo.

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Objective

T tages the safety of PN 200-110 administered orally in multiple doses compared to placebo in healthy male volunteers.

Population

Healthy male volunteers, 18 - 45 years of age were selected for the trial. All subjects had to be healthy with no clinically significant abnormal physical or laboratory findings. Exclusion criteria were those subjects with significant clinical illness within two weeks of study entry, anyone who had received an investigational drug four weeks prior to entry, required concomitant medications including aspirin, history of drug or alcohol abuse within previous year or intolerance to calcium antagonists or any condition that could interfere with absorption, metabolism or excretion of drug.

Study Plan

This was a randomized, double-blind, parallel group, placebo controlled study with 41 subjects. The study was conducted in four stages (I-IV) with each stage assessing safety of a multiple dose schedule. No subject completed more than one stage. All participants were housed at study site for duration of each stage.

Dosage tested was separated in
Stage I: 20 mg/day
Stage II: 10 mg/day
(10 mg bid)
Stage III: 7.5 mg/day
mg/day (5 mg
(7.5 mg

Doses were changed from original protocol by means of amendments 1, 2 and 3. These amendments were made to provide for a reduction in dose following reports of adverse reactions after 10 mg bid schedule in Stage I. The other amendments were for safety and tolerance purposes. Later dosing adjustments were made depending on results from the previous stage.

Eight subjects received PN 200-110 in stage I and 7 were in each of the other stages. Three received placebo in each stage. During bid period, drug was given 8.00 am and 8.00 pm while ~~during tid period, it was administered 7.00 am, 1.00 pm and 7.00~~ pm. No food was permitted from midnight until 2 hours after 8.00 am (or 7.00 am) dose. Subjects were followed for 32 hours post dose. No subject could participate in more than one stage and no stage began until the preceeding one had been completed and safety of that dose schedule established. The time interval between stages was at least four days.

Evaluation

Subjects were evaluated as per schedule in Table 1. Safety was assessed by clinical signs, ECGs, clinical laboratory tests, vital signs etc. Vital signs of sitting blood pressure and pulse rate were recorded at 0.5, 1, 2, 4 and 8 hours after morning dose in stage I and 0.5, 1, 2 and 4 hours after evening dose. For other stages, recordings were obtained at 0.5, 1, 2 and 4 hours post dose. Standing blood pressures and pulse rates were recorded prior to each dose and 1, 2 and 4 hours post dose. ECG was obtained at screening and at 10 am daily.

Results

A total of 41 subjects were enrolled and all but one completed. One discontinued for personal reasons on day 2 of Stage I after receiving a total dose of 20 mg. There were no significant differences found between groups for any demographic variable.

There were no newly occurring abnormalities in physical examinations for any subject. Tables 3 - 6 present results from sitting vital signs. In stage I, there were no statistically significant differences from placebo up to 8 hours post dose. There was an increase in pulse rate with statistical significance from 0.5 to 2 hours post dose.

In stage II there were dose related decreases in diastolic blood pressure [illegible] hours post dose and [illegible] 12 hours post dose [illegible]

Stage III results showed no statistically significant differences from placebo and the three PN 200-110 doses up to 8 hours. There was a dose related increase in pulse rate at all times post dose but only 7.5 mg tid was statistically significant compared to placebo at 8 hours.

Stage IV showed no differences from placebo at any dose level except diastolic pressure at 1 hour for 5 mg tid.

There were no significant changes in respiratory rate in any stage. There were no differences from placebo in standing blood pressures. There was a significant increase in body weight in stage IV group (4.7 lbs) compared to placebo.

ECG Changes

Tables 8 - 12 show ECG changes from baseline. Stage I showed statistically significant increases in atrial and ventricular rates 2 hours post dose compared to baseline and to placebo. There was also a statistically significant increase in P-R interval compared to placebo. In stage II, there was a dose related increase in atrial and ventricular rates which were statistically significant from placebo. There were no other statistical differences between groups, except for decrease in Q-T interval with 10 mg bid. Stage III again shows a dose related increase in atrial and ventricular rates but only 7.5 mg tid was statistically significantly different from placebo. There were additional changes in other parameters but only Q-T interval were significantly decreased. Stage IV results are similar to stage III.
Table 12 presents results from final ECGs recorded, day 4 and day 8. These ECGs were recorded 12 hours post dose.

Clinical Laboratory Results.

Tables 14 - 16 summarize results of laboratory tests. In active group, 4/29 had an increase in SGPT, 3 being in stage IV group. There were 2/12 in placebo group with elevated SGPT. Both groups show a mean increase of 25 units on day 8 compared to baseline; PN 200-110 increased 24.7 units and placebo by 25 units. Investigator could not determine etiology of this occurrence. None returned for blood tests after the study was completed. There [illegible] increases in blood glucose and LDH.

Adverse Reactions

Table [illegible] reported during the study. No subjects [illegible]

Discussion.

There were no statistically significant changes in systolic blood pressures compared to placebo at any time point. Diastolic pressures were similar although in doses > 15 mg/day, there were differences from placebo. There were statistically significant differences in pulse rates compared to placebo with a maximum mean increase of 19 bpm in stage II. and 18 bpm in stage III.

Reviewer's Comments.

There are a few points to be aware of in this study:

1. It appears that unless the drug is titrated carefully, subjects experience undue side effects.

2. PN 200-110 causes increases in both atrial and ventricular rates at all strengths.

3. At higher doses there appears to be increases in SGPT. Even though this occurred in placebo subjects as well, it is something that should be carefully monitored.

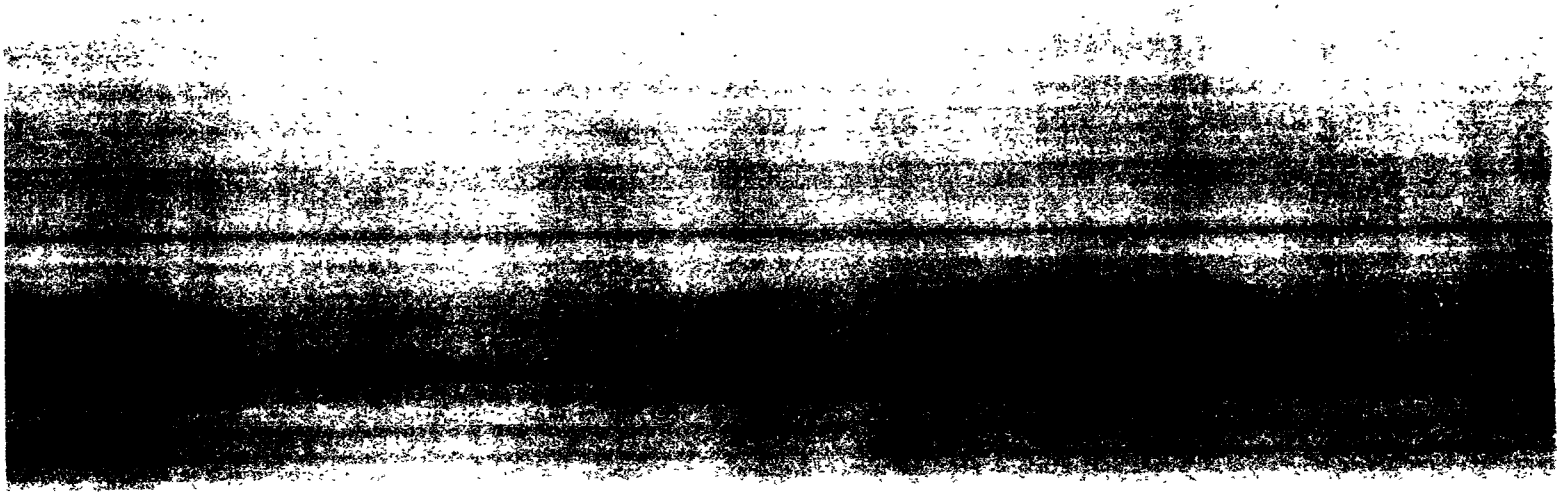

TABLE 1

PN 200-110 STUDY NO. 2

EVALUATION SCHEDULE FOR STAGES I - III (3 DAYS ON DRUG) AND STAGE IV (7 DAYS ON DRUG)

Parameter Evaluated	Screening Evaluations (Within 14 days prior to Dosing)	Evaluations Performed on Study Days No. —			
		Stage I	Stage II	Stage III	Stage IV
Background Information (CRF BK)	X				
Checklist for Subject Selection (CRF IE)	X				
Physical Examination (CRF PE)	X	4	4	4	8
Vital Signs (CRF VS)	X	1-4[b]	1-4[b]	1-4[c,d]	1-8[c,d]
ECG (CRF ECG)	X	1-4	1-4[e]	1-4[e]	1-8
Clinical Laboratory Tests (CRF LAB)	X	4	4	4	4,8
Chest X-ray (CRF CX)	X[a]				
Ophthalmologic Examination (CRF OP)	X	4	4	4	8
Adverse Reaction (CRF AR)		1-4	1-4	1-4	1-8
End of Study Information (CRF ES)		4	4	4	8

[a]The X-ray was taken at any time within 6 months of study entry.

[b]For Stages I and II, vital signs were obtained just prior to each dose and repeated at 0.5, 1, 2, 4, and 8 hours after each morning dose, and at 0.5, 1, 2, and 4 hours after each evening dose.

[c]For Stages III and IV, vital signs were obtained just prior to each dose and repeated at 0.5, 1, 2, and 4 hours after each dose.

[d]In Stages III and IV, standing blood pressures and pulse rates were recorded just prior to each dose and repeated at 0.5, 1, 2 and 4 hours post-dose on Days when the subjects were receiving the maximum dose administered (i.e., Day 3 for Stage III and Days 5-7 for Stage IV).

[e]In addition to the daily 10 A.M. ECG, ECG's were obtained in Stage II at 10 P.M. (days 1-3), and in Stage III at 4 P.M. and 10 P.M. (days 1-3).

