

## BLOOD CHEMISTRY

Parameter (Normal Range)	Subject No.	Pre-Treatment	Post-Treatment
Inorganic Phosphorus (2.5-4.5 mg/dl)	011	3.8	4.8 (H)
	012	3.7	4.6 (H)
	018	4.7 (H)	3.8
Glucose (65-120 mg/dl)	006	85	59 (L)
	010	86	134 (H)
	017	95	130 (H)
Sodium (135-145 mEq/l)	002	140	146 (H)
	009	142	146 (H)
Cholesterol (140-260 mg/dl)	009	190	126 (L)
	011	147	139 (L)
	013	317 (H)	Not Available
CO <sub>2</sub> (22-33 mEq/l)	013	27	19 (L)
Creatinine (0.7-1.4 mg/dl)	005	1.2	1.6 (H)
	009	1.5 (H)	1.1
	017	1.5 (H)	1.4

(H) Denotes value above the normal range limits.

(L) Denotes value below the normal range limits.

Deviations are of little or no significance.

**TABLE 4**  
**FN 200-110 STUDY NO. 319**  
**LABORATORY TEST DATA - SUBJECTS WITH**  
**VALUES OUTSIDE THE NORMAL RANGE**  
**HEMATOLOGY**

Parameter (Normal Range)	Subject No.	Pre-Treatment	Post-Treatment
Hemoglobin (13.0-17.4 gm/dl)	014	17.7 (H)	17.0
Hematocrit (36.3-49.2%)	005	52.0 (H)	50.0 (H)
	014	51.0 (H)	50.0 (H)
	015	48.0	50.0 (H)
WBC (3.8-10.9x10 <sup>3</sup> cu.mm.)	018	9.1	3.1 (L)
Neutrophils (47-76%)	001	65.0	31.0 (L)
Lymphocytes (16-44%)	001	27	7.0 (L)

(H) Denotes value above the normal range limits.  
(L) Denotes value below the normal range limits.

**FN 200-110 STUDY NO. 319**  
**BACKGROUND DATA SUMMARY**

Variable	Range	Number of Subjects	Percent	Descriptive Statistics
Sex	Male	10	100%	
	Female	0	0%	
Age (years)	21-25	8	44%	mean 25.2 std.dev. 3.49 range 21-29
	26-30	10	56%	
Weight (lbs.)	120-140	1	6%	mean 169.8 std.dev. 22.27 range 120-201
	141-160	6	33%	
	161-180	6	33%	
	181-200	4	22%	
	201	1	6%	
Height (inches)	55-65	1	6%	mean 70.3 std.dev. 3.86 range 57-74
	66-70	9	44%	
	71-75	9	50%	
Body Frame	Small	2	11%	
	Medium	14	78%	
	Large	2	11%	
Race	Caucasian	17	94%	
	Oriental	1	6%	

The demography and blood pressure from the studies 310 and 319 are virtually interchangeable.

## PH 300-110 STUDY NO. 319

## SITTING BLOOD PRESSURE AND RADIAL PULSE

Variable	Dose	Number of Subjects	Baseline Pre-Dose		Mean Change From Baseline ± S.D.			
					2 Hours Post-Dose		12 Hours Post-Dose	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.
Systolic Blood Pressure (mm Hg)	2.5 mg	17	116.3	9.63	-6.6	8.97	+6.3	8.10
	5 mg	16	121.6	11.31	-7.3	9.60	+1.8	10.63
	10 mg	17	118.2	7.60	-3.8	9.63	+3.1	9.91
Diastolic Blood Pressure (mm Hg)	2.5 mg	17	76.2	9.61	-6.1	9.63	-4.3	7.69
	5 mg	16	76.3	9.65	-7.9	9.86	-8.1	9.61
	10 mg	17	76.1	5.79	-3.1	7.63	-1.7	7.11
Radial Pulse (beats/min.)	2.5 mg	17	66.1	10.33	-1.9	6.65	+1.8	7.16
	5 mg	16	66.4	7.24	-8.6	6.95	+1.8	9.78
	10 mg	17	68.8	6.65	+3.3	7.99	+6.7	8.80

Elevations of liver enzymes are not impressive and do not approach those encountered in Study 310.

**Conclusion:** No evidence from this study indicates the drug is unsafe in the doses given.

PH 200-110 STUDY NO. 319

LABORATORY TEST DATA - SUBJECTS WITH VALUES OUTSIDE THE NORMAL RANGE

LIVER FUNCTION TESTS\*

Parameter (Normal Range)	Subject No.	Test Day	Pre-Treatment	Post-Treatment
SGOT (1-41 units)	001	Pre-Study	22 °	
		1	17	15
		2	21	17
		3	23	16
		Post-Study		16
		2 wk Follow-up		24
		4 wk Follow-up		48 (H)
	6 wk Follow-up		27	
	007	Pre-Study	26	
		1	13	12
		2	22	15
		3	20	15
		Post-Study		12
		2 wk Follow-up		24
4 wk Follow-up			46 (H)	
6 wk Follow-up		23		
SGPT (1-31 units)	007	Pre-Study	17	
		1	12	14
		2	17	16
		3	23	18
		Post-Study		16
		2 wk Follow-up		20
		4 wk Follow-up		34 (H)
6 wk Follow-up		47		
Total Bilirubin (0.1-1.2 mg/dl)	008	Pre-Study	1.3 (H)	
		1	2.1 (H)	2.0 (H)
		2	1.9 (H)	1.4 (H)
		3	2.0 (H)	1.8 (H)
		Post-Study		1.1
		2 wk Follow-up		1.4 (H)
		6 wk Follow-up		1.2

\*All laboratory data is listed if subject demonstrated at least one laboratory abnormality.

(H) Denotes value above the normal range limits.

(L) Denotes value below the normal range limits.

**Conclusions:** The essential pharmacokinetic data have been collected for the pharmacokinetic characterization of this drug. The findings, consistent with animal and other clinical studies, demonstrate a rapid, complete absorption, large first pass effect and quantitative rate of elimination. The drug appears to be safe except for a question of hepatotoxicity.

#### PHARMACODYNAMICS

The data from the following limited studies as well as from the large trials are treated by parametric and categorical analyses. The categories of blood pressure response referred to here and in the other studies are: category 1, sitting diastolic blood pressure less than 85 mm with a decrease of 10 mm or more from the baseline; category 2, sitting diastolic blood pressure greater than 85 with a decrease of 10 or more mm from baseline; category 3, sitting diastolic blood pressure greater than 85 with 5 or more mm departure, but less than 10 mm HG from the baseline; category 4, sitting diastolic blood pressure greater than 85 with a decrease of less than 5 or and increase. Category 1 would be considered a complete success, and category 4 a total failure and those intermediate are qualified successes or failures.

Blinding was carefully designed and has been uncompromised. A question of whether a correlation exists between side effects and blood pressure response is tested with the data from Study#7. This problem and other such matters are discussed in the Statistical Review.

