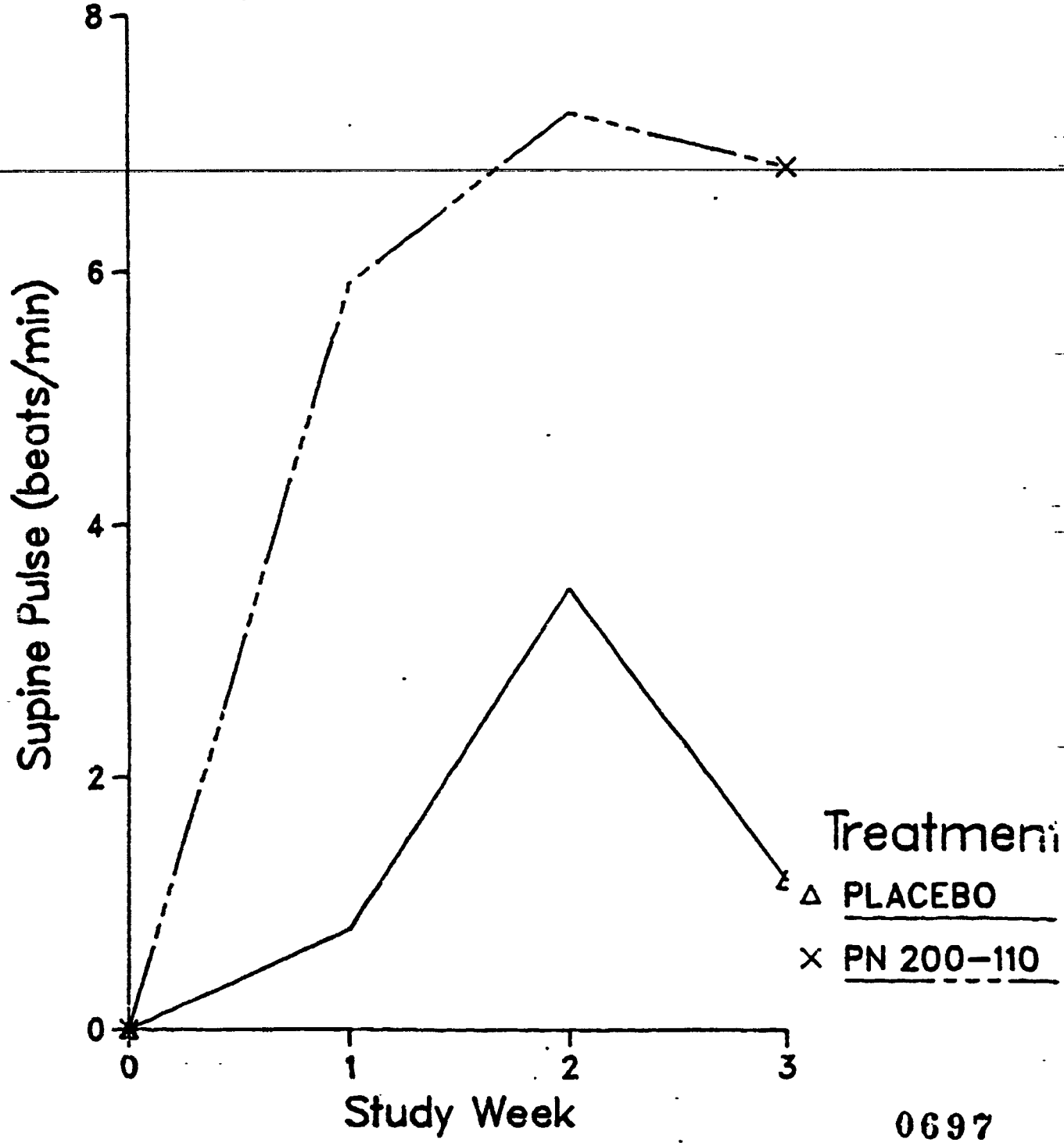
Figure 3

PN 200-110 Study #11
Supine Pulse
Change From Baseline – Valid Patients

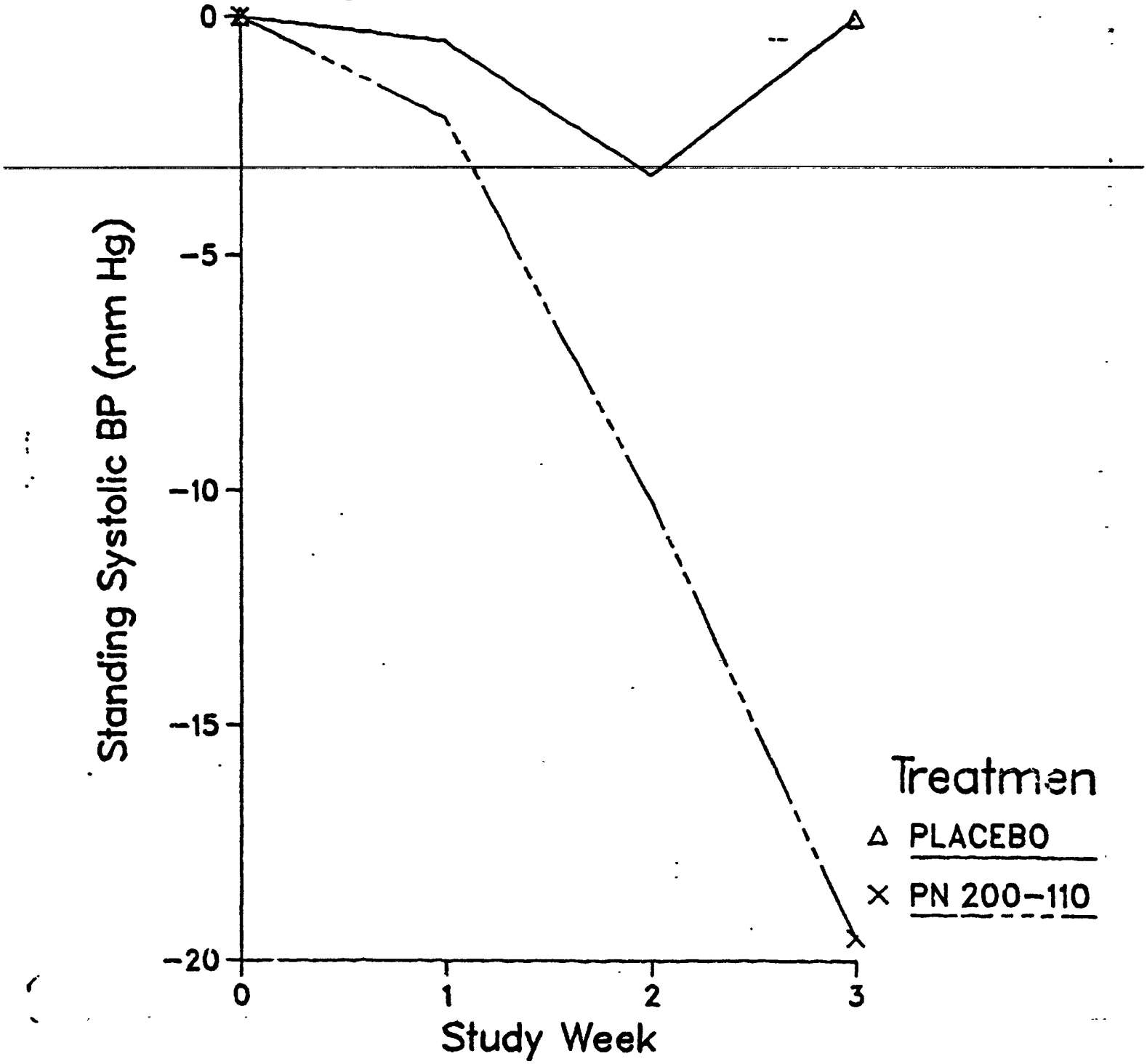


0697

07-01080

Figure 4

PN 200-110 Study #11
Standing Systolic Blood Pressure
Change From Baseline – Valid Patients



07-0661

Figure 5

PN 200–110 Study #11
Stand. Diastolic Blood Pressure
Change From Baseline – Valid Patients

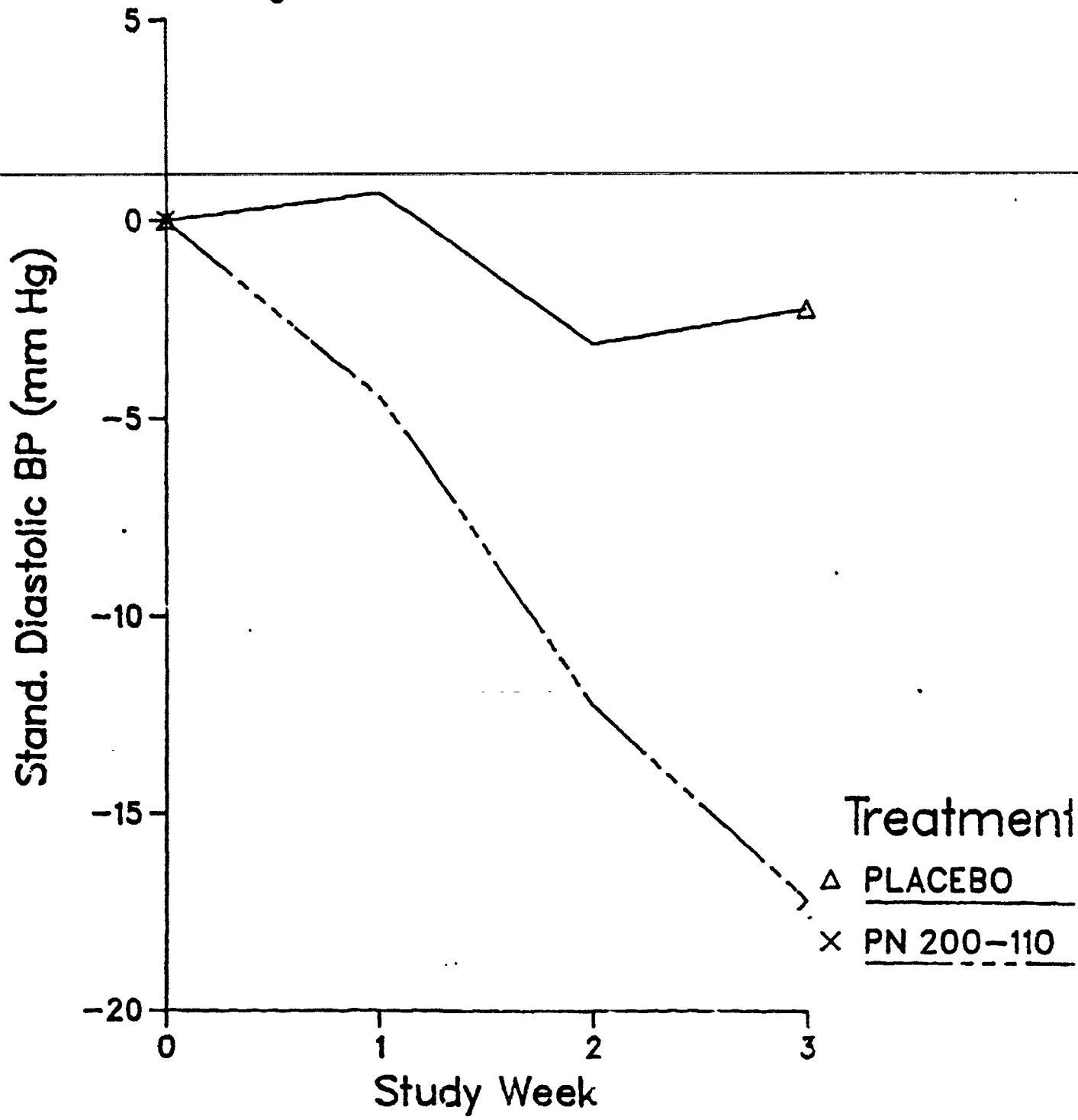
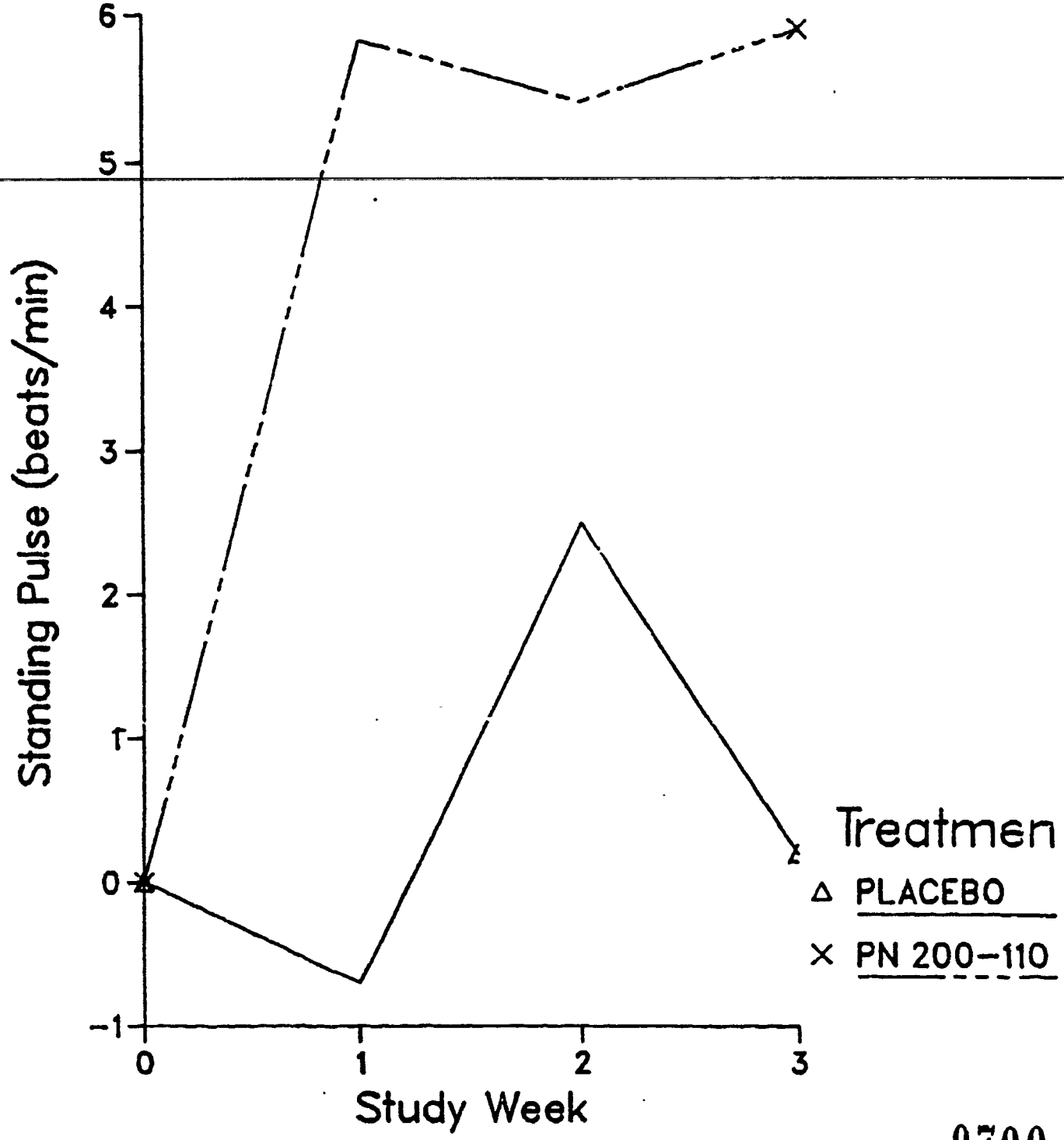


Figure 6

PN 200–110 Study #11
Standimg Pulse
Change From Baseline – Valid Patients



0700
07-01083

BEST POSSIBLE COPY

Protocol 324

Title

A Study to Evaluate the Effects of PN 200-110 vs Placebo on Reproductive Hormone Levels in Healthy Male Volunteers

Investigator

Emile F. Wamsteker, M.D.
Medical Director
Clinical Concepts, Inc
689 Front St
Teaneck, NJ 07666

Objective

To assess the effects of PN 200-110 on male reproductive hormone levels in man.