TAL 3
PN 200-110 STUDY NO. 2
VITAL SIGNS - SITTING
STAGE I
ANALYSIS OF VARIANCE†

Variable	Dose (bid)	No. Sub-jects	Baseline Mean (pre-initial dose)	Mean Change From Baseline at Hours Post Dose						Mean Change Over Hours 0.5-12
				Hour 0.5	Hour 1	Hour 2	Hour 4	Hour 8	Hour 12	
Systolic Blood Pressure (mm Hg)	PN 10 mg	6	112.0	4.0	7.3(*)	5.8(*)	4.3*	5.2	5.2(*)	5.3(*)
	Placebo	12	112.0	3.0	2.6	1.5	3.0	4.3	-0.5	2.3
Diastolic Blood Pressure (mm Hg)	PN 10 mg	8	79.0	-5.8**	-7.0**	-5.6*	-5.3*	-6.1*	-1.3	-5.2*
	Placebo	12	78.2	-4.7*	-4.0(*)	-3.4(*)	-4.8*	-4.8*	-8.0***	-5.0*
Pulse (per min.)	PN 10 mg	8	73.5	4.3	8.3* (*)	8.3*	9.6**	8.9**	3.0(*)	7.0*
	Placebo	12	68.0	6.4**	6.3**	5.3**	9.8***	7.8**	5.2**	7.3**
Respiratory Rate (per min.)	PN 10 mg	8	16.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Placebo	12	16.0	0.0	0.0	0.0	0.0	0.0	-0.1(*)	0.0(*)

(*) p<.10, * p<.05, ** p<.01, *** p<.001

†Standard deviations and additional descriptive statistics can be found in the Statistical Appendix.

TAble 4
PN 200-110 STUDY NO. 2
VITAL SIGNS - SITTING
STAGE II
ANALYSIS OF VARIANCE†

Variable	Dose (bid)	No. Subjects	Baseline Mean (pre-initial dose)	Mean Change From Baseline at Hours Post Dose						Mean Change Over Hours 0.5-12
				Hour 0.5	Hour 1	Hour 2	Hour 4	Hour 8	Hour 12	
Systolic Blood Pressure (mm Hg)	PN 5 mg	7	112.6	0.0	2.1	1.0	7.6*	6.6(*)	-0.6	2.8
	PN 10 mg	7	112.6	3.9*	5.3*	2.0	1.9	3.3	4.4	3.5(*)
	Placebo	12	112.0	3.0	2.6	1.5	3.0	4.3	-0.5	2.3
Diastolic Blood Pressure (mm Hg)	PN 5 mg	7	78.9	-7.9*	-6.0**	-5.9**	-5.4(*)	0.3	-5.3**	-5.0**
	PN 10 mg	7	78.9	-4.1	-6.3**	-8.5**	-7.4**	-4.7*	-4.6**	-5.9**
	Placebo	12	78.2	-4.7*	-4.0(*)	-3.4(*)	-4.8*	-4.8*	-4.0***	-5.0*
Pulse (per min.)	PN 5 mg	7	63.4	10.6**	12.9***	10.6**	13.1***	13.1*	7.7*	11.3**
	PN 10 mg	7	63.4	10.6*	13.1*	16.1***	19.1***	17.1**	11.9**	14.7**
	Placebo	12	68.0	6.4**	6.3**	5.3**	9.8***	7.8**	8.2**	7.3**
Respiratory Rate (per min.)	PN 5 mg	7	16.0	0.0	0.0	0.0	0.0	0.0	-0.3	-0.1
	10 mg	7	16.0	-0.1	-0.1	0.0	0.0	0.0	-0.1	-0.1
	Placebo	12	16.0	0.0	0.0	0.0	0.0	0.0	-0.1(*)	0.0(*)

(*) p<.10, * p<.05, ** p<.01, *** p<.001

†Standard deviations and additional descriptive statistics can be found in the Statistical Appendix.

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PN 200-11 UD[illegible] 1. 2
VITAL SIGN[illegible] NG
STAG[illegible] .I
ANALYSIS OF VARIANCE†

Variable	Dose (tid)	No. Sub-jects	Baseline Mean (pre-initial dose)	Mean Change From Baseline at Hours Post Dose					Mean Change Over Hours 0.5-8
				Hour 0.5	Hour 1	Hour 2	Hour 4	Hour 8	
Systolic Blood Pressure (mm Hg)	PN 2.5 mg	7	117.4	-0.7	0.9	-3.3	-1.1	2.2	-0.4
	PN 5 mg	7	117.4	-0.1	-1.2	0.1	-0.1	4.9	0.7
	PN 7.5 mg	7	117.4	1.6	2.8	-1.6	3.1	4.0	1.7
	Placebo	12	112.0	3.0	2.6	1.5	3.0	4.3	2.3
Diastolic Blood Pressure (mm Hg)	PN 2.5 mg	7	81.1	-5.1*	-7.2**	-6.7*	-5.5*	-7.5*	-6.4**
	PN 5 mg	7	81.1	-5.4	-7.8**	-5.7(*)	-7.2*	-0.3	-5.3(*)
	PN 7.5 mg	7	81.1	-6.6*	-8.2*	-8.0*	-6.9*	-5.1(*)	-7.1*
	Placebo	12	78.2	-4.7*	-4.0(*)	-3.4(*)	-4.8*	-4.8*	-5.0*
Pulse (per min.)	PN 2.5 mg	7	64.6	3.1	5.4*	2.4	8.4*	8.3**	5.5*
	PN 5 mg	7	64.6	10.6***	9.4*	9.7*	11.6**	8.1(*)	9.9**
	PN 7.5 mg	7	64.6	12.6*	13.3*	10.3*	13.6**	18.0**	13.3**
	Placebo	12	68.0	6.4**	6.3**	5.3**	9.8***	7.8**	7.3**
Respiratory Rate (per min.)	PN 2.5 mg	7	15.7	0.3	0.3	0.3	0.3	0.2	0.3
	PN 5 mg	7	15.7	0.3	0.3	0.3	0.3	0.3	0.3
	PN 7.5 mg	7	15.7	0.3	0.3	0.3	0.3	0.3	0.3
	Placebo	12	16.0	0.0	0.0	0.0	0.0	0.0	0.0(*)

(*) p<.10, * p<.05, ** p<.01, *** p<.001
†Standard deviations and additional descriptive statistics can be found in the Statistical Appendix.

TABLE
PN 200-110 2
VITAL SIGNS -
STAGE I\
ANALYSIS OF VARIANCE†

ıriable	Dose (tid)	No. Sub-jects	Baseline Mean (pre-initial dose)	Mean Change From Baseline at Hours Post Dose					MeanChange Over Hours 0.5-8
				Hour 0.5	Hour 1	Hour 2	Hour 4	Hour 8	
ıtolic od ıssure ı Hg)	PN 2.5 mg	7	114.0	2.2	-1.0	-1.6	2.9	0.9	0.7
	PN 5 mg	7	114.0	-0.1	-0.9	1.1	2.3	3.7	1.2
	PN 7.5 mg	7	114.0	2.6	3.0	3.4	4.7	3.0	3.6
	Placebo	12	112.0	3.0	2.6	1.5	3.0	4.3	2.3
ıstolic od ıssure ı Hg)	PN 2.5 mg	7	76.3	-5.0(*)	-4.4	-4.7	-5.5	-3.2	-4.5
	PN 5 mg	7	76.3	-6.6(*)	-7.4(*)	-4.0	-3.3	-1.1	-4.5
	PN 7.5 mg	7	76.3	-2.9 (*)	-4.5 *	-3.5	-4.3	-2.9	-3.5
	Placebo	12	78.2	-4.7*	-4.0(*)	-3.4(*)	-4.8*	-4.8*	-5.0*
se r min.)	PN 2.5 mg	7	68.6	2.7	1.9	0.6 (*)	2.4 **	2.6 *	2.0 *
	PN 5 mg	7	68.6	6.7*	7.0* (*)	5.7(*)	7.7**	5.1(*)	6.5*
	PN 7.5 mg	7	68.6	6.9**	7.4**	7.9**	8.1***	5.7*	6.7**
	Placebo	12	68.0	6.4**	6.3**	5.3**	9.8***	7.8**	7.3**
piratory e r min.)	PN 2.5 mg	7	16.0	0.0	0.0	0.0	0.0	0.0	0.0
	PN 5 mg	7	16.0	-0.1	0.0	0.0	0.0	0.0	0.0(*)
	PN 7.5 mg	7	16.0	0.0	0.0	0.0	0.0	0.0	0.0
	Placebo	12	16.0	0.0	0.0	0.0	0.0	0.0	0.0(*)

p<.10, * p<.05, ** p<.01, *** p<.001
andard deviations and additional descriptive statistics can be found in the Statistical Appendix.

TABLE 8
PN 200-110 STUDY NO. 2
ECG DATA - STAGE I
ANALYSIS OF VARIANCE

Variable	Dose (bid)	No. Subject	Baseline Mean (Pre-initial dose)	S.D.	Mean Change From Baseline 2 Hours Post-Dose	S.D.
Atrial Rate (per min.)	PN 10 mg	8†	58.9	6.20	8.40*	7.88
	Placebo	12	59.2	7.38	-0.09	6.11
Ventricular Rate (per min.)	PN 10 mg	8†	58.9	6.20	8.40*	7.88
	Placebo	12	59.2	7.38	-0.09	6.11
P-R Interval (sec.)	PN 10 mg	8†	0.180	0.01	0.005	0.01
	Placebo	12	0.168	0.02	0.002	0.01
QRS Duration (sec.)	PN 10 mg	8†	0.079	0.01	-0.001	0.00
	Placebo	12	0.072	0.01	0.005	0.01
Interval (sec.)	PN 10 mg	8†	0.380	0.02	-0.009	0.01
	Placebo	12	0.385	0.03	-0.004	0.02

(*) $p<.10$, *$p<.05$, **$p<.01$, ***$p<.001$

†Subject No. 106 dropped out of the study at Day 2.

