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Protocol 7

Title:

Evaluation of the Safety and Efficacy of Sandoz Compound PN 200-110 Administered Orally for the Treatment of Hypertension

Investigator:

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Objective

To determine the blood pressure lowering effect of PN 200-110 (2.5mg, 5.0 mg and 10.0 mg, bid) compared with placebo in patients with hypertension. Additionally, the safety of PN 200-110 would be evaluated in terms of physical and cardiopulmonary examinations, vital signs, ECGs, laboratory evaluations and adverse reactions.

Design

This was a randomized, double-blind, placebo controlled, parallel group study.

Population

Patients of either sex, 18 years and older with previously treated or newly diagnosed benign essential hypertension were eligible for the trial. A supine diastolic blood pressure of > 95 mm Hg during the washout period was required for entry into the study. There was to be no manifestation of a decreasing trend in blood pressure during the washout period. If average supine diastolic blood pressure at each evaluation day of the washout phase was less than the previous day's values and the Time 0 diastolic pressure had decreased by more than 10 mm Hg compared to first day, patient was excluded from the study.

Exclusion criteria included patients with secondary or malignant hypertension, patients who were unable to be evaluated before 11.00 a.m. on visit day, angina pectoris, CHF uncontrolled by digitalis alone, MI in previous six months, cardiac arrhythmias requiring treatment with medications other than digitalis, bradycardia < 50 bpm, A-V conduction impairment, other investigational drugs in 4 weeks prior to enrollment, any significant clinical conditions that could interfere in evaluation, certain drugs and patients with a history of drug abuse or cerebral insufficiency.

Trial Plan

Study design is shown in Tables 1 and 2. There was an initial single blind, 3 week placebo washout period, followed by a 4 week randomized, double-blind, placebo controlled active treatment period. A protocol amendment allowed an additional two weeks, double-blind phase, during which PN 200-110 was compared to

placebo were administered once daily. The dosage in this phase was to be the same as that achieved during the bid administration phase. This amendment was implemented after 12 patients had already completed the study, leaving only 11 for possible entry into the extension phase.

Medication

Study drug consisted of identically appearing capsules of PN 200-110 2.5 mg or 5.0 mg or placebo. Dosage schedule is found in Table 1. During initial 3 weeks placebo washout, all received one capsule bid before breakfast and supper. Those satisfying entry requiremens were then randomized to active drug or placebo.

PN 200-110 patients received 2.5 mg bid during week 1; this was increased to 5 mg bid and then to 10 mg bid if supine diastolic blood pressure (SDBP) was > 90 mm Hg at end of weeks 1 and 2 respectively. If SDBP was < 90 mm Hg, the dose producing this response was used for the remainder of the study. No further dose titration was permitted after the third week.

Patients in the two week extension period, continued receiving their randomly assigned drug but, from week 5, the dose was administered once daily before breakfast. Dosage was adjusted, if necessary, at end of week 5 and given for week 6. At no time could total daily dose exceed 20 mg. On clinic day, the morning dose was not to be taken in order to evaluate the once daily regimen.

Evaluation

Patients were evaluated at weekly intervals during the study. Schedule is shown in Table 2. Plasma renin activity was determined at Time 0. Efficacy was assessed by change in vital signs from Time 0 evaluation. During once a day phase, vital signs were measured 24 hours after last dose. There was a protocol amendment evaluating ambulatory blood pressure over 24 hours at end of week 6. Only 4 patients participated in this aspect.
Safety evaluation included physical examinations, cardiopulmonary evaluations, ECGs, vital signs, laboratory tests, chest x-rays and adverse reactions. An adjustment was made for those patients reporting ADRs during both washout and double-blind periods. These patients were eliminated from frequency count during active phase. (Is this an acceptable practice ?).

Results

A total of 23 patients entered the study; 11 received placebo and 12 received active drug. (How many were actually enrolled ?) Data from 8 were determined to be partially or totally invalid for efficacy analysis because they did not completed the double-blind treatment phase as specified in protocol. Thus, only 9 PN and 6 placebo patients were considered valid. Reasons for the exclusion of the 8 invalid patients were:

Partially valid:

PN 200-110: n=3	ADR 1; unacceptable concomitant medication 1; patient completed study but did not take morning dose at visit 4.
Placebo n =2	Completed study but did not take morning dose at visit 4; study drug ineffective.

Totally Invalid:

PN 200-110: n=0	
Placebo: n=3	Nonqualifying BP at Time 0; completed study but non compliant for weeks 1 and 3; completed study but did not take morning dose at Time 0.

There were 11 patients who entered the extension protocol and 3 completed. Of these, 5 received active drug.

Demography

The only statistically significant difference in demographic characteristics was for body frame for all patients. There were no other statistical differences either for all patients or for valid group only. There were 7/12 (58%) males in active group and 10/11 (91%) in placebo group. Actives were 83% caucasian compared to 100% placebo. Mean age for PN group was 52.8 years (range 37 - 68) and for placebo 55.9 (range 47 - 69).

Dose

The average daily dose by week, is presented in Table 6. The mean daily dose was 4.9 mg at week 1, 6.9 mg at week 2, 9.6 mg at week 3 and 10.1 mg at week 4.

Efficacy

1. Valid Patients

Table 7 summarizes mean changes from baseline in supine and standing blood pressures and pulse rates for weeks 1, 2, 3 and 4 for the 15 valid patients. After week 1, there were statistically significant decreases from baseline in active group for both supine and standing systolic and diastolic blood pressures. This was especially seen in SDBP for weeks 2, 3 and 4 and for standing DBP for weeks 3 and 4. For placebo, there was a statistically significant decrease in supine systolic blood pressure. By week 2, the decreases for both groups were also statistically significant from baseline for all blood pressure variables. There were no

statistically significant between group differences for weeks 1 and 2. At week 4, there was a statistically significant difference from placebo for SDBP. The mean changes at weeks 3 and 4 from baseline were:

		n=	Week 3	Week 4
Supine Systolic	PN	9	-16.3	-24.2
	Placebo	6	-19.0	-10.3
Supine Diastolic	PN	9	-12.9	-16.8
	Placebo	6	- 8.3	- 4.7
Standing Systolic	PN	9	-13.9	-18.2
	Placebo	6	-14.0	- 4.3
Standing Diastolic	PN	9	-10.8	-10.2
	Placebo	6	- 4.0	- 1.7

The active group also had a statistically significant greater increases in supine and standing pulse rates from baseline than did placebo at week 3.

Changes in blood pressure and pulse by week for valid patients are shown graphically in figures 1 - 6.

Mean change and adjusted mean change from baseline over plateau period for valid patients are seen in Table 8. Active group had statistically significantly greater decreases in supine and standing diastolic pressure compared to placebo. SDBP (active) decreased by 15.4 mm Hg at weeks 3-4 compared to 6.5 mm Hg for placebo. Standing diastolic decreases were 11.0 mm Hg and 2.8 mm Hg respectively.

There was a mean increase in supine and standing pulse rates with PN which was statistically significantly different from placebo.

2. All Patients

Tables 9, 10 and 11 present vital signs for all patients in the study at weeks 1, 2, 3 and 4. Similar results were observed as for valid patients only. Statistically significant between group differences were achieved for both supine and standing diastolic pressures for weeks 3 and 4. The SDBP for PN decreased by 14.1 mm Hg compared to 3.78 mm Hg for placebo. PN also tended to produce greater decreases in other blood pressure variables than placebo, but those differences were not statistically [illegible] statistically significant difference from baseline in supine pulse rate with PN (+6.7 bpm).

Table 12 summarizes changes in endpoint analyses for all patients. Only PN had statistically significant decreases from baseline for both supine and standing systolic and diastolic blood pressures. There was a statistically significant between group difference for these parameters.

Table 13 presents catergorical analysis of SDBP at week 4 for valid patients. 89% of PN group versus 34% placebo showed a decrease of at least 10 mm Hg for SDBP from baseline.

Extension Study

Patients in the once a day extension study continued having consistent reductions in their blood pressures compare to placebo (Table 14). Sponsor maintains that these results were clinically relevant but due to small number of patients only descriptive statistics were done. These reductions were not seen at week 6 and it was felt that blood pressure control was not maintained with a once daily dosage. There were no increases in supine or standing pulse rates. The average daily dose in this phase was 11.2 mg.

Three patients, two active and one placebo, were withdrawn from the extension phase. One active patient experienced "extra heart beats" which apparantly increased during week 5 and investigator withdrew the patient. The second active patient withdrew due to ADR, edema and tingling of lower extremities. The placebo patient withdrew due to elevated blood pressure 200/118 mm Hg.

Safety

There was a statistically significant difference in the number of patients with baseline heart abnormalities. No PN patient had an abnormality while 5/11 placebo were noted to have an atrial (S4) gallop sound. No newly occurring abnormalities were noted in either group.

ECG results are shown in Table 16. A statistically significant increase in atrial and ventricular rate was seen with PN at week 3 only (+ 9.0 bpm). One placebo patient developed a first degree AV block at week 1. One patient in each group had newly diagnosed ST-T wave changes at week 5. Table 18 presents ECG data for extension trial.

There were no significant changes in either group for respiratory rate, body weight or temperature

Clinical Laboratory Tests.

Table 21 - 27 present data on laboratory tests. Statistically significant between group differences were noted only for alkaline phosphatase.

Adverse Reactions

Table 31 lists all ADRs during the study. Thirteen of the twenty-three patients reported an ADR. Table 32 compares frequency of each ADR by treatment. One PN patient was withdrawn due to moderately severe headache and tachycardia. (What about the patient withdrawn due to edema during extension trial ?). Most frequently reported ADRs with PN were palpitations and headaches.

Discussion

~~There were significantly greater reductions in supine and~~ standing diastolic blood pressures with PN than with placebo. The mean daily dose was 10.8 mg. There were no serious ADR reported.

Reviewer's Comments

1. This single center, small study, presents data showing that PN 200-110, administered twice daily, reduces blood pressure significantly from baseline and more than placebo. It also appears that results are only significant after about 3 weeks.

2. There are no clinically significant liver function abnormalities in this small study

3. No results are presented for the ambulatory blood pressure recordings.

4. No mention is made as to how many patients were originally enrolled and how many were discontinued during the washout period.

TABLE 1

FN 200-110 STUDY NO. 7

STUDY DESIGN

Treatment Group	Single-Blind Placebo Washout Period Weeks -3,-2,-1	Double-Blind					
		Week 1	Week 2	Week 3	Week 4	Extension† Week 5	Extension† Week 6
FN 200-110	one (1) Pcb cap (bid) ac*	one (1) FN 200-110 2.5 mg cap (bid) ac	one (1) FN 200-110 2.5 mg cap (bid) ac if diastolic BP ≤90 OR one (1) FN 200-110 5.0 mg cap (bid) ac if diastolic BP >90	one (1) FN 200-110 2.5 mg cap (bid) ac if diastolic BP ≤90 one (1) FN 200-110 5.0 mg cap (bid) ac if diastolic BP >90 one (1) FN 200-110 5.0 mg cap (bid) ac if diastolic BP ≤ 90 two (2) FN 200-110 5.0 mg caps (bid) ac if diastolic BP >90	Same dosage regimen Same dosage regimen Same dosage regimen Same dosage regimen	one (1) to four (4) FN 200-110 5.0 mg caps once-a-day**	one (1) to four (4) FN 200-110 5.0 mg caps once-a-day**
	Total Daily Dose:	5.0 mg	5-10.0 mg	5-20.0 mg	5-20.0 mg	5-20.0 mg	5-20.0 mg
Placebo	one (1) Pcb cap (bid) ac	one (1) Pcb cap (bid) ac	one (1) Pcb cap (bid) ac	one (1) Pcb cap (bid) ac	Same dosage regimen	one (1) to four (4) Pcb caps once-a-day**	one (1) to four (4) Pcb caps once-a-day
			appropriately packaged and titrated to maintain double-blind study design				

*Before breakfast and supper.

**Before breakfast.

†Eleven (11) patients entered the double-blind, two week extension, Weeks 5 and 6. Patients continued to receive the same study medication as received during the initial active treatment phase but the full daily dose was administered on a once-a-day regimen. During Week 5, titration was allowed to achieve the maximum tolerated once-a-day dose as determined by the investigator. No dose titration was allowed during Week 6. The highest allowable dose was 20.0 mg/day.

TABLE 2
PN 200-110 STUDY NO. 7
SCHEDULE OF PATIENT EVALUATIONS

	Patient Visits									
					Active Treatment Period					
	Day 1 of Weeks				Twice-a-Day				Once-a-Day Extension	
	Initial Visit	Placebo Period		Time	End of Weeks					
	-3	-2	-1	0	1	2	3	4	5	6
Background Information (BK, BK-2)†	X								--	
Physical Exam (PE)†	X									X
Exclusion Checklist (IE)†				X						
Vital Signs (VS)†	X	X	X	X	X	X	X	X	X	X
Cardiopulmonary Exam (CP)†				X	X	X	X	X	X	
ECG Evaluation (ECG)†	X			X	X	X	X	X	X	X
Chest X-Ray (CX)†	X[1]									
Concomitant Medication (CM)†	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) (LAB)†	X			X[2]				X		X
Comments (COM)†	X	X	X	X	X	X	X	X	X	X
Medication Check (MC)†		X	X	X	X	X	X	X	X	X
Adverse Reactions (AR)†		X	X	X	X	X	X	X	X	X
End of Study Information (ES)†								X[3]		X[3]

[1]The baseline chest X-ray was taken any time during the placebo washout period. A chest X-ray obtained within six (6) months prior to entering the trial served as baseline for the study and was not repeated at the initial visit provided the X-ray was normal and a clinical condition requiring a repeat film had not occurred during this interval.
[2]Laboratory evaluation at Time 0 included 24 hour urine collection and plasma sample for plasma renin assay.
[3]Or upon early discontinuation from study.
†Case report form identifiers.