Population

Healthy, male volunteers aged 21 - 35 were selected. Subjects exhibited no abnormal clinical or laboratory signs. They were excluded if they had any significant illness in previous 2 weeks; history of any significant disease; bradycardia; history of alcoholism or drug abuse.

Trial Plan

This was a randomized double-blind, parallel group, placebo controlled study. A total of 28 patients were entered into the study. PN was supplied as identically appearing capsules of 2.5, 5 or 7.5 mg or placebo. Patients were randomized into one of two groups.

During Period I, days 1 - 7, all subjects received placebo one capsule tid. During Period II, days 8 - 14, one group continued receiving placebo tid and the second group received PN 2.5 mg on days 8 and 9, 5 mg tid on days 10 and 11 and 7.5 mg tid on days 12, 13 and 14. On day 14 only the first two doses were administered. (Table 1).

Table 2 shows schedule of evaluations. On each study day, urine samples were collected for determination of urinary FSH and LH levels. On days 1 - 6 and 8 - 13, a 3 hour total urine sample was collected at 7 a.m concluding at 10 a.m On days 7 and 14, 3 successive 3 hour urine samples were collected, for a total of 9 hours. Table 3 summarizes this schedule. On days 7 and 14, 9 hourly blood samples were obtained for serum FSH, LH, testosterone, and prolactin.

Results

Twenty eight subjects were enrolled in two separate periods. Subjects 1 - 17 were completing study days 8 - 14 and final evaluation day 15 when subjects 19 - 18 were reaching day 8. One subject was withdrawn prior to active phase when cocaine was found in his urine.

Soon after second set of subjects were randomized, an unusual number of elevated SGPTs were noted in both sets of volunteers. It was later determined that the incidence of elevated SGPTs was the same in PN and placebo groups. At the time, however, investigator was unaware of the randomization and it was decided to discontinue the study when subjects 19 - 28 had completed study day 9 i.e end of second day of randomization. Of the subjects entered, 27 had been randomized, 14 to PN and 13 to placebo; 9 PN and 8 placebo completed the trial.

Subjects were aged 21 to 33 years, mean 25.0; all were male and 19 were white and 9 black. There were no clinically significant differences between the two groups. There was a statistically significant difference for height. Seventeen subjects, 9 PN and 8 placebo, were included in analysis to assess effects of PN on male reproductive hormone levels.

Analysis of hormone level data is presented in Tables 8 - 12. Serum FSH, LH, Testosterone and Prolactin levels are given in Table 8. This table presents data collected at each hour during study day 14 compared to average of 9 hour collection on day 7. Table 9 presents same data for 9 hour average of day 14 compared to similar 9 hour average at baseline day 7. Except for LH, statistically significant within group changes from baseline were noted in hormone levels for PN and/or placebo groups at various times 1 - 8 hours post dose. Statistically significant between group differences occurred only for prolactin at 1, 2 and 3 hours post dose and LH at 8 hours post dose. There was a greater decrease in prolactin with placebo than with PN.

For the 9 hour averages for days 7 and 14, the only statistically significant changes were within group mean decreases in prolactin in both groups. There was no indication that PN resulted in clinically significant changes in serum hormone levels.

Urine FSH and LH levels are shown in Table 10. The only statistically significant between group differences occurred with FSH on day 9. The within group changes from baseline were not statistically significant for either group. Table 11 presents data for 3 hour specimens of active versus placebo periods. Table 12 presents data from urine samples collected during a 9 hour period on day 14 compared to day 9. No statistically significant differences were seen between groups.

Consultant's Review.

Dr Wayne Bardin, Director, Population Council, NY City, was used as a consultant. Dr Bardin concluded "...you have performed a rigorous examination of the effects of PN 200-110 on gonadotropin, testosterone and prolactin secretion. Under the conditions of your study, no significant changes were seen. In my view, it seems unlikely that a different study design or method of sampling could have revealed the diffeence that would not have been detected in this study. "

Safety

Three PN and 6 placebo subjects reorted changes in their physical examinations but none were clinically significant, mainly bruising at site of venipuncture. There were slight changes in blood pressure and pulse rate in both groups, but these were not significant. ECG changes are shown in Table 17.

Clinical Laboratory Tests

Results of all tests are presented in Tables 18 - 28. Tables 20, 23 and 26 list all instances of newly occurring or deteriorating abnormal laboratory tests excluding SGPT, which is presented in Tables 27 and 28. Twenty one subjects exhibited elevated SGPT values. Nine PN and 7 placebo had newly occurring or deteriorating SGPT values. There were statistically significant elevations in both treatment groups. but not between groups. Hepatitis profiles were obtained and Table 30 lists those patients with positive findings.

Adverse Reactions

Table 32 lists all ADRs reported. Table 33 lists total frequency of newly occurring events. Most frequent event was headache.

Discussion

There were no clinically significant effects of PN on male reproductive hormones as compared to placebo. There were a number of subjects who developed elevated SGPT levels during the study both with PN and placebo. It was felt that there was no drug relationship involved but that this was due to laboratory error or to contact with hepatitis.

Reviewer's Comments.

1. The elevated SGPT levels is a cause for alarm, but this abnormality was investigated in protocol 398 and was found not to be drug related. From reports in 398 it appears that subjects were housed in a motel and school dormitory and possibly contracted sub clinical hepatitis. There was no evidence of liver damage on rechallenge with PN

2. This study appears to demonstrate that there is no effect on male reproductive hormones with PN.

TABLE 1
PN 200-110 STUDY NO. 324

DOSAGE SCHEDULE*

Treatment Group	PERIOD I	PERIOD II							Final Evaluation Day 15
	Placebo Phase (Single-Blind)	Active Treatment (Double-Blind)**							
	Study Days 1-7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14***	
Group A (PN 200-110)	One (1) placebo capsule tid	PN 2.5 mg tid	PN 2.5 mg tid	PN 5.0 mg tid	PN 5.0 mg tid	PN 7.5 mg tid	PN 7.5 mg tid	PN 7.5 mg tid	No study medication administered
Group B (Placebo)	One (1) placebo capsule tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	Pcb tid	No study medication administered
	<—— Single-Blind ——>	<—— Double-Blind ——>							

PN = PN 200-110 Capsule
Pcb = Placebo Capsule

*Study medication administered tid at 7:00 AM, 12 noon, and 5:00 PM at least one (1) hour prior to the respective meals. Any subject who could not tolerate the dosage regimen of study medication was to be discontinued from the study at that time; no alteration in the prescribed dosage regimen was permitted.

**Dose indicated was according to a t.i.d. dose regimen (i.e., respective daily doses required for PN 200-110 were 2.5 mg tid = 7.5 mg, 5.0 mg tid = 15 mg, and 7.5 mg tid = 22.5 mg).

***The final dose (5:00 PM) was not scheduled for administration on Study Day 14.

TABLE 2
PN 200-110 STUDY NO. 324
SUMMARY OF EVALUATIONS TO BE PERFORMED

Parameter	Initial Evaluation (within two weeks)	PERIOD I (Placebo Phase)							PERIOD II (Active Treatment Phase)								Two-Week Follow-Up Visit
		Study Day 1	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7	Study Day 8	Study Day 9	Study Day 10	Study Day 11	Study Day 12	Study Day 13	Study Day 14	Study Day 15	
Background Information (CRF BK)	X																
Hepatitis Profile (CRF HP)	X	X[a]															
Urinary Drug Screen (CRF DS)	X	X[a]							X								
Physical Exam (CRF PE)	X															X	
Inclusion/ Exclusion Criteria (CRF IE)	X	X[b]															
Chest X-Ray (CRF CX)	X[c]																
Vital Signs (CRF VS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG Evaluation (CRF ECG)	X															X	
Laboratory Evaluations (CRF LAB)	X	X[a]							X							X	X[d]
Adverse Reactions (CRF AR)		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Comment (CRF COM)	X	- RECORDED AS REQUIRED -														X	X
Sample Collections for Hormone Levels (CRF HD)		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]		
End of Study Information (CRF ES)																X	

[a]Blood and urine samples were collected and stored in the frozen state should the need for subsequent analysis arise.
[b]Each subject was interviewed to insure that the inclusion/exclusion requirements were still satisfied.
[c]Documentation of a normal chest X-ray performed within 6 months was accepted in lieu of the pretreatment X-ray.
[d]Liver function tests only: LDH, total bilirubin, SGOT, SGPT, alkaline phosphatase.
[e]A 3-hour total urine specimen for determination of hormone levels (FSH and LH) was collected beginning at the time of the first dose (7:00 AM) of the day and concluding three (3) hours later (10:00 AM).
[f]Three (3) successive 3-hour urine specimens for the determination of hormone levels (FSH and LH) were collected for a total of nine (9) hours, beginning at the time of the 7:00 AM dose on each of these study days and concluding 4-hours after the noon dose; i.e., 4:00 PM. Ten (10) ml blood samples were also collected hourly for a total [illegible] hours following the 7:00 AM dose for assay of serum FSH, LH, testosterone [illegible] selection.

0280

07-00294

TABLE 3
PN 200-110 STUDY NO. 324

SCHEDULE FOR COLLECTION OF URINE SPECIMENS FOR THE DETERMINATION OF HORMONE LEVELS (FSH AND LH)

Study Day	Sample Number	Urine Sample Collections (Times)
1 2 3 4 5 6	1 2 3 4 5 6	Beginning 7:00 AM; Concluding 10:00 AM
7+	7 8 9	~~Beginning 7:00 AM; Concluding 10:00 AM~~ Beginning 10:00 AM; Concluding 1:00 PM Beginning 1:00 PM; Concluding 4:00 PM
8 9 10 11 12 13	10 11 12 13 14 15	Beginning 7:00 AM; Concluding 10:00 AM
14+	16 17 18	Beginning 7:00 AM; Concluding 10:00 AM Beginning 10:00 AM; Concluding 1:00 PM Beginning 1:00 PM; Concluding 4:00 PM

+Three (3) successive 3-hour total urine specimens were obtained for a total of nine (9) hours. The subject voided at 7:00 AM ("0-hour") immediately prior to dosing, then all urine was collected during the next nine (9) hours at intervals of every three (3) hours. The subject voided at the end of each 3-hour period, and this volume was added to the urine volume that had been collected during the preceding 3 hours.

TABLE 8

PN 200-110 STUDY NO. 32A

ANALYSIS OF HORMONE LEVELS DETERMINED BY SERUM (BLOOD) SAMPLES
AVERAGE OF DAY 7 BASELINE (9 HOUR AVG) COMPARED TO DAY 14 (EACH HOUR POST-DOSE)

Variable	Treatment Group	N	Baseline Mean	Mean Change on Day 14 - Hour Post Dose								
				1	2	3	4	5	6	7	8	9
FSH mIU/ml	PN 200-110	9	8.35	-0.46	-0.23	0.32	-0.96	-0.57 (↓)	-0.79(*)	-0.12	-0.68	0.54
	Placebo	8	8.31	-1.06*	-1.18*	-0.06	-0.68	-1.80	-0.68	-0.31	-0.68	0.07
LH mIU/ml	PN 200-110	9	4.86	0.75	1.81	0.42	0.09	2.14 (↓)	-0.47	1.81	-1.91(*)	0.09
	Placebo	8	4.82	-0.26	-1.26	-0.13	-1.44	-1.26	0.81	1.49	1.31	-0.38
Testosterone ng/dl	PN 200-110	9	614.20	75.47(*) (↓)	44.91	-63.09	-32.64	-75.86(*)	-54.64	-124.42**	-138.64** (↓)	-63.42
	Placebo	8	550.43	275.19*	77.57	0.82	48.94	-26.81	-26.93	-46.31	-66.81*	-35.56
Prolactin ng/ml	PN 200-110	9	7.82	-0.43 (↓)	-1.04 (↓)	-0.15 (↓)	-1.93*** (↓)	-3.77***	-4.2***	-0.89	0.01	-0.04
	Placebo	8	8.72	-2.47**	-3.60**	-1.72**	-3.10***	-3.78**	-4.66***	-1.41	-1.20	-0.78

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

07-00306

0825

TABLE 9

PN 200-110 STUDY NO. 324

ANALYSIS OF HORMONE LEVELS DETERMINED BY SERUM (BLOOD) SAMPLES
AVERAGE OF DAY 7 BASELINE (9 HOUR AVG) COMPARED TO DAY 14 (9 HOUR AVG)

Variable	Treatment Group	N	Baseline Mean	Mean Change	S.D.
FSH mIU/ml	PN 200-110	9	8.35	-0.33	1.03
	Placebo	8	8.31	-0.71	1.20
LH mIU/ml	PN 200-110	9	4.86	0.52	1.34
	Placebo	8	4.82	-0.13	2.18
Testosterone ng/dl	PN 200-110	9	614.20	-48.04(*)	73.27
	Placebo	8	550.43	22.01	106.75
Prolactin ng/ml	PN 200-110	9	7.82	-1.38***	0.70
	Placebo	8	8.72	-2.53***	0.96