TABLE 9
PN 200-110 STUDY NO. 2
ECG DATA - STAGE II
ANALYSIS OF VARIANCE

Variable	Dose (bid)	No. Subject	Baseline Mean (Pre-initial dose)	S.D.	Mean Change From Baseline 2 Hours Post-Dose	S.D.
Atrial Rate (per min.)	PN 5 mg	7	58.1	9.96	3.50	7.74
	PN 10 mg	7	58.1	9.96	9.14**	6.12
	Placebo	12	59.2	7.38	-0.09	6.11
Ventricular Rate (per min.)	PN 5 mg	7	58.1	9.96	3.50	7.35
	PN 10 mg	7	58.1	9.96	9.14**	6.12
	Placebo	12	59.2	7.38	-0.09	6.11
P-R Interval (sec.)	PN 5 mg	7	0.173	0.01	0.005	0.01
	PN 10 mg	7	0.173	0.01	0.002	0.00
	Placebo	12	0.168	0.02	0.002	0.01
QRS Duration (sec.)	PN 5 mg	7	0.076	0.01	0.003	0.01
	PN 10 mg	7	0.076	0.01	0.001	0.01
	Placebo	12	0.072	0.01	0.005	0.01
QT Interval (sec.)	PN 5 mg	7	0.389	0.03	-0.001	0.02
	PN 10 mg	7	0.389	0.03	-0.016*(*)	0.01
	Placebo	12	0.385	0.03	-0.004	0.02

(*) p<.10, *p<.05, **p<.01, ***p<.001

TABLE 10
PN 200-110 STUDY NO. 2
ECG DATA - STAGE III
ANALYSIS OF VARIANCE

Variable	Dose (tid)	No. Subject	Baseline Mean (Pre-initial dose)	S.D.	Mean Change From Baseline 2 Hours Post-Dose	S.D.
Atrial Rate (per min.)	PN 2.5 mg	-	56.3	4.03	3.09(*)	3.69
	PN 5 mg	7	56.3	4.03	5.95(*)	7.11
	PN 7.5 mg	7	56.3	4.03	9.71** (*)	7.48
	Placebo	12	59.2	7.38	-0.09	6.11
Ventricular Rate (per min.)	PN 2.5 mg	7	56.3	4.03	3.09(*)	3.69
	PN 5 mg	7	56.3	4.03	5.95(*)	7.11
	PN 7.5 mg	7	56.3	4.03	9.71** (*)	7.48
	Placebo	12	59.2	7.38	-0.09	6.11
Interval (sec.)	PN 2.5 mg	7	0.154	0.02	0.012*	0.01
	PN 5 mg	7	0.154	0.02	0.006	0.01
	PN 7.5 mg	7	0.154	0.02	0.018** (*)	0.01
	Placebo	12	0.168	0.02	0.002	0.01
QRS Duration (sec.)	PN 2.5 mg	7	0.063	0.01	0.016***	0.01
	PN 5 mg	7	0.063	0.01	0.015** (*)	0.01
	PN 7.5 mg	7	0.063	0.01	0.016**	0.01
	Placebo	12	0.072	0.01	0.005	0.01
QT Interval (sec.)	PN 2.5 mg	7	0.391	0.02	0.010	0.01
	PN 5 mg	7	0.391	0.02	-0.012* **	0.01
	PN 7.5 mg	7	0.391	0.02	-0.024** **	0.01
	Placebo	12	0.385	0.03	-0.004	0.02

(*)p<.10, *p<.05, **p<.01, ***p<.001

TABLE 11
PN 200-110 STUDY NO. 2
ECG DATA - STAGE IV
ANALYSIS OF VARIANCE

Variable	Dose (tid)	No. Subject	Baseline Mean (Pre-initial dosn)	Std. Dev.	Mean Change From Baseline 2 Hours Post-Dose	Std. Dev.
Atrial Rate (per min.)	PN 2.5 mg	7	52.1	12.24	1.00	8.34
	PN 5 mg	7	52.1	12.24	6.07	10.48
	PN 7.5 mg	7	52.1	12.24	10.33*	10.81
	Placebo	12	59.2	7.38	-0.09	6.11
Ventricular Rate (per min.)	PN 2.5 mg	7	52.1	12.24	1.00	8.34
	PN 5 mg	7	52.1	12.24	6.07	10.48
	PN 7.5 mg	7	52.1	12.24	10.33*	10.81
	Placebo	12	59.2	7.38	-0.09	6.11
Interval (sec.)	PN 2.5 mg	7	0.163	0.03	0.009	0.02
	PN 5 mg	7	0.163	0.03	0.014	0.02
	PN 7.5 mg	7	0.163	0.03	0.010	0.02
	Placebo	12	0.168	0.02	0.002	0.01
QRS Duration (sec.)	PN 2.5 mg	7	0.083	0.01	-0.001	0.00
	PN 5 mg	7	0.083	0.01	-0.001	0.01
	PN 7.5 mg	7	0.083	0.01	0.001	0.00
	Placebo	12	0.072	0.01	0.005	0.01
QT Interval (sec.)	PN 2.5 mg	7	0.397	0.03	0.005	0.03
	PN 5 mg	7	0.397	0.03	-0.005	0.03
	PN 7.5 mg	7	0.397	0.03	-0.017	0.03
	Placebo	12	0.385	0.03	-0.004	0.02

(•) p<.10, *p<.05, **p<.01, ***p<.001

PN 200-11 ...Y NO. 2
ECG ...TA
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable	Treatment Group	No. Subjects	Baseline Mean (Pre-Initial Dose)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Atrial Rate (Per Min.)	PN 200-110:					
	Stage I	8	58.9	6.20	5.63*	7.78
	Stage II	7	58.1	9.96	4.57	7.89
	Stage III	7	56.3	4.03	6.86	9.77
	Stage IV	7	52.1	12.24	12.29*	9.64
	Placebo	12	59.2	7.38	6.50*	9.20
Ventricular Rate (Per Min.)	PN 200-110:					
	Stage I	8	58.9	6.20	5.63*	7.78
	Stage II	7	58.1	9.96	4.57	7.89
	Stage III	7	56.3	4.03	6.86	9.77
	Stage IV	7	52.1	12.24	12.29*	9.64
	Placebo	12	59.2	7.38	6.50*	9.20
P-R Interval (Sec.)	PN 200-110:					
	Stage I	8	0.180	0.01	0.000	0.01
	Stage II	7	0.173	0.01	-0.010*	0.01
	Stage III	7	0.154	0.02	0.021**	0.01
	Stage IV	7	0.163	0.03	0.014	0.02
	Placebo	12	0.168	0.02	0.003	0.02

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV.

(*) p<.10, *p<.05, ** p<.01, *** p<.001

TABLE ,nt'd)
PN 200-11u STUDY NO. 2
ECG DATA
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable	Treatment Group	No. Subjects	Baseline Mean (Pre-Initial Dose)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
QRS Duration (Sec.)	PN 200-110:					
	Stage I	8	0.079	0.01	0.002	0.01
	Stage II	7	0.076	0.01	-0.010*	0.01
	Stage III	7	0.063	0.01	0.017**	0.01
	Stage IV	7	0.083	0.01	0.000	0.01
	Placebo	12	0.072	0.01	0.001	0.01
Q-T Interval (Sec.)	PN 200-110:					
	Stage I	8	0.380	0.02	-0.013(*)	0.02
	Stage II	7	0.389	0.03	-0.011*	0.02
	Stage III	7	0.391	0.02	-0.023·	0.02
	Stage IV	7	0.397	0.03	-0.027(*)	0.03
	Placebo	12	0.385	0.03	-0.023***	0.02

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV.

(*) p<.10, *p<.05, ** p<.01, *** p<.001

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TABLE 14
PN 200-110 STUDY NO. 2
LAB DATA - HEMATOLOGY
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Hemoglobin gm/dl (14-18)	PN 200-110:					
	Stage I	8	14.8	1.21	0.16	0.82
	Stage II	7	15.8	1.09	-0.27	0.68
	Stage III	7	15.8	0.81	-0.06	0.58
	Stage IV	7	15.8	1.54	-0.10	1.14
	Placebo	12	15.7	1.32	0.47	1.39
Hematocrit % (42-52)	PN 200-110:					
	Stage I	8	44.3	3.11	-1.00	3.02
	Stage II	7	45.1	2.41	2.86*	2.91
	Stage III	7	47.0	3.11	-0.14	1.68
	Stage IV	7	46.3	4.89	0.57 (•)	3.69
	Placebo	12	46.3	4.33	2.42	5.16
WBC x 10^3 cu. mm (4.8-10.8)	PN 200-110:					
	Stage I	8	6.5	1.36	0.09	1.31
	Stage II	7	5.9	1.25	0.83	1.41
	Stage III	7	8.5	2.76	-1.21 (•)	2.48
	Stage IV	7	7.7	1.82	1.20*	1.29
	Placebo	12	6.9	1.49	1.18*	1.81

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(•) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

TABLE 14 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - HEMATOLOGY
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Bands % (0-8)	PN 200-110:					
	Stage I	8	2.8	1.83	-0.13	1.55
	Stage II	7	2.0	1.00	1.14	1.86
	Stage III	7	1.6	0.79	0.43 (•)	1.27
	Stage IV	7	2.9	2.27	-0.14	2.85
	Placebo	12	1.9	1.08	-0.58	1.62
Neutrophils % (50-75)	PN 200-110:					
	Stage I	8	55.9	6.06	-5.00•	5.93
	Stage II	7	52.7	5.44	-3.14	9.92
	Stage III	7	57.7	12.84	-3.29	10.89
	Stage IV	7	61.9	7.84	3.14	7.36
	Placebo	12	59.3	7.60	-4.25	10.39
Lymphocytes % (20-40)	PN 200-110:					
	Stage I	8	36.0	6.70	3.50	6.07
	Stage II	7	40.3	5.02	1.00	10.26
	Stage III	7	36.0	13.65	1.43	10.66
	Stage IV	7	29.6	9.00	-3.43	9.71
	Placebo	12	33.1	7.23	3.75	9.44

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(•) $p<.10$, •$p<.05$, •• $p<.01$, ••• $p<.001$

TABLE 14 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - HEMATOLOGY
ALL STAGES - EM[illegible]t
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Monocytes % (0-8)	PN 200-110:					
	Stage I	8	3.8	2.25	-0.13	2.85
	Stage II	7	3.3	0.95	1.29	2.50
	Stage III	7	2.6	1.72	1.43	2.07
	Stage IV	7	3.4	2.37	0.43	2.23
	Placebo	12	3.8	2.45	1.50	3.53
Eosinophils% (0-4)	PN 200-110:					
	Stage I	8	1.5	0.93	1.75*	1.91
	Stage II	7	1.7	0.95	-0.29	1.50
	Stage III	7	2.1	2.34	0.00	1.63
	Stage IV	7	2.3	2.29	0.00	1.00
	Placebo	12	1.9	1.56	-0.50	2.07
Basophils % (0-2)	PN 200-110:					
	Stage I	8	0.1	0.35	0.00	0.54
	Stage II	7	0.0	0.00	0.00	0.00
	Stage III	7	0.0	0.00	0.00	0.00
	Stage IV	7	0.0	0.00	0.00	0.00
	Placebo	12	0.0	0.00	0.08	0.00

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(•) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

TA
PN 200-110 STUDY NO. 2
LAB DATA - URINALYSIS
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Specific Gravity (1.001-1.035)	PN 200-110:					
	Stage I	8	1.011	0.007	0.005	0.009
	Stage II	7	1.019	0.007	0.001	0.012
	Stage III	7	1.011	0.007	0.007(*)	0.008
	Stage IV	7	1.012	0.008	0.003	0.010
	Placebo	12	1.017	0.007	-0.003	0.007
pH (5.0-8.0)	PN 200-110:					
	Stage I	8	6.0	0.76	-0.88*	0.84
	Stage II	7	6.1	1.17	-0.29	1.47
	Stage III	7	7.3	0.57	-1.21**	0.64
	Stage IV	7	6.6	0.38	-1.21** **	0.86
	Placebo	12	5.9	1.19	-0.46	1.36

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV.