TABLE 6

PN 200-110 STUDY NO. 7

SUMMARY OF AVERAGE DAILY DOSE
OF PN 200-110 BY WEEK

For Valid Patients

Statistic	Week 1	Week 2	Week 3	Week 4
n	9	9	9	9
Mean	4.9	6.9	9.6	10.1
S.D.	0.35	2.51	4.94	5.78
Median	5.0	5.3	10.0	10.0
Minimum	4.3	3.9	3.8	3.4
Maximum	5.4	10.0	20.0	20.0

For All Patients

Statistic	Week 1	Week 2	Week 3	Week 4
n	12	10	10	10
Mean	4.9	7.2	10.6	10.8
S.D.	0.34	2.48	5.57	5.88
Median	5.0	7.0	10.0	10.0
Minimum	4.3	3.9	3.8	3.4
Maximum	5.4	10.0	20.0	20.0

TABLE 7

PN 200-110 STUDY NO. 7

VITAL SIGNS
ANALYSIS OF VARIANCE
VALID PATIENTS

Variable	Treatment Group	N	Baseline		Mean Change From Baseline At			
			Mean	S.D.	Week 1	Week 2	Week 3	Week 4
Supine Systolic B.P. (mm Hg)	PN 200-110	9	160.0	21.82	-13.78*	-17.00*	-16.25(*)	-24.22**
	Placebo	6	155.7	17.57	-15.33*	-15.67*	-19.00**	-10.33
Supine Diastolic B.P. (mm Hg)	PN 200-110	9	100.1	5.53	-9.67**	-14.11***	-13.88***	-16.78***
	Placebo	6	99.3	5.47	-5.33	-7.00**	-8.33*	-4.67
Supine Pulse Rate (beats/min)	PN 200-110	9	67.6	9.04	-1.44	5.00(*)	10.25*	4.22
	Placebo	6	75.8	4.79	-2.50	-1.67	-8.17	-2.50
Standing Systolic B.P. (mm Hg)	PN 200-110	9	157.3	20.88	-13.11*	-12.00*	-13.88*	-18.22*
	Placebo	6	151.0	21.38	-8.33	-10.33*	-14.00*	-4.33
Standing Diastolic B.P. (mm Hg)	PN 200-110	9	97.3	7.28	-7.44**	-8.00(*)	-10.75**	-10.22**
	Placebo	6	99.7	7.42	-3.33	-4.33	-4.00	-1.67
Standing Pulse Rate (beats/min)	PN 200-110	9	73.6	11.47	0.89	4.00	7.50	3.89
	Placebo	6	85.5	10.43	-2.00	-5.33	-9.17	-5.50

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

TABLE 8

PN 200-110 STUDY NO. 7

VITAL SIGNS
ANALYSIS OF VARIANCE
VALID PATIENTS

Variable	Treatment Group	N	Baseline		Plateau Period (Weeks 3-4)		
			Mean	S.D.	Mean Change	S.D.	Adjusted Mean Change†
Supine Systolic B.P. (mm Hg)	PN 200-110	9	160.0	21.82	-20.22*	18.77	-19.08
	Placebo	6	155.7	17.57	-14.67(*)	14.75	-16.37
Supine Diastolic B.P. (mm Hg)	PN 200-110	9	100.1	5.53	-15.44***	3.88	-15.32
	Placebo	6	99.3	5.47	-6.50*	5.43	-6.69
Supine Pulse Rate (beats/min)	PN 200-110	9	67.6	9.04	6.67*	6.76	
	Placebo	6	75.8	4.79	-5.33	9.21	
Standing Systolic B.P. (mm Hg)	PN 200-110	9	157.3	20.88	-15.72*	15.50	-14.27
	Placebo	6	151.0	21.38	-9.17	12.22	-11.34
Standing Diastolic B.P. (mm Hg)	PN 200-110	9	97.3	7.28	-11.00**	6.82	-11.61
	Placebo	6	99.7	7.42	-2.83	7.03	-1.92
Standing Pulse Rate (beats/min)	PN 200-110	9	73.6	11.47	4.83	10.21	2.77
	Placebo	6	85.5	10.43	-7.33(*)	8.47	-4.24

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

†Presented only when analysis of covariance assumptions were met.

TABLE 9

PN 200-110 STUDY NO. 7

VITAL SIGNS
ANALYSIS OF VARIANCE
ALL PATIENTS

Variable	Treatment Group	N	Baseline		Week 1		
			Mean	S.D.	Mean Change	S.D.	Adjusted Mean Change†
Supine Systolic B.P. (mm Hg)	PN 200-110	12	160.3	23.48	-9.67*	14.44	-10.17
	Placebo	11	164.5	19.39	-10.91*	15.16	-10.36
Supine Diastolic B.P. (mm Hg)	PN 200-110	12	99.8	5.13	-7.67**	6.61	-7.97
	Placebo	11	100.5	6.31	-4.36	9.03	-4.04
Supine Pulse Rate (beats/min)	PN 200-110	12	66.3	8.12	-1.75	4.48	-2.94 (↓)
	Placebo	11	71.0	7.29	1.73	11.01	3.02
Standing Systolic B.P. (mm Hg)	PN 200-110	12	156.1	21.69	-7.58	15.13	-8.83
	Placebo	11	163.5	22.47	-9.00*	13.29	-7.65
Standing Diastolic B.P. (mm Hg)	PN 200-110	12	97.8	7.36	-4.58(*)	8.79	-5.41
	Placebo	11	102.0	6.76	-4.09(*)	6.20	-3.19
Standing Pulse Rate (beats/min)	PN 200-110	12	72.4	10.18	-0.33	6.51	
	Placebo	11	76.8	12.85	4.09	10.07	

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

†Presented only when analysis of covariance assumptions were met.

TABLE 10

PN 200-110 STUDY NO. 7

VITAL SIGNS
ANALYSIS OF VARIANCE
ALL PATIENTS

Variable	Treatment Group	N	Baseline		Week 2		
			Mean	S.D.	Mean Change	S.D.	Adjusted Mean Change†
Supine Systolic B.P. (mm Hg)	PN 200-110	10	158.0	21.52	-16.50*	18.25	-18.20
	Placebo	11	164.5	19.39	-10.36(*)	17.55	-8.82
Supine Diastolic B.P. (mm Hg)	PN 200-110	10	99.6	5.46	-12.80***	6.32	-13.13 (**)
	Placebo	11	100.5	6.33	-4.55(*)	7.22	-4.25
Supine Pulse Rate (beats/min)	PN 200-110	10	67.4	8.54	5.50*	6.40	4.64
	Placebo	11	71.0	7.29	2.55	9.60	3.32
Standing Systolic B.P. (mm Hg)	PN 200-110	10	154.8	21.25	-11.00*	14.46	-12.65
	Placebo	11	163.5	22.47	-9.91(*)	14.78	-8.41
Standing Diastolic B.P. (mm Hg)	PN 200-110	10	96.6	7.25	-7.00(*)	11.82	-9.21 (*)
	Placebo	11	102.0	6.75	-4.82*	5.91	-2.81
Standing Pulse Rate (beats/min)	PN 200-110	10	73.0	10.95	5.20	9.94	4.15
	Placebo	11	76.8	12.85	-0.09	5.84	0.87

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

†Presented only when analysis of covariance assumptions were met.

TABLE 11

PN 200-110 STUDY NO. 7

VITAL SIGNS
ANALYSIS OF VARIANCE
ALL PATIENTS

Variable	Treatment Group	N	Baseline		Plateau Period (Weeks 3-4)		
			Mean	S.D.	Mean Change	S.D.	Adjusted Mean Change†
Supine Systolic B.P. (mm Hg)	PN 200-110	10††	158.0	21.52	-18.81**	16.26	-19.59
	Placebo	9	161.3	19.65	-12.78*	14.91	-11.90
Supine Diastolic B.P. (mm Hg)	PN 200-110	10††	99.6	5.46	-14.10***	5.61	
	Placebo	9	100.2	5.78	-3.78	6.42	
Supine Pulse Rate (beats/min)	PN 200-110	10††	67.4	8.54	6.70**	6.37	
	Placebo	9	71.9	7.25	0.33	11.44	
Standing Systolic B.P. (mm Hg)	PN 200-110	10††	154.8	21.25	-13.75*	15.89	-14.61
	Placebo	9	158.3	[illegible]	[illegible]11*	11.87	-10.16
Standing Diastolic B.P. (mm Hg)	PN 200-110	10††	96.6	7.25	-9.40**	8.18	-10.68
	Placebo	9	100.9	6.8[illegible]	-2.67	6.00	-1.24
Standing Pulse Rate (beats/min)	PN 200-110	10††	73.0	10.95	5.20	9.70	3.70
	Placebo	9	78.9	13.01	-2.33	10.09	-0.67

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

†Presented only when analysis of covariance assumptions were met.

††Patient No. 122 missing Week 3 data, however, his Week 4 evaluation was included in this analysis.

TABLE 12

PN 200-110 STUDY NO. 7

VITAL SIGNS - ENDPOINT OF ENTIRE STUDY PERIOD

ALL PATIENTS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint				
			Mean	S.D.	Mean Change	S.D.	Adjusted Mean Change†	Mean	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	12	160.3	23.48	-18.5**	20.18		141.8	23.10
	Placebo	11	164.5	19.39	-5.5	19.45		159.1	27.73
Supine Diastolic B.P. (mm Hg)	PN 200-110	12	99.8	5.13	-13.2***	8.4.		86.7	9.00
	Placebo	11	100.5	6.33	-	9.51		99.1	10.56
Pulse Rate (per min.)	PN 200-110	12	66.3	8.12	3.3	7.44		69.7	11.37
	Placebo	11	71.0	7.29	3.5	10.79		74.5	6.38
Standing Systolic B.P. (mm Hg)	PN 200-110	12	156.1	21.69	-12.4*	19.11	-13.8	143.7	16.00
	Placebo	11	163.5	22.47	-7.9(*)	13.93	-6.4	155.6	22.91
Standing Diastolic B.P. (mm Hg)	PN 200-110	12	97.8	7.36	-7.3*	9.32	-8.4	90.5	8.01
	Placebo	11	102.0	6.75	-1.5	9.05	-0.4	100.5	9.95
Standing Pulse Rate (per min.)	PN 200-110	12	72.4	10.18	3.0	8.43	2.0	75.4	10.96
	Placebo	11	76.8	12.85	0.3	10.58	1.4	77.1	8.04

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

†Presented when analysis of covariance assumptions are met.

TABLE 13

PN 200-110 STUDY NO. 7

CATEGORICAL ANALYSIS OF SUPINE DIASTOLIC B.P. (MM HG)

AT WEEK 4

VALID PATIENTS - CHANGE FROM BASELINE

Treatment Group	No. of Patients	Response Categories			
		≥10 mm Hg Decrease		5-<10 mm Hg Decrease	<5 mm Hg Decrease
		≤85 mm Hg	>85 mm Hg		
		N (%)	N (%)	N (%)	N (%)
PN 200-110	9	7 (78)	1 (11)	0 (0)	1 (11)
Placebo	6	1 (17)	1 (17)	1 (17)	3 (50)

Pearson Chi-Square = 6.146

D.F. = 3

p = 0.105

TABLE 13

0627

TABLE 14

PN 200-110 STUDY NO. 7

DESCRIPTIVE STATISTICS FOR BLOOD PRESSURE AND PULSE
TWO-WEEK EXTENSION PERIOD

Variable (≥ 24 hours after last dose)	Treatment Group	Week 5					Week 6				
		N	Baseline Mean	S.D.	Mean Change	S.D.	N	Baseline Mean	S.D.	Mean Change	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	7	156.3	23.71	-20.29	27.12	5	158.4	27.62	4.00	26.68
	Placebo	4	164.0	24.71	-6.50	9.71	3	158.7	27.30	-12.00	10.39
Supine Diastolic B.P. (mm Hg)	PN 200-110	7	100.1	6.28	-16.71	14.08	5	101.2	7.16	-3.20	11.63
	Placebo	4	101.5	5.97	5.00	13.12	3	98.7	2.31	0.67	10.07
Supine Pulse (per min)	PN 200-110	7	66.3	10.11	-0.29	8.92	5	65.2	11.99	-0.60	10.81
	Placebo	4	72.5	8.35	-3.25	11.98	3	75.7	6.66	-8.67	15.31
Standing Systolic B.P. (mm Hg)	PN 200-110	7	156.9	25.06	-18.86	23.97	5	163.2	26.93	-1.50	19.46
	Placebo	4	156.3	27.91	-9.75	13.38	3	151.3	29.69	-2.67	13.01
Standing Diastolic B.P. (mm Hg)	PN 200-110	7	97.4	7.37	-14.00	17.36	5	100.0	7.21	-1.20	11.97
	Placebo	4	100.0	8.33	3.50	5.00	3	96.7	6.11	-2.00	16.37
Standing Pulse (per min)	PN 200-110	7	70.6	11.75	1.14	6.67	5	69.4	13.63	-1.40	15.21
	Placebo	4	80.5	20.21	-0.50	13.82	3	85.3	21.73	-7.67	30.35