#### Study #7

1. **Objective:** To determine the effect on mild hypertension of PN-200 in oral doses of 215,510 and 10 mg bid
2. **Design:** Randomized placebo controlled parallel dose titration study of 3 weeks duration.
3. **Materials and Methods:** Patients selected for randomization on the basis of supine diastolic blood pressure greater than 95 and less than 114 mm of mercury. At the end a single blind placebo run in. Patients during run-in whose blood pressure was falling were not randomized. Inclusion/exclusion criteria were appropriate, selecting for uncomplicated benign essential increase in blood pressure. The design of the experiment is shown in the table.

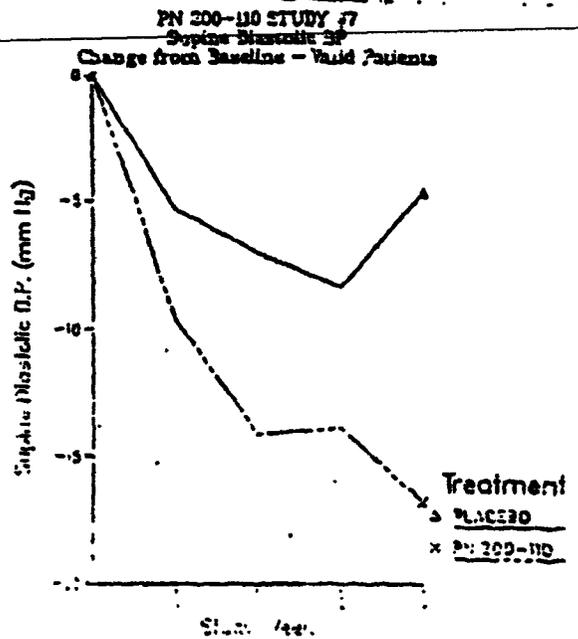
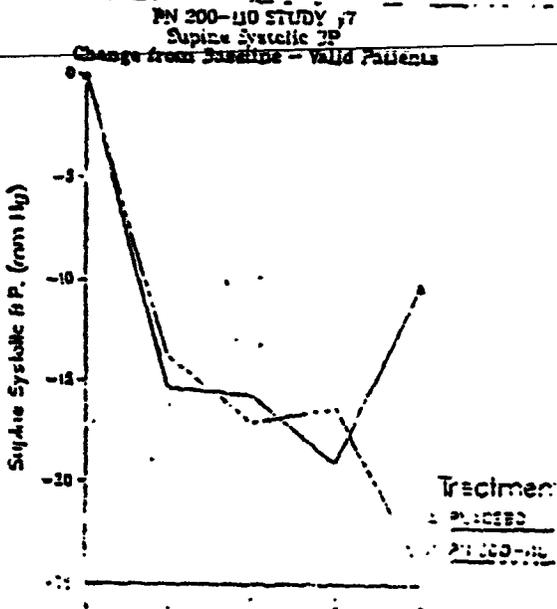
Subject Group	Single-Dose Protocol Number (1, 2, 3)	Blinding					
		Week 1	Week 2	Week 3	Week 4	Estimate Week 5	Estimate Week 6
200-110	one (1) Pn cap (bid) AC	one (1) Pn 200-110 2.5 mg cap (bid) AC	one (1) Pn 200-110 2.5 mg cap (bid) AC IF diastolic BP > 90	one (1) Pn 200-110 2.5 mg cap (bid) AC IF diastolic BP > 90	Same dosage regimen	one (1) to four (4) Pn 200-110 5.0 mg caps twice-a-day	one (1) to four (4) Pn 200-110 5.0 mg AC twice-a-day
			OR	one (1) Pn 200-110 3.0 mg cap (bid) AC IF diastolic BP > 90	Same dosage regimen		
			one (1) Pn 200-110 3.0 mg cap (bid) AC IF diastolic BP > 90	one (1) Pn 200-110 3.0 mg cap (bid) AC IF diastolic BP > 90	Same dosage regimen		
	Total Daily Dose:	5.0 mg	5-10.0 mg	5-10.0 mg	5-20.0 mg	5-20.0 mg	5-20.0 mg
2000	one (1) Pn cap (bid) AC	one (1) Pn cap (bid) AC	one (1) Pn cap (bid) AC	one (1) Pn cap (bid) AC	Same dosage regimen	one (1) to four (4) Pn caps twice-a-day	one (1) to four (4) Pn caps twice-a-day
			appropriately increased and titrated to maintain diastolic study design				