(*) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

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TABLE 16
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Calcium mg/dl (8.5-10.8)	PN 200-110:					
	Stage I	8	10.1	0.44	-0.26(•)	0.38
	Stage II	7	10.2	0.37	-0.21	0.37
	Stage III	7	10.2	0.25	-0.21•	0.20
	Stage IV	7	10.2	0.35	-0.26(•)	0.33
	Placebo	12	10.3	0.41	-0.20	0.47
Inorganic Phosphorus mg/dl (2.5-4.5)	PN 200-110:					
	Stage I	8	3.8	0.48	0.46•	0.52
	Stage II	7	3.5	0.57	0.26	0.58
	Stage III	7	3.4	0.62	0.33	0.56
	Stage IV	7	3.4	0.25	-0.01	0.60
	Placebo	12	3.3	0.36	0.23	0.58
BUN mg/dl (10-25)	PN 200-110:					
	Stage I	8	11.6	2.97	4.13••	3.14
	Stage II	7	13.7	4.96	1.86	4.22
	Stage III	7	11.7	3.09	2.71(•)	3.50
	Stage IV	7	12.3	3.99	2.71(•)	3.09
	Placebo	12	12.8	3.60	1.58(•)	2.97

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(•) $p<.10$, •$p<.05$, •• $p<.01$, ••• $p<.001$

TABLE 16 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Uric Acid mg/dl (2.5-8.5)	PN 200-110:					
	Stage I	8	6.0	0.83	-0.73**	0.58
	Stage II	7	6.0	1.14	-1.37**	0.78
	Stage III	7	5.6	0.95	-0.39	0.56
	Stage IV	7	6.2	1.42	-1.00*	1.06
	Placebo	12	6.6	0.63	-0.78**	0.76
Glucose mg/dl (70-110)	PN 200-110:					
	Stage I	8	92.9	7.92	7.25(*)	8.88
	Stage II	7	97.3	9.07	-0.57	6.40
	Stage III	7	89.4	12.10	15.29**	10.32
	Stage IV	7	95.1	9.30	4.14	8.17
	Placebo	12	92.0	6.47	8.92**	7.35
Total Protein gm/dl (6.0-8.5)	PN 200-110:					
	Stage I	8	7.2	0.42	-0.06	0.33
	Stage II	7	7.4	0.32	-0.37**	0.24
	Stage III	7	7.3	0.38	-0.21(*)	0.27
	Stage IV	7	7.3	0.44	-0.16	0.30
	Placebo	12	7.4	0.41	-0.05	0.45

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(*) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

TABLE 16 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Albumin gm/dl (3.2-5.5)	PN 200-110:					
	Stage I	8	4.7	0.24	-0.14*	0.14
	Stage II	7	4.7	0.32	-0.07	0.26
	Stage III	7	4.7	0.16	-0.19(*)	0.25
	Stage IV	7	4.8	0.23	-0.10	0.17
	Placebo	12	4.7	0.27	-0.07	0.27
Total Bilirubin mg/dl (0.2-1.1)	PN 200-110:					
	Stage I	8	0.5	0.22	-0.13	0.24
	Stage II	7	0.6	0.24	-0.30*	0.23
	Stage III	7	0.5	0.21	-0.20*	0.15
	Stage IV	7	0.7	0.40	-0.30*	0.25
	Placebo	12	0.6	0.24	-0.23**	0.21
Cholesterol mg/dl (140-320)	PN 200-110:					
	Stage I	8	185.9	24.75	-9.38	16.64
	Stage II	7	185.0	33.94	-10.00(*)	12.18
	Stage III	7	183.3	23.19	-7.71	19.31
	Stage IV	7	178.9	33.30	-5.00	29.12
	Placebo	12	180.0	25.17	-2.25	17.83

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(*) p<.10, *p<.05, ** p<.01, *** p<.001

TABLE 16 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Alkaline Phosphatase Units (30-115)	PN 200-110:					
	Stage I	8	93.0	27.18	-5.38(*)	7.35
	Stage II	7	79.6	27.42	-4.57	9.52
	Stage III	7	74.1	22.92	-7.43(*)	8.12
	Stage IV	7	91.3	18.02	-7.71(*)	8.98
	Placebo	12	89.3	15.36	-1.58	8.22
LDH Units (80-225)	PN 200-110:					
	Stage I	8	172.0	27.99	3.50	25.53
	Stage II	7	161.4	37.99	-35.29**	19.33
	Stage III	7	177.0	25.35	-16.29(*)	19.85
	Stage IV	7	171.0	17.62	-6.29	23.47
	Placebo	12	130.5	27.25	-24.75**	21.34
SGOT Units (0-41)	PN 200-110:					
	Stage I	8	17.1	5.54	-0.50	7.80
	Stage II	7	18.0	4.12	-2.43	5.06
	Stage III	7	15.3	5.65	7.29(*)	8.06
	Stage IV	7	21.4	7.81	6.86(*)	8.19
	Placebo	12	23.8	11.66	0.75	12.86

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(*) p<.10, *p<.05, ** p<.01, *** p<.001

TABLE 16 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
SGPT Units (0-45)	PN 200-110:					
	Stage I	8	21.8	6.76	9.38**	6.59
	Stage II	7	29.4	10.52	2.29	9.30
	Stage III	7	23.1	11.88	9.71(*)	10.78
	Stage IV	7	29.1	7.73	24.71*	21.60
	Placebo	12	30.5	11.91	11.25*	14.04
Sodium mEq/l (135-145)	PN 200-110:					
	Stage I	8	142.5	0.93	-0.38	1.30
	Stage II	7	141.7	1.60	-2.29**	1.11
	Stage III	7	142.0	1.29	0.00	1.16
	Stage IV	7	140.6	1.51	2.71**	1.50
	Placebo	12	142.1	1.93	0.42	1.83
Potassium mEq/l (3.5-5.0)	PN 200-110:					
	Stage I	8	4.7	0.36	-0.38(*)	0.48
	Stage II	7	4.8	0.35	-0.40	0.56
	Stage III	7	4.4	0.34	-0.06	0.41
	Stage IV	7	4.6	0.28	-0.17*	0.16
	Placebo	12	4.8	0.33	-0.42**	0.43

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(*) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

TABLE 16 (Cont'd)
PN 200-110 STUDY NO. 2
LAB DATA - CHEMISTRIES
ALL STAGES - ENDPOINT†
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Subjects	Baseline Mean (Screening)	S.D.	Mean Change From Baseline At Endpoint†	S.D.
Chloride mEq/l (95-108)	PN 200-110:					
	Stage I	8	104.0	1.07	0.88	1.89
	Stage II	7	103.9	1.86	0.71	2.29
	Stage III	7	103.4	1.51	1.86*	1.95
	Stage IV	7	103.0	1.92	2.29(*)	2.50
	Placebo	12	102.8	2.52	1.17	2.76
CO_2 mEq/l (24-32)	PN 200-110:					
	Stage I	8	27.1	1.25	-2.25*	1.83
	Stage II	7	27.0	1.29	-0.71	1.80
	Stage III	7	27.6	0.98	-0.14	1.46
	Stage IV	7	27.9	0.90	-0.86	1.35
	Placebo	12	27.7	1.44	-0.50	1.31
Creatinine mg/dl	PN 200-110:					
	Stage I	8	1.0	0.08	0.03	0.07
	Stage II	7	1.0	0.13	-0.04	0.11
	Stage III	7	0.9	0.14	0.03	0.08
	Stage IV	7	1.1	0.13	-0.06	0.21
	Placebo	12	1.1	0.14	-0.02	0.11

†Endpoint is Day 4 for Stages I-III, Day 8 for Stage IV
(*) $p<.10$, *$p<.05$, ** $p<.01$, *** $p<.001$

TABLE 23
PN 200-110 STUDY NO. 2
SUMMARY OF ADVERSE REACTIONS

Subject	PN 200-110 Treatment Group	Adverse Reaction	Severity	Study Day Occurring	Due to Drug
102	Stage I	Headache	Mild	1,2	Yes
103	Stage I	Headache	Mild	1	Yes
106	Stage I	Inc. Heart Beat	Mild	1	Uncertain
		Headache	Mild	1,2	Yes
		Nausea	Mild	1	Yes
107	Stage I	Weakness	Mild	1	Uncertain
		Headache	Moderate	1,2,3	Yes
		Warm & Clammy	Mild	1	Uncertain
		Nausea	Mild	1,2,3	Yes
		Emesis	Mild	1	Yes
108	Stage I	Inc. Heart Beat	Mild	1	Uncertain
		Lightheadedness	Mild	3	Yes
109	Stage I	Inc. Heart Beat	Mild	1	Mild
		Headache	Mild	1	Yes
110	Stage I	Tingling	Mild	1,2	Yes
		Warm Sensation	Mild	1,2	Yes
		Headache	Mild	1,2,3	Yes
		Tiredness	Mild	1	Uncertain
		Jittery Feeling	Mild	2	Uncertain
		Weakness	Mild	2	Uncertain
112	Stage I	Drowsiness	Mild	1	Yes
		Headache	Mild	1	Yes
		Abdominal Disc.	Mild	2	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction 8/8 = 100%					
201	Stage II	Headache	Mild	2	Yes
		Tiredness	Mild	3	Uncertain
202	Stage II	Lightheadedness	Mild	1	Yes
		Headache	Mild	2	Yes
207	Stage II	Headache	Mild	1,2	Yes
210	Stage II	Drowsiness	Mild	1	Uncertain
		Inc. Heart Beat	Mild	1,2	Yes
		Pressure Head	Mild	1	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction 4/7 = 57%					