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

07-00307

0826

TABLE 10

PN 200-110 STUDY NO. 324

ANALYSIS OF HORMONE LEVELS DETERMINED FROM URINE SAMPLES
AVERAGE OF PERIOD I (DAY 1 - DAY 7) COMPARED TO EACH DAY OF
PERIOD II (DAY 8-14)
0-3 HR. SAMPLES

				Mean Change at Study Day						
Variable	Treatment Group	N	Baseline Mean	8	9	10	11	12	13	14
FSH mIU/ml	PN 200-110	9	6.88	0.34	-1.32	-0.55	-1.10	0.23	-0.99	2.23
	Placebo	8	7.64	0.11	-0.89	-1.02	-0.02	-0.64	-1.89	-0.39
FSH mIU/hr	PN 200-110	9	531.29	194.49	101.16	53.05	70.94	100.60	-4.95	127.60
	Placebo	8	577.70	-27.57	-104.82	-65.07	-49.57	-112.70 (*)	-25.57	26.55
LH mIU/ml	PN 200-110	9	19.25	-1.81	-5.81*	-3.25	-2.92	-4.14	-5.37	-0.37
	Placebo	8	14.88	1.50	-1.75	-4.63*	1.25	-1.50	-0.75	-0.63
LH mIU/hr	PN 200-110	9	1518.90	323.65	[illegible]3.97	183.32	76.43	-97.02	36.21	80.65
	Placebo	8	1162.21	98.54	-286.34	-305.71(*) (*)	-131.71	-314.84	-21.34	-52.59

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

Table 10

TABLE 11

PN 200-110 STUDY NO. 324

ANALYSIS OF HORMONE LEVELS DETERMINED FROM URINE SAMPLES
AVERAGE OF PERIOD I (DAY 1-7) COMPARED TO AVERAGE OF
PERIOD II (DAY 8-14)
0-3 HR. SAMPLES

Variable	Treatment Group	N	Baseline Mean	Mean Change	S.D.
FSH mIU/ml	PN 200-110	9	6.88	-0.17	0.77
	Placebo	8	7.64	-0.68	1.98
FSH mIU/hr	PN 200-110	9	531.29	91.84 (*)	198.55
	Placebo	8	577.70	-51.25(*)	75.34
LH mIU/ml	PN 200-110	9	19.25	-3.38	5.77
	Placebo	8	14.88	-0.93	4.34
LH mIU/hr	PN 200-110	9	1518.90	105.30	395.68
	Placebo	8	1162.21	-144.86	291.23

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

TABLE 12

PN 200-110 STUDY NO. 324

ANALYSIS OF HORMONE LEVELS DETERMINED FROM URINE SAMPLES
AVERAGE OF DAY 7 (9 HOUR AVG) COMPARED TO DAY 14

Variable	Treatment Group	N	Baseline Mean	Mean Change at Hours Post Dose			
				0-3	3-6	6-9	0-9
FSH mIU/ml	PN 200-110	9	7.06	2.06	0.72	-0.06	0.91
	Placebo	8	6.27	0.98**	-0.77	-0.90	-0.23
FSH mIU/hr	PN 200-110	9	709.33	-50.44	-150.22(*)	-79.89	-93.52
	Placebo	8	546.79	57.46	-200.67*	36.21	-35.67
LH mIU/ml	PN 200-110	9	19.37	-0.48	-3.04	-5.59	-3.04
	Placebo	8	10.42	3.83(*)	-1.29	-2.54	0.00
LH mIU/hr	PN 200-110	9	1757.78	-158.22	-618.89(*)	-508.44	-428.52
	Placebo	8	902.88	206.75(*)	-319.50*	-118.75	-77.17

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

07-00310

0829

TABLE 21

PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR URINALYSIS DATA
SUBJECTS 1-17

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change at			
					Day 15	S.D.	Day 29	S.D.
Specific Gravity (1.005-1.032)	PN 200-110	9	1.014	0.005	0.006*	0.007	0.005	0.005
	Placebo	8	1.013	0.004	0.007***	0.003	0.007**	0.007
pH (5.0-7.0)	PN 200-110	9	6.00	0.50	0.22	0.97	-0.56(*)	0.88
	Placebo	8	5.50	0.53	0.38	0.74	0.50	1.07

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

07-00321

0830

TABLE 22

PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR URINALYSIS DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10	11	12	13	14	15††	21	29
Specific Gravity (1.005-1.032)	PN 200-110	5	1.0174	0.0052	0.001	0.001	0.000	0.005	0.003	0.009	0.000	0.005(*)
	Placebo	5	1.0166	0.0052	0.002	0.001	0.000	-0.003	0.001	0.007	0.000	0.002
pH (5.0-7.0)	PN 200-110	5	6.00	0.00	0.00	2.80***	0.40	-0.20	-1.00	0.00	-0.20	0.20
	Placebo	5	5.80	0.45	0.40	1.20(*)	0.40	0.60	0.40	0.00	0.40	0.40

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.

†S.D. can be found in the statistical appendix.

††N=4 for the placebo treatment group

Table 22

07-00322

0831

TABLE 23
PM 200-110 STUDY NO. 324

LABORATORY DATA - URINALYSIS
NEWLY-OCCURRING AND WORSENING** ABNORMALITIES

			Pre-PM 200-110		During and Post PM 200-110			
Treatment Group	Subject No.	Variables (Normal Range)	Number of Determinations	Values*	Number of Determinations	Duration (Days) From Baseline	Values*	Abnormal High (H) or Low (L)
PM 200-110	5	Bile (0-0)	2	0, 0	2	19	1, 0	H
	9	Bile (0-0)	2	0, 0	3	35	0, 1, 0	H
	19	pH (5.0-7.0)	2	4, 4	8	21	6, 9, 8, 5, 5, 6, 7, 6	H
	22	pH (5.0-7.0)	2	6, 6	8	26	5, 9, 6, 5, 5, 5, 6, 5, 6	H
		Bile (0-0)	2	0, 0	8	26	0, 0, 0, 2, 1, 0, 0, 0	H
	24	pH (5.0-7.0)	2	5, 6	8	26	8, 9, 6, 6, 5, 6, 6, 6,	H
	24	Bile (0-0)	2	0, 0	8	26	0, 0, 0, 0, 1, 0, 0, 0	H
	26	pH (5.0-7.0)	2	6, 6	8	22	6, 9, 6, 7, 5, 6, 5, 6	H
		Bile (0-1)	2	0, 0	8	22	1, 0, 0, 1, 3, 0, 0, 0	H
Placebo	2	WBC/HPF* (0-1)	2	0, 0	4	28	2, 2, 2, 2	H
		RBC/HPF* (0-1)	2	0, 0	4	28	1, 2, 1, 1	H
	6	Bile (0-0)	2	0, 0	3	21	0, 2, 0	H
		WBC/HPF* (0-1)	2	1, 1	3	21	1, 1, 2	H
	8	pH (5.0-7.0)	2	7, 6	3	24	7, 9, 8	H
		Bile (0-0)	2	0, 0	3	24	0, 1, 0	H
	12	Bile (0-0)	2	0, 0	3	21	1, 0, 0	H
	20	pH (5.0-7.0)	2	6, 6	8	26	6, 9, 6, 6, 5, 6, 6, 6	H
	28	Bile (0-0)	2	0, 0	8	20	0, 0, 0, 1, 1, 0, 0, 0	H

*Underlined values are outside the ±15% adjusted normal range.
**Abnormal at baseline and worsening by at least 15%.

*Coded as the following: (0)=none, (1)=1-5, (2)=6-25, (3)=26-50

07-00323

0832

TABLE 24
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
SUBJECTS 1-17

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change at Day 15	S.D.	Day 29	S.D.
Calcium mg/dl (8.6-10.6)	PN 200-110	9	10.02	0.31	0.04	0.29	-0.08	0.36
	Placebo	8	10.14	0.31	-0.29(*)	0.40	-0.44*	0.37
Inorganic Phosphorus mg/dl (2.5-4.5)	PN 200-110	9	5.09	0.54	-0.32	0.57	-1.54***	0.43
	Placebo	8	5.43	0.64	-0.20	1.06	-1.88***	0.63
BUN mg/dl (10-25)	PN 200-110	9	10.89	2.71	.89**	2.37	4.44*	5.20
	Placebo	8	11.38	2.62	4.13**	2.85	3.88**	2.03
Uric Acid mg/dl (2.5-8.5)	PN 200-110	9	5.63	0.62	-0.09	0.51	0.72*	0.88
	Placebo	8	5.36	0.81	-0.21	0.56	-0.06	0.65
Glucose mg/dl (65-110)	PN 200-110	9	92.44	6.25	-3.67	9.26	8.78	15.67
	Placebo	8	93.13	8.94	-5.00	10.70	3.63	9.81
Total Protein gm/dl (6.0-8.5)	PN 200-110	9	6.92	0.34	0.33	0.31	0.50*	0.45
	Placebo	8	7.44	0.37	-0.41*	0.40	-0.18	0.51
Albumin gm/dl (3.5-5.5)	PN 200-110	9	4.48	0.27	-0.03	0.50	0.39**	0.26
	Placebo	8	4.70	0.23	-0.35*	0.33	0.01	0.31
Total Bilirubin mg/dl (0.0-1.5)	PN 200-110	9	0.51	0.23	0.08(*)	0.12	0.17*	0.21
	Placebo	8	0.40	0.08	0.01	0.08	0.19(*)	0.23
Cholesterol mg/dl (150-300)	PN 200-110	9	191.78	30.87	6.44	20.37	8.22	20.44
	Placebo	8	223.63	38.99	-17.63(*)	24.97	-21.00*	22.95

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

07-00324

0522

TABLE 24 (CONTINUED)
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
SUBJECTS 1-17

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change at Day 15	S.D.	Day 29	S.D.
Alkaline Phosphatase Units (20-115)	PN 200-110	9	45.22	7.24	-6.78*	7.41	-3.67(*)	5.10
	Placebo	8	60.50	14.29	-11.75**	9.11	-9.50*	8.11
LDH Units (100-300)	PN 200-110	9	143.11	22.05	12.56(*)	17.47	29.11**	24.18
	Placebo	8	161.88	44.56	15.88	28.38	9.38	35.86
SGOT Units (10-50)	PN 200-110	9	28.78	11.30	3.89	16.02	-3.33	13.02
	Placebo	8	35.50	21.04	-7.25	13.74	-15.50(*)	18.72
GPT Units (0-38)	PN 200-110	9	25.33	10.43	59.89*	56.87	8.56(*)	13.37
	Placebo	8	27.75	13.96	48.88*	46.14	0.00	13.22
Sodium mEq/l (132-146)	PN 200-110	9	142.11	1.76	2.44*	2.88	0.00	1.41
	Placebo	8	143.78	1.06	1.13(*)	1.55	-2.75*	2.25
Potassium mEq/l (3.8-5.5)	PN 200-110	9	4.83	0.40	-0.50*	0.48	-0.08	0.66
	Placebo	8	4.83	0.37	-0.54*	0.46	-0.26	0.56
Chloride mEq/l (96-106)	PN 200-110	9	101.22	2.82	0.78	2.54	0.00	2.69
	Placebo	8	101.75	1.58	1.25	2.82	-0.63	3.42
CO_2 mEq/l (19-32)	PN 200-110	9	26.56	3.13	-4.00*	4.33	1.78(*)	2.77
	Placebo	8	27.25	2.61	-4.38**	2.72	-1.00	3.85
Creatinine mg/dl (0.6-1.5)	PN 200-110	9	1.10	0.11	-0.06(*)	0.07	0.11**	0.09
	Placebo	8	1.04	0.17	-0.01	0.08	0.10*	0.09

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

TABLE 25
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10	11	12	13	14	15††	21	29
Calcium mg/dl (8.6-10.6)	PN 200-110	5	9.72	0.38	0.34	0.02	-0.14	-0.20	0.08	-0.10	0.14	0.02
	Placebo	5	10.02	0.27	0.08	0.32(*)	-0.38*	-0.68(*)	-0.02	-0.05	0.02	-0.28
Inorganic Phosphorus mg/dl (2.5-4.5)	PN 200-110	5	4.08	0.65	-0.42	0.40	1.08**	0.40*	0.70**	0.12	0.48	-0.32 (↓)
	Placebo	5	3.92	0.13	-0.34	0.18	0.80*	0.30	0.98**	0.38*	-0.08	0.32
BUN mg/dl (10-25)	PN 200-110	5	12.60	1.67	0.60	2.00	5.00*	1.40	2.00	0.40	2.00 (↓)	1.00 (↓)
	Placebo	5	12.00	3.81	0.20	1.80**	3.00(*)	0.20	1.20	1.25	-2.00	-1.40
Uric Acid mg/dl (2.5-8.5)	PN 200-110	5	6.08	1.03	-1.18 (↓)	-0.38	0.30	-0.74*	0.10	-0.40	-0.44(*)	-0.24
	Placebo	5	5.34	0.96	-0.24	0.24	0.36	-0.18	0.16	0.33	0.06	0.22
Glucose mg/dl (65-110)	PN 200-110	5	100.40	6.69	-16.60*	-4.60	0.60	-6.00(*)	5.00	-2.80	-2.88	-13.00
	Placebo	5	101.80	20.74	-11.40	0.60	-3.00	-7.60	-8.20	-3.75	-13.40	-9.20

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.

†S.D. can be found in the statistical appendix.

††N=4 for the placebo treatment group

07-00326

TABLE 25 (CONTINUED)
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10	11	12	13	14	15††	21	29
Total Protein gm/dl (6.0-8.5)	PN 200-110	5	7.00	0.68	0.22	-0.22	-0.40(*)	-0.12	0.06	-0.26(*)	0.68*	0.34**
	Placebo	5	7.08	0.34	0.32	-0.32*	-0.12	-0.18	0.32	-0.03	0.30	0.28
Albumin gm/dl (3.5-5.5)	PN 200-110	5	4.04	0.31	0.48	0.20(*)	0.20	0.42*	0.28	0.54**	0.08**	0.64**
	Placebo	5	4.26	0.39	0.40*	-0.04	0.16	0.08	0.36*	0.45	0.64(*)	0.40(*)
Total Bilirubin mg/dl (0.0-1.5)	PN 200-110	5	0.50	0.12	-0.00	0.04	0.10*	0.16	0.08	0.22*	0.02	0.04
	Placebo	5	0.48	0.22	0.04	0.14	0.12	0.08	0.06	0.08	0.02	0.16(*)
Cholesterol mg/dl (150-300)	PN 200-110	5	176.80	33.32	-1.20	0.00	7.00	5.60	21.00	15.60	6.40	23.60(*)
	Placebo	5	206.80	30.06	13.80	-4.00	6.40	-1.80	18.80	11.50	6.20	9.60

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.