**Study #7 (Continued)**

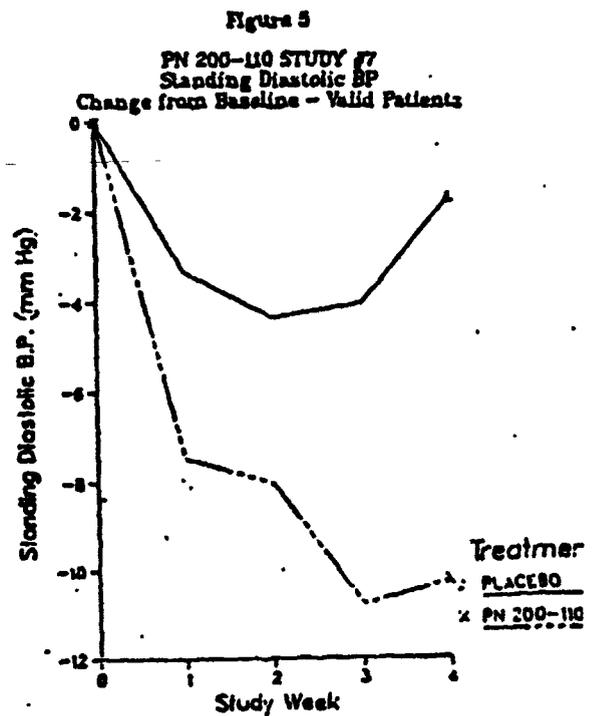
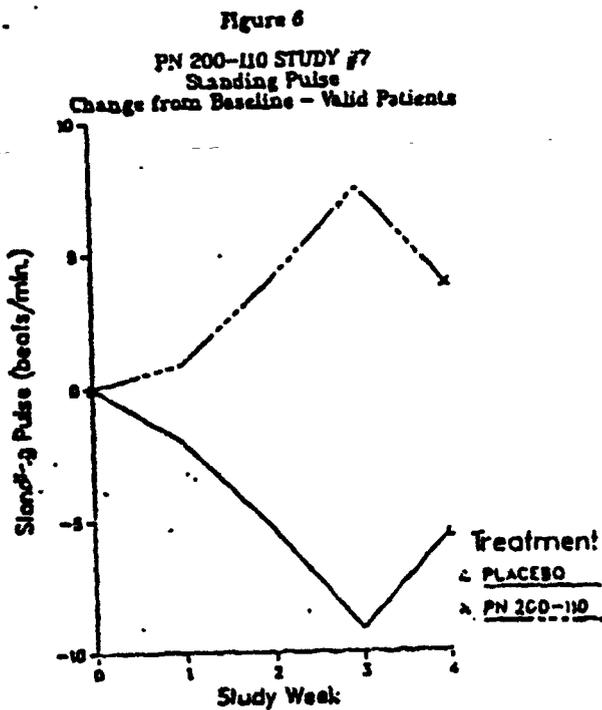
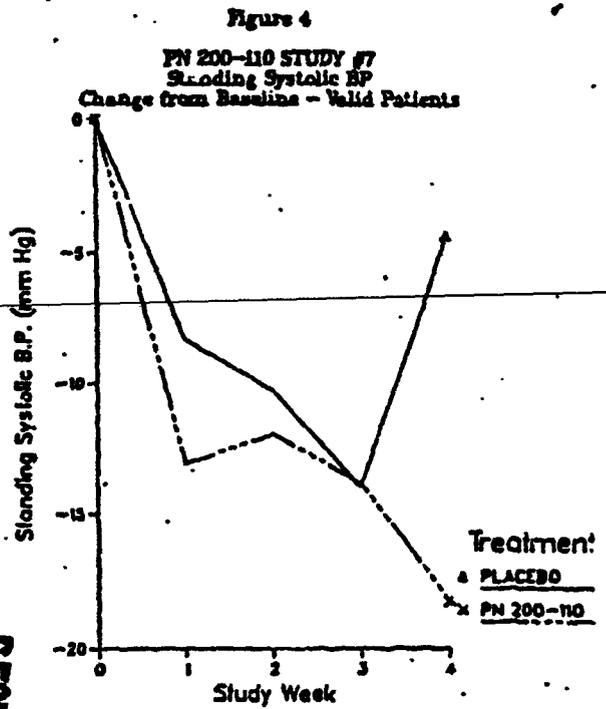
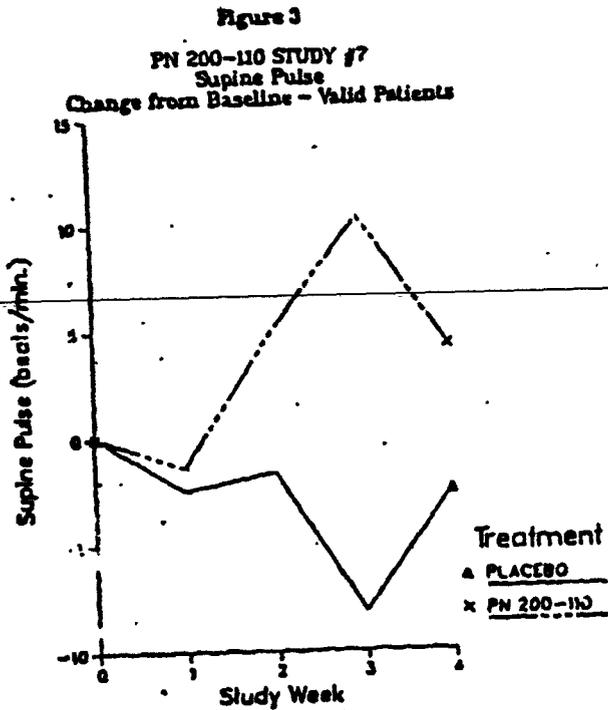
In addition to measurement of blood pressure and standard laboratory including x-ray and ECG, PRA and 24 hour urine sodium were measured at time of randomization. Blinding was insured by appropriate measures. Pill taken between 7 and 8 each morning during telephone contact at home. with visits to occur before 11:00 in the morning, between 2 - 3 hours after dose.

Twenty-four patients were randomized, no information on how many internal screening, 22 patients were included in the analysis. Two placebos were unaccounted for. Group slightly unbalanced with respect to race, the white were more numerous than the black, endocrine greater than normal, skin trouble greater than normal for the PN group, baseline average blood pressure, 102.3 - 102.9 supine diastolic for the PN and placebo groups respectively. Nearly all subjects received the maximum dose of 20 mg (that is 10 mg bid). Three patients remained at the dose level of 5 mg a day.

4. Results: The statistical differences shown in the blood pressure response, both the placebo and treatment were in the early phase of the study. A statistical difference is apparent between the active drug and placebo at the end of 3 weeks. A statically significant rise in the pulse was demonstrated with PN though the change is so slight as to be of doubtful clinical importance. At 2 week extension of the study, no effect on blood pressure was evident in the small group receiving a single daily dose of PN 200. Blood pressure responses are shown in the graphic display.



BEST POSSIBLE COPY



EST PASSED 1/10/11

5. Safety: No serious side effects were reported. Adverse reactions are summarized in the tables.

PM 200-110 STUDY NO. 7  
ADVERSE REACTION LISTING

Treatment Group	Patient Number	Adverse Reaction	Date and Severity of		
			First Occurrence	Last Occurrence	Worst Occurrence
PM 200-110	181VVT	Headache TACHYCARDIA	1 - Moderate		
	183	Headache	2 - Mild	8 - Mild	
	188	Fatigue	2 - Mild	8 - Mild	
	114VVT	Ringing in ear Palpitations	2 - Mild 2 - Mild	3 - Moderate 3 - Severe	3 - Moderate
		Lightheaded	1 - Mild		
		Thumping in chest	2 - Moderate	6 - Mild	
		Flushing of face	2 - Mild	6 - Mild	
		Headache	3 - Mild	6 - Mild	
		Tingling; numbness	3 - Moderate		
			3 - Moderate		
	123	Headache	4 - Mild		
	104	Diarrhea	4 - Moderate		
107	Shin pain	2 - Mild	3 - Mild		
111	Blurring of vision	2 - Mild			
113	Rash, erythema Headache Burning/aching eyes Ecema under eye Upper respiratory infection	2 - Mild 0 - Moderate 2 - Mild 2 - Mild 3 - Mild	0 - Mild 6 - Mild	1 - Moderate	
119	Sore Throat	3 - Mild			
121	Dizziness Staph infection, thumb	2 - Mild 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 severe reaction.  
 ††††Discontinued after Week 3 because of severe reactions.

BEST PRACTICE COPY

PM 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	PM 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

6. Conclusions: The drug is safely tolerated in doses up to 20 mg a day and there is a significant fall in b.p. B.i.d. appears to be optimal dose schedule.

Dose related reduction in b.p. followed single doses of 2.5, 5, 10, 20 mg. A statistically significant difference in 10 mg, 20 mg dose was not shown. Maximum response was seen approximately 6 hrs with some b.p. reduction remaining approximately 12-21 hrs. B.I.D. dosages appears the most effective schedule. Safety data indicate the drug is tolerated safely in the doses given.

### Study #9

1. Objective: To measure dose response of blood pressure to oral PN-200-110 in patients with mild to moderate hypertension.

2. Design: Randomized 4 X 4 Latin square. placebo controlled 2 week outpatient 3 day inpatient single blind washout, and 9 day double blind inpatient study

3. Materials and Methods: Results: Sixteen patients (100% black, 75% w. men) selected according the established criteria for inclusion and exclusion were randomized to four groups and given the medication according to the the schedule outlined in the table. See Table 1. Each pt received 4 single daily doses ranging from 2.5 to 20mg separated by one day of placebo according to the following sequence:

The 4 X 4 Latin square used 4 R<sub>x</sub> multiple crossover sequences:

Sequence 1: 5 mg, 2.5 mg, 20 mg, 10 mg,	pts # 1, 6, 10, 17
Sequence 2: 2. mg, 10 mg, 5 mg, 10 mg, 20 mg,	pts # 2, 5, 9, 16
Sequence 3: 20 mg, 5 mg, 10 mg, 2.5 mg	pts # 3, 7, 12, 14
Sequence 4: 10 mg, 20 mg, 2.5 mg, 5 mg,	pts # 4, 8, 11, 15

These patients were treated as two Latin squares, the 1/2 receiving med on even, the other on odd days. In the 3rd week titration was stopped at the discretion of the investigator and a lower dose maintained without compromising the double blind. During the two week extension the dose being given at the end of the total 9th week was continued in a single a.m. dose 4.