TABLE 16

PN 200-110 STUDY NO. 7

EKG EVALUATION
ANALYSIS OF VARIANCE

Variable	Treatment Group	Completers Only									Endpoint - All Patients				
					Mean Change From Baseline At										
		N	Baseline Mean	S.D.	Week 1	Week 2	Week 3	Week 4	Weeks 1-4	S.D.	N	Baseline Mean	S.D.	Mean Change	S.D.
Atrial Rate (per min)	PN 200-110	9	70.8	6.92	3.0	2.1	9.0**	5.6	4.9(*)	7.45	12	68.7	7.96	4.6	11.94
	Placebo	9	71.8	8.32	-0.1	1.7	-0.3	3.2	1.1	9.51	11	71.0	7.72	3.1	12.01
Ventricular Rate (per min)	PN 200-110	9	70.8	6.92	3.0	2.1	9.0**	5.6	4.9(*)	7.45	12	68.7	7.96	4.6	11.94
	Placebo	9	71.8	8.32	-0.1	1.7	-0.3	3.2	1.1	9.51	11	71.0	7.72	3.1	12.01
P-R Interval (sec)	PN 200-110	9	0.163	0.014	-0.003	0.001	0.000	-0.001	-0.001	0.007	12	0.172	0.019	-0.002	0.011
	Placebo	9	0.174	0.017	-0.003	0.004	-0.012*	-0.007	-0.004	0.012	11	0.172	0.016	-0.005	0.010
QRS Duration (sec)	PN 200-110	9	0.081	0.003	0.002	-0.001	0.002	0.001	0.001	0.005	12	0.082	0.006	0.001	0.007
	Placebo	9	0.088	0.019	-0.001	0.002 (*)	0.003(*)	-0.002	0.001	0.005	11	0.086	0.017	-0.001	0.008
QT Interval (sec)	PN 200-110	9	0.398	0.025	-0.007	-0.009	-0.020	-0.008	-0.011	0.025	12	0.398	0.022	-0.009	0.027
	Placebo	9	0.387	0.017	0.007	-0.004	0.000	-0.004	-0.001	0.014	11	0.387	0.016	-0.004	0.027

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

TABLE 16

TABLE 18

PN 200-110 STUDY NO. 7

ECG EVALUATION
DESCRIPTIVE STATISTICS FOR TWO-WEEK
EXTENSION PERIOD (QD DOSING)

Variable	Treatment Group	Week 5					Week 6				
		N	Baseline Mean	S.D.	Mean Change	S.D.	N	Baseline Mean	S.D.	Mean Change	S.D.
Atrial Rate (per min)	PN 200-110	7	68.1	5.24	3.3	13.23	5	66.4	4.98	-5.8	9.01
	Placebo	4	70.5	12.56	-0.5	15.84	3	69.0	14.93	-5.0	19.98
Ventricular Rate (per min)	PN 200-110	7	68.1	5.24	3.3	13.23	5	66.4	4.98	-5.8	9.01
	Placebo	4	70.5	12.56	-0.5	15.84	3	69.0	14.93	-5.0	19.98
P-R Interval (sec)	PN 200-110	7	0.164	0.016	-0.006	0.011	5	0.166	0.019	0.002	0.018
	Placebo	4	0.170	0.020	0.002	0.005	3	0.160	0.000	0.000	0.000
QRS Duration (sec)	PN 200-110	7	0.084	0.008	-0.003	0.010	5	0.086	0.009	-0.004	0.011
	Placebo	4	0.090	0.020	0.003	0.005	3	0.093	0.023	0.000	0.000
Q-T Interval (sec)	PN 200-110	7	0.403	0.024	-0.017	0.029	5	0.400	0.028	-0.010	0.036
	Placebo	4	0.385	0.019	0.005	0.010	3	0.380	0.020	0.000	0.000

TABLE 21

PN 200-110 STUDY NO. 7

LAB DATA - HEMATOLOGY

ANALYSIS OF CHANGES FROM BASELINE (WEEK 0) TO WEEK 4

Variable (Normal Range)	Treatment Group	No. of Patients++	Baseline Mean	S.D.	Mean Change at Week 4+	S.D.
Hemoglobin gm/dl (12-18)	PN 200-110	10	14.9	1.47	0.62*	0.73
	Placebo	9	15.3	0.82	0.54(*)	0.72
Hematocrit % (37-52)	PN 200-110	10	44.8	4.44	1.80(*)	2.70
	Placebo	9	45.8	3.15	1.89**	1.62
WBC x 10^3 cu.mm (4.0-11.0)	PN 200-110	10	6.2	1.74	0.25	1.18
	Placebo	9	7.2	2.14	0.36	2.31
Neutrophils % (40-75)	PN 200-110	10	59.2	8.42	-1.30	7.36
	Placebo	9	61.6	4.88	1.44	7.44
Lymphocytes % (15-45)	PN 200-110	10	32.4	7.56	1.20	6.94
	Placebo	9	29.8	4.24	0.11	6.68
Monocytes % (0-10)	PN 200-110	10	4.7	0.82	-0.40	1.71
	Placebo	9	4.2	1.86	-0.33	1.41
Eosinophils % (0-5)	PN 200-110	10	2.5	1.18	0.10	1.29
	Placebo	9	2.7	1.12	-0.44	1.24
Basophils % (0-1)	PN 200-110	10	1.2	1.75	-0.20	1.87
	Placebo	9	0.9	0.78	-0.22	0.83

(*)p<0.10, *p<.05, **p<.01, ***p<.001

+Patient #101 (PN 200-110) evaluated at Week 1 and Patient #116 (placebo) evaluated at Week 2 (discontinuing patients).

++Four patients did not have final evaluations.

TABLE 22

PN 200-110 STUDY NO. 7

LAB DATA - URINALYSIS

ANALYSIS OF CHANGES FROM BASELINE (WEEK 0) TO WEEK 4

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 4*	S.D.
Specific Gravity (1.001-1.035)	PN 200-110	10	1.017	0.005	0.002	0.009
	Placebo	9	1.020	0.007	-0.001	0.009
pH (5.0-6.0)	PN 200-110	10	5.2	0.34	0.15	0.47
	Placebo	9	5.2	0.44	0.17	0.79

(*)p<0.10, *p<.05, **p<.01, ***p<.001

*Patient #101 evaluated at week 1 and Patient #116 evaluated at Week 2.

TABLE 23

PN 200-110 STUDY NO. 7

LAB DATA - CHEMISTRY
ANALYSIS OF CHANGES FROM BASELINE (WEEK 0) TO WEEK 4

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 4*	S.D.
Calcium mg/dl (8.5-11.0)	PN 200-110	10	9.9	0.41	0.10	0.42
	Placebo	9	9.8	0.35	0.09	0.33
Inorganic Phosphorus mg/dl (2.5-4.5)	PN 200-110	10	3.4	0.29	-0.11	0.46
	Placebo	9	3.4	0.38	-0.03	0.54
BUN mg/dl (7-26)	PN 200-110	10	16.4	3.37	0.60	3.53
	Placebo	9	14.0	3.46	0.22	3.56
Uric Acid mg/dl (2.0-9.0)	PN 200-110	10	6.6	1.28	-0.37 (+)	0.91
	Placebo	9	6.2	1.98	0.62	1.27
Glucose mg/dl (60-115)	PN 200-110	10	123.4	64.30	-1.70	5.98
	Placebo	9	120.3	47.98	-5.56	18.58
Total Protein gm/dl (6.0-8.5)	PN 200-110	10	7.2	0.30	0.07	0.39
	Placebo	9	7.3	0.36	0.21	0.35
Albumin gm/dl (3.0-5.5)	PN 200-110	10	4.4	0.23	0.03	0.26
	Placebo	9	4.3	0.36	0.09	0.26
Total Bilirubin mg/dl (0.1-1.2)	PN 200-110	10	0.7	0.26	-0.04	0.13
	Placebo	9	0.5	0.20	0.00	0.19
Cholesterol mg/dl (150-300)	PN 200-110	10	195.2	23.33	6.10	20.91
	Placebo	9	236.9	37.73	9.22*	9.69

(+)p<0.10, *p<.05, **p<.01, ***p<.001

*Patient #101 evaluated at Week 1 and Patient #116 evaluated at Week 2.

TABLE 23 (Continued)

PN 200-110 STUDY NO. 7

LAB DATA - CHEMISTRY
ANALYSIS OF CHANGES FROM BASELINE (WEEK 0) TO WEEK 4

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 4*	S.D.
Alkaline Phosphatase Units (20-125)	PN 200-110	10	79.4	25.11	-1.70	8.69
	Placebo	9	79.3	17.27	9.22*	11.[illegible]6
LDH Units (75-250)	PN 200 110	10	202.6	36.86	7.00	26.31
	Placebo	9	174.9	22.72	11.56	18.66
SGOT Units (0-50)	PN 20[illegible]-110	10	23.0	10.92	2.80	7.18
	Placebo	9	21.4	9.53	-1.44	6.54
SGPT Units (0-50)	PN 200-110	10	41.1	50.08	3.10	1[illegible]
	Placebo	9	28.3	18.19	-2.22	[illegible]
Sodium mEq/l (135-148)	PN 200-110	10	141.2	2.25	1.40	2.68
	Placebo	9	141.8	3.23	-1.00	3.39
Potassium mEq/l (3.5-5.5)	PN 200-110	10	4.4	0.30	-0.12	0.37
	Placebo	9	4.3	0.23	0.07	0.38
Chloride mEq/l (94-108)	PN 200-110	10	104.6	2.50	-0.30	2.11
	Placebo	9	103.9	2.62	-0.44	1.42
Creatinine mg/dl (0.5-1.5)	PN 200-110	10	1.0	0.13	-0.01	0.09
	Placebo	9	1.1	0.24	-0.01	0.16

(*)p<0.10, *p<.05, **p<.01, ***p<.001

*Patient #101 evaluated at Week 1 and Patient #116 evaluated at Week 2.

TABLE 24

PN 200-110 STUDY NO. 7

LAB DATA - HEMATOLOGY

DESCRIPTIVE STATISTICS FOR TWO-WEEK
EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 6*	S.D.
Hemoglobin gm/dl (12-18)	PN 200-110	7	15.4	1.11	0.17	0.50
	Placebo	4	15.4	1.25	0.73	0.96
Hematocrit % (37-52)	PN 200-110	7	46.1	3.34	1.14	2.04
	Placebo	4	46.3	4.72	1.25	4.50
WBC x 10^3 cu.mm (4.0-11.0)	PN 200-110	7	6.1	1.77	0.07	0.50
	Placebo	4	8.2	2.69	0.05	2.00
Neutrophils % (40-75)	PN 200-110	7	56.7	8.60	-2.00	6.68
	Placebo	4	64.8	3.78	-0.50	9.82
Lymphocytes % (15-45)	PN 200-110	7	34.1	8.07	1.17	5.25
	Placebo	4	26.8	3.10	2.25	10.31
Monocytes % (0-10)	PN 200-110	7	4.6	0.98	-0.43	1.51
	Placebo	4	4.0	1.83	-0.50	1.29
Eosinophils % (0-5)	PN 200-110	7	2.4	1.51	1.14	1.77
	Placebo	4	2.5	1.73	-0.75	1.71
Basophils % (0-1)	PN 200-110	7	1.6	1.99	-0.43	2.07
	Placebo	4	0.8	0.96	0.00	0.82

*Patient Nos. 114, 117 and 120 evaluated at Week 5.

TABLE 25

PN 200-110 STUDY NO. 7

LAB DATA - URINALYSIS

DESCRIPTIVE STATISTICS FOR TWO-WEEK
EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 6+	S.D.
Specific Gravity (1.001-1.035)	PN 200-110	7	1.019	0.007	0.004	0.010
	Placebo	4	1.018	0.008	-0.002	0.005
pH (5.0-6.0)	PN 200-110	7	5.0	0.00	0.14	0.38
	Placebo	4	5.0	0.00	0.50	1.00

+Patient Nos. 114, 117 and 120 evaluated at Week 5.

TABLE 26

PN 200-110 STUDY NO. 7

LAB DATA - CHEMISTRY
DESCRIPTIVE STATISTICS FOR TWO-WEEK
EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 6*	S.D.
Calcium mg/dl (8.5-11.0)	PN 200-110	7	9.8	0.56	0.04	0.26
	Placebo	4	9.8	0.48	0.15	0.62
Inorganic Phosphorus mg/dl (2.5-4.5)	PN 200-110	7	3.5	0.30	0.24	0.64
	Placebo	4	3.6	0.24	-0.35	0.47
BUN mg/dl (7-26)	PN 200-110	7	16.1	3.63	-0.14	2.61
	Placebo	4	12.5	4.44	-0.25	2.97
Uric Acid mg/dl (2.0-9.0)	PN 200-110	7	6.2	1.33	-0.14	0.90
	Placebo	4	6.7	2.41	0.48	1.25
Glucose mg/dl (60-115)	PN 200-110	7	[illegible]5.1	78.48	-10.86	27.05
	Placebo	4	116.8	35.73	-21.00	28.13
Total Protein gm/dl (6.0-8.5)	PN 200-110	7	7.1	0.44	-0.16	0.56
	Placebo	4	7.2	0.30	0.08	0.33
Albumin gm/dl (3.0-5.5)	PN 200-110	7	4.3	0.33	0.00	0.25
	Placebo	4	4.3	0.46	0.10	0.36
Total Bilirubin mg/dl (0.1-1.2)	PN 200-110	7	0.7	0.26	-0.09	0.16
	Placebo	4	0.5	0.06	0.05	0.06
Cholesterol mg/dl (150-300)	PN 200-110	7	196.7	22.29	-9.57	19.85
	Placebo	4	220.8	37.70	16.50	16.90

*Patient Nos. 114, 117 and 120 evaluated at Week 5.