†S.D. can be found in the statistical appendix.

††N=4 for the placebo treatment group

Table 25 (cont.)

TABLE 25 (CONTINUED)
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10	11	12	13	14	15††	21	29
Alkaline Phosphatase Units (20-115)	PN 200-110	5	51.80	10.85	3.20	-5.80	-3.20	-2.40	0.20	-8.20(*)	-4.20	7.00**
	Placebo	5	55.00	11.49	5.20(*)	-9.60*	-0.60	-2.80	-3.20	0.25	1.80	2.00
LDH Units (100-300)	PN 200-110	5	114.80	29.42	8.80(*)	12.80(*)	15.80	19.60(*)	18.20*	8.40*	76.20	25.00
	Placebo	5	126.00	26.43	4.20	-5.60	-0.60	2.00	14.60*	20.00	41.40*	26.40
SGOT Units (10-50)	PN 200-110	5	28.60	12.24	7.40	3.20	4.00	3.00	8.00	-1.40	26.40	17.20
	Placebo	5	25.20	7.19	6.20	4.20	2.00	6.60	3.40	2.50	3.80	0.00
SGPT Units (0-38)	PN 200-110	5	72.00	62.39	-2.00	-1.40	1.60	6.20	8.80	2.80	-14.80	-14.20
	Placebo	5	51.00	24.06	-4.40	-11.60*	2.80	-3.00	-0.60	-2.50	-3.80	-20.80
Sodium mEq/l (132-146)	PN 200-110	5	144.40	1.52	-1.60	-1.20	-2.00(*)	-5.80***	-2.20(*)	-1.60	-1.20	-3.60**
	Placebo	5	143.20	2.17	0.20	-1.60	-2.60(*)	-6.00*	-1.00	-1.50	-0.80	-2.20(*)

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.
†S.D. can be found in the statistical appendix.
††N=4 for the placebo treatment group

Table 25 (cont.)

07-00328
0326

TABLE 25 (CONTINUED)
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR CHEMISTRY DATA
PATIENTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day 10	11	12	13	14	15††	21	29
Potassium mEq/l (3.8-5.5)	PN 200-110	5	4.74	0.34	-0.12	-0.24	-0.08	-0.04	-0.08	-0.14	-0.36	-0.14
	Placebo	5	4.88	0.28	-0.32	-0.24*	-0.38*	-0.12	0.00	-0.48(*)	-0.34	-0.44(*)
Chloride mEq/l (96-106)	PN 200-110	5	100.40	1.14	2.00*	2.60**	3.40(*)	-2.40*	1.80	1.80(*)	4.00*	2.60
	Placebo	5	101.80	2.59	1.40	-0.40	1.20	-2.00	-2.60	0.50	1.80	-3.00**
CO_2 mEq/l (19-32)	PN 200-110	5	29.00	1.87	-4.00**	-0.60	-3.40	0.20	-4.40(*)	-3.60	-5.40*	-5.20
	Placebo	5	26.60	4.16	-0.20	2.60	0.80	2.20*	0.40	-3.00	-1.80	1.00
Creatinine mg/dl (0.6-1.5)	PN 200-110	5	1.10	0.07	-0.04	-0.02	0.00	0.00	0.08	0.02	0.04	0.04
	Placebo	5	1.12	0.13	-0.04	-0.04	0.00	-0.02	-0.02	0.00	0.00	-0.00

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.

†S.D. can be found in the statistical appendix.

††N=4 for the placebo treatment group

Table 25 (cont.)

TABLE 26
PN 200-110 STUDY NO. 324

LABORATORY DATA - CHEMISTRY
NEWLY-OCCURRING AND WORSENING ABNORMALITIES

			Pre-PN 200-110		During and Post PN 200-110			
Treatment Group	Subject No.	Variables (Normal Range)	Number of Determinations	Values*	Number of Determinations	Duration (Days) From Baseline	Values*	Abnormal High (H) or Low (L)
PN 200-110	4	Glucose mg/dl (65-110)	2	103, 101	3	29	90, 93, 144	H
	7	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.4, 3.0	2	20	5.5, 3.9	H
	19	SGOT units (10-50)	2	34, 51	8	21	62, 42, 50, 55, 52, 42, 50, 59	H
	22	Inorganic Phosphorus mg/dl (2.5-4.5)	2	4.4, 4.9	8	26	3.9, 5.7, 6.4, 5.3, 5.6, 4.8, 6.4, 4.1	H
		Glucose mg/dl (65-110)	2	96, 108	8	26	90, 112, 122, 101, 99, 96, 127, 80	H
		LDH units (100-300)	2	166, 109	9	26	106, 120, 123, 129, 134, 123, 348, 146, 147	H
		SGOT units (10-50)	2	37, 23	9	26	23, 26, 27, 31, 45, 32, 154, 103, 29	H
	24	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.3, 3.6	8	26	3.5, 3.9, 4.7, 4.1, 4.3, 3.9, 6.8, 3.6	H
	27	Glucose mg/dl (65-110)	2	114, 105	8	26	108, 75, 101, 91, 142, 93, 84, 74	H
Placebo	10	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.1, 4.9	3	21	6.0, 3.4, 3.3	H
	12	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.5, 4.6	3	21	6.1, 4.0, 3.6	H
	20	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.3, 3.8	8	26	3.8, 4.1, 4.3, 3.5, 5.2, 4.4, 4.5, 4.5	H

Underlined values are outside the ±15% adjusted normal range.
Abnormal at baseline and worsening by at least 15%.

07-00330

0828

TABLE 26 (CONTINUED)
PN 200-110 STUDY NO. 324

LABORATORY DATA - CHEMISTRY
NEWLY-OCCURRING AND WORSENING ABNORMALITIES

			Pre-PN 200-110		During and Post PN 200-110			
Treatment Group	Subject No.	Variables (Normal Range)	Number of Determinations	Values*	Number of Determinations	Duration (Days) from Baseline	Values*	Abnormal High (H) or Low (L)
Placebo	21	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.3, 4.1	8	21	3.3, 4.7, 5.3, 4.3, 4.8, 4.6, 3.5, 3.8	H
	25	Glucose mg/dl (65-110)	2	89, 92	9	26	82, 87, 91, 85, 81, 84, 74, 102, 95	H
	28	Inorganic Phosphorus mg/dl (2.5-4.5)	2	3.3, 3.8	8	20	4.6, 3.9, 3.4, 5.4, 4.6, 4.3, 3.6, 4.0	H
		SGOT units (10-50)	2	30, 35	6	20	30, 34, 31, 51, 66, 31, 46, 37	H

*Underlined values are outside the 2 1SD adjusted normal range.
†Abnormal at baseline and worsening by at least 15%.

07-00331

0020

PH 200-1 . 27A

Summary of SCPT . ted Subjects

Subject No. (Treatment)	Subject I.D.	Lab Data	PLACEBO						ACTIVE TREATMENT								FOLLOW-UP													
			Days																											
			-14		1-6	7		8		9		10,11	12	13		14		15			16,17	18		19	20		21		22		-	29	
			A	B		--	B	A	B	A	B	--	--	A	B	A	B	A	B	C	--	A	B	--	A	B	A	B	A	B	-	A	B
2 (PL)	BEA	SCPT	12	QNS			7	15	8								4	23	QNS	15							26	15				17	10
3 (PL)	SRB		30	6			9	22	17								31	110	45	39							59	QNS				91	14
6 (PL)	C-S		17	8			66	53	87	125	81					100	53	149	73	--												33	17
8 (PL)	H-B		20	QNS			15	31	21								61	151	QNS	52		70	55									21	[illegible]
10 (PL)	PSS		13	9			11	20	[illegible]								12	25	18	--					21	0						23	[illegible]
12 (PL)	BWB		17	12			11	20	17								4	29	16	--									31	18		21	17
14 (PL)	GYY		32	6			17	33	18								10	57	21	--												24	27
15 (PL)	B-B		22	8			11	22	22								22	50	QNS	--					38	QNS						34	--
1 (PH)	DLJ	SCPT	13	QNS			5	11	6								3	12	8	11							17	8				15	[illegible]
4 (PH)	LRT		20	QNS			6	12	10								21	62	24	--									38	28		34	[illegible]
5 (PH)	A-C		12	5			8	17	6								10	38	20	--												22	[illegible]
7 (PH)	T-L		13	QNS			17	29	20								17	95	51	33												23	15
9 (PH)	SAB		34	10			28	35	32								31	111	QNS	--							63	46				66	24
11 (PH)	T-C		35	8			26	51						-- 24	QNS		18	238	117	93												51	32
13 (PH)	E-L		10	QNS			16	34	21								28	81	QNS	--												21	10
16 (PH)	BMB		23	10			16	20	20								22	24	QNS	--												61	29
17 (PH)	JYD		44	3			15	27	20								16	48	36	--												61	21

(PL) = Randomized to placebo treat[illegible] group
(PH) = Randomized to PH 200-110 treatment group

+ = Diluted specimen to obtain sufficient column.

++ = Scheduled 3 Week Follow-up Visit; Subject nos. 3 and 7 were evaluated on Day 28, and Subject no. 5 was evaluated on Day 27.

* A = Rockland Medicine - Pomona, N.Y. ——— SCPT (0-38)
B = Roche Biomedical Laboratory ; ——— SCPT (0-50)
C = CLINPAIR - Hackensack, N.J. ; SCPT (5-4).
D = Corp Endocrine Laboratory - Horsham, PA. ; ——— SCPT (0-35)

07-00332

0540

PN 200-110 Study No. 324
Summary of SGPT Data - Discontinued Subjects

Subject NO. (Treatment)	Subject I.D.	Lab Data	PLACEBO - Days - -14 A*	-14 B*	2 - 6 A*	2 - 6 B*	7 -	7 B*	8 A*	8 B*	8 C*	9	FOLLOW-UP 10 A*	10 B*	11 A*	11 B*	12 A*	12 B*	13 A*	13 B*	14 A*	14 B*	15 A*	15 B*	21 A*	21 B*
20 (PL)	[illegible]	SGPT	35	13				15	31	14	-		34	16	20	13	28	13	28		31	22	28	23	49	26
21 (PL)	BAB		21	8			[illegible]	5	28	4	-	[illegible]	28	18	21	15	25	12	28	[illegible]	27	12	28	17	16	15
23 (PL)	D-P		17	6			[illegible]	14	54	QNS	-	[illegible]	57	29	66	12	53	24	55	[illegible]	61	36	71	41	59	28
25 (PL)	BJB		58	38	-		[illegible]	26	88	QNS	41	[illegible]	67	41	66	36	79	37	76	[illegible]	77	47	84	41	81	37
28 (PL)	BEB		23	9			[illegible]	4	54	25	28	[illegible]	57	29	55	21	58	30	56	[illegible]	56	38	51 56	32	51	35
							[illegible]					[illegible]								[illegible]						
19 (PN)	BJB	SGPT	51	1	QNS	- 16	QNS	[illegible]	91	181	QNS	32	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
22 (PN)	CDE		64	(7-)29			[illegible]	34	67	QNS	-	[illegible]	60	48	63	3[illegible]	72	45	75	[illegible]	86	69	81	64	99	37
24 (PN)	JMB		30	17			[illegible]	14	60	28	-	[illegible]	56	36	67	30	62	37	66	[illegible]	76	57	71	45	59	23
26 (PN)	W.J		20	11			[illegible]	13	31	5	-	[illegible]	38	23	43	26	53	26	53	[illegible]	68	31	53	26	69	36
27 (PN)	B-V		22	11				20	61	QNS	-		36	27	35	15	37	19	40		3[illegible]	18	28	22	22	19

(PL) = Randomized to placebo treatment group.
(PN) = Randomized to PN 200-110 treatment group.

† = Diluted specimen to obtain sufficient volume.

** = Active Treatment Period - Subjects received double-blind study medication on Study Days 8 and 9 only. Dosing was discontinued because of aminotransferase elevations.

* A - [illegible]kland Medlabs - Pomona, N.Y. ; ———— [illegible]PT (0-38)
B - [illegible] Biomedical ; ———— SGPT (0-50)
C - CLINPATH - Hackensack, N.J. ; SGPT (5-45)
B - Corporate Reference Laboratory - Hershey, PA. ; ———— SGPT (0-35)

Table 28

07-00333

TABLE 29
PN 200-110 STUDY NO. 324

FREQUENCY OF ALL NEWLY-OCCURRING
LABORATORY ABNORMALITIES†

Variable		PN 200-110 (N=14)	Placebo (N=13)
Hematology:			
WBC	Low	0	1
WBC	High	1	1
Neutrophils %	Low	3	3
Lymphocytes	High	3	5
Eosinophils %	High	2	3
Basophils %	High	0	1
Urinalysis:			
pH	High	4	2
WBC/HPF	High	0	2
RBC/HPF	High	0	1
Bile	High	5	4
Chemistry:			
Inorganic Phosphorus mg/dl	High	3	5
Glucose mg/dl	High	3	1
LDH units	High	1	0
SGOT units	High	2	1
SGPT units	High	9	7

†Defined as an abnormality reported during the double-blind period that was not present during the placebo washout or an abnormality reported during the placebo washout that worsened during the treatment period. The methods used to classify a variable as "abnormal" are described in the Statistical Methodology Section of this report (pp. 6 through 7).