4. Results: Measurements of b.p. and weekly evaluations are summarized in Table 2. Details of analysis are found in Statistical Review.

TABLE 1  
 PM 200-110 STUDY NO. 9  
 SBMV DESIGN

Period I	Period II	Period III												
		Washed ("Outrained") Weeks 1, 2	Washed ("Outrained") Days 1, 2, 3	Active Treatment (Inpatient)*										
				Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9		
Ten (2) placebo capsules every day before breakfast	Ten (2) placebo capsules every day before breakfast	Pre-Dose												
		BELOW PREVIOUS SUCCESSIVE TREATMENTS	D <sub>1</sub>	P	D <sub>2</sub>	P	D <sub>3</sub>	P	D <sub>4</sub>	P	D <sub>5</sub>	P	D <sub>6</sub>	P
		INCLUSIVE EXCLUSION CRITERIA FORM COMPLETED.	P	D <sub>1</sub>	P	D <sub>2</sub>	P	D <sub>3</sub>	P	D <sub>4</sub>	P	D <sub>5</sub>	P	D <sub>6</sub>

← single-blind →      ← single-blind →      ← double-blind →

D<sub>1</sub>-D<sub>6</sub> = four different dose levels of PM 200-110 (2.5 mg, 5 mg, 10 mg, 20 mg) in random order. The individual doses consisted of two capsules, either PM 200-110 and/or placebo administered before breakfast, at approximately 7:00 A.M.; P = placebo.

\*The out-patient washout period was decreased to six days in one newly diagnosed hypertensive patient who had never previously been treated for hypertension.

TABLE 1

5. **Safety:** Safety was assessed by those 6 parameters used throughout, viz background PE, ECG, chest film adverse reactions, and clinical laboratory tests. There were no dropouts.

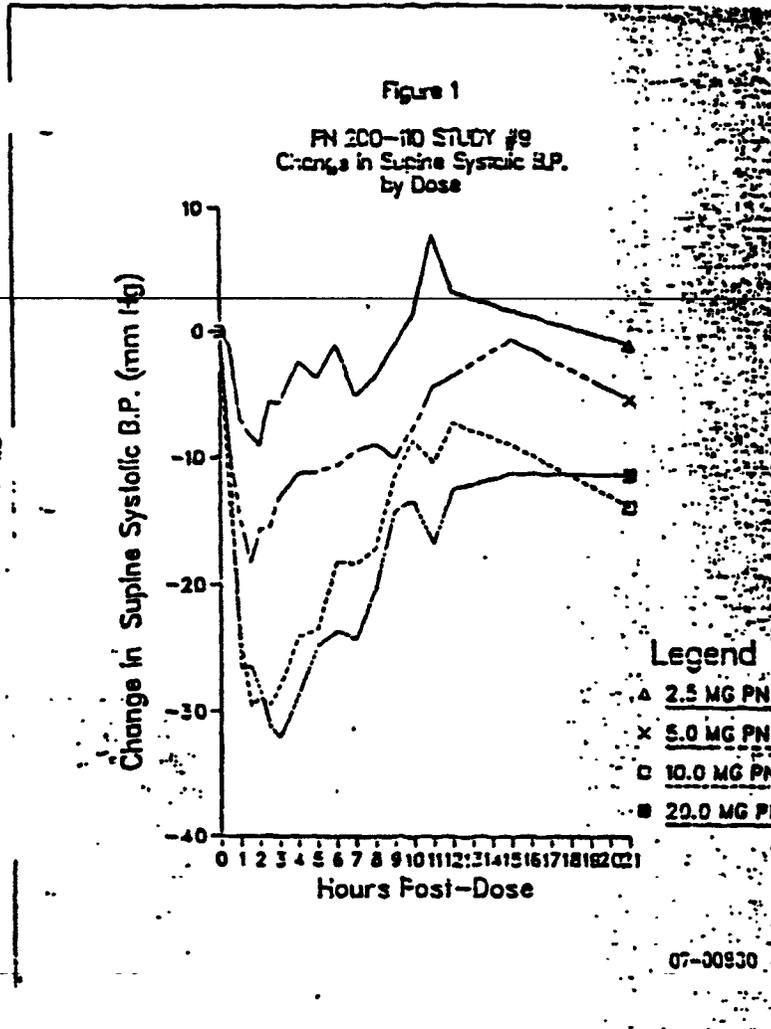
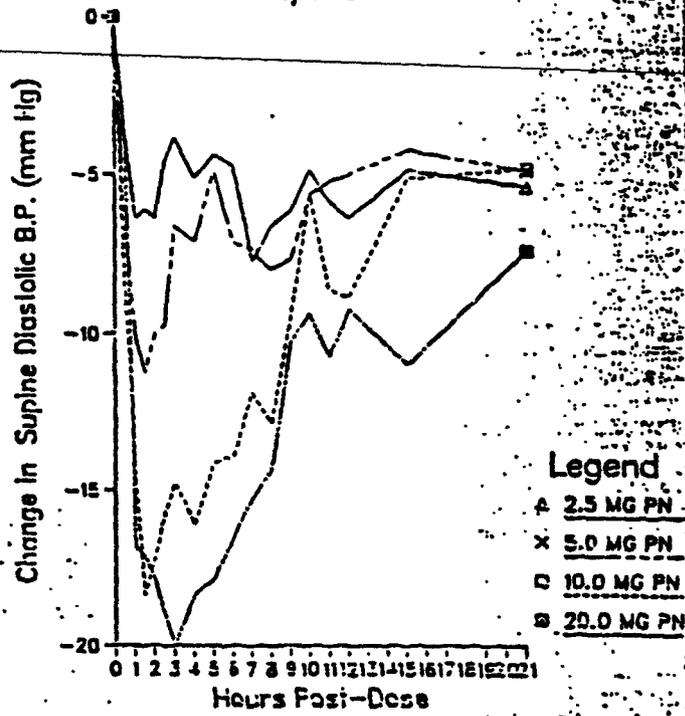
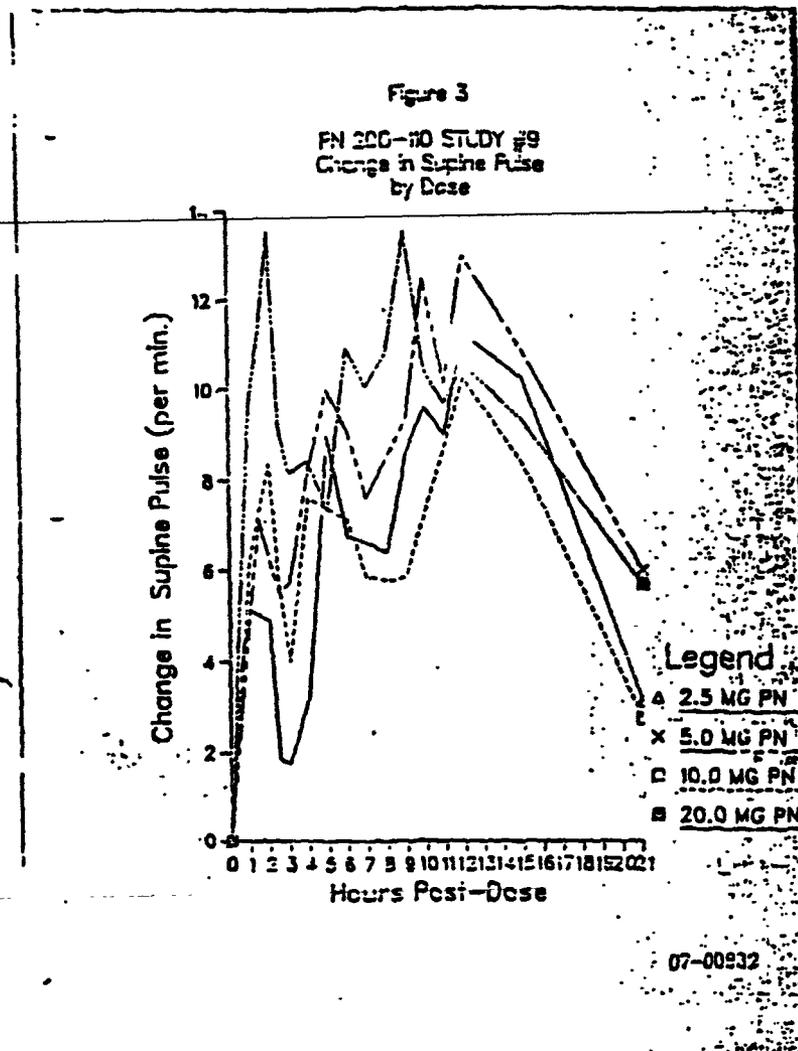