TABLE 23 (Cont'd)
PN 200-110 STUDY NO. 2
SUMMARY OF ADVERSE REACTIONS

Subject	PN 200-110 Treatment Group	Adverse Reaction	Severity	Study Day Occurring	Due to Drug
303	Stage III	Headache	Mild	1	Yes
		Tiredness	Mild	1	No
305	Stage III	Headache	Moderate	2,3	Yes
306	Stage III	Emesis	Mild	1	Yes
		Headache	Mild	2	Yes
		Nausea	Mild	2	Yes
Ratio of Subjects Reporting at Least One Adverse Reaction 3/7 = 43%					
401	Stage IV	Headache	Mild	1	Yes
402	Stage IV	Drowsiness	Mild	1	Uncertain
		Lightheadedness	Mild	1	Yes
		Diaphoresis	Mild	2,3	Uncertain
404	Stage IV	Drowsiness	Mild	1	Uncertain
		Headache	Mild	1,2	Yes
		Tiredness	Mild	3	Uncertain
405	Stage IV	Drowsiness	Mild	1	Uncertain
		Emesis	Mild	4	Yes
		Nausea	Mild	4	Yes
		Abdominal Cramps	Mild	4	Yes
		Headache	Mild	4	Yes
		Diarrhea	Mild	7	Yes
407	Stage IV	Feels Mellow	Mild	1,5	Uncertain
		Yawning	Mild	1,2,3,4	Uncertain
		Lightheadedness	Mild	1,2,3,4,5,6	Yes
		Weakness	Mild	2,3	Uncertain
		Fatigue	Mild	4	Uncertain
408	Stage IV	Nausea	Mild	4	Yes
		Headache	Mild	4,5	Yes
		Eyelid Disorder	Mild	7	No
Ratio of Subjects Reporting at Lease One Adverse Reaction 6/7 = 86%					

TABLE 23 (Cont'd)
PN 200-110 STUDY NO. 2
SUMMARY OF ADVERSE REACTIONS

Subject	Placebo Treatment Group	Adverse Reaction	Severity	Total Duration (Hours)	Due to Drug
208	Stage II	Headache	Mild	1,2,3	Yes
		ABD Pain-Lower	Mild	2	No
		Lightheadedness	Mild	2	Yes
307	Stage III	Feels Mellow	Mild	1	No
		Abdominal Cramp	Mild	1,3	Yes
		Lower Back Pain	Mild	2	No
		Headache	Mild	4	Uncertain
308	Stage III	Lightheadedness	Mild	1	Yes
		Tight in Chest	Mild	1,2	Uncertain
403	Stage IV	Pressure Sensation	Mild	7	No
406	Stage IV	Tiredness	Mild	1	No
		Light Sensitivity	Mild	2	Uncertain
		Lightheadedness	Mild	3,4,5,7	Yes
		Feels Mellow	Mild	3,5,6,7	Uncertain
		Feels Relaxed	Mild	3	Uncertain
		Dry Mouth	Mild	4,5	Uncertain
		Drowsiness	Mild	4,7	Uncertain
410	Stage IV	Tiredness	Mild	2	Uncertain
		Lightheadedness	Mild	3	Yes
		Headache	Mild	3,6	Yes
		Stomachache	Mild	3	Yes
		Nausea	Mild	4,5	Yes
		Emesis	Mild	4	Yes
		Dry Heaves	Mild	4	Yes
		Diaphoresis	Mild	4	Uncertain
		Right Eye Pain	Mild	7	No

Ratio of Subjects Reporting at Least One Adverse Reaction 6/12 = 50%

TABLE 24
PN 200-110 STUDY NO. 2
COMPARATIVE FREQUENCY OF SUBJECTS REPORTING
AN ADVERSE REACTION

Adverse Reactions	PN 200-110 Treatment Group				Placebo
	Stage I (N=8)	Stage II (N=7)	Stage III (N=7)	Stage IV (N=7)	Stages I-IV (N=12)
Miscellaneous	--				
Eyelid Disorders	0	0	0	1	0
Eye Discomfort	0	0	0	0	1
Musculoskeletal					
Back, Ache/Pain	0	0	0	0	1
Extremities, Ache/Pain	0	0	0	0	1
Respiratory					
Respiration Abnormal	0	0	0	1	0
Cardiovascular					
hest Pain	0	0	0	0	1
chycardia	3	1	0	0	0
astro-Intestinal					
Abdominal Discomfort	1	0	0	1	3
Diarrhea	0	0	0	1	0
Eructation	0	0	0	0	1
Nausea	2	0	1	2	1
Vomiting	1	0	1	1	1
Central Nervous System					
Weakness	2	0	0	1	0
Calm Feeling	0	0	0	1	2
Dizziness	1	1	0	2	4
Drowsy	1	1	0	3	1
Fatigue	1	1	1	2	2
Headache	7	3	3	4	3
Head, Misc. Abnormalities	0	1	0	0	0
Nervousness	1	0	0	0	0
Light Sensitive	0	0	0	0	1
Tranquilized	0	0	0	0	1
Autonomic Nervous System					
Mouth	0	0	0	0	1
perhidrosis	0	0	0	1	1
ngling	1	0	0	0	0
Warm Feeling	2	0	0	0	0

TABLE 25
PN 200-110 STUDY NO. 2
COMPARATIVE FREQUENCY OF SUBJECTS REPORTING
AT LEAST ONE ADVERSE REACTION

Treatment Group	N	Number of Subjects With at Least One Adverse Reaction	Number of Subjects With No Adverse Reactions
PN 200-110:			
Stage I	8	8	0
Stage II	7	4	3
Stage III	7	3	4
Stage IV	7	6	1
Placebo	12	6	6

(*) p<.10, * p<.05, ** p<.01, *** p<.001

Protocol 398

Title:

A Re-Challenge Study of PN 200-110 to Determine Possible Liver Toxicity

Investigators:

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Background:

A number of studies have been conducted with PN 200-110 without any apparant adverse reactions. One month after conclusion of study 310, a volunteer returned to participate in an unrelated study. On screening it was found that the subject had elevated aminotransferases. A similar result was then obtained in a second subject resulting in the recall of all 18 subjects from the study. It was found that seven subjects had elevated aminotransferases ranging from 200 to 1600 units and four had minimal liver enzyme elevations < 200 units. Four subjects were found to have positive hepatitis B core antibodies with negative hepatitis B surface antigen. Most of the affected subjects were clinically well. Four complained of mild fatigue and one had slight anorexia. Two reported a period of dark urine and light stools and one had morning nausea. It was several months before the elevated liver enzymes returned to normal.
A number of subjects had histories associated with liver disease e.g. alcoholism, male prostitution and drug abuse. All had been housed in a motel and school dormitory and the timing suggested exposure to a common hepatotoxic or infectious agent.
Elevated enzymes had also beem observed in a few subjects in other studies but had returned to normal within 1 - 3 weeks post study. As a result of the above, a rechallenge study was conducted.

Objective:

To assess the liver toxicity of PN 200-110 by rechallenging normal male subjects who demonstrated elevated liver enzymes after dosing with [illegible] PN 200-110 oral solution or capsules.

Population

Eleven male subjects who had [illegible] liver enzyme elevations after PN 200-110 administration in studies 310, 313 and 318 were enrolled in the [illegible]

[illegible]

unavailable for [illegible] to follow up and was unable to [illegible]

Study Plan

All qualified subjects who were enrolled remained in the study unit for the full 18 days of the trial. Liver function tests and CBC were determined daily for three to four days prior to dosing. If aminotransferases were normal (+ 15% of upper limit of normal), subjects received PN 200-110 10 mg. Subjects with aminotranferases outside normal limits remained at study site for the full time and were evaluated in the same way as the "normal" subjects.

Dosing

On study day 1, subjects received a single 10 mg capsule of PN 200-110 at 8 a.m. One subject received placebo as a control.

Evaluation

Vital signs were recorded at screening, day 1 and day 14. ECGs were done at screening and laboratory evaluations done at screening, daily from day -4 to day 8 and then either daily or every second day to day 14.

Results

There were 11 subjects entered into this study, 9 of whom were rechallenged with 10 mg PN 200-110 and one who received placebo. The remaining subject received nothing. There were no findings in past medical history that were considered to interfere with study objectives. Table 3 lists history of drug abuse etc for all subjects. (Did original protocols not exclude this type of volunteer ? Is it certain that drug abuse, alcoholism etc will not interfere in evaluation ?).

Tables 4 and 5 give the results of the liver function tests. Table 4 lists data for those subjects who were rechallenged and Table 5 gives data for the two subjects not receiving active drug. These latter two subjects were not rechallenged due to persistent aminotransferase elevations during baseline period. Table 6 compares maximum enzyme levels during study 398 with those from earlier trial.

SGOT and SGPT data were plotted for each subject, figures 1 - 11. Two subjects developed elevations of SGOT and SGPT on several test days. The values for subject 3 became elevated on day 4 reaching a maximum on days 7 - 10 and then returning to normal. On day 13, a liver biopsy was done and indicated non specific reactive hepatitis (report supplied). Subject 11 had elevated enzymes on day 6, peaking at day [illegible] and returned to normal on day 10. He refused [illegible] the remaining subjects, no consistent elevations were observed.

Plasma concentrations were determined one hour post dose for some [illegible] Table 7 [illegible]

Safety Data

There were no new clinical abnormalities observed nor were there significant changes in ECGs or chest x-rays.

Adverse Reactions

Tables 14 and 15 list ADRs and their frequency. The most frequent complaint was headache, reported by 7/9 of subjects. Other ADRs included nausea and vomiting, chest pain and backache.

Discussion

There were no clinically significant changes in physical examination, ECG or vital signs. No serious adverse reactions were reported. Sponsor concludes that 7/9 subjects did not demonstrate clinically significant elevations in their enzymes or other liver parameters. Two subjects did exhibit changes following rechallenge. Sponsor concludes that since 7/9 subjects "did not demonstrate meaningful elevations in serum transaminases during rechallenge, it is unlikely that the elevations observed previously in these subjects were due to PN 200-110."

Reviewer's Comments

1. It is difficult to understand why subjects with potential liver problems, (alcoholism, drug abuse etc) were enrolled in a clinical study, especially a phase I study.

2. Elevations of enzymes did occur in a number of subjects, but not to a clinically significant level. These subjects, however, only received one dose of medication. What would the result be with chronic use ?

3. Review of data by consultants tend to point to a non drug relationshipp. It appears likely that subjects contracted (sub-clinical) hepatitis.