TABLE 30

PN 200-110 STUDY NO. 324

LISTING OF ALL POSITIVE FINDINGS ON THE HEPATITIS PROFILES

Subject Number	Treatment Group	Study Day	Detected Antibody or Antigen
19	PN 200-110	10	Hepatitis B Surface Ag Hepatitis B Antigen
		21	Hepatitis B Surface Ag Hepatitis B Antigen
		29	Hepatitis B Surface Ag Hepatitis B Antigen
6	Placebo	-14	Hepatitis B Core Antibody Hepatitis B Surface Antibody
		14	Hepatitis B Core Antibody Hepatitis B Surface Antibody
		29	Hepatitis B Core Antibody Hepatitis B Surface Antibody
8	Placebo	18	Hepatitis A Antibody (convalescent)
15	Placebo	29	Hepatitis A Antibody (convalescent)

TABLE 31

PN 200-110 STUDY NO. 324

LISTING OF ALL POSITIVE FINDINGS
ON THE URINARY DRUG SCREENINGS

Subject Number	Treatment Group	Study Day	Detected Substance
18	Placebo	-14	Cocaine Positive

TABLE 32
PN 200-110 STUDY NO. 324

ADVERSE REACTION LISTING

Treatment Group	Subject Number	Adverse Reaction	Day and Severity of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110	1	Headache	10 - Mild	12 - Mild	
	5	Headache	13 - Mild		
		Nasal Congestion	15 - Mild		
	13	Cold Symptoms	15 - Mild		
	15	Headache	8 - Mild		
	19	Headache	1 - Mild	2 - Mild	
		Lightheadedness	1 - Mild		
		Gas Pain in Chest/Abdomen	5 - Mild		
		URI Symptoms	10 - Mild	14 - Mild	11 - Moderate
		Cough	10 - Mild	14 - Mild	11 - Moderate
	22	Neck Pain	12 - Moderate	13 - Mild	
	24	Headache	1 - Mild	14 - Severe	
	26	Drained Feeling	6 - Moderate		
		Headache	6 - Mild		
		Upset Stomach	6 - Mild		
Placebo	3	Headache	5 - Moderate		
	8	Tired	8 - Mild		
		URI Symptoms	11 - Moderate	14 - Mild	
	10	Sore Throat	9 - Moderate	14 - Mild	
	14	Congestion	14 - Mild		
	15	Headache	1 - Mild	13 - Moderate	
		Nasal Congestion	14 - Mild		
	20	Diarrhea	2 - Mild	14 - Mild	
		Stuffy Nose	11 - Mild		
		Elevated Temperature	11 - Mild		
	21	Sharp Abdominal Pain	5 - Moderate		
		Cold Symptoms	8 - Mild	13 - Mild	
		Coughing	10 - Mild	14 - Mild	
		Headache	14 - Moderate		
	23	Headache	13 - Mild		
	28	Headache	5 - Mild	14 - Mild	

*Presented only if there are multiple occurrences.
**Presented only if different from information presented under first and last occurrence.

07-00337

0845

TABLE 33
PN 200-110 STUDY NO. 324

NEWLY-OCCURRING ADVERSE REACTIONS+

Adverse Reaction	Frequency	
	PN 200-110 (N=14)	Placebo (N=14)
Miscellaneous		
Temperature Abnormal	0	1
Musculo-skeletal		
Neck, pain/sore/stiff	1	0
Respiratory		
Coughing	1	1
Nasal Congestion	1	3
Throat, pain/numb	0	1
Central Nervous System		
Fatigue	0	1
Headache	4	1
Total number of subjects with at least one newly-occurring adverse reaction	6	6

+First reported during (or within 3 days following) double-blind treatment or increasing in severity over that reported during the single-blind placebo period.

TABLE 19
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR HEMATOLOGY DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10††	11†††	12	13	14	15††††	21ˣ	29
Hemoglobin gm/dl (14-18)	PN 200-110	5	15.74	0.36	-0.08	0.23	0.30	-0.06	0.10	0.08	0.30	0.20
	Placebo	5	16.24	0.64	-0.80	-0.42	-0.56	-0.72(*)	0.06	-0.60(*)	-0.52	-0.42
Hematocrit % (42-52)	PN 200-110	5	44.60	0.89	1.00	2.00	1.80	0.60	0.60	2.20*	2.50(*)	1.80
	Placebo	5	46.40	1.52	-0.75	0.20	-0.40	-1.40	1.00	0.75	0.20	1.20
WBC x 10^3 cu mm (4.8-10.8)	PN 200-110	5	7.76	0.60	0.50	0.33	0.14	0.12	0.26	-0.38	2.40	-0.90(*)
	Placebo	5	10.84	2.99	0.40	0.08	0.38	-1.18(*)	-1.08(*)	-2.45	-1.14	-1.30
Bands % (0-3)	PN 200-110	5	0.00	0.00	0.25	0.00	0.00	0.00	0.00	0.60	1.00	0.40
	Placebo	5	0.20	0.45	-0.25	0.00	0.00	-0.20	-0.20	0.25	-0.20	-0.20

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

*Final day of dosing was on Study Day 9 Data presented is post-treatment data.

**N=4 for the placebo treatment group

†S.D. can be found in the statistical appendix

††N=4 for the placebo treatment group

†††N=3 for the PN 200-110 treatment group

ˣN=4 for the PN 200-110 treatment group

TABLE 19 (CONTINUED)
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR HEMATOLOGY DATA
SUBJECTS 19-28*

Variable (Normal Range)	Treatment Group	N	Baseline Mean	S.D.	Mean Change† at Day							
					10**	11††	12	13	14	15†††	21×	29
Neutrophils % (50-80)	PN 200-110	5	54.00	8.92	-7.50	-0.67	6.40(*)	8.80*	3.20	-4.80	-7.75	-2.40
	Placebo	5	57.40	8.91	-2.50	-3.80	3.00	0.60	-4.20	-7.50*	-0.80	2.20
Lymphocytes % (15-40)	PN 200-110	5	41.20	11.39	-13.00	1.33	-5.40	-10.20	-3.80	3.00	3.00	2.40
	Placebo	5	34.20	9.50	5.50	8.00	-0.60	2.40	7.00	9.25	3.40	1.40
Monocytes % (0-10)	PN 200-110	5	2.80	2.28	2.25	-0.33	-0.80	1.80	0.60	1.40	0.00	0.60
	Placebo	5	5.60	1.52	-1.75	-4.20*	-3.20*	-1.20	-2.80(*)	-2.25(*)	-1.80(*)	-2.40
Eosinophils % (0-5)	PN 200-110	5	2.00	3.08	0.25	-0.33	-0.20	-0.40	-0.20	-0.40	-1.50	-1.20
	Placebo	5	2.40	0.55	-0.75	0.20	1.00	-1.40(*)	0.40	0.50	-0.40	-0.80
Basophils % (0-3)	PN 200-110	5	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.20	0.25	0.20
	Placebo	5	0.20	0.45	-0.25	-0.20	-0.20	-0.20	-0.20	-0.25	-0.20	-0.20

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

*Final day of dosing was on Study Day 9. Data presented is post-treatment data.

**N=4 for each treatment group

†S.D. can be found in the statistical appendix.

††N=4 for the placebo treatment group

†††N=3 for the PN 200-110 treatment group

×N=4 for the PN 200-110 treatment group

TABLE 20
FM 200-110 STUDY NO. 324

LABORATORY DATA - HEMATOLOGY
NEWLY-OCCURRING AND WORSENING ABNORMALITIES

			Pre-Active Treatment Period		During and Post Active Treatment Period			
Treatment Group	Subject No.	Variables (Normal Range)	Number of Determinations	Values*	Number of Determinations	Duration (Days) From Baseline	Values*	Abnormal High (H) or Low (L)
FM 200-11C	4	Eosinophils % (0-5)	2	4.0, 3.0	3	29	0.0, 10.0, 0.0	H
	9	Eosinophils % (0-5)	3	6, 0, 2	3	33	2, 8, 1	H†
	13	Neutrophils % (50-80)	2	64.0, 56.0	2	20	34.0, 50.0	L
		Lymphocytes % (15-40)	2	33, 39	2	20	63, 44	H
	19	Neutrophils % (50-80)	2	50, 41	7	22	4, 55, 58, 57, 50, 49, 42	L†
	22	WBCx10^3 cu.mm. (4.8-10.8)	3	8.3, 8.8, 7.7	9	26	7.5, 7.7, 7.8, 8.8, 8.6, 7.8, 16.4, 6.5, 7.1	H
		Neutrophils % (50-80)	3	42, 40, 56	9	26	44, 51, 65, 65, 47, 40, 61, 35, 33	L†
		Lymphocytes % (15-40)	3	50, 52, 41	9	26	48, 46, 37, 29, 50, 55, 36, 60, 59	H†
	24	Lymphocytes % (15-40)	1	35.0	8	26	26, 31, 35, 30, 35, 43, 51, 47	H
Placebo	2	Lymphocytes % (15-40)	2	45, 38	3	28	34, 38, 48	H
	8	WBCx10^3 cu.mm. (4.8-10.8)	2	4, 5.2	4	24	4.9, 3.6, 3.3, 4	L†
		Neutrophils % (50-80)	2	64, 67	4	24	60, 35, 60, 39	L
		Lymphocytes % (15-40)	2	34, 26	4	24	35, 44, 36, 32	H
		Eosinophils % (0-5)	2	0.0, 2.0	4	24	0.0, 0.0, 2.0, 7.0	H
	8	Basophils % (0-3)	2	0.0, 0.0	4	24	5, 1.0, 0.0, 0.0	H

*Underlined values are outside the ±15% adjusted normal range.
†Abnormal at baseline and worsening by at least 15%.

07-00319

0849

TABLE 20 (CONTINUED)
FM 200-110 STUDY NO. 324

LABORATORY DATA - HEMATOLOGY
NEWLY-OCCURRING AND WORSENING ABNORMALITIES

			Pre-Active Treatment Period		During and Post-Active Treatment Period			
Treatment Group	Subject No.	Variables (Normal Range)	Number of Determinations	Values*	Number of Determinations	Duration (Days) From Baseline	Values*	Abnormal High (H) or Low (L)
Placebo	20	Lymphocytes % (15-40)	1	23.0	8	26	48, 43.0, 25.0, 24.0, 32.0, 48, 39.0, 47	H
		Neutrophils % (30-80)	1	74.0	8	26	45, 52.0, 71.0, 71.0, 60.0, 41, 51.0, 48	L
	23	Eosinophils % (0-3)	3	3.0, 5, 2	8	21	0, 2.0, 6.0, 0.0, 3.0, 2.0, 1, 4.0	H
	25	Lymphocytes % (15-40)	2	24.0, 26	8	26	35, 48.0, 25.0, 48.0, 34.0, 47.0, 46, 32.0	
	28	WBCx10^3 cu.mm. (4.8-10.8)	2	9.1, 9.8	8	20	13, 10.7, 10.4, 14.2, 9.5, 10.6, 13, 11.6	H
		Neutrophils % (30-80)	2	54.0, 51.0	7	20	59.0, 43.0, 53.0, 56.0, 36.0, 70, 78.0	L
		Lymphocytes % (15-40)	2	44.0, 40.0	8	20	37, 38.0, 45.0, 37.0, 35.0, 37.0, 23, 22.0	H
		Eosinophils (0-3)	2	0.0, 3.0	8	20	3, 2.0, 9.0, 6.0, 2.0, 3.0, 3, 0.0	H

*Underlined values are outside the ±15% adjusted normal range.
†Abnormal at baseline and worsening by at least 15%.

07-00320

TABLE 17

PN 200-110 STUDY NO. 324

SUMMARY COMPARATIVE RESULTS FOR ECG VARIABLES

Variable	Treatment Group	N	Baseline Mean	S.D.	Endpoint Mean Change	S.D.
Atrial Rate (beats/min.)	PN 200-110	14	65.4	12.19	9.2**	11.16
	Placebo	13	64.0	10.12	12.2***	9.63
Ventricular Rate (beats/min.)	PN 200-110	14	65.4	12.19	9.2**	11.16
	Placebo	13	64.0	10.12	12.2***	9.63
QRS Duration (sec.)	PN 200-110	14	0.079	0.003	0.001	0.003
	Placebo	13	0.082	0.006	-0.001	0.003
QT Interval (sec.)	PN 200-110	14	0.387	0.037	-0.017*	0.028
	Placebo	13	0.395	0.027	-0.032*	0.049

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

TABLE 18
PN 200-110 STUDY NO. 324

SUMMARY OF COMPARATIVE RESULTS
FOR HEMATOLOGY DATA
SUBJECTS 1-17

Variable (Normal Range)	Treatment Group	N	Baseline Mean (Day 9)	S.D.	Mean Change at Day 15	S.D.	Day 29†	S.D.
Hemoglobin gm/dl (14.0-18.0)	PN 200-110	9	15.04	0.80	-0.04	0.37	0.40	0.77
	Placebo	8	15.65	1.13	-0.41	0.65	-0.38	0.71
Hematocrit % (42-52)	PN 200-110	9	42.78	2.44	0.38	1.77	3.44	2.13
	Placebo	8	44.25	3.50	-0.13	2.53	1.50	2.62
WBC x 10^3 cu mm (4.8-10.8)	PN 200-110	9	7.21	2.01	0.36	1.05	-0.72	1.43
	Placebo	8	7.16	2.30	0.54(*)	0.73	-0.30	1.27
Bands % (0-3)	PN 200-110	9	0.11	0.33	-0.13	0.35	-0.11	0.33
	Placebo	8	0.13	0.35	-0.13	0.35	-0.13	0.35
Neutrophils % (50-80)	PN 200-110	9	59.33	9.55	-3.38 (*)	11.15	-0.22	10.63
	Placebo	8	56.50	10.03	5.88	10.41	1.25	9.66
Lymphocytes % (15-40)	PN 200-110	9	34.78	7.12	00	10.01	-0.78	9.69
	Placebo	8	36.88	9.83	-4.63	12.60	0.00	9.94
Monocytes % (0-10)	PN 200-110	9	3.78	1.39	0.63	3.20	1.78	2.77
	Placebo	8	4.38	2.00	-1.25	3.15	-0.63	2.20
Eosinophils % (0-5)	PN 200-110	9	2.00	2.50	-1.13	2.64	-0.89	3.33
	Placebo	8	2.00	1.31	-0.50	1.85	-0.50	1.77
Basophils % (0-3)	PN 200-110	9	0.00	0.00	0.00	0.00	0.22	0.44
	Placebo	8	0.13	0.35	0.63	1.85	0.00	0.54

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

†A complete follow-up laboratory evaluation was performed approximately two (2) weeks following the final evaluation visit (Study Day 15).

ISRADIPINE - SAFETY UPDATE

OVERALL SUMMARY

This safety update is a review of worldwide safety profile of isradipine using data compiled since the previous update of November 22, 1988. US and foreign data are supplied separately. This report also includes initial marketing experience since isradipine has now been approved in 8 countries and is marketed in Great Britian.