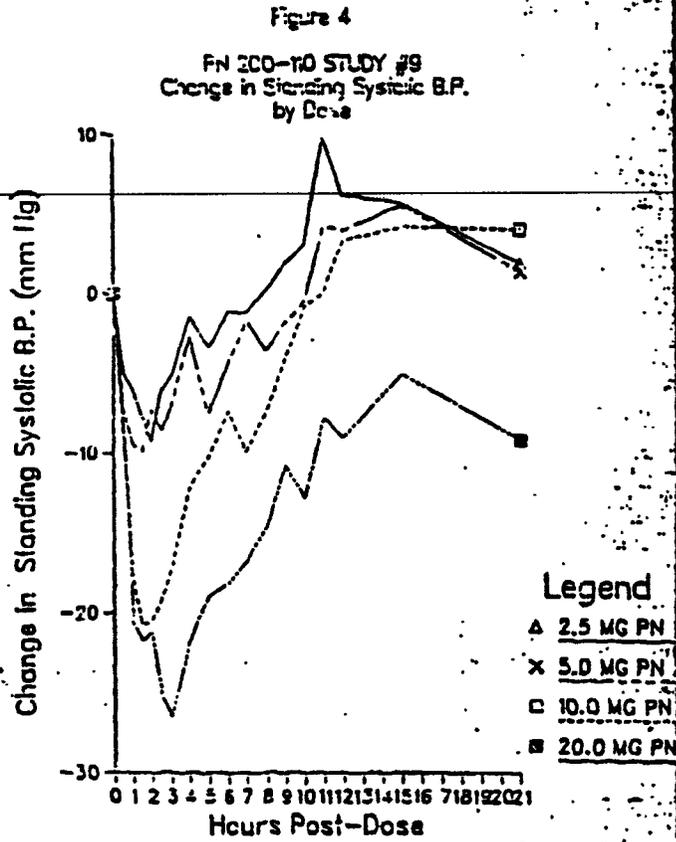
Figure 2  
FN 200-10 STUDY 49  
Change in Supine Diastolic B.P.  
by Dose



Legend  
▲ 2.5 MG PN  
× 5.0 MG PN  
□ 10.0 MG PN  
■ 20.0 MG PN

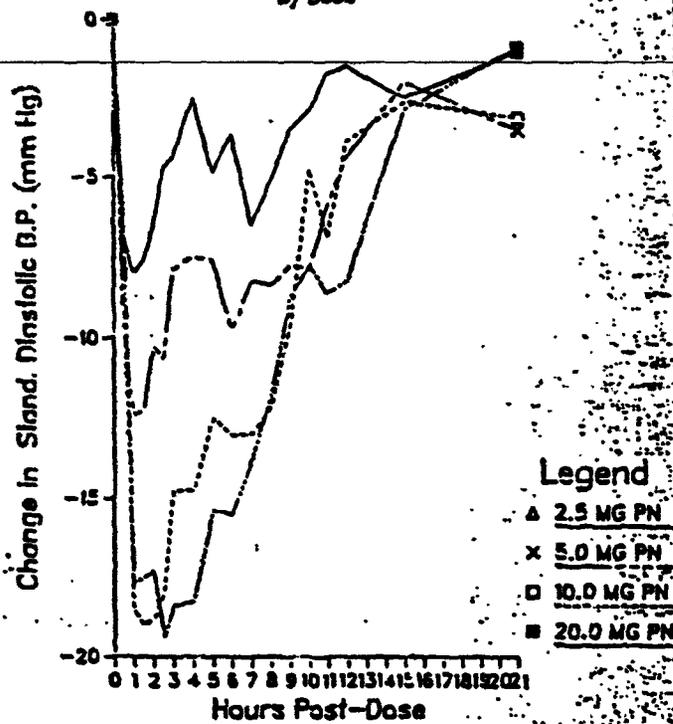
07-30931





07-00933

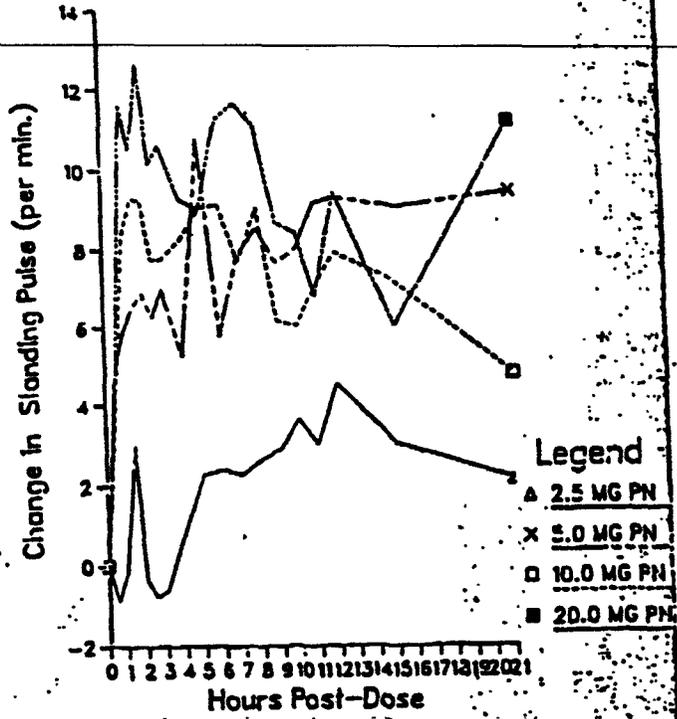
Figure 3  
FN 200-10 STUDY #9  
Change in Standing Diastolic B.P.  
by Dose



Legend  
▲ 2.5 MG PN  
× 5.0 MG PN  
□ 10.0 MG PN  
■ 20.0 MG PN

07-00934

Figure 6  
PN 200-110 STUDY #9  
Change in Standing Pulse  
by Dose



07-00935

Significant fall in b.p. compared to placebo indicates dose response relationship between PN and b.p. These data are displayed in Table and Figure 5. Changes in pulse rate are clinical or statistical significance. Table 10 displays categorical analysis. The data from qd study insufficient for analysis indicate lack of b.p. control by single daily dose of PN.