TABLE 26 (Continued)

PN 200-110 STUDY NO. 7

LAB DATA - CHEMISTRY
DESCRIPTIVE STATISTICS FOR TWO-WEEK
EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline Mean	S.D.	Mean Change at Week 6+	S.D.
Alkaline Phosphatase Units (20-125)	PN 200-110	7	70.3	19.19	-4.14	9.97
	Placebo	4	72.5	14.45	-8.50	11.39
LDH Units (75-250)	PN 200-110	7	203.4	35.48	-8.71	21.62
	Placebo	4	184.8	26.24	-12.25	22.41
SGOT Units (0-50)	PN 200-110	7	22.9	12.85	3.57	4.69
	Placebo	4	19.0	12.04	-6.00	7.26
SGPT Units (0-50)	PN 200-110	7	47.3	59.34	3.71	15.03
	Placebo	4	21.0	11.75	-4.75	12.42
Sodium mEq/l (135-148)	PN 200-110	7	140.7	2.43	1.43	1.27
	Placebo	4	141.3	2.50	1.00	4.08
Potassium mEq/l (3.5-5.5)	PN 200-110	7	4.4	0.29	0.07	0.38
	Placebo	4	4.3	0.33	0.20	0.90
Chloride mEq/l (94-108)	PN 200-110	7	105.4	2.30	0.00	3.70
	Placebo	4	105.0	1.63	-2.00	2.31
Creatinine mg/dl (0.5-1.5)	PN 200-110	7	1.0	0.15	-0.03	0.08
	Placebo	4	1.0	0.29	0.03	0.17

+Patient Nos. 114, 117 and 120 evaluated at Week 5.

TABLE 27

PN 200-110 STUDY NO. 7

LABORATORY DATA - NEWLY OCCURRING ABNORMALITIES[a]

Treatment Group	Variable (Normal Range)	Patient Number	Washout Period		Double-Blind Period		Abnormal High (H) or Low (L)
			Week -3	Time 0	Week 4	Week 6	
Hematology							
PN 200-110	Eosinophils (%) (0-5)	114	1	2	1	6[c]	H
	WBC x 10^3 cu mm (4-11)	120	N.D.[d]	4.3	2.8[c]	4.4	L
	Basophils (%) (0-2)	120	N.D.	0	2	1	H
		122	2	1	2	2	H
Placebo	Platelet Est. (Normal)	117	Normal	Normal	Normal	Decreased	L
Urinalysis							
PN 200-110	Specific Gravity (1.001-1.035)	122	1.033	1.029	1.040	1.046	H
	WBC/HPF (0-1)	122	0	1-5	26-50	0	H
Placebo	pH (5-6)	11	5	5	6	7	H
	RBC/HPF (0-1)	119	1-5	0	1-5	6-25	H
Chemistry							
PN 200-110	LDH (62-250)	105	201	261	303	N.D.	H[f]
	SGPT (0-53)	101	29	30	61[c]	N.D.	H
		118	22	26	44,62	54	H
Placebo	Uric Acid (2.0-9.0)	113	7.7	10.0	13.5	12.3	H[f]

[a]Defined as all pre-dose evaluations being normal and at least one abnormal post-dose evaluation based on adjusted normal limits or an abnormal baseline evaluation that worsened by at least 15%.

[b]Normal ranges presented here encompass all ranges used in this study. It should be noted however that the laboratory performing these assays changed the normal ranges as of Oct. 17, 1983. In addition, patient 122 went to a separate laboratory for his Week -3 evaluation and so had a different reference normal range for this time point. The exact normal range specific to each patient's evalutions were used in determining newly-occurring abnormalities.

[c]Patient 114's final evaluation performed at Week 5.
Patient 101's final evaluation performed at Week 1.
N.D. denotes evaluation not done.

[e]Underlined values denote an abnormality.

[f]Abnormal at baseline and worsening by at least 15%.

TABLE 31
PN 200-110 STUDY NO. 7

ADVERSE REACTION LISTING

Treatment Group	Patient Number	Adverse Reaction	Week and Severity of		
			First Occurrence	Last Occurrence†	Worst Occurrence††
PN 200-110	101†††	Headache	1 - Moderate		
		Tachycardia	1 - Moderate		
	105	Headache	-2 - Mild	0 - Mild	
	~~108~~	~~Fatigue~~	~~-2 - Mild~~	~~0 - Mild~~	
	114††††	Ringing in ear	-2 - Mild	5 - Moderate	3 - Moderate
		Palpitations	-2 - Mild	5 - Severe	
	118	Lightheaded	1 - Mild		
		Thumping in chest	2 - Moderate	6 - Mild	
		Flushing of face	2 - Mild	6 - Mild	
		Headache	3 - Mild	6 - Mild	
	120††††	Edema; legs, ankles	5 - Moderate		
		Tingling; extremities	5 - Moderate		
	123	Headache	4 - Mild		
Placebo	104	Diarrhea	4 - Moderate		
	107	Skin pain	-2 - Mild	3 - Mild	
	111	Blurring of vision	2 - Mild		
	113	Rash, erythema	-2 - Mild	0 - Mild	-1 - Moderate
		Headache	0 - Moderate	6 - Mild	
		Burning/aching eyes	2 - Mild		
		Edema under eye	2 - Mild		
		Upper respiratory infection	5 - Mild		
	119	Sore Throat	3 - Mild		
	121	Dizziness	-2 - Mild		
		Staph infection, thumb	-2 - Mild		

†Presented only if there were multiple occurrences.
††Presented only if different from information recorded under first or last occurrence.
†††Discontinued after Week 1 because of adverse reaction.
††††Discontinued after Week 5 because of adverse reactions.

TABLE 32

PN 200-110 STUDY NO. 7

COMPARATIVE FREQUENCY OF PATIENTS
REPORTING NEWLY-OCCURRING
ADVERSE REACTIONS

(AFTER ADJUSTING FOR ADVERSE REACTIONS
REPORTED DURING THE PLACEBO WASHOUT PERIOD)

Adverse Reaction	PN 200-110 (N = 12)	Placebo (N = 11)
Miscellaneous		
Eyes, Burning	0	1
Cardiovascular		
Edema	1	1
Palpitations	2	0
Tachycardia	1	0
Gastrointestinal		
Diarrhea	0	1
Central Nervous System		
Dizziness	1	0
Headache	3	0
Tinnitus	1	0
Autonomic Nervous System		
Flushing	1	0
Tingling	1	0
Visual Disturbance	0	1
Number of Patients Reporting at Least One Newly-Occurring Adverse Reaction	5/12	3/11