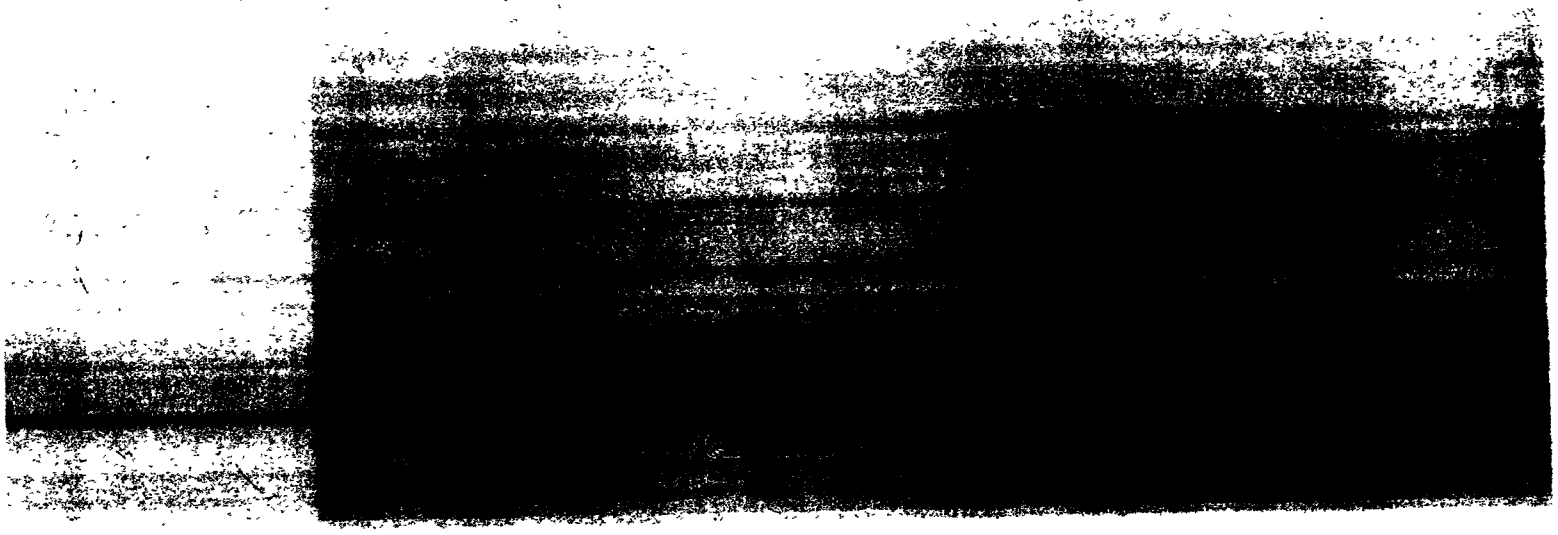

TABLE 3

PN 200-110 STUDY NO. 398

ADVERSE REACTIONS AND OTHER OBSERVATIONS

ALL SUBJECTS

Subject No.	Subject No./Study No. Previous Study	Adverse Reactions/Observations
1	Subject No. 7 Study No. 318	No complaints reported; admitted to being bisexual, but denied recent contacts. Subject sprayed his apartment heavily with Lysol spray a few days before receiving the second dose of PN 200-110 in Study No. 318.
2	Subject No. 14 Study No. 313	No complaints reported.
3	Subject No. 16 Study No. 310	Complained of headaches 5 mins. post-dose which lasted 1.5 hrs. This subject smoked some of the same cigarettes which were being smoked by Subject No. 6.
4	Subject No. 7 Study No. 310	Complained of nausea and headache 1 hr. post-dose and vomited 3.5 hrs. post-dose.
5	Subject No. 8 Study No. 310	No complaints reported; admitted to being homosexual and was arrested in the past as a male prostitute. He also indicated that he participated in 7-8 drug trials within the last year.
6 Not dosed with PN 200-110	Subject No. 9 Study No. 310	Did not receive PN 200-110 during the re-challenge. On questioning, this subject gave a long history of drug use: oral, nasal, and IV use of PCP (angel dust) during the summer, 1973; biphetamine 20 (black beauty) during the same interval; cocaine use in 1974 and 2-3 times/yr. since then; marijuana use (joint/day) even during the past year; heavy alcohol use between the ages of 17-22 (he is now 36).
7	Subject No. 2 Study No. 310	Complained of headache and nausea 5 hrs. post-dose and vomited 5 hrs. post-dose. Under questioning following completion of the study, he indicated that there was some drug abuse by the subjects at the site, but this is unsubstantiated, as the subjects were searched on entry and all personal possessions and clothes were removed. This subject is known to lie.
8	Subject No. 5 Study No. 310	Complained of headache 52 hrs. post-dose and backache as a result of a previous motorcycle accident. Codeine was prescribed.
9 Dosed with Placebo, not PN 200-110	Subject No. 3 Study No. 310	Did not receive PN 200-110 during the [illegible]. On single placebo capsule, single-blind [illegible] Subject admitted to a history of [illegible] of taking all sorts of drugs [illegible]
10	Subject No. 10 Study No. 310	Complained of headache [illegible] after receiving the dose of PN 200-110 [illegible] history of [illegible]
11	Subjects No. 11 Study No. 310	Complained of [illegible] PN 200-110 and [illegible] quitting some [illegible] his ECG was normal.

Protocol 398

Title:

A Re-Challenge Study of PN 200-110 to Determine Possible Liver Toxicity

Investigators:

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A number of subjects had histories associated with liver disease e.g. alcoholism, male prostitution and drug abuse. All had been housed in a motel and school dormitory and the timing suggested exposure to a common hepatotoxic or infectious agent.

Elevated enzymes had also beem observed in a few subjects in other studies but had returned to normal within 1 - 3 weeks post study. As a result of the above, a rechallenge study was conducted.

Objective:

To assess the liver toxicity of PN 200-110 by rechallenging normal male subjects who demonstrated elevated liver enzymes after dosing with either PN 200-110 oral solution or capsules.

Population

Eleven male subjects who had demonstrated liver enzyme elevations after PN 200-110 administered in studies 310, 313 and 318 were enrolled in this rechallenge trial. All liver function tests had returned to normal prior to study entry. Subjects were required to have no clinically significant abnormal findings at screening. Two subjects who had had elevated liver enzymes were unavailable for this study, one was lost to follow up and one was unable to take time from work.

Study Plan

All qualified subjects who were enrolled remained in the study unit for the full 18 days of the trial. Liver function tests and CBC were determined daily for three to four days prior to dosing. If aminotransferases were normal (+ 15% of upper limit of normal), subjects received PN 200-110 10 mg. Subjects with aminotranferases outside normal limits remained at study site for the full time and were evaluated in the same way as the "normal" subjects.

Dosing

On study day 1, subjects received a single 10 mg capsule of PN 200-110 at 8 a.m. One subject received placebo as a control.

Evaluation

Vital signs were recorded at screening, day 1 and day 14. ECGs were done at screening and laboratory evaluations done at screening, daily from day -4 to day 8 and then either daily or every second day to day 14.

Results

There were 11 subjects entered into this study, 9 of whom were rechallenged with 10 mg PN 200-110 and one who received placebo. The remaining subject received nothing. There were no findings in past medical history that were considered to interfere with study objectives. Table 3 lists history of drug abuse etc for all subjects. (Did original protocols not exclude this type of volunteer ? Is it certain that drug abuse, alcoholism etc will not interfere in evaluation ?).
Tables 4 and 5 give the results of the liver function tests. Table 4 lists data for those subjects who were rechallenged and Table 5 gives data for the two subjects not receiving active drug. These latter two subjects were not rechallenged due to persistent aminotransferase elevations during baseline period. Table 6 compares maximum enzyme levels during study 398 with those from earlier trial.
SGOT and SGPT data were plotted for each subject, figures 1 - 11. Two subjects developed elevations of SGOT and SGPT on several test days. The values for subject 3 became elevated on day 4 reaching a maximum on days 7 - 10 and then returning to normal. On day 13, a liver biopsy was done and indicated non specific reactive hepatitis (report supplied). Subject 11 had elevated enzymes on day 6, peaking at days 7 and 8 and returned to normal on day 10. He refused a liver biopsy. For the remaining subjects, no consistent elevations were observed.

Plasma concentrations were determined one hour post dose for some subjects. Table 7 presents these results.
Six subjects were positive for hepatitis B core antibody (Table 8)

Safety Data

There were no new clinical abnormalities observed nor were there significant changes in ECGs or chest x-rays.

Adverse Reactions

Tables 14 and 15 list ADRs and their frequency. The most frequent complaint was headache, reported by 7/9 of subjects. Other ADRs included nausea and vomiting, chest pain and backache.

Discussion

There were no clinically significant changes in physical examination, ECG or vital signs. No serious adverse reactions were reported. Sponsor concludes that 7/9 subjects did not demonstrate clinically significant elevations in their enzymes or other liver parameters. Two subjects did exhibit changes following rechallenge. Sponsor concludes that since 7/9 subjects "did not demonstrate meaningful elevations in serum transaminases during rechallenge, it is unlikely that the elevations observed previously in these subjects were due to PN 200-110."

Reviewer's Comments

1. It is difficult to understand why subjects with potential liver problems, (alcoholism, drug abuse etc) were enrolled in a clinical study, especially a phase I study.

2. Elevations of enzymes did occur in a number of subjects, but not to a clinically significant level. These subjects, however, only received one dose of medication. What would the result be with chronic use ?

3. Review of data by consultants tend to point to a non drug relationshipp. It appears likely that subjects contracted (sub-clinical) hepatitis.