The commonest adverse reactions were headache, dizziness, and abdominal discomfort. There was no apparent relationship between dose and frequency of side effects.

5. Conclusions: Dose response is clear over the range of 2.5-20mg. The drug is safe given in these doses, though there is little difference in the response to 10 and 20mg doses. Dose response curves indicate that PN-200 is effective when given twice daily but probably is not suitable for single daily dosage.

#### Study #11

1. Objective: To measure the effect of PN in ascending dose in pts with essential hypertension.
2. Design: Double-blind, placebo controlled 3 week ascending dose study.
3. Materials and Methods: Twenty-four patients after two week placebo washout, were randomized to active treatment and placebo groups. Those in the active treatment received fixed doses increasing in weekly increments from 5.0 to 20 mg daily given in two daily doses. Titration was stopped at the discretion of the investigator and a lower dose maintained without compromising the double blind. All 24 patients completed the three week trial, but two were not evaluated for efficacy due to protocol violation. During a two week extension, the dose being given at the end of the total 9th week was continued in 7 patients in a single a.m. dose. Blood pressure measurements and safety evaluations were made weekly. A third of the placebo group and none of the actively treated group was black.

The design of the study is outlined in Table 1.

TABLE I  
 PN 200-110 STUDY NO. 11  
 STUDY DESIGN

Treatment Group	Placebo (Pcb) Washout Period	Week 1	Week 2	Week 3 †	Extension ††	Extension ††
	Weeks -3,-2,-1				Week 4	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→

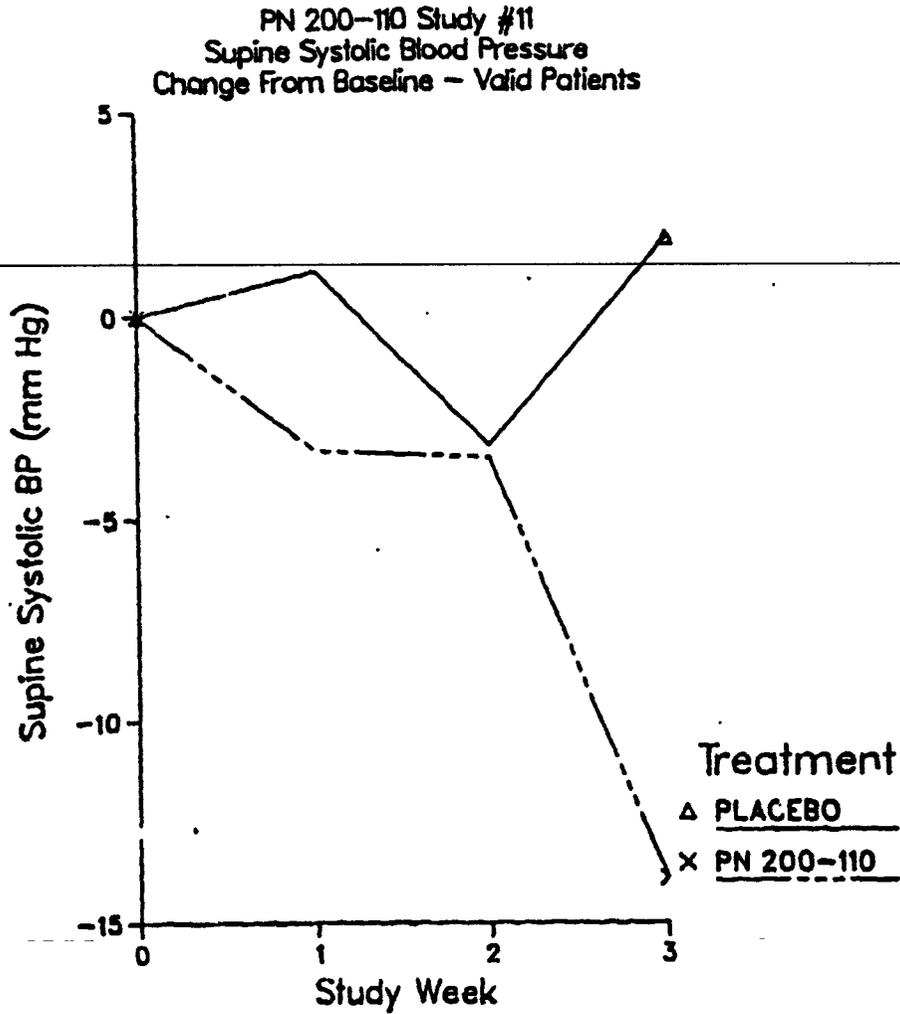
\*ac - Before breakfast and supper.

\*\*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.

4. Results: Response of blood pressure with increasing dose and time is drawn in the curve which shows the disappearance of placebo effect with time.



5. Conclusions: Isradipine produced a significantly greater fall in b.p. than b.i.d. placebo and in the doses of 5 to 20mg daily was safely tolerated. Single daily dosing was ineffective confirming impressions from earlier study.

6. Summary: These three crucial hemodynamic studies establish dose responsiveness of hypertension to PN-200-110, indicate a safe range and likely dosing interval. There is no suggestion from these studies that the drug is unsafe.

Study #301

This is one of two pivotal studies and was conducted by Albert Core of Atlanta, Georgia, Michael Davidoff of Falls Church, Virginia Bruce Hamilton of Baltimore, Maryland, Harold Schnapper of Birmingham, Alabama, Manual Valaxces of Milwaukee, Wisconsin, and Alexander Sheppard of San Antonio, Texas.

1. Objective: To determine the safety and efficacy of four doses of PN-200 in patients with mild to moderate hypertension.