Figure 1

PN 200–110 STUDY #7
Supine Systolic BP
Change from Baseline – Valid Patients

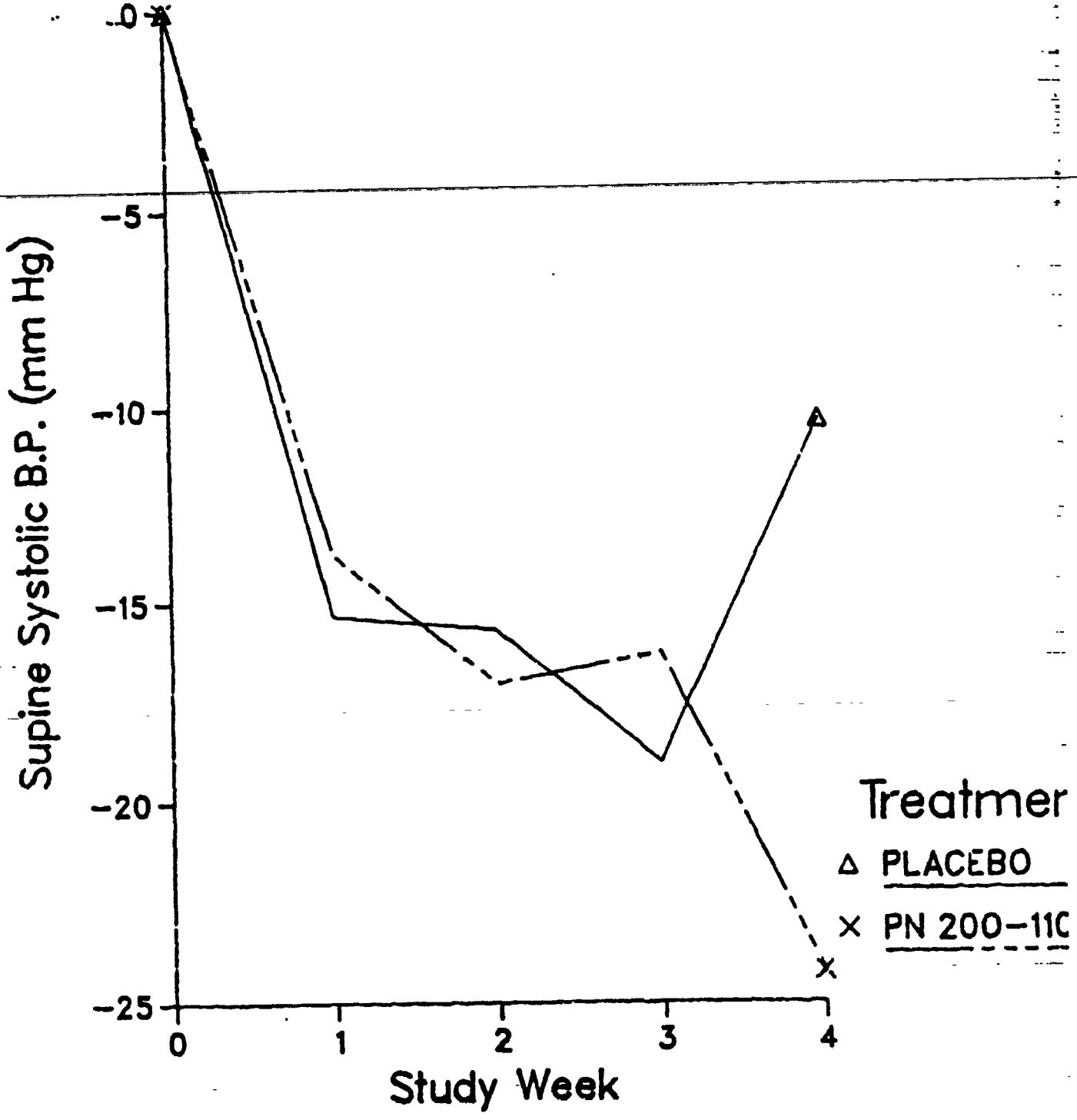

Figure 2

PN 200–110 STUDY #7
Supine Diastolic BP
Change from Baseline – Valid Patients

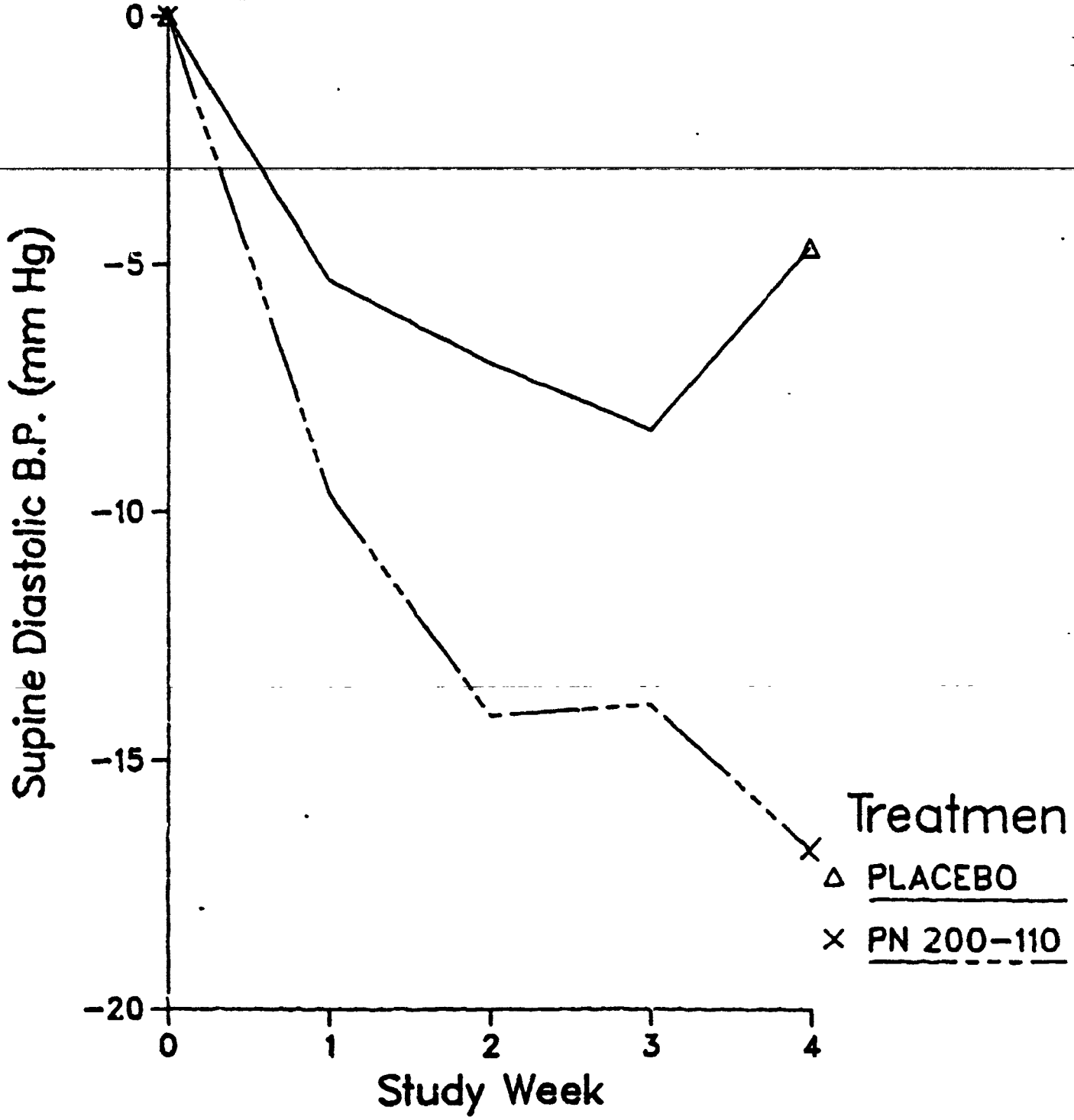

Figure 3

PN 200-110 STUDY #7
Supine Pulse
Change from Baseline – Valid Patients

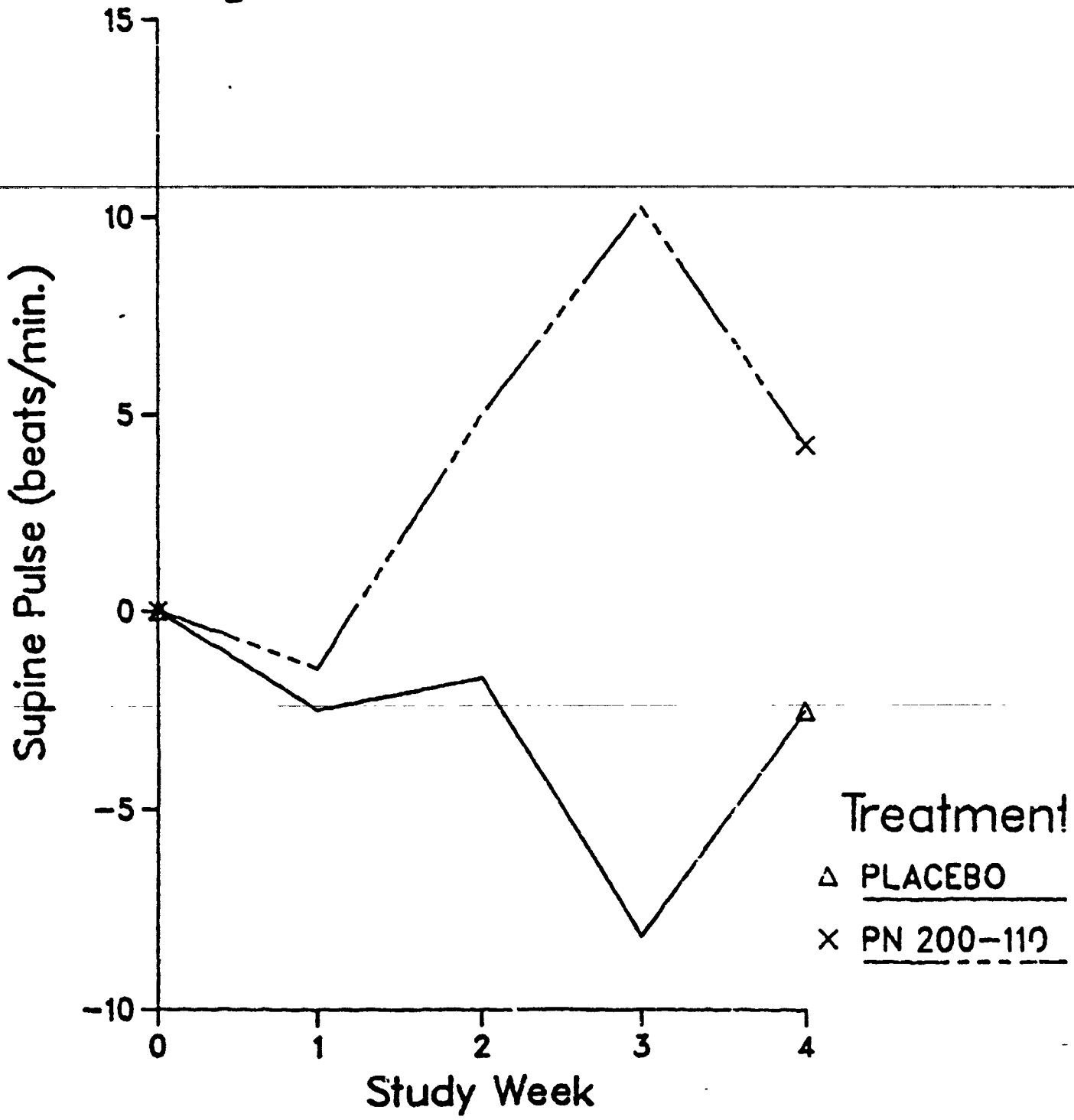

Figure 4

PN 200–110 STUDY #7
Standing Systolic BP
Change from Baseline – Valid Patients

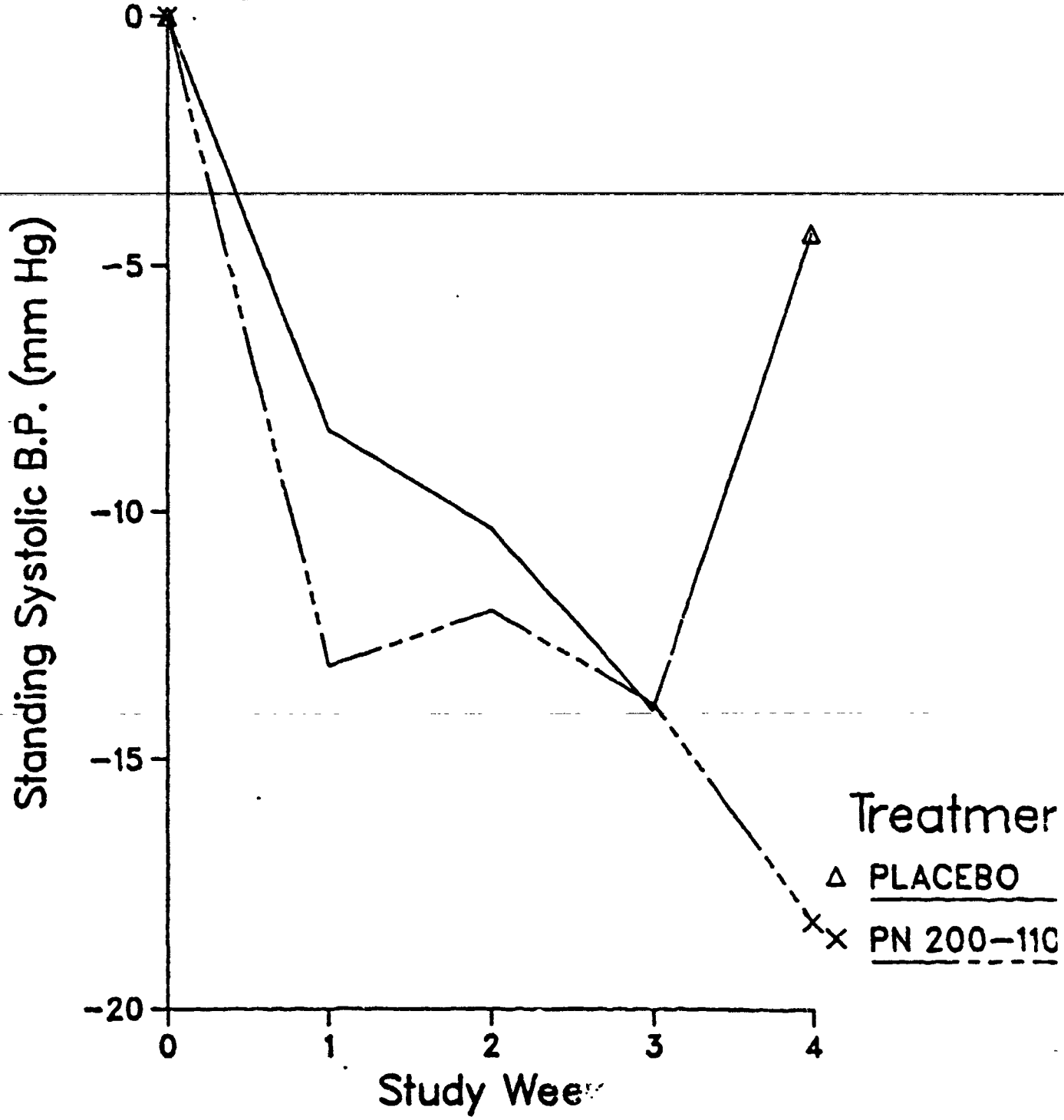

Figure 5

PN 200–110 STUDY #7
Standing Diastolic BP
Change from Baseline – Valid Patients

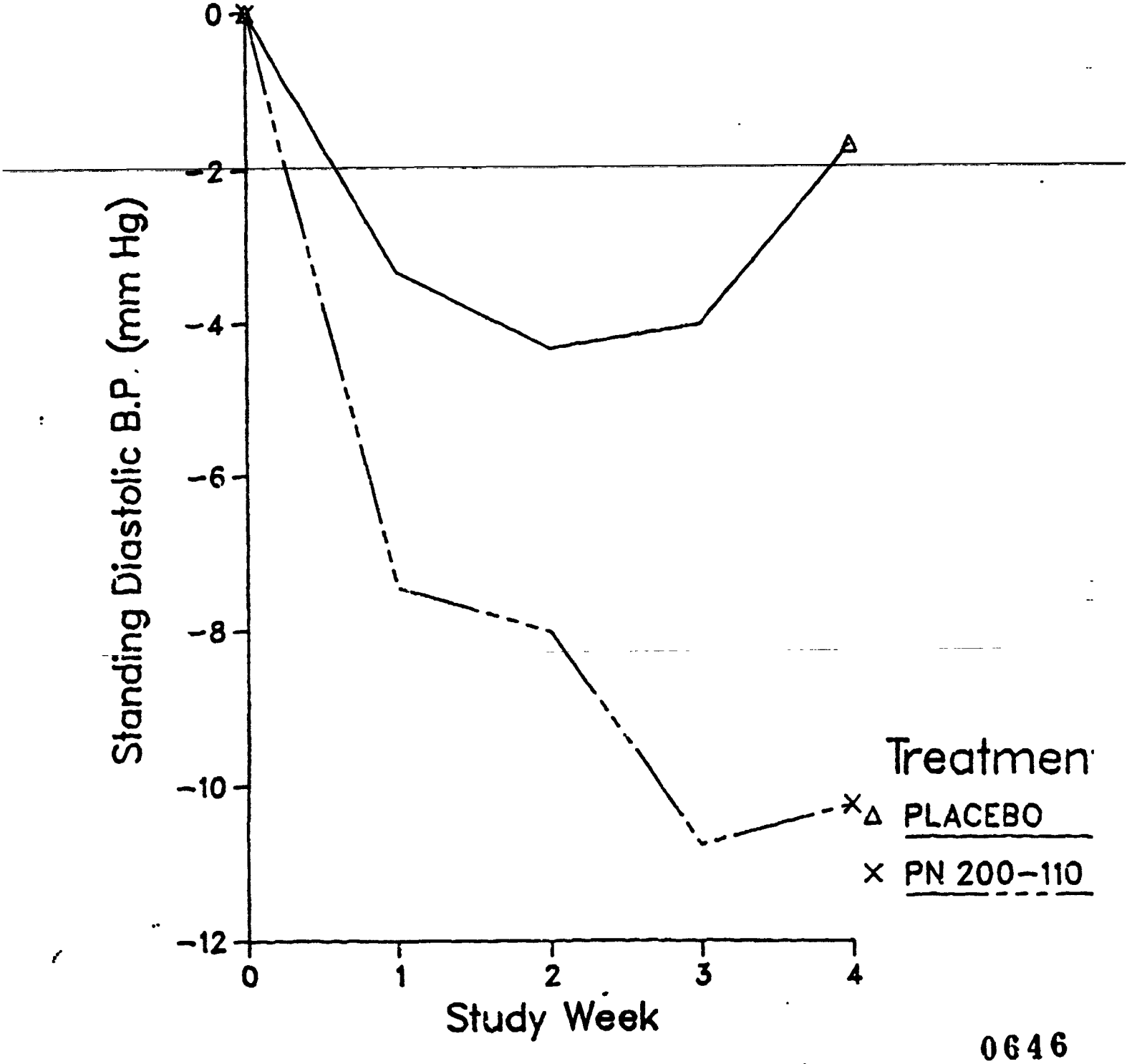

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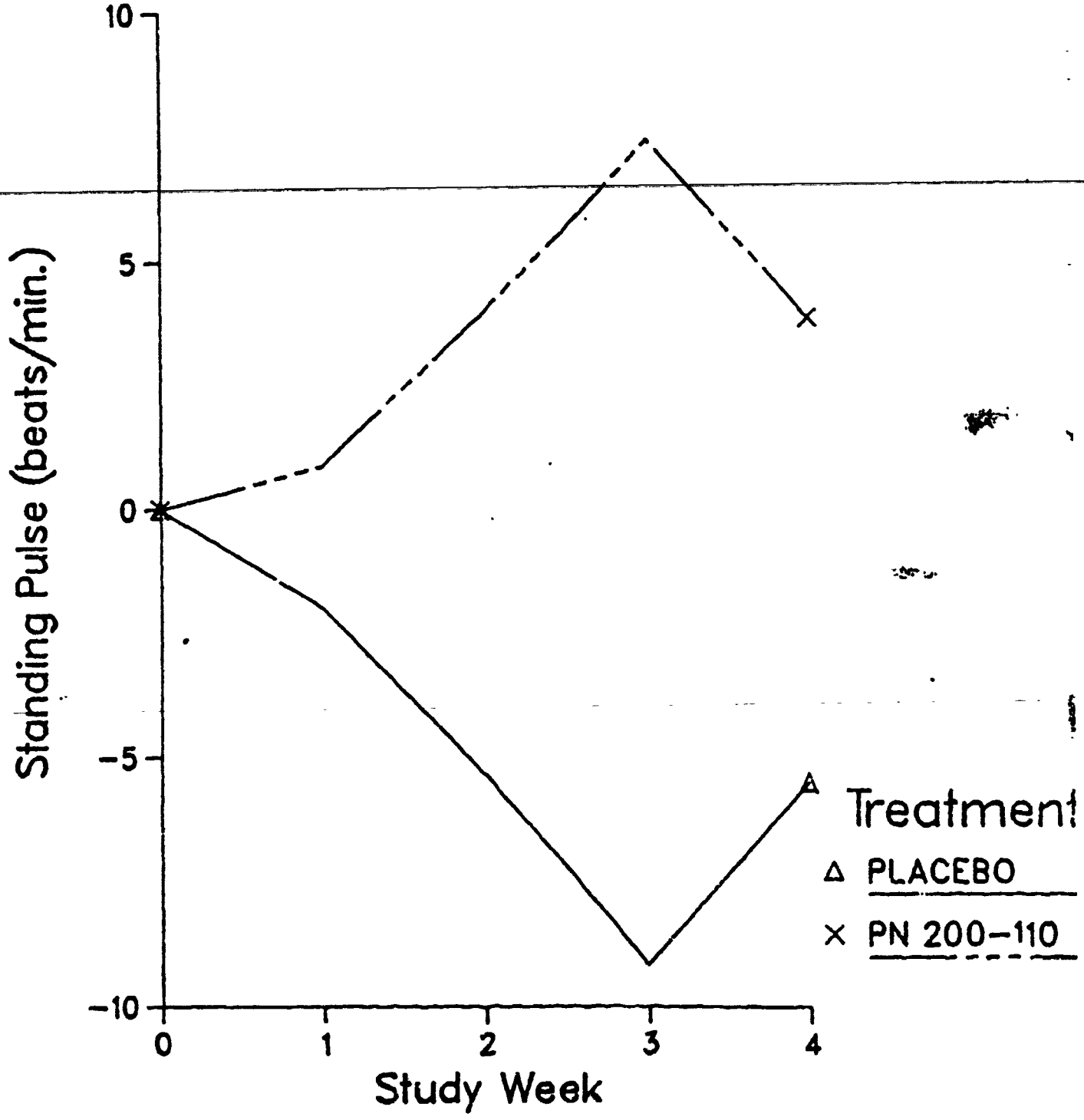
Figure 6

PN 200–110 STUDY #7
Standing Pulse
Change from Baseline – Valid Patients



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Protocol 11

Title

The Evaluation of the Safety and Efficacy of Sandoz PN 200-110 Administered Orally in Ascending Doses for the Treatment of Hypertension

Investigator

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Objective

To determine the blood pressure lowering effect of PN 200-110 administered according to a fixed dosing schedule, compared with placebo in twenty four outpatients with hypertension.

Design

This was a randomized, double-blind, parallel group, placebo controlled study.

Population

Patients of either sex, over the age of 18 years, with benign essential hypertension were selected for the study. For the double-blind period, patients had to have a supine diastolic blood pressure (SDBP) of > 95 mm Hg on two consecutive visits during the initial three week washout period. There was to be no manifestation of a decreasing trend in blood pressure during the washout period. The average SDBP for each evaluation day could not be less than that of the previous evaluation day and the Time 0 SDBP could not have decreased by more than 10 mm Hg compared to first evaluation day. Patients were to be evaluated before 11.00 a.m. each visit day.

Exclusion criteria included non benign essential hypertension, SDBP > 114 mm Hg on two occassions, history of alcoholism, drug abuse, cerebral insufficiency, angina pectoris (except stable, exertional angina controlled by sublingual nitroglycerin alone), CHF uncontrolled by digitalis, MI in previous 6 months, cardiac arrhythmias, bradycardia, PR interval > 0.25 sec, 2nd or 3rd degree heart block, use of other investigational drugs in the 4 weeks preceding the study, conditions that [illegible] effect absorption, metabolism or excretion of the drug and certain concomitant medications.

Trial Plan

[illegible] randomized [illegible]

[illegible] Patients [illegible]

[illegible] washout period and a 3 week [illegible]

being given twice daily. The protocol was, however, amended to add on an additional 2 weeks during which the drug was administered once daily. This amendment became effective after 15 patients had already concluded the trial.

Medication

Drug was supplied as identically appearing capsules of PN 2.5 or 5 mg or placebo. During the first 6 weeks of the study, medication was administered twice daily, before breakfast and supper. Morning dose was to be taken 2-3 hours before visit.

During first week, all patients received 2.5 mg bid. Dose was automatically increased to 5 mg bid for week 2 and to 10 mg bid for week 3. If investigator felt that the patient could not tolerate 20 mg per day, dose was not titrated at week 3. During the two week extension period, patients continued with their medication but the total daily dose was now administered once daily before breakfast. Dose could be adjusted at week 4, but could not exceed 20 mg daily. On the day of clinic visit, dose was not taken until after blood pressures had been recorded.

Evaluations

Patients were seen at weekly intervals during the study with evaluation schedule being shown in Table 2.

Results

A total of 24 patients entered the double blind phase of the study and all completed the bid portion of the protocol. (How many were initially enrolled ?) Twenty two were considered totally valid for efficacy evaluation and two were invalid. One of the latter did not take morning dose at week 0, and the other did not take morning dose at week 1. Seven patients entered the two week extension period, only 3 received PN and no inference tests were done due to small number of patients.

There were 12 patients in each group. Mean age of PN group was 52.3 years (range 44 - 67) and for placebo group 48.8 years (range 28 - 67). PN had 11 whites and 1 other while placebo was 8 white and 4 black; There were 10 males in each group. Mean daily dose was 4.8 mg at week 1, 9.7 mg at week 2 and 17.0 mg at week 3. During extension period, dose was [illegible] mg week 4 and 11.9 mg at week 5.

Valid Patients

Results of analysis of variance for [illegible] below. In PN group, there were [illegible] differences from baseline at week 3 for [illegible] supine and standing and these [illegible] significantly different from placebo [illegible]

were averaged over the 3 weeks, PN resulted in a statistically significant greater reduction in standing systolic blood pressure and supine and standing diastolic blood pressures compared to placebo.

The reductions from baseline were:

	Week 1		Week 2		Week 3		Mean change weeks 1 - 3.	
	PN	P1	PN	P1	PN	P1	PN	P1
n =	12	10	12	10	12	10	12	10
Supine Systolic	-3.3	1.1	- 3.5	-3.2	-13.9	1.9	-6.9	-0.1
Supine Diastolic	-5.9	-0.5	-11.8	-7.8	-14.8	-4.5	-10.8	-4.3
Supine Pulse	5.9	0.8	7.3	3.5	6.8	1.2	6.7	1.8
Standing Systolic	-2.1	-0.5	-10.3	-3.3	19.5	0.0	-10.6	-1.3
Standing Diastolic	-4.4	0.7	-12.3	-3.1	-17.2	-2.2	-11.3	-1.5
Standing Pulse	5.8	-0.7	5.4	2.5	5.09	0.2	5.7	0.7