TABLE 3

PN 200-110 STUDY NO. 398

ADVERSE REACTIONS AND OTHER OBSERVATIONS

ALL SUBJECTS

Subject No.	Subject No./Study No. Previous Study	Adverse Reactions/Observations
1	Subject No. 7 Study No. 318	No complaints reported; admitted to being bisexual, but denied recent contacts. Subject sprayed his apartment heavily with Lysol spray a few days before receiving the second dose of PN 200-110 in Study No. 318.
2	Subject No. 14 Study No. 313	No complaints reported.
3	Subject No. 16 Study No. 310	Complained of headaches 5 mins. post-dose which lasted 1.5 hrs. This subject smoked some of the same cigarettes which were being smoked by Subject No. 6.
4	Subject No. 7 Study No. 310	Complained of nausea and headache 1 hr. post-dose and vomited 3.5 hrs. post-dose.
5	Subject No. 8 Study No. 310	No complaints reported; admitted to being homosexual and was arrested in the past as a male prostitute. He also indicated that he participated in 7-8 drug trials within the last year.
6 Not dosed with PN 200-110	Subject No. 9 Study No. 310	Did not receive PN 200-110 during the re-challenge. On questioning, this subject gave a long history of drug use: oral, nasal, and IV use of PCP (angel dust) during the summer, 1973; biphetamine 20 (black beauty) during the same interval; cocaine use in 1974 and 2-3 times/yr. since then; marijuana use (joint/day) even during the past year; heavy alcohol use between the ages of 17-22 (he is now 36).
7	Subject No. 2 Study No. 310	Complained of headache and nausea 5 hrs. post-dose and vomited 5 hrs. post-dose. Under questioning following completion of the study, he indicated that there was some drug abuse by the subjects at the site, but this is unsubstantiated, as the subjects were searched on entry and all personal possessions and clothes were removed. This subject is known to lie.
8	Subject No. 5 Study No. 310	Complained of headache 52 hrs. post-dose and backache as a result of a previous motorcycle accident. Codeine was prescribed.
9 Dosed with Placebo, not PN 200-110	Subject No. 3 Study No. 310	Did not receive PN 200-110 during the re-challenge, but a single placebo capsule, single-blind on Day 2. This subject admitted to a history of heavy alcohol use and to taking all sorts of drugs for several years.
10	Subject No. 10 Study No. 310	Complained of headache intermittently for three days after receiving the dose of PN 200-110, and also admitted to a history of heavy alcohol use and to taking all sorts of drugs. This subject had a liver biopsy performed in 1982 because of elevated transaminases from alcohol use.
11	Subject No. 18 Study No. 310	Complained of headache shortly after receiving the dose of PN 200-110 and chest discomfort and tingling radiating down his arm eleven days following dosing; his ECG was normal.

Table

PH 200-110 STUDY NO. 3 — SINGLE TRIAL

SUBJECTS CHALLENGED WITH PH 200-110

RESULTS OF THE LIVER FUNCTION TESTS

Subject No.	Test	Study Days																	
		-4	-3	-2	-1	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
001	SGOT		27	27	25	31	37	26	37	22	27	30	30	25	14	17	16	13	22	25
E.T.	SGPT		44	45	44	38	43	44	52	45	45	40	45	40	38	33	29	24	26	32
	Alk Ph		82	75	74	72	64	72	77	72	74	75	77	80	82	79	75	69	74	76
	LDH		170	160	148	159	157	130	201	146	140	132	135	122	145	127	125	114	154	164
	T. Bili		0.3	0.3	0.5	0.4	0.7	0.5	0.3	0.4	0.5	0.4	0.5	0.2	1.0	0.5	0.5	0.5	0.4	0.6
002	SGOT (3-40 U/L)		30	26	27	28	20	24	15	26	14	24	13		17		16		11	-
	SGPT (5-40 U/L)		30	28	31	25	24	26	18	9	18	14	13		15		18		14	-
J.N.	Alk Ph (38-115 U/L)		97	96	104	100	92	87	103	97	90	97	93		90		89		97	-
	LDH (100-225 U/L)		127	131	127	128	114	105	109	110	111	118	115		135		141		157	-
	T. Bili (0.1-1.2 mg%)		0.3	0.4	0.3	0.4	0.3	0.3	0.4	0.3	0.4	0.3	0.3		0.5		0.6		0.7	-
003	SGOT		11	13	13	10	18	36	59	71	72	66	98**		65	48	26		30	-
F.G.	SGPT		6	13	17	6	45	39	97	186	219	226	304		360	222	161		102	-
	Alk Ph		61	64	66	63	68	67	64	71	66	82	84		79	78	76		80	-
	LDH		133	145	150	144	141	145	180	170	174	159	175		159	141	124		146	-
	T. Bili		0.9	0.8	0.7	0.5	0.5	0.6	0.7	0.6	0.8	0.5	0.5		0.6	0.9	0.7		1.2	-
004	SGOT		25	28	13	25	27	19	23	23	28	29	25**		26	31	41	37	25	-
J.K.	SGPT		-	40	17	51	57	37	29	45	38	38	60		52	62	58	38	43	-
	Alk Ph		110	110	66	104	97	92	98	96	97	109	108		104	111	819	111	107	-
	LDH		115	147	150	151	120	134	118	120	124	121	116		110	114	129	143	135	-
	T. Bili		0.8	1.0	0.7	0.5	0.8	0.9	0.9	1.0	1.1	0.9	0.4		0.8	0.9	1.3	1.5	1.1	-
005	SGOT		25	25	22	21	28	17	28	24	24	31	72**		27	24	18	19	16	-
B.T.	SGPT		32	25	25	24	26	20	45	36	31	28	96		44	27	32	15	30	-
	Alk Ph		64	63	67	58	71	52	59	57	55	62	62		59	59	59	60	66	-
	LDH		140	162	132	141	140	131	153	133	123	118	103		115	133	113	155	130	-
	T. Bili		0.7	0.7	0.9	1.1	0.6	1.0	0.9	0.8	1.1	0.9	0.5		1.2	0.9	0.9	0.7	0.8	-
007	SGOT		45	39	31	25	22	11	27	26	32	28	26**		19	25	14	21	23	-
A.L.	SGPT		40	39	50	44	44	36	27	42	42	40	45		33	27	31	16	29	-
	Alk Ph		66	79	108	74	64	55	61	56	57	65	56		52	54	53	53	55	-
	LDH		174	165	144	154	139	140	171	157	175	186	167		145	159	147	180	167	-
	T. Bili		0.8	0.7	1.0	0.5	0.7	0.5	0.7	0.6	0.8	0.5	0.6		0.5	0.9	0.7	0.7	0.6	-

NOSAMP / NOSAMPLE

Normal Range Unless Indicated Otherwise	
SGOT	5-50 U/L
SGPT	0-45 U/L
Alk Ph	30-115 U/L
LDH	90-225 U/L
T. Bili	0.1-1.5 mg%

*Day 1 = Day of dosing. Results on Day 1 and earlier are pre-dose results. All remaining values represent post-dose data.

**These samples were collected and prepared as usual, but were refrigerated overnight and were picked up and assayed the following day.

NB: Subject No. 03 was seen by G.I. specialist, Dr. N. Siegel, on Day 10 and liver biopsy was obtained on Day 13. Diagnosis: Non-specific reactive hepatitis.

Table 4

Table 4 (Cont.)

PN 200-110 STUDY NO. 398: RECHALLENGE TRIAL
SUBJECTS RECHALLENGED WITH PN 200-110
RESULTS OF THE LIVER FUNCTION TESTS

Subject No.	Test	Study Days																	
		-4	-3	-2	-1	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
108	SGOT	NO	7	15	17	14	14	16	18	13	10	44	51**	NO	28	19	18	45	15	-
I.N.	SGPT	SAMPLE	-	9	7	6	2	1	11	20	10	36	63	SAMPLE	46	6	8	41	14	-
	Alk Ph		93	103	99	109	99	85	102	91	92	115	119		99	94	92	98	104	-
	LDH		117	148	141	185	119	128	179	118	116	180	140		118	116	129	292	125	-
	T. Bili		0.2	0.2	0.7	0.1	0.2	0.3	0.2	0.3	0.4	0.2	0.2		0.2	0.4	0.3	0.1	0.2	-
110	SGOT	45		34	30	27	20	22	27	32	25	33	36	29	33**	34	32(37)**	28	34**	-
INP	(15-50 U/L)		S																	
	SGPT	81	P	59	59	46	47	49	39	44	50	49	59	53	55	56	56(59)	53	47	-
	(10-75 U/L)		C																	
	Alk Ph	39	C	37	37	44	36	42	41	38	35	44	30	37	35	39	56(50)	34	36	-
	(15-45 U/L)		I																	
	LDH	149	N	139	134	141	157	176	133	163	153	121	133	136	251	142	143(217)	112	266	-
	(110-240 U/L)		E																	
	T. Bili	0.39	N	0.31	0.'9	0.36	0.50	0.47	0.42	0.59	0.68	0.58	0.66	0.63	0.60	0.64	0.50(0.50)	0.75	0.78	-
	(0.3-1.5 mg%)		S																	
111	SGOT	N	N	25	31	29	31	29	39	42	70	66	65	53	33**	25	25(28)**	N	26**	-
INP	(15-50 U/L)	O	I															O		
	SGPT		S	29	39	39	44	42	41	59	105	119	120	110	23	58	59(63)		44	-
	(10-60 U/L)	S	P															S		
	Alk Ph	A	L	39	41	32	36	30	44	30	33	29	35	32	26	32	32(29)	A	26	-
	(15-90 U/L)	M	A															M		
	LDH	P	C	144	165	137	212	138	145	174	194	185	165	162	177	133	152(174)	P	177	-
	(110-240 U/L)	L	E															L		
	T. Bili	E	D	0.71	0.91	0.89	0.94	0.71	0.71	1.04	1.68	1.53	1.36	1.13	0.62	0.70	0.61(0.60)	E	1.54	-
	(0.3-1.6 mg%)																			

Normal Range Unless Indicated Otherwise

SGOT	5-50 U/L
SGPT	0-45 U/L
Alk Ph	30-115 U/L
LDH	90-225 U/L
T. Bili	0.1-1.5 mgs

*Day 1 = Day of dosing. Results on Day 1 and earlier are pre-dose results. All remaining values represent post-dose data.
**These samples were collected and prepared as usual, but were refrigerated overnight and were picked up and assayed the following day. Those in parentheses are duplicates of samples assayed on the day of collection.
NB:Subject No. 11 was seen by Dr. Seigel on Day 13 but refused to consent to a liver biopsy.

Table 4 (cont.)