In the US, both Sandoz and [redacted] are conducting studies with immediate release Dynacirc but for this report only data from completed studies have been included. Studies currently ongoing with this formulation or completed studies using other dosage forms, eg modified release or intravenous dosage forms, were not analyzed for this report. There have been no serious or unexpected adverse reactions (ADRs) with any dosage form since the last report.

In the present update, data from an additional 281 patients are analyzed from Sandoz sponsored trials. Of this number, only 181 received isradipine. The total number of isradipine patients is listed below; this combines the numbers included in the original NDA submision and this safety update. (The safety cutoff date for Sandoz sponsored trials is June 30, 1989. According to Mr Bitz, Sandoz, no [redacted] data are included as their studies were still ongoing at the time this report was finalized).

Total No isradipine randomized patients/Intent-to-Treat 2065

Total Number Actually Treated by Duration of Therapy:

< 2 Weeks	2039
2 Weeks or more	1510
10 Weeks	880
6 Months	485
12 Months	367
24 Months	98
> 24 Months	84

As may be seen from this Table, 2039 received at least one dose of drug with 1510 receiving it for two weeks or more.

The previous update included data from 1321 non US patients and this update includes data from an additional 590 foreign patients being treated for chronic angina pectoris. By combining US and foreign data, a total of 3950 isradipine treated patients are analyzed.

Sponsor states that the results show that isradipine is safe and well tolerated. No deaths or serious ADRs implicated isradipine, according to the investigators.

Since January 1989, isradipine has been approved for marketing in 9 countries, Great Britian, Belgium, Colombia, Ireland, Switzerland, Chile, Uruguey, Czechoslavakia and Egypt. It has only been launched in Britian. Post marketing experience is, therefore, limited.

- In addition to these reports, this safety update presents sections for worldwide regulatory actions, marketing history, package inserts etc. A summary of worldwide literature is also included.

Sponsor concludes that "Based on the review of the large clinical experience with isradipine including clinical trials conducted in both the US and overseas and the initial postmarketing experience with isradipine in Great Britain, it is concluded that isradipine continues to be a safe and well tolerated drug."

JAN 3 . 1989

Division of Cardio-Renal Drug Products
Medical Review

Number: NDA 19546
Drug Name: Dynacirc(isradipine)
Sponsor: Sandoz
Submission Type: Clinical Report
Submission Date: Oct 28, 1988
Date of Receipt:
Review Complete: Dec. 29, 1988

Pharmacologic Class: Dihydropyridine calcium channel blocker

~~Dosage Form and Strength: 5-20mg capsules~~

Route of Administration: P.O.

Dosage Regimen: Once daily

~~Proposed Clinical Use: Hypertension~~

Title of Study: Study # 308 The Multicenter Evaluation of the Safety and Efficacy of PN 200-100 Administration Once-Daily in the Treatment of Hypertension Compared to Placebo.

Investigator(s): Center A: Walter KIrkendall, M.D. Houston TX. Center B: Gilbert McMahon New Orleans LA. Center C: Frank Canosa, M.D. Center D: Nathaniel Hiner, M.D. Kansas City, MO Center E: Andrew Lewin, M.:D. Los Angeles, CA. Center F: Albert Carr, M.D. Augusta GA

Rationale:

I. Introduction and Objectives: Isradipine has been shown effective in controlling mild to moderate hypertension. In the large clinical trials the maximum daily dose seemed to be 20mg. Little further hypotensive effect was achieved above this level and above this dose the incidence of the side effects resulting from vasodilation was considered unacceptable. In one trial demonstrating efficacy of bid medication, once daily dosing failed to maintain control of blood pressure. The dose was not pushed to a maximum and the study was of limited scope. Clinical experience with this drug indicate that it is best given twice daily. Pharmacokinetic data are not entirely inconsistent with once-a-day dosage and first order kinetics implies duration will increase with dose as dose is increased. The objective of this study, then, is to determine whether the maximum tolerable daily dose is effective when given at

one time.

II. Materials and Methods: Two hundred and eight patients were selected according to the established inclusion criteria and with diastolic blood pressures between 100 and 120 torr. One hundred and seventy of these were randomized after three weeks placebo washout to active treatment or placebo group. The balance between the two groups with respect to all demographic characteristics examined is nearly perfect. From the summarized data no correlation is apparent between any of these variables and a response to treatment. Such a correlation is sought in examination of the individual CRF

Study plan shown in diagram is detailed in Table I.

III. Results: The inter-dosing interval was close to the intended 24h ~~with a mean of 24.9 and median of 24.1 hours. Ninety-two percent. fell~~ between 23 and 25 hours. Eleven outside this interval were eliminated from the study for other reasons. Seventy per cent. were titrated to the full dose in the active and 78% in the placebo group. The fall in mean systolic and diastolic blood pressures was significant in both groups from the first week of the study. After the the first two weeks the difference between the ~~effect of drug and placebo appeared and and remained significantly different~~ throughout the study even though placebo effect was significant through the plateau period. Change with time in supine diastolic blood pressures are displayed in the curves derived from the tabulated data given in tables 10-16

The categorical response to treatment is shown in the table below.

Treatment Group	Total N	Number of Patients (%)			
		Category*			
		1	2	3	4
PN 200-110	60	19 (32)	14 (23)	16 (27)	11 (18)
Placebo	64	10 (16)	10 (16)	18 (28)	26 (41)

*Category 1: supine diastolic ≤90 mm Hg with at least a 10 mm Hg decrease; Category 2: ≥10 mm Hg decrease, but still >90 mm Hg; Category 3: ≥5-<10 mm Hg decrease; and Category 4: <5 mm Hg decrease or an increase.

The difference in response between the placebo and isradipine groups is statistically significant. The response is good in about half the population,

and marginally effective or ineffective in the rest.

IV: Safety: There were 21 drop-outs from the isradipine and 23 from the placebo group. The reasons for discontinuation are given in the table.

Reason	IN 200-110 Group		Placebo Group	
	Patient Number	No. of Patients (% Total N=84)	Patient Number	No. of Patients (% Total N=86)
Lost to Follow-Up	263	1 (1%)	256	1 (1%)
Adverse Reaction	259 412 261 606 266 614 312 654 351	9 (11%)	204 315 516 659	4 (5%)
Uncooperative Noncompliant	201 572 505	3 (4%)	314 657	2 (2%)
Ineffectiveness of Study Drug	203 276 456 651	4 (5%)	202 303 205 410 208 416 264 457 265 656 268	11 (13%)
Other	207 358 251 414 274 453	6 (7%)	275 352 517	3 (4%)
TOTAL	23/84 (27%)		21/86 (24%)	

The ADRs attributable to the drug were for the most part mild to moderate. Headache was the most frequent of these. Those symptoms described as severe and resulting in discontinuation occurred twice in each group. The frequency of side effects is not dose related and the study raises no new safety issues.

V. Discussion: The claim that this study shows isradipine to be effective in controlling blood pressure in many patients may be accepted with reservation. The data do not permit an unqualified statement that the drug is effective when given once daily. In this study about half the patients with mild to moderate hypertension responded to qd dosage. Nearly all the patients studied (90%) were obese and 40% had normal eyegrounds. There were 17 diabetics and about half the patients were elderly. Many of these, it can be argued, do not need medicinal treatment for hypertension. It would be of interest to determine what relationship exists between those who may not need isradipine and those who do not respond to the drug.

It does seem reasonable to mention in labeling that with titration of the dose when beginning treatment isradipine may be given once daily with blood pressure measurements taken twenty-four hours post dose. The argument for once daily dosage can be strengthened by considering that improvement may continue after the 2 week regimen followed in the other clinical efficacy studies.

Summary and Conclusions: Study #332 quantitatively supports with peak and trough data the efficacy of bid dosage. Study # 308 dose not claim efficacy for qd dosage, but does show that some patients may respond to a small dose once daily and that a reasonable approach to treatment with this drug may to begin with a minimum dose given once daily for maximum time before increasing the dose and beginning conventional bid dosage.

RKimball

~~cHFD110~~
HFD-110
~~HFD-110/CSO~~
HFD-110/RKimball
wang #0111Y

N 200-110
Study No. 308

TABLE 1

DOSAGE SCHEDULE†

Treatment Group	Placebo Washout	Active Treatment††					
	Weeks -3, -2, -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo	One, Pcb* capsule once-daily	One, Pcb capsule once-daily	One or Two, Pcb capsules once-daily	One, Two or Three, Pcb capsules once-daily	One, Two, Three or Four, Pcb capsules once-daily	--->	
PN 200-110	One, Pcb capsule once-daily	One, 5 mg capsule once-daily	One or Two, 5 mg capsules once-daily	One, Two or Three, 5 mg capsules once-daily	One, Two, Three or Four, 5 mg capsules once-daily	--->	
	Total Dose/Day	5 mg	5-10 mg	5-15 mg	5- 20 mg		

<— Single-Blind —><——— Double-Blind ———>

*Pcb = placebo

†All study doses were administered once-daily before 12:00 noon, except on the day of each clinic evaluation when the study drug was taken after the required blood pressure measurements had been recorded by the investigator and his staff. Evaluations must have been performed before 1:00 PM on each clinic evaluation day (within 23 to 25 hours after the previous day's dose).

††The dose was increased by one capsule/day at weekly intervals until Week 4 if the average supine diastolic B.P was >95 mm Hg or had not decreased by at least 10 mm Hg from baseline without administration of the prescribed daily medication dose; otherwise the dose remained unchanged for the next interval. At the end of Week 4, a final titration to the next available dose level was permitted if the patient, previously maintained at a lower dose regimen of 1 to 3 capsules once-daily, did not satisfy the B.P. criteria at that time. Beginning with Week 5, the dose remained unchanged unless an adverse reaction occurred necessitating a dosage reduction.

08-0033

PH 200-110
Study No. 303

TABLE 2

FLOW CHART

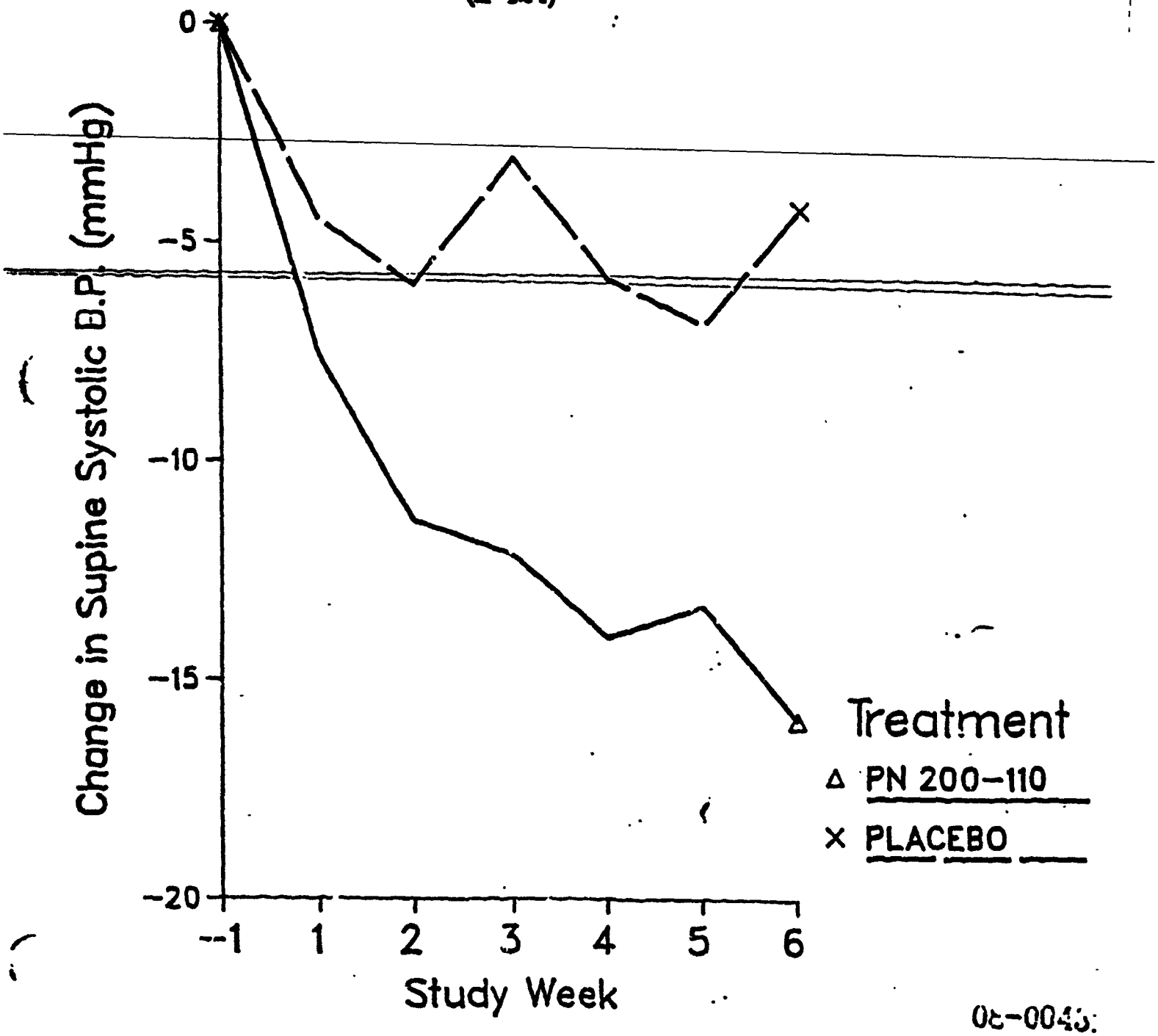
	Initial Visit	END OF WEEK									
		Single-Blind			Double-Blind						
		Placebo Washout†			Active Treatment Period						
	-4	-3	-2	-1 Time 0	1	2	3	4	5	6 Final Evaluation**	8 Follow-up Visit
Background Information CRF BK	X										
Physical Exam CRF PE	X									X**	
Cardiovascular Evaluation CRF CV	X			X			X			X**	
Patient Inclusion/Exclusion Criteria CRF IE				X							
Blood Pressure; Vital Signs CRF VS††	X	X	X	X	X	X	X	X	X	X**	
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) CRF LAB	X			X			X*			X**	X*
ECG Evaluation CRF ECG	X			X			X			X**	
Chest X-Ray CRF CX	X†††										
Concomitant Medication CRF CM	X	- AS REQUIRED -									
Comment CRF COM	X	X	X	X	X	X	X	X	X	X**	
Medication Check CRF MC		X	X	X	X	X	X	X	X	X**	
Adverse Reaction CRF AR		X	X	X	X	X	X	X	X	X**	
End of Study Information CRF ES										X**	

*Patients must have been evaluated before 1:00 PM, except possibly at the initial visit.
*Liver function tests only: LDH, total bilirubin, SGOT, SGPT and alkaline phosphatase.
**If upon discontinuation from the study.
†The placebo washout period may have been extended by as much as 2 weeks in order for patients to meet the entry blood pressure criteria.
††The vital signs were recorded before the daily medication dose was administered.
†††A chest X-ray obtained within six (6) months prior to the patient entering the trial may have served as baseline for the study and need not have been repeated at the initial visit provided that the chest X-ray was normal or that any abnormalities noted were minor and not considered by the investigator to be clinically relevant, and a clinical condition requiring a chest X-ray had not occurred during that interval. Otherwise an X-ray should have been obtained.