These data are displayed graphically in figures 1 - 6.

All Patients

Results for all patients are shown below:

	Week 1		Week 2		Week 3		Mean change weeks 1 - 3.	
	PN	P1	PN	P1	PN	P1	PN	P1
n =	12	12	12	12	12	12	12	12
Supine Systolic	-3.3	2.2	- 3.5	0.2	-13.9	4.3	-6.9	2.2
Supine Diastolic	-5.9	[illegible]	-11.8	-6.5	-14.8	[illegible]	[illegible]	[illegible]
Supine Pulse	5.9	[illegible]	7.3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Standing Systolic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Standing Diastolic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Standing [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Categorical Analysis of Blood Pressure

Categorical analysis of SDBP at week 3 for all patients is shown below. Seventy five percent (75%) of PN patients versus 8% placebo showed a clinically relevant decrease of at least 10 mm Hg.

Group	n=	Response Categories							
		> 10 mm Hg Decrease				Decrease of		< 5 mm H	
		< 85 mm Hg		> 85 mm Hg		5- < 10 mm Hg		Decrease	
PN	12	3	25%	6	50%	1	8%	2	16%
Placebo	12	0	0%	1	8%	7	58%	4	33%

Once Daily Dosage

No inference tests were done due to small number of patients. Data seem to indicate that qd dosing did not effectively control blood pressure. (Table 12).

Safety

There were no significnat changes in the physical examinations of patients. There were 5 patients with newly occurring cardiovascular abnormalities, 4 in PN group and one placebo. Of the 4 PN patients, two (PVCs and chest pain) had a previous history of the events. The other two PN events were ankle edema and pre-syncope. The placebo event was a left radial pulse deficit.

ECGs

Table 14 presents variable for ECG changes. There was a statistically significant difference from placebo for P- R interval at weeks 1 and 2, and for the mean over weeks 1 - 3. There were no other statistical differences for other variables. Two PN patients had rhythm abnormalities during screening and there were two newly occurring rhythm abnormalities. [illegible] placebo had one new abnormality.

Clinical Laboratory [illegible]

Tables [illegible]
[illegible]
second case

Adverse Reactions

Table 29 lists all ADRs reported in the study. Table 30 compares frequency of events in the two groups. Fatigue was the most commonly reported event. There were 7 PN patients with at least one new ADR compared to 4 placebo.

Discussion

PN 200-110 significantly reduced blood pressure in this short study. The reductions appeared to be dose related and were statistically significantly different from baseline and from placebo in most cases. It seems that once daily dosage is not effective.

Reviewer's Comments

1. This appears to be a well designed, well conducted study. Active drug shows efficacy in reducing blood pressure in hypertensive cases, more than did placebo.

2. There is no mention as to how many patients were originally enrolled and how many, if any, did not qualify for the double-blind phase.

TABLE 1

PN 200-110 STUDY NO. 11

STUDY DESIGN

Treatment Group	Placebo (Pcb) Washout Period Weeks -3,-2,-1	Week 1	Week 2	Week 3 †	Extension †† Week 4	Extension †† Week 5
Group I PN 200-110	one (1) Pcb. cap (bid) ac*	one (1) PN 200-110 2.5 mg cap (bid) ac*	two (2) PN 200-110 2.5 mg caps (bid) ac*	two (2) PN 200-110 5.0 mg caps (bid) ac*	one (1) to four (4) PN 200-110 5.0 mg caps once-a-day**	one (1) to four (4) PN 200-110 5.0 mg caps once-a-day**
Group II Placebo	one (1) Pcb. cap (bid) ac*	one (1) Pcb. cap (bid) ac*	two (2) Pcb. caps (bid) ac*	two (2) Pcb. caps (bid) ac*	one (1) to four (4) placebo caps once-a-day**	one (1) to four (4) placebo caps once-a-day**

<—single-blind—><————————————double-blind————————————>

*ac - Before breakfast and supper.

**Before breakfast.

†If the investigator felt the patient could not tolerate the maximum dose of 20 mg/day: starting with Week 3, the dose could be maintained at 10 mg/day (5 mg bid) or reduced to 5 mg/day (2.5 mg bid).

††Seven patients (Pt. Nos. 16-22) entered the double-blind, two week extension, Weeks 4 and 5. Group I patients continued to receive PN 200-110 but the full daily dose was administered on a once-a-day regimen and Group II patients received placebo on a once-a-day regimen. During Week 4, titration was allowed to achieve the maximal tolerated once-a-day dose as determined by the investigator and during Week 5 the patients were maintained on this dose. The highest allowable dose was 20.0 mg/day.

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TABLE 2

PN 200-110 STUDY NO. 11

EVALUATION SCHEDULE

	Placebo Period			Active Treatment Period Twice-A-Day				Once-A-Day Extension	
	Day 1 of Weeks			End of Weeks				End of Weeks	
	-3	-2	-1	Time 0	1	2	3	4	5
Background Information (BK)	X								
Physical Examination (PE)	X								X
Inclusion/Exclusion Checklist (IE)				X					
Vital Signs (VS)	X	X	X	X	X	X	X	X	X
Cardiovascular Evaluation (CV)	X			X	X	X	X		
ECG Evaluation (ECG)	X			X	X	X	X	X	X
Chest X-Ray (CX)	[1] X								
Concomitant Medication (CM)	X	X	X	X	X	X	X	X	X
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) (LAB)	X			[2] X			[2] X		X
Comments (COM)	X	X	X	X	X	X	X	X	X
Medication Check (MC)		X	X	X	X	X	X	X	X
Adverse Reactions (AR)		X	X	X	X	X	X	X	X
End of Study Information (ES)							[3] X		[3] X

[1] The baseline chest X-ray could be taken any time during the placebo washout period. A chest X-ray obtained within six (6) months prior to entering the trial could serve as baseline for the study and was not repeated at the initial visit provided the X-ray was normal and a clinical condition requiring a repeat film had not occurred during this interval.

[2] Laboratory evaluation at Time 0 included 24-hour urine collection and plasma sample for plasma renin assay.

[3] Or upon early discontinuation from study.