2. Design: Double-blind randomized placebo controlled fixed ascending dose trial.

3. Materials and Methods: A total of 203 patients were entered in the study. Patients were male 18 years or older with diagnosis of essential hypertension. Diastolic pressure was determined to be greater than 100 or was shown to have a trend toward 100 after the period of washout from active treatment. Patients had received reserpine or guanethidine required a 4 week washout. Patients with bp greater than 120 mmHg were excluded.. Criteria for exclusion are as follows:

malignant, accelerated, or severe hypertension, and patients with secondary forms of hypertension

angina pectoris, other than infrequent angina controlled by sublingual nitroglycerin PRN only

history of myocardial infarction within 6 months to initiating the cardiac arrhythmias of sufficient severity as to place the patient at risk or interfere with the objectives of the study

patients who received within 4 weeks prior to entering the study any other investigational new drug

congestive heart failure uncontrolled by digitalis glycosides alone

bradycardia (heart rate less than 50 beats per minute) first degree heart block or a PR interval 0.25 sec or a functionally significant accessory atrioventricular conducting pathway

history of alcohol or drug abuse during the two years prior to entry into the study, mental dysfunction, or a language barrier

cerebral vascular insufficiency

known adverse reaction or hypersensitivity to any calcium blocking study

any disease or abnormal condition which resulted in altered absorption or distribution or impairment or metabolism or excretion of PN 200-110 or its metabolites

required use of disallowed concurrent medication

patients who received within 3 months prior to entry into the study, medications that were known to be particularly toxic to a major organ system, such as those causing blood dyscrasias, nephrotoxicity, hepatotoxicity, and/or neurotoxicity

patients with creatinine 2.0 mg or clinically significant laboratory abnormalities

pregnant or lactating females

medications which could interfere with the evaluation of safety and efficacy were disallowed at the beginning of the washout period and throughout the duration of the trial of the trial. These included the following:

all agents used for the treatment of hypertension such as diuretics, beta-blockers, and calcium channel blocking agents, or agents under investigation for the treatment of hypertension except the study drugs. Guanethidine and reserpine were discontinued at least 4 weeks prior to initiating the active treatment phase.

adrenergic augmenting drugs of the MAO inhibitor class such as isocarboxazid (marplan), nialamide

adrenolytic drugs of the dibenzazepine class (tri-cyclic antidepressants)

(Niamid), phenelzine (nardil), tranylcypromine (parlate)

antiarrhythmic drugs such as diphenylhydantoin (Dilantin), procainamide (Pronestyl), quinidine, bretylium, lidocaine, disopyramide (Norpace), or verapamil (Isoptin)

psychotropic drugs (major tranquilizers, anti-depressants, central nervous system stimulants, and depressants)

oral contraceptives

At the time of randomization, the patients were stratified according to diastolic blood pressure between 100 and 105 and those greater than 105 and these distributed uniformly amongst the 5 groups. The schedule for the five groups is shown below in the table. No investigator treatment, treatment x time and treatment x investigator x time affected the analysis of efficacy. Efficacy with increasing dose is shown in the curves abstracted from the tabulation of mean blood pressure changes during the course of the study.

Treatment Group	Placebo		Active Treatment*			
	Weeks -3,-2,-1-	week 1	Week 2	Week 3	Week 4	Week 5
Group 1 Placebo	One, Pcb** capsule bid	One, Pcb capsule bid	Dose continued			
Group 2 PN 200-110 5 mg	One, Pcb capsule bid	One, 7.5 mg PN 200-110 capsule bid	Dose continued			
Total Dose/Day		7 mg	Dose continued			
Group 3 PN 200-110 10 mg	One, Pcb capsule bid	One, 7.5 mg PN 200-110 capsule bid	One, 7.5 mg PN 200-110 capsule bid	Dose continued		
Total Dose/Day		7 mg	10 mg	Dose continued		
Group 4 PN 200-110 15 mg	One, Pcb capsule bid	One, 7.5 mg PN 200-110 capsule bid	One, 7.5 mg PN 200-110 capsule bid	One, 7.5 mg PN 200-110 capsule bid	Dose continued	
Total Dose/Day		7 mg	10 mg	15 mg	Dose continued	
Group 5 PN 200-110 20 mg	One, Pcb capsule bid	One, 7.5 mg PN 200-110 capsule bid	One, 7.5 mg PN 200-110 capsule bid	One, 10.0 mg PN 200-110 capsule bid	Dose continued	
Total Dose/Day		7 mg	10 mg	15 mg	20 mg	Dose continued

\*Dose of 10 mg  
 \*\*Dose of 15 mg  
 \*\*\*Dose of 20 mg  
 \*\*\*\*Dose of 25 mg  
 \*\*\*\*\*Dose of 30 mg  
 \*\*\*\*\*Dose of 35 mg  
 \*\*\*\*\*Dose of 40 mg  
 \*\*\*\*\*Dose of 45 mg  
 \*\*\*\*\*Dose of 50 mg  
 \*\*\*\*\*Dose of 55 mg  
 \*\*\*\*\*Dose of 60 mg  
 \*\*\*\*\*Dose of 65 mg  
 \*\*\*\*\*Dose of 70 mg  
 \*\*\*\*\*Dose of 75 mg  
 \*\*\*\*\*Dose of 80 mg  
 \*\*\*\*\*Dose of 85 mg  
 \*\*\*\*\*Dose of 90 mg  
 \*\*\*\*\*Dose of 95 mg  
 \*\*\*\*\*Dose of 100 mg

4. Results: The effect of the medication compared to placebo is shown in comparison by group and category in the table below. In all doses the drug is shown to be superior to placebo.

BEST POSSIBLE COPY

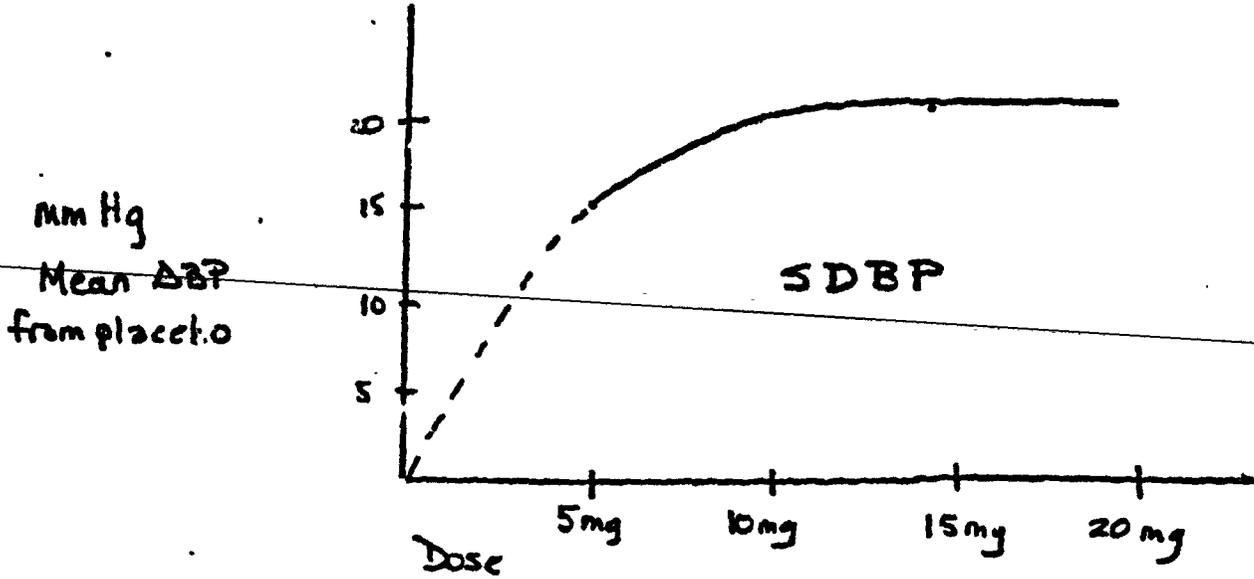
Tabulation of mean dose indicates departure from planned dosage schedule. The mean dose was calculated from the ratio of caps returned/caps dispensed weekly.