08-00339

Figure 1

PN 200-110 : UDY #308
Supine Systolic BP
Change from Baseline
Valid Patients
(n=124)



08-0045

Figure 2

PN 200-110 STUDY #308
Supine Diastolic BP
Change from Baseline
Valid Patients
(n=124)

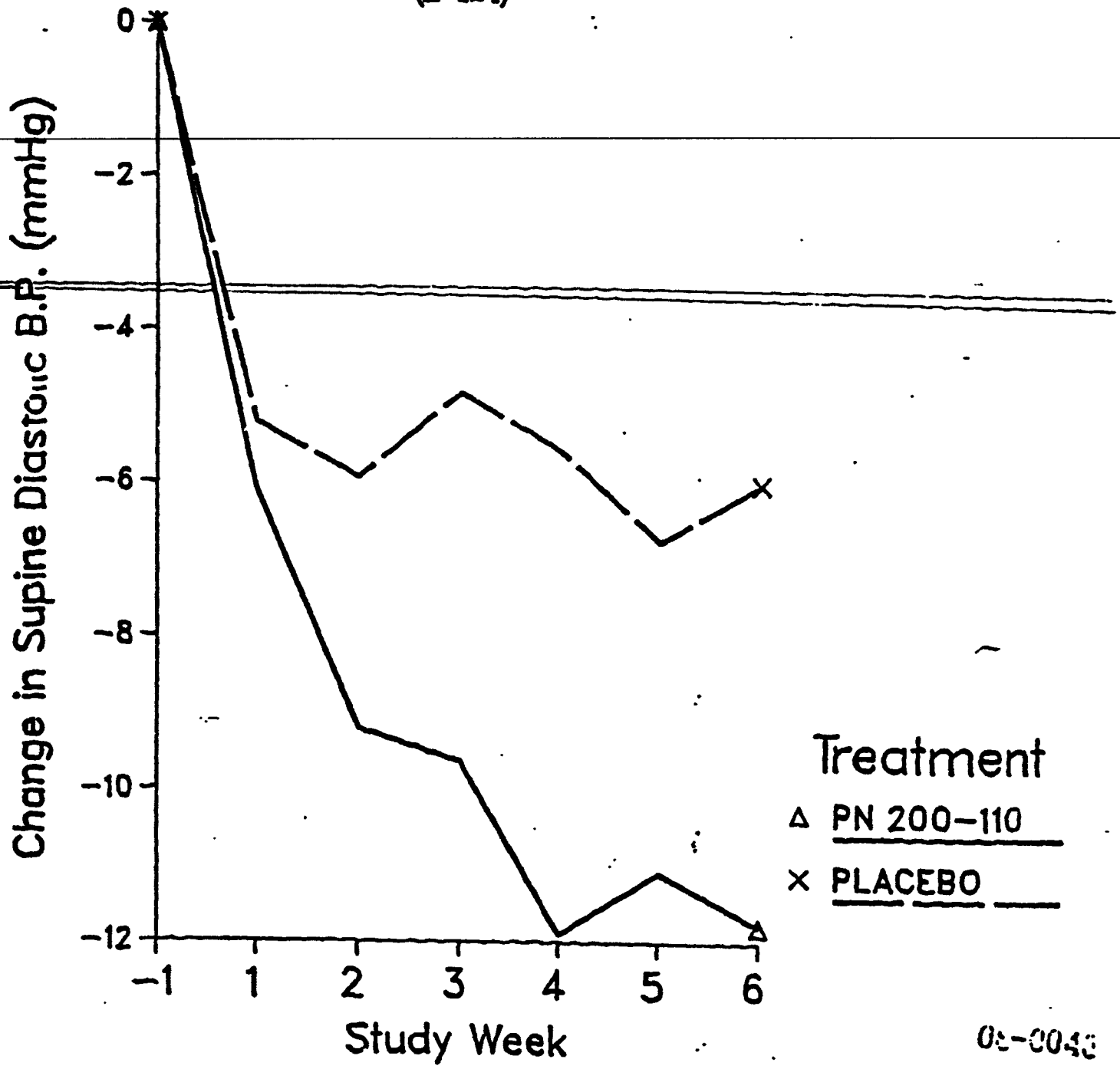
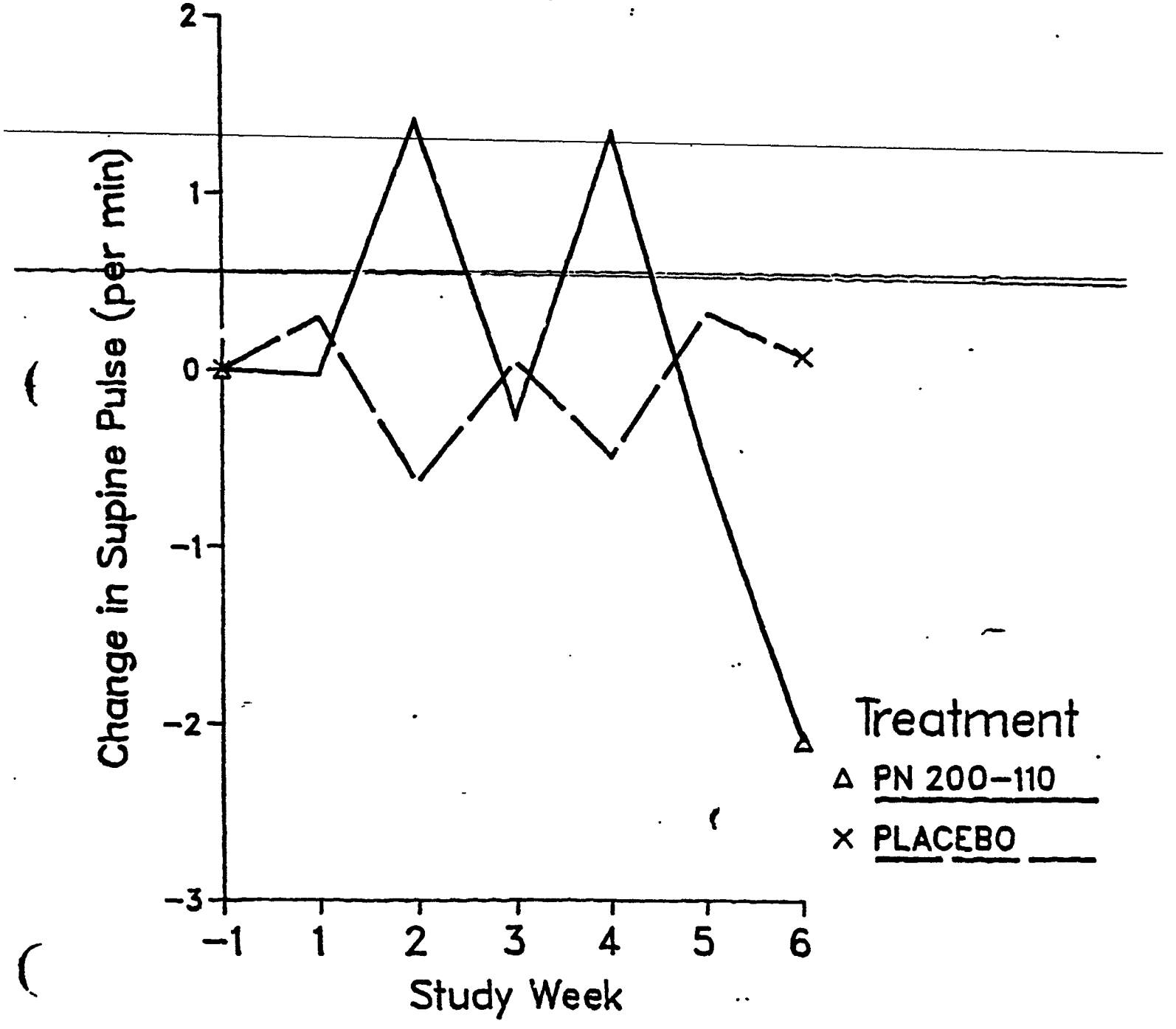


Figure 3

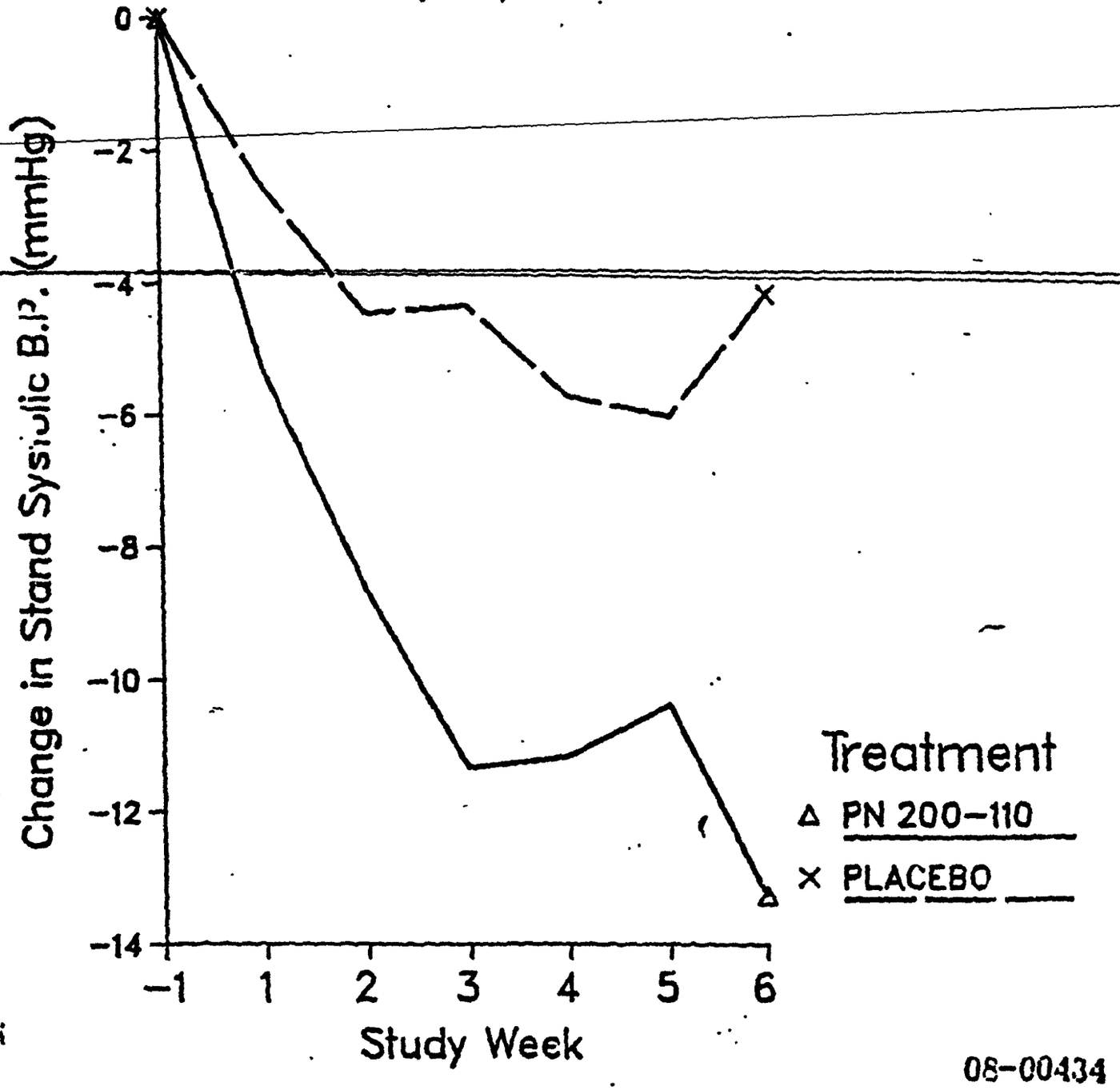
PN 200-110 STUDY #308
Supine Pulse
Change from Baseline
Valid Patients
(n=124)