TABLE 5

PN 200-110 STUDY NO. 11

ANALYSIS OF VARIANCE RESULTS FOR BLOOD PRESSURE AND PULSE

VALID PATIENTS

Variable/ Treatment Group	N	Baseline Mean	S.D.	Mean Change At			Mean Change Over Weeks 1-3	S.D.
				Week 1	Week 2	Week 3		
Supine Systolic BP (mm Hg)								
PN 200-110	12	149.0	11.61	-3.3	-3.5	-13.9**	-6.9(*)	13.21
Placebo	10	151.7	14.67	1.1	-3.2	1.9	-0.1	6.22
Supine Diastolic BP (mm Hg)								
PN 200-110	12	102.3	5.99	-5.9*	-11.8**	-14.8***	-10.8***	5.71
Placebo	10	102.9	3.67	-0.5	-7.8***	-4.5*	-4.3**	3.72
Supine Pulse Rate (per min)								
PN 200-110	12	68.3	6.37	5.9*	7.3*	6.8(*)	6.7*	8.86
Placebo	10	67.3	11.16	0.8	3.5(*)	1.2	1.8(*)	2.91
Standing Systolic BP (mm Hg)								
PN 200-110	12	143.0	13.56	-2.1	-10.3*	-19.5***	-10.6**	9.85
Placebo	10	144.6	10.81	-0.5	-3.3	0.0	-1.3	7.02
Standing Diastolic BP (mm Hg)								
PN 200-110	12	100.4	6.97	-4.4	-12.3***	-17.2***	-11.3***	6.49
Placebo	10	101.6	6.69	0.7	-3.1(*)	-2.2	-1.5	3.79
Standing Pulse Rate (per min)								
PN 200-110	12	78.4	7.88	5.8(*)	5.4	5.9	5.7(*)	10.79
Placebo	10	78.7	13.45	-0.7	2.5	0.2	0.7	3.96

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

TABLE 12

PN 200-110 STUDY NO. 11

DESCRIPTIVE STATISTICS FOR BLOOD PRESSURE AND PULSE

TWO-WEEK EXTENSION PERIOD (QD DOSING)

EVALUATIONS RECORDED ≥ 24 HOURS AFTER LAST DOSE

Variable	Treatment Group	Week 4					Week 5				
		N	Baseline Mean*	S.D.	Mean Change	S.D.	N	Baseline Mean*	S.D.	Mean Change	S.D.
Supine Systolic B.P. (mm Hg)	PN 200-110	3	149.0	10.58	-12.67	24.58	2	147.0	14.14	3.50	20.51
	Placebo	4	142.5	7.14	10.50	18.66	4	142.5	7.14	6.25	14.61
Supine Diastolic B.P. (mm Hg)	PN 200-110	3	105.0	4.36	-24.67	16.26	2	106.5	4.95	-4.50	3.54
	Placebo	4	104.0	2.94	-3.50	4.04	4	104.0	2.94	-2.00	6.98
Supine Pulse (per min)	PN 200-110	3	75.0	6.56	6.33	13.80	2	78.5	3.54	-6.00	1.41
	Placebo	4	67.5	7.68	15.50	11.62	4	67.5	7.68	10.25	6.60
Standing Systolic B.P. (mm Hg)	PN 200-110	3	143.7	9.07	-17.67	7.51	2	147.0	9.90	-4.50	9.19
	Placebo	4	148.8	11.79	-10.00	8.76	4	148.8	11.79	-3.25	7.93
Standing Diastolic B.P. (mm Hg)	PN 200-110	3	104.0	6.25	-22.67	7.10	2	106.5	6.36	-5.00	2.83
	Placebo	4	105.0	4.97	-6.50	6.25	4	105.0	4.97	-3.75	5.50
Standing Pulse (per min)	PN 200-110	3	83.0	8.72	10.33	22.37	2	88.0	1.41	-4.00	7.07
	Placebo	4	77.8	11.15	6.50	9.68	4	77.8	11.15	8.75	15.71

*Week 0

TABLE 14

PN 200-110 STUDY NO. 11
ECG: QUANTITATIVE VARIABLES
ANALYSIS OF VARIANCE

ALL PATIENTS

Variable	Treatment Group	No. Patients	Baseline		Mean Change At			Mean Changes At Weeks 1-3	S.D.
			Mean	S.D.	Week 1+	Week 2	Week 3		
Atrial Rate (per min)	PN 200-110	12	67.5	8.25	3.82	6.00(*)	4.58	4.93	9.93
	Placebo	12	65.3	10.20	0.33	2.92	0.08	1.11	5.58
Ventricular Rate (per min)	PN 200-110	12	67.5	8.25	3.82	6.00(*)	4.58	4.93	9.93
	Placebo	12	65.3	10.20	0.33	2.92	0.08	1.11	5.58
T Interval c)	PN 200-110	12	0.161	0.026	-0.005	-0.010	-0.003	-0.007	0.014
	Placebo	12	0.152	0.020	0.009(*)	0.010(*)	0.004	0.008(*)	0.015
QRS Duration (sec)	PN 200-110	12	0.088	0.010	0.000	0.001	0.002	0.001	0.011
	Placebo	12	0.086	0.009	0.002	0.002	-0.001	0.001	0.011
Q-T Interval (sec)	PN 200-110	12	0.391	0.019	-0.005	-0.003	0.001	-0.002	0.018
	Placebo	12	0.392	0.025	-0.001	-0.011	0.005	-0.002	0.021

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

+Patient No. 1 (PN 200-110) is missing Week 1 evaluation.

TABLE 18

PN 200-110 STUDY NO. 11

HEMATOLOGY

ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Patients	Baseline Mean	S.D.	Mean Change at Week 3	S.D.
Hemoglobin gm/dl (11.5-18.0)	PN 200-110	12	15.8	1.45	0.08	1.04
	Placebo	12	15.5	0.63	-0.42 (*)	0.78
Hematocrit % (37-54)	PN 200-110	12	47.1	4.48	1.25 (*)	3.60
	Placebo	12	47.2	2.41	-1.25	2.96
WBC x 10^3 cu mm (3.8-11.0)	PN 200-110	12	6.3	1.49	0.42 (*)	0.79
	Placebo	12	6.3	1.72	0.06	0.91
Bands % (0-6)	PN 200-110	12	0.0	0.00	0.00	0.00
	Placebo	12	0.0	0.00	0.00	0.00
Neutrophils % (40-80)	PN 200-110	12	58.1	7.76	-0.17	4.04
	Placebo	12	56.5	8.32	1.67	6.21
Lymphocytes % (15-50)	PN 200-110	12	33.5	7.50	0.33	3.11
	Placebo	12	33.9	7.42	-0.67	4.42
Monocytes % (2-11)	PN 200-110	12	5.5	1.00	-0.25	0.75
	Placebo	12	5.4	1.62	-0.92	2.58
Eosinophils % (1-7)	PN 200-110	12	2.7	1.16	0.08	1.31
	Placebo	12	3.9	2.50	-0.33	1.56
Basophils % (0-1)	PN 200-110	12	0.3	0.45	0.00	0.60
	Placebo	12	0.3	0.45	0.17	0.72

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

TABLE 19

PN 200-110 STUDY NO. 11

URINALYSIS

ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Patients	Baseline Mean	S.D.	Mean Change at Week 3	S.D.
Specific Gravity (1.002-1.030)	PN 200-110	12	1.017	0.006	-0.001	0.005
	Placebo	12	1.014	0.007	0.002	0.008
pH (4.8-7.8)	PN 200-110	12	6.2	0.72	-0.08	0.82
	Placebo	12	6.0	0.92	0.08	0.63

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

TABLE 20
PN 200-110 STUDY NO. 11
CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Patients	Baseline Mean	S.D.	Mean Change at Week 3	S.D.
Calcium mg/dl (8.5-11.0)	PN 200-110	12	9.4	0.41	0.15	0.57
	Placebo	12	9.6	0.27	-0.09	0.33
Inorganic Phosphorus mg/dl (2.2-4.5)	PN 200-110	12	3.2	0.44	0.04	0.39
	Placebo	12	3.2	0.37	-0.08	0.31
BUN mg/dl (9-26)	PN 200-110	12	13.3	2.70	0.17	2.13
	Placebo	12	12.8	3.60	-0.33	2.31
Uric Acid mg/dl (2.2-9.0)	PN 200-110	12	6.0	0.96	-0.31	0.69
	Placebo	12	6.0	1.23	0.36(*)	0.64
Glucose mg/dl (65-115)	PN 200-110	12	97.3	15.22	3.75	15.78
	Placebo	12	100.4	17.21	0.58	9.14
Total Protein gm/dl (6.0-8.5)	PN 200-110	12	6.9	0.38	0.13	0.52
	Placebo	12	7.1	0.50	-0.13	0.28
Albumin gm/dl (3.5-5.5)	PN 200-110	12	4.5	0.21	-0.01	0.35
	Placebo	12	4.3	0.22	-0.03	0.22
Total Bilirubin mg/dl (0.2-1.5)	PN 200-110	12	0.7	0.19	0.00	0.13
	Placebo	12	0.6	0.26	0.03	0.11
Cholesterol mg/dl (150-300)	PN 200-110	12	211.3	41.58	1.00	22.15
	Placebo	12	234.3	25.37	-6.67	15.79
Alkaline Phosphatase Units (30-115)	PN 200-110	12	79.7	16.89	6.67**	6.26
	Placebo	12	72.2	19.86	0.75	6.70

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

TABLE 20 (Continued)
PN 200-110 STUDY NO. 1.
CHEMISTRIES
ANALYSIS OF VARIANCE

Variable (Normal Range)	Treatment Group	No. Patients	Baseline Mean	S.D.	Mean Change at Week 3	S.D.
LDH Units (60-225)	PN 200-110	12	180.2	32.49	-3.00	23.97
	Placebo	12	169.5	25.04	1.75	17.70
SGOT Units (0-41)	PN 200-110	12	20.2	5.77	1.92	7.10
	Placebo	12	22.7	11.25	-0.50	6.07
SGPT Units (0-46)	PN 200-110	12	29.8	15.21	1.58	13.28
	Placebo	12	32.1	20.73	-2.67	14.32
Sodium mEq/l (135-145)	PN 200-110	12	141.8	1.80	-1.50(*)	2.47
	Placebo	12	141.9	2.02	-0.92	2.02
Potassium mEq/l (3.5-5.5)	PN 200-110	12	4.2	0.28	-0.09	0.22
	Placebo	12	4.2	0.41	-0.05	0.33
Chloride mEq/l (96-108)	PN 200-110	12	103.3	2.19	-1.75*	2.22
	Placebo	12	102.8	2.34	-0.25	2.93
CO_2 mEq/l (22-30)	PN 200-110	12	24.6	1.24	0.83	2.25
	Placebo	12	24.9	1.51	0.67	2.39
Creatinine mg/dl (0.5-1.7)	PN 200-110	12	1.1	0.24	0.01	0.07
	Placebo	12	1.1	0.19	0.06	0.16

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

TABLE 21

PN 200-110 STUDY NO. 11

HEMATOLOGY VARIABLES

DESCRIPTIVE STATISTICS FOR TWO-WEEK

EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. Patients	Baseline		Week 5	
			Mean	S.D.	Mean	S.D.
Hemoglobin gm/dl (11.5-18.0)	PN 200-110	3	14.9	0.44	0.00	0.78
	Placebo	4	15.8	0.42	-0.60	1.14
Hematocrit % (37-54)	PN 200-110	3	43.3	1.53	1.33	2.52
	Placebo	4	47.3	2.99	-1.25	3.10
WBC x 10^3 cu mm (3.8-11.0)	PN 200-110	3	6.7	1.86	0.73	0.82
	Placebo	4	6.4	1.17	-0.63	0.95
Bands % (0-6)	PN 200-110	3	0.00	0.00	0.00	0.00
	Placebo	4	0.00	0.00	0.00	0.00
Neutrophils % (40-80)	PN 200-110	3	60.3	1.16	-1.33	3.22
	Placebo	4	53.8	6.99	1.75	4.27
Lymphocytes % (15-50)	PN 200-110	3	31.7	2.08	2.00	2.65
	Placebo	4	37.5	7.33	-0.50	2.52
Monocytes % (2-11)	PN 200-110	3	5.0	1.00	-1.33	1.16
	Placebo	4	5.0	1.83	-0.75	0.96
Eosinophils % (1-7)	PN 200-110	3	2.7	0.58	0.33	0.58
	Placebo	4	3.5	1.00	-0.50	0.58
Basophils % (0-1)	PN 200-110	3	0.3	0.58	0.33	0.58
	Placebo	4	0.3	0.50	0.00	0.82

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

TABLE 22

PN 200-110 STUDY NO. 11

URINALYSIS VARIABLES

DESCRIPTIVE STATISTICS FOR TWO-WEEK

EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. Patients	Baseline		Week 5	
			Mean	S.D.	Mean	S.D.
Specific Gravity (1.002-1.030)	PN 200-110	3	1.020	0.006	0.004	0.007
	Placebo	4	1.011	0.007	0.007	0.006
pH (4.8-7.8)	PN 200-110	3	6.3	0.58	-0.67	0.58
	Placebo	4	6.0	1.16	-0.25	0.96

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

TABLE 23

PN 200-110 STUDY NO. 11

CHEMISTRY VARIABLES

DESCRIPTIVE STATISTICS FOR TWO-WEEK

EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 5	
			Mean	S.D.	Mean	S.D.
Calcium mg/dl (8.5-11.0)	PN 200-110	3	9.0	0.35	0.77	0.15
	Placebo	4	9.8	0.19	-0.10	0.25
Inorganic Phosphorus mg/dl (2.2-4.5)	PN 200-110	3	3.3	0.44	0.67	0.55
	Placebo	4	3.2	0.24	0.33	0.70
BUN mg/dl (9-26)	PN 200-110	3	12.0	3.00	4.67	3.06
	Placebo	4	9.8	2.99	2.75	2.87
Uric Acid mg/dl (2.2-9.0)	PN 200-110	3	5.9	0.25	0.07	1.11
	Placebo	4	5.9	1.86	0.43	0.56
Glucose mg/dl (65-115)	PN 200-110	3	99.0	7.00	7.33	22.90
	Placebo	4	94.0	12.99	-0.50	14.84
Total Protein gm/dl (6.0-8.5)	PN 200-110	3	6.8	0.59	0.30	0.36
	Placebo	4	7.2	0.75	0.03	0.57
Albumin gm/dl (3.5-5.5)	PN 200-110	3	4.5	0.06	0.00	0.10
	Placebo	4	4.3	0.26	0.05	0.44
Total Bilirubin mg/dl (0.2-1.5)	PN 200-110	3	0.7	0.06	-0.03	0.06
	Placebo	4	0.6	0.40	-0.13	0.44
Cholesterol mg/dl (150-300)	PN 200-110	3	213.3	23.12	-4.33	12.42
	Placebo	4	231.3	41.87	-6.75	20.02