**MEAN DAILY DOSE (IN MG)  
VALID PATIENTS**

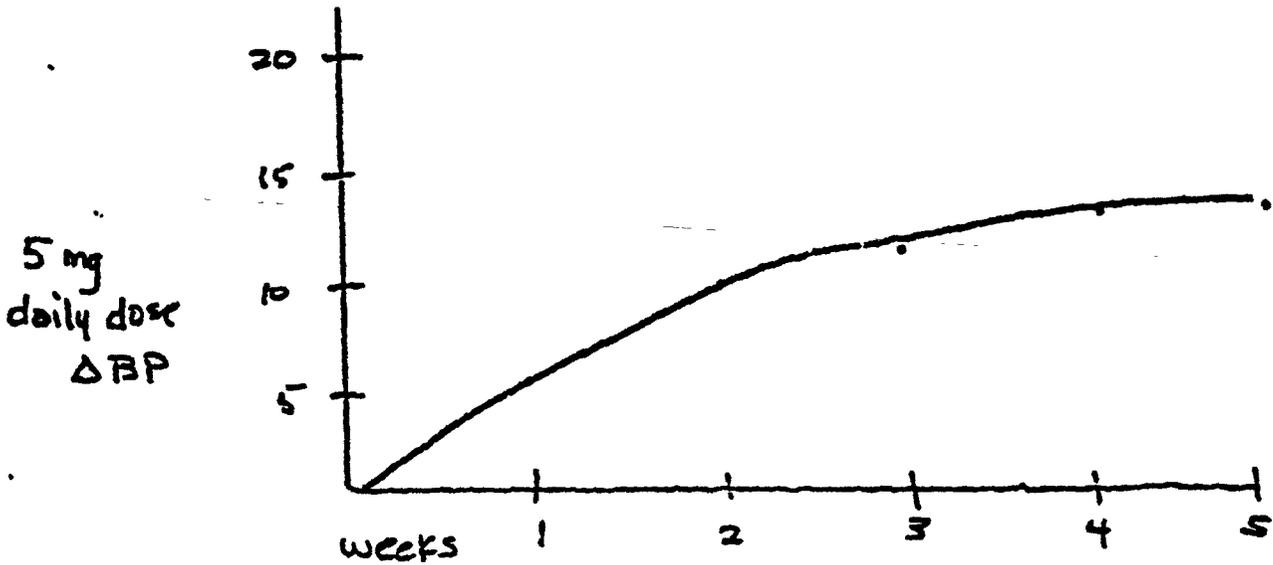
	P# 200-110 Randomized Treatment Group			
	5 mg	10 mg	15 mg	20 mg
<b>Week 1</b>				
N	35	34	38	41
Mean	4.94	4.95	4.92	9.88
S.D.	0.37	0.37	0.45	0.88
Min	4.29	3.93	3.93	6.50
Max	6.07	5.71	6.25	12.86
<b>Week 2</b>				
N	35	34	38	41
Mean	5.00	9.85	9.39	13.46
S.D.	0.20	1.21	1.47	3.49
Min	4.29	5.00	4.29	4.69
Max	5.42	12.86	10.71	16.88
<b>Week 3</b>				
N	35	34	38	41
Mean	4.87	9.38	13.93	17.50
S.D.	0.24	1.35	3.14	5.37
Min	4.06	5.00	5.00	4.29
Max	5.00	10.71	16.50	25.71
<b>Week 4</b>				
N	35	34	38	41
Mean	4.90	9.26	14.33	17.17
S.D.	0.34	1.57	3.94	5.03
Min	2.57	5.00	4.64	4.79
Max	5.71	10.83	30.00	21.43
<b>Week 5</b>				
N	35	34	37*	41
Mean	4.88	9.45	13.88	17.07
S.D.	0.22	1.60	3.41	5.22
Min	4.29	4.77	4.64	3.21
Max	5.00	11.67	24.64	22.86

\*Patient No. 254 failed to return the medication bottle for Week 5 so his average daily dose could not be determined for this interval.

Dose effect relationship is indicated by the curves:



Little change in response occurs beyond 10 mg/day.



Similar changes in response is seen with the other doses tested.

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

Supine Diastolic B.P. (mm Hg)	PN 5 mg	39	104.2	4.47	-10.0***	7.74	94.2	9.05
	PN 10 mg	38	104.0	4.18	-10.1***	7.09	93.9	7.72
	PN 15 mg	39	103.6	3.64	-8.6***	9.04	95.0	8.12
	PN 20 mg	41	103.5	3.95	-14.8***	8.64	89.1	9.28
	Placebo	41	103.9	4.36	-4.5***	5.68	99.4	9.77

These notations are used throughout all the clinical studies

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

B.P. (mm Hg)	PN 5 mg	38	104.3	4.51	-11.8***	7.07	92.9	9.17
	PN 10 mg	37	104.1	4.19	-14.6***	6.61	89.5	7.95
	PN 15 mg	39	103.6	3.64	-12.1***	8.05	91.5	7.16
	PN 20 mg	41	103.5	3.95	-16.0***	6.22	87.5	7.35
	Placebo	41	103.9	4.36	-3.3***	6.98	98.4	7.98

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSES  
MEAN OVER PLATEAU PERIOD (WEEKS 3-5) - VALID PATIENTS ONLY

TABLE 13  
PN 200-110 STUDY NO. 301

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSES  
ENDPOINT ANALYSIS FOR THE PLATEAU PERIOD  
VALID AND PARTIALLY VALID PATIENTS

Supine Diastolic B.P. (mm Hg)	PN 5 mg	38	104.3	4.51	-13.6***	8.43	-13.5	90.7	9.04
	PN 10 mg	34	104.3	4.35	-17.4***	8.21	-17.3	85.9	8.04
	PN 15 mg	39	103.6	3.64	-17.8***	7.89	-17.6	86.2	7.89
	PN 20 mg	41	103.5	3.95	-17.1***	8.87	-17.2	86.4	8.58
	Placebo	40	103.9	4.40	-6.5***	8.19	-6.5	97.4	8.47

(\*) p<.10, \*\*p<.05, \*\*\*p<.01, \*\*\*\*p<.001  
Results are presented according to pre-determined randomized treatment group pooling together all patients randomized to the treatment group.  
represented only when analysis of covariance assumptions are met.

BEST POSSIBLE COPY

The response to the drug was monitored for 24 hours in a small group of patients.

5. Safety: Safety was monitored by physical examination, cardiovascular examination, ECG, a chest x-ray, and clinical laboratory examination. There were 14 dropouts. Patients who did not complete the study and were considered partially valid were included in safety. Only valid patients were included for evaluation of efficacy. (Special attention was given to liver function in view of Study #310. There was no suggestion liver toxicity. The occasional elevation of alk phosphatase can be safely disregarded.

6. Conclusions: The effect on blood pressure is clearly greater than that of placebo. A clear-cut dose response is demonstrated and a cumulative therapeutic effect is shown to exist over a period of over 2-3 weeks. The drug appears to be safely tolerated. There were no serious side effects, specifically no evidence of hepatotoxicity and the symptoms encountered were for