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Table 5

PN 200-110 STUDY NO. 398: RECHALLENGE TRIAL
SUBJECTS NOT RECHALLENGED WITH PN 200-110

RESULTS OF THE LIVER FUNCTION TESTS

Subject No.	Test	Study Days																	
		-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
5	SGOT	NO	194	217	184	159	113	118	110	109	145	179	209*	NO	370	NO	380	241	214	-
6	SGPT	SAMPLE	430	470	420	418	360	350	258	278	378	370	460	SAMPLE	760	SAMPLE	930	700	650	-
	Alk Ph		101	109	104	101	86	93	83	76	76	88	83		93		112	110	117	-
	LDH		194	204	198	203	168	170	164	172	181	200	208		253		205	267	217	-
T DOSED	T. Bili		1.1	1.0	1.0	0.5	0.6	0.5	0.9	0.6	0.6	0.6	0.9		1.2		0.7	1.5	1.1	-
9†	SGOT	47	S	39	55	50	53	58	60	43	43	61	65	51	54*	31	33(40)*	N	54*	-
7	(15-45 U/L)		A M															O		
	SGPT	75	N I	79	91	78	109	107	96	97	92	108	144	113	85	77	82(82)		120	-
DOSED	(10-75 U/L)		P S															S		
H PN	Alk Ph	27	L P	19	15	18	23	27	30	21	18	22	15	20	17	22	20(20)	A	27	-
-110;	(15-45 U/L)		E L															M		
EIVED	LDH	143	S A	125	200	124	133	217	135	123	128	136	17	126	148	113	122(192)	P	180	-
CEBO	(110-240 U/L)		C															L		
DAY 2,	T. Bili	0.66	E	0.26	0.48	0.46	0.30	0.70	0.54	0.36	0.25	0.35	0.2	0.39	0.40	0.47	0.34(0.39)	E	0.66	-
9/85	(0.3-1.5 mg%)		D																	

mal Range Unless
icated Otherwise

T	5-50 U/L
T	0-45 U/L
Ph	30-115 U/L
	90-225 U/L
Bili	0.1-1.5 mg%

*These samples were collected and prepared as usual, but were refrigerated overnight and were picked up and assayed the following day. Those in parenthesis are duplicates of samples assayed on the day of collection.

†Subject No. 9 was not dosed with PN 200-110, but received placebo, 1 matching capsule, single-blind on Day 2. Therefore, results on Day 2 and earlier are pre-placebo results for this subject, and all remaining values represent post-placebo data.

NB: Subject No. 6 was seen by Dr. Siegel on Day 3 and liver biopsy was obtained on Day 11. Diagnosis: Non-Specific reactive hepatitis. Subject No. 9 was seen by Dr. Seigel on Day 13 and a liver biopsy was obtained. Findings: scattered lipoid granuloma.

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Table 5

TABLE 6

PN 200-110 STUDY #398: RE-CHALLENGE TRIAL
ALL SUBJECTS

MAXIMUM SGOT AND SGPT
LEVELS RECORDED

Subjects Re-Challenged with PN 200-110

Subject No.	SGOT (U/L) Re-Challenge Study #398	SGOT (U/L) Previous Maximum (Study#)	SGPT (U/L) Re-Challenge Study #398	SGPT (U/L) Previous Maximum (Study#)
1	37	415 (#318)	52	240 (#318)
2	26	1470 (#313)	26	321 (#313)
3	98	545 (#310)	360	1230 (#310)
4	41	88 (#310)	62	204 (#310)
5	72	610 (#310)	94	990 (#310)
7	32	815 (#310)	45	1625 (#310)
8	51	600 (#310)	63	1070 (#310)
10	36	17 (#310)	59	42 (#310)
11	70	855 (#310)	120	1260 (#310)

Subjects NOT Re-Challenged with PN 200-110

Subject No.	SGOT (U/L) Re-Challenge Study #398	SGOT (U/L) Previous Maximum (Study#)	SGPT (U/L) Re-Challenge Study #398	SGPT (U/L) Previous Maximum (Study#)
6	380	68 (#310)	93	142 (#310)
9	65	55 (#310)	144	79 (#310)

TABLE 7

PN 200-110 STUDY #398

PN 200-110 PLASMA CONCENTRATIONS (NG/ML)

FOLLOWING 10 MG DOSE PN 200-110

Subjects Re-Challenged with PN 200-110

Subject No.	Study #398*	Study #310†	
Study #398	1-Hr. Post-Dose	1-Hr. Post-Dose	Peak Concentration Observed (Time Post-Dose)
3	7.6	4.8	18.7 (20 mins.)
4	9.8	8.6	17.4 (20 mins.)
5	6.2	12.3	25.4 (20 mins.)
7	5.4	3.9	7.4 (20 mins.)
8	4.8	15.7	20.1 (20 mins.)
10	5.1	6.0	23.8 (20 mins.)
11	7.0	5.1	23.8 (40 mins.)

Subjects NOT Re-Challenged with PN 200-110

Subject No.	Study #398*	Study #310†	
6	NOT DOSED	8.1	46.5 (20 mins.)
9	Received Placebo, Single-Blind	9.5	20.3 (20 mins.)

*10 mg PN 200-110 capsule administered orally

†10 mg PN 200-110 solution administered orally

TABLE

PH 200-110 51 63

RESULTS OF THE LIVER FUNCTION TESTS FROM PREVIOUS STUDIES

Subjects Re-Challenged in Study No. 398

Subject No. Study #398	Subject No./ Study No. Previous Study	Date	Remarks	LDH U/L	Alkaline Phosphatase U/L	Total Bilirubin (mg %)	SGOT U/L	SGPT U/L
1	Subject No. 7			(90-225)+	(30-115)+	(0.1-1.1)+	(5-50)+	(0-45)+
	Study No. 318	10/19/84	Screening	191	75	0.3	11	12
		10/30/84	Test Day 1 - Pre-Dose	170	62	0.7	27	40
			Test Day 1 - Post-Dose	161	67	0.5	33	43
		11/6/84	Test Day 2 - Pre-Dose	822	75	0.7	415	194
			Test Day 2 - Post-Dose	527	93	0.3	370	240
		11/9/84	Follow-up	168	100	0.3	104	122
		11/12/84	Follow-up	214	78	0.4	54	101
2	Subject No. 14			(100-225)+	(30-115)+	(0.1-1.2)+	(0-40)+	(5-40)+
	Study No. 313	10/8/84	Screening	142	103	0.6	18	11
		10/11/84	Test Day 1 - Pre-Dose	162	108	0.7	22	16
		10/12/84	Test Day 1 - Post-Dose	129	128	0.3	21	23
		10/18/84	Test Day 2 - Pre-Dose	125	115	0.4	11	19
		10/19/84	Test Day 2 - Post-Dose	109	116	0.3	15	21
		10/25/84	Test Day 3 - Pre-Dose	129	101	0.3	15	17
		10/26/84	Test Day 3 - Post-Dose	120	118	0.2	16	41
		10/31/84	Follow-up	1470	138	2.0	1470	321
		11/12/84	Follow-up	175	100	0.5	25	28
3	Subject No. 16			(60-200)+	(36-126)+	(0.2-1.2)+	(0-40)+	(0-45)+
	Study No. 310	5/11/84	Screening or Pre 1st Dose	183	59	0.8	16*	17*
		6/3/84	Post Study	138	81	0.4	18*	25*
		8/13/84	Follow-up	-	160	1.2	545	1230
		8/14/84	Follow-up	-	-	1.5	-	-
4	Subject No. 7	5/11/84	Screening or Pre 1st Dose	177	117	0.6	34*	37*
	Study No. 310	6/3/84	Post Study	150	106	0.4	32*	32*
		8/14/84	Follow-up	-	13	1.4	88	204
5	Subject No. 8	5/11/84	Screening or Pre 1st Dose	204	65	0.8	26*	30*
	Study No. 310	6/3/84	Post Study	163	75	0.5	19*	17*
		7/24/84	Follow-up	-	155	1.3	610	990
		8/2/84	Follow-up	-	-	0.8	52	-
		8/14/84	Follow-up	-	85	0.8	39	55
7	Subject No. 2	5/11/84	Screening or Pre 1st Dose	241	64	0.7	17*	22*
	Study No. 310	6/3/84	Post Study	310	65	0.4	51*	54*
		8/6/84	Follow-up	-	202	2.0	815	1625
		8/14/84	Follow-up	-	125	0.9	69	394
8	Subject No. 5	5/11/84	Screening or Pre 1st Dose	184	117	0.9	19*	17*
	Study No. 310	6/3/84	Post Study	148	114	0.9	13*	23*
		7/5/84	Follow-up	-	272	0.9	600	1070
		8/9/84	Follow-up	-	114	0.2	417	26

+Normal Range

*Assays performed by a different lab on samples collected during the study and stored frozen. Normal ranges are slightly different than those listed and dates are different than those listed.

Table 9

TABLE 9 (CONT.)
PN 200-110 STUDY #398
RESULTS OF THE LIVER FUNCTION TESTS FROM PREVIOUS STUDIES

Subjects Re-Challenged in Study No. 398

bject No. udy #398	Subject No./ Study No. Previous Study	Date	Remarks	LDH U/L	Alkaline Phosphatase U/L	Total Bilirubin (mg %)	SGOT U/L	SGPT U/L
10	Subject No. 10 Study No. 310			(60-200)+	(36-126)+	(0.2-1.2)+	(0-40)+	(0-45)+
		5/16/84	Screening or Pre 1st Dose	147	140	1.0	11*	42*
		6/3/84	Post Study	-	123	1.1	17*	30*
		8/6/84	Follow-up	-	160	-	-	-
11	Subject No. 18 Study No. 310	5/23/84	Screening or Pre 1st Dose	225	117	0.8	46*	34*
		6/7/84	Post Study	210	118	0.6	18*	27*
		6/15/84	Follow-up	180	122	1.4	855	1260
		8/9/84	Follow-up	218	218	3.2	142	544
		8/13/84	Follow-up	154	154	2.2	-	-

rmal Range
says performed by a different lab on samples collected during the study and stored frozen. Normal ranges are slightly different an those listed and dates are different than those listed.

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Table 9 (cont.)

Table 10

PN 200-110 STUDY #398
RESULTS OF THE LIVER FUNCTION TESTS FROM PREVIOUS STUDIES

Subjects NOT Re-Challenged in Study No. 398

Subject No. Study #398	Subject No./ Study No. Previous Study	Date	Remarks	LDH U/L	Alkaline Phosphatase U/L	Total Bilirubin (mg %)	SGOT U/L	SGPT U/L
6	Subject No. 9 Study No. 310	5/17/84	Screening or Pre 1st Dose	264	74	0.3	35*	22*
		6/3/84	Post Study	211	80	1.0	16*	52*
		8/13/84	Follow-up	-	107	0.3	41	50
		8/14/84	Follow-up	-	90	0.5	68	142
9	Subject No. 3 Study No. 310	5/19/84	Screening or Pre 1st Dose	215	101	0.3	55*	55*
		6/2/84	Post Study	183	108	0.3	3.*	36*
		8/13/84	Follow-up	-	82	0.3	53	79

*Normal Range
*Assays performed by a different lab on samples collected during the study and stored frozen. Normal ranges are slightly different than those listed and dates are different than those listed.

Table 10