TABLE 23 (Continued)

PN 200-110 STUDY NO. 11

CHEMISTRY VARIABLES

DESCRIPTIVE STATISTICS FOR TWO-WEEK

EXTENSION PERIOD (QD DOSING)

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 5	
			Mean	S.D.	Mean	S.D.
Alkaline Phosphatase Units (30-115)	PN 200-110	3	61.7	22.23	6.33	6.35
	Placebo	4	82.8	26.18	-10.25	9.03
LDH Units (60-225)	PN 200-110	3	167.0	37.75	15.67	15.01
	Placebo	4	172.0	33.10	6.75	24.10
SGOT Units (0-41)	PN 200-110	3	16.0	6.08	13.67	10.02
	Placebo	4	24.5	10.34	-5.75	6.80
SGPT Units (0-46)	PN 200-110	3	26.3	14.84	16.33	7.37
	Placebo	4	32.8	23.13	-3.75	5.06
Sodium mEq/l (135-145)	PN 200-110	3	140.0	1.00	1.67	0.58
	Placebo	4	142.5	2.65	-0.50	4.20
Potassium mEq/l (3.5-5.5)	PN 200-110	3	4.0	0.31	0.00	0.27
	Placebo	4	4.5	0.27	0.08	0.36
Chloride mEq/l (96-108)	PN 200-110	3	102.7	2.31	0.00	1.00
	Placebo	4	102.3	2.06	0.50	3.51
CO_2 mEq/l (22-30)	PN 200-110	3	24.0	1.00	1.00	0.00
	Placebo	4	25.3	2.06	1.00	1.41
Creatinine mg/dl (0.5-1.7)	PN 200-110	3	1.0	0.06	0.07	0.12
	Placebo	4	1.0	0.26	0.08	0.15

TABLE 29
PN 200-110 STUDY NO. 11

ADVERSE REACTION LISTING

Treatment Group	Patient Number	Adverse Reaction	Week and Severity of		
			First Occurrence	Last Occurrence†	Worst Occurrence††
PN 200-110	1	Diarrhea	2 - Severe		
	4	Dizziness	-2 - Mild	1 - Mild	
	5	Headache	1 - Mild		
		Upset Stomach	1 - Moderate		
		Ankle and feet edema	2 - Mild		
		Fatigue	3 - Moderate		
		Muscle cramping	3 - Moderate		
		Sleeplessness	3 - Moderate		
		Itching	3 - Moderate		
		Rash	3 - Moderate		
		Restlessness	3 - Moderate		
	9	Fatigue	3 - Moderate		
	12	Decreased energy	1 - Moderate		
		Syncope	2 - Moderate		
		Numbness, right foot	3 - Mild		
	15	Diarrhea	-2 - Moderate		
		Facial flushing	1 - Mild	3 - Mild	
		Fatigue	3 - Moderate		
	19	Inflammed, tender neck	2 - Moderate	3 - Mild	
		Dizziness	4 - Severe		
		Cramps in calves	5 - Mild		
	21	Cramp, calf muscle	-2 - Moderate	0 - Mild	
		Pain, right shoulder	0 - Moderate		
		Shoulder, face pressure	0 - Moderate		
		Fatigue	3 - Moderate		
		Cramp, left calf	4 - Moderate		
		Dizziness	4 - Mild		
	23	Headache, neck pain	-2 - Moderate		
		Chest pain	0 - Severe	3 - Moderate	
Placebo	2	Headache	-2 - Mild		
	3	Back and arm rash	1 - Mild		
	16	Cough	-1 - Moderate	3 - Mild	
		Loose stools	1 - Mild		
		Wheezing	1 - Moderate		
	20	Lightheadedness	-2 - Mild		
		Headache	-2 - Mild	3 - Mild	
		Swelling in ankles	-2 - Mild		
		Sore throat	-2 - Mild		
		Pain, left shoulder	0 - Mild	1 - Mild	
		Abdominal pain	1 - Moderate		
		Rectal bleeding	2 - Mild	3 - Mild	
	22	Diarrhea	2 - Mild		
		Lightheadedness	4 - Mild		
	24	Headache	0 - Mild	3 - Moderate	2 - Moderate

†Presented only if there were multiple occurrences.
††Presented only if different from information recorded under first or last occurrence.

TABLE 30
PN 200-110 STUDY NO. 11
COMPARATIVE ADVERSE REACTION FREQUENCY (NO. OF PATIENTS)
ADJUSTED FOR BASELINE (PLACEBO WASHOUT) EFFECTS

Side Effect	PN 200-110 (N = 12)	Placebo (N = 12)
Skin		
Pruritus	1	0
Rash	1	1
Musculoskeletal		
Neck Pain/Sore/Stiff	1	0
Respiratory		
Wheezing	0	1
Cardiovascular		
Edema	1	0
Cramps Leg/Foot	1	0
Cramps, Muscle	1	0
Gastrointestinal		
Abdominal Discomfort	0	1
Diarrhea	1	1
Nausea	1	0
Rectal Bleeding	0	1
Stools, Loose	0	1
Central Nervous System		
Dizziness	2	1
Fatigue	4	0
Headache	1	1
Insomnia	1	0
Decreased Energy	1	0
Nervousness	1	0
Syncope	1	0
Autonomic Nervous System		
Flushing	1	0
Numbness	1	0
Total Number of Patients Reporting At Least One Newly-Occurring Adverse Reaction	7/12 (58%)	5/12 (42%)

Figure 1

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

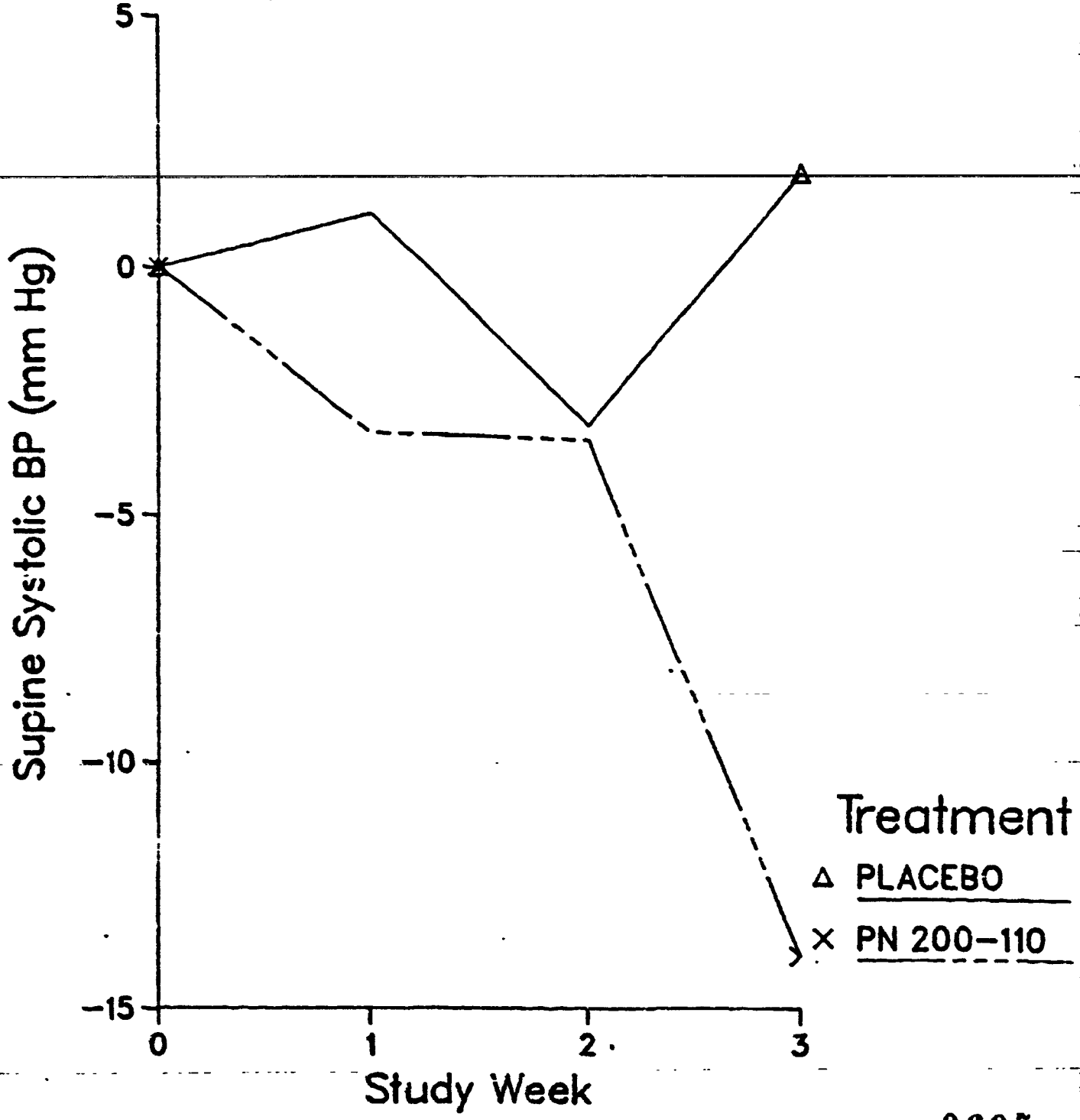

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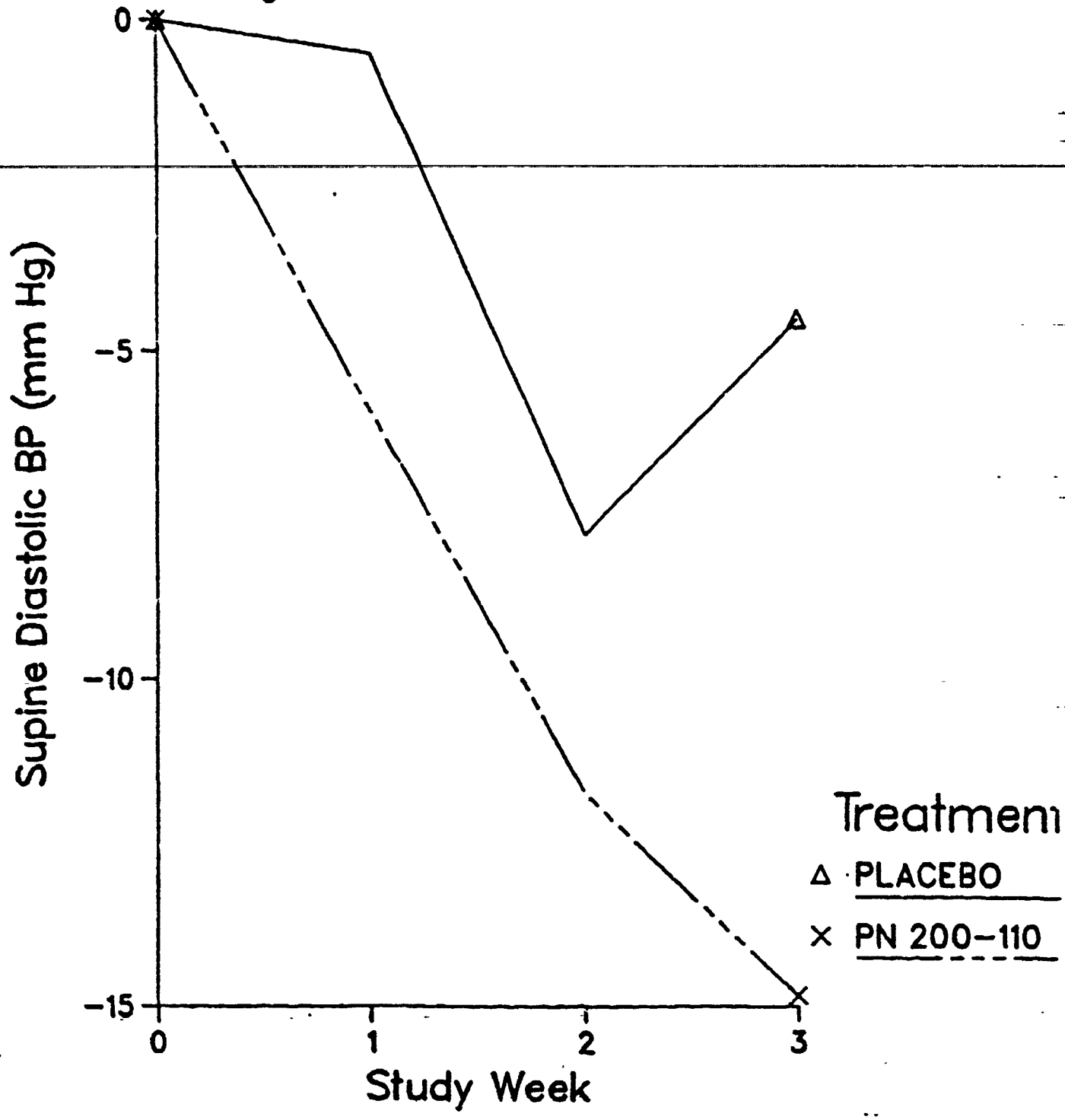
Figure 2

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