08-0043

Figure 4

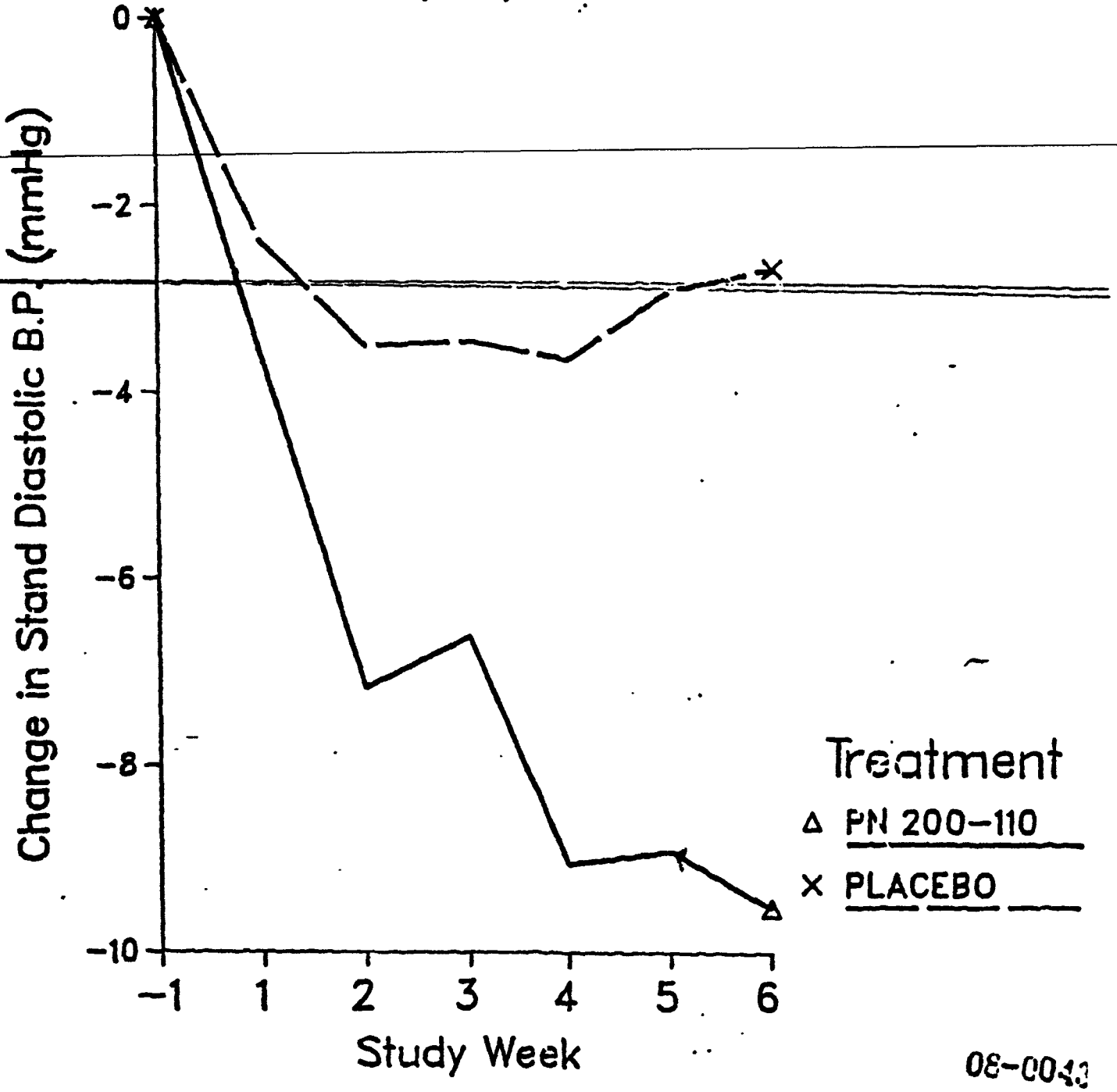
PN 200-110 STUDY #308
Standing Systolic BP
Change from Baseline
Valid Patients
(n=124)



08-00434

Figure 5

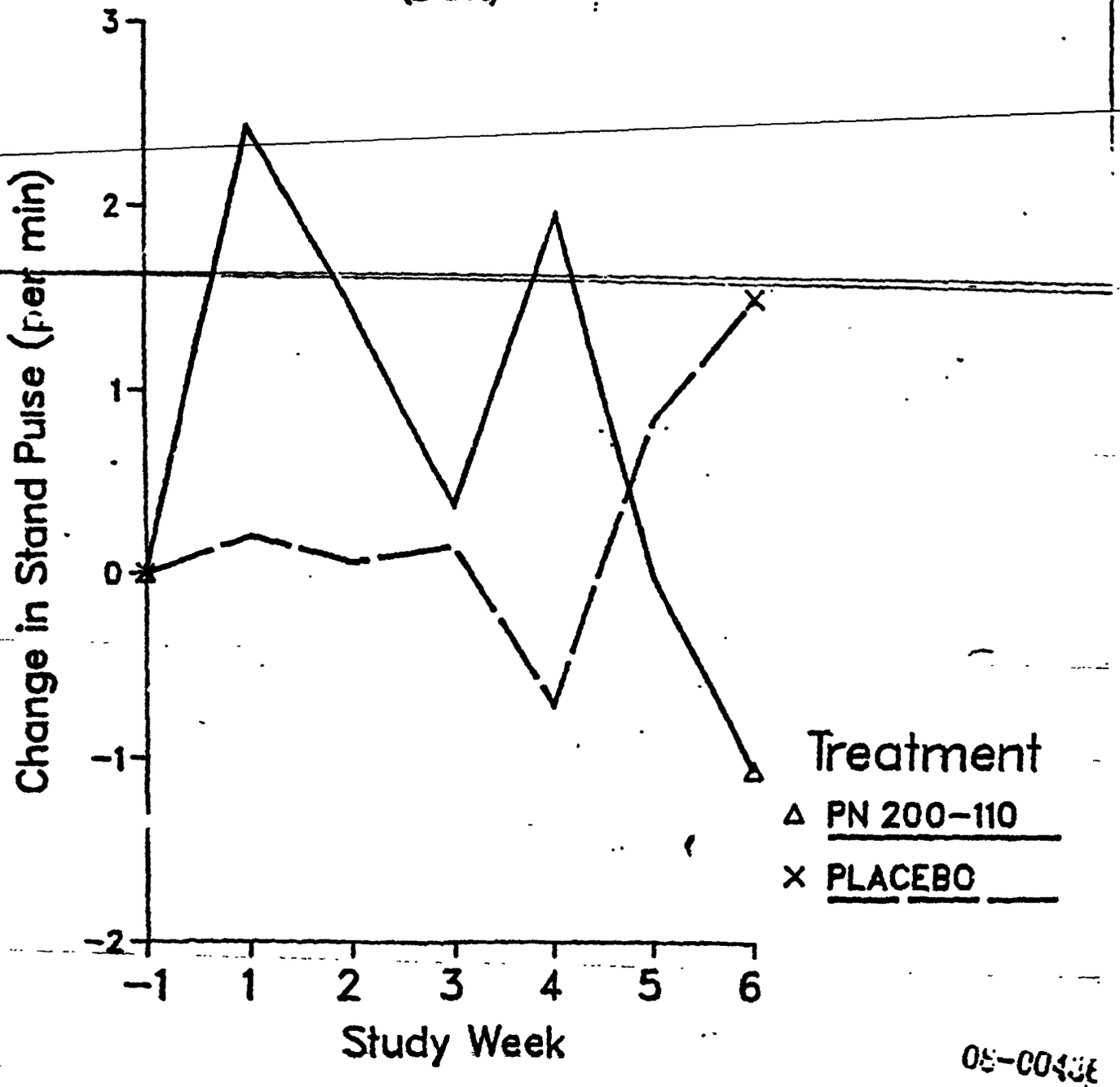
PN 200-110 STUDY #308
Standing Diastolic BP
Change from Baseline
Valid Patients
(n=124)



08-0043

Figure 6

PN 200-110 STUDY #308
Standing Pulse
Change from Baseline
Valid Patients
(n=124)



08-0043E

TABLE 10
PN 200-110 STUDY NO. 108

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
WEEK 1 - VALID AND PARTIALLY VALID PATIENTS

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change+	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	77	163.7	18.17	-8.21*** (*)	12.69	-8.13 (*)	155.5	17.38
	Placebo	84	163.0	19.76	-4.76***	12.51	-4.83	158.2	21.13
Supine Diastolic B.P. (mm Hg)	PN 200-110	77	104.7	4.86	-5.34***	6.18		99.3	7.88
	Placebo	84	105.3	5.59	-5.01***	6.14		100.3	8.31
Supine Pulse (per min)	PN 200-110	77	75.1	8.21	-0.02	7.74	0.16	75.1	8.13
	Placebo	84	74.4	8.06	0.17	7.86	0.01	74.5	8.34
Standing Systolic B.P. (mm Hg)	PN 200-110	77	159.5	20.31	-5.75***	14.16	-5.82	153.7	18.12
	Placebo	84	159.9	22.02	-3.19*	12.83	-3.12	156.8	21.00
Standing Diastolic B.P. (mm Hg)	PN 200-110	77	103.9	7.81	-3.43***	6.92	-3.57	100.4	9.08
	Placebo	84	105.3	9.29	-2.65***	6.61	-2.52	102.7	10.06
Standing Pulse (per min)	PN 200-110	77	79.2	9.14	2.14*	8.54	2.13	81.3	8.57
	Placebo	84	79.2	9.03	0.08	8.90	0.09	79.3	10.42

(*) p<.10, * p<.05, ** p<.01, *** p<.001
+Presented only when analysis of covariance assumptions were met.

08-003

TABLE 11
PN 200-110 STUDY NO. 308

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
WEEK 2 - VALID AND PARTIALLY VALID PATIENTS

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change+	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	75	163.0	17.71	-10.83***	12.38	-10.83	152.2	16.90
	Placebo	82	163.0	20.00	-5.04**	13.84	-5.04	157.9	18.19
Supine Diastolic B.P. (mm Hg)	PN 200-110	75	104.5	4.76	-8.72***	6.70		95.8	8.18
	Placebo	82	105.2	5.57	-4.75**	7.64		100.5	9.33
Supine Pulse (per min)	PN 200-110	75	75.1	8.30	1.04	9.54		76.1	9.14
	Placebo	82	74.4	8.09	-0.35	7.58		74.0	9.18
Standing Systolic B.P. (mm Hg)	PN 200-110	75	158.5	19.63	-8.79***	13.86	-9.02	149.7	16.55
	Placebo	82	159.9	22.18	-4.43**	15.10	-4.12	155.5	21.35
Standing Diastolic B.P. (mm Hg)	PN 200-110	75	103.5	7.58	-6.96***	7.60	-7.13	96.6	9.51
	Placebo	82	105.2	9.39	-3.43**	7.68	-3.28	101.8	10.85
Standing Pulse (per min)	PN 200-110	75	79.2	9.26	1.28	8.85	1.29	80.5	9.91
	Placebo	82	79.1	9.12	0.31	9.10	0.30	79.4	9.88

*) p<.10, * p<.05, ** p<.01, *** p<.001
+Presented only when analysis of covariance assumptions were met.

08-00356

TABLE 12
PN 200-110 STUDY NO. 308

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
WEEK 3 - VALID AND PARTIALLY VALID PATIENTS

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change*	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	7*	163.4	17.93	-11.41***	12.48	-11.39***	152.0	20.53
	Placebo	80	163.1	20.22	-2.79(*)	13.72	-2.81	160.3	21.37
Supine Diastolic B.P. (mm Hg)	PN 200-110	71	104.6	4.85	-8.40***	7.20		96.2	8.63
	Placebo	80	105.3	5.63	-3.94***	7.99		101.3	9.94
Supine Pulse (per min)	PN 200-110	71	75.3	8.38	-0.61	8.15	-0.41	74.7	8.88
	Placebo	80	74.3	8.05	0.41	7.88	0.23	74.7	9.12
Standing Systolic B.P. (mm Hg)	PN 200-110	71	158.9	19.90	-11.34***	13.11	-11.48***	147.5	20.33
	Placebo	80	160.0	22.46	-3.60*	14.12	-3.47	156.4	20.54
Standing Diastolic B.P. (mm Hg)	PN 200-110	71	103.5	7.75	-6.39***	7.53	-6.53**	97.1	9.36
	Placebo	80	105.2	9.50	-3.23***	7.70	-3.10	102.0	11.54
Standing Pulse (per min)	PN 200-110	71	79.3	9.37	0.32	8.89	0.34	79.6	9.79
	Placebo	80	79.2	9.08	-0.07	8.87	-0.08	79.1	10.38

(*) p<.10, * p<.05, ** p<.01, *** p<.001
*Presented only when analysis of covariance assumptions were met.

08-0035

TABLE 13
PN 200-110 STUDY NO. 308

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
WEEK 4 - VALID AND PARTIALLY VALID PATIENTS

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change+	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	69	163.5	17.87	-13.52***	13.74	-13.22	150.0	19.31
	Placebo	76	161.6	19.73	-4.50**	13.74	-4.78	157.1	16.76
Supine Diastolic B.P. (mm Hg)	PN 200-110	69	104.5	4.90	-11.03***	7.51		93.5	9.19
	Placebo	76	105.1	5.44	-4.60***	7.81		100.5	9.29
Supine Pulse (per min)	PN 200-110	69	75.1	8.42	0.64	9.39	0.90	75.8	8.79
	Placebo	76	74.2	8.20	-0.20	8.21	-0.44	74.0	8.36
Standing Systolic B.P. (mm Hg)	PN 200-110	69	159.1	19.95	-11.58***	14.61	-11.43	147.5	18.17
	Placebo	76	158.2	20.93	-5.57***	13.44	-5.70	152.7	18.11
Standing Diastolic B.P. (mm Hg)	PN 200-110	69	103.3	7.64	-8.30***	7.83	-8.41	95.0	10
	Placebo	76	104.8	9.22	-3.42***	7.44	-3.32	101.3	10.83
Standing Pulse (per min)	PN 200-110	65	79.0	9.36	1.57	9.38	1.52	80.6	9.40
	Placebo	76	79.3	9.22	-0.61	8.86	-0.55	78.7	9.94

(*) p<.10, * p<.05, ** p<.01, *** p<.001
+Presented only when analysis of covariance assumptions were met.

TABLE 14
PN 200-110 STUDY NO. 308

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
MEAN OVER PLATEAU PERIOD (WEEKS 5-6) - VALID PATIENTS ONLY

Variable	Randomized Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change+	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	60	162.2	17.14	-14.62***	12.30	-14.50***	147.6	14.58
	Placebo	64	162.0	19.63	-5.56**	13.36	-5.60	156.4	17.25
Supine Diastolic B.P. (mm Hg)	PN 200-110	60	104.1	4.54	-11.43***	6.71		92.6	7.40
	Placebo	64	104.7	5.34	-6.39***	6.01		98.3	8.77
Supine Pulse (per min)	PN 200-110	60	75.1	8.18	-1.32	7.61	-1.09	73.8	8.10
	Placebo	64	73.7	7.77	0.20	5.88	-0.11	73.9	6.31
Standing Systolic B.P. (mm Hg)	PN 200-110	60	157.6	20.30	-11.81***	16.28	-11.98*	145.8	16.19
	Placebo	64	158.3	22.24	-5.09**	14.93	-4.93	153.2	17.99
Standing Diastolic B.P. (mm Hg)	PN 200-110	60	102.7	7.46	-9.22***	8.71	-9.31***	93.5	9.87
	Placebo	64	103.5	9.22	-2.79**	7.10	-2.70	100.7	10.30
Standing Pulse (per min)	PN 200-110	60	79.1	9.33	-0.54	8.04	-0.28	78.6	9.09
	Placebo	64	77.9	8.11	1.17	7.11	0.93	79.1	7.24

(*) p<.10, * p<.05, ** p<.01 *** p<.001
+Presented only when analysis of covariance assumptions were met

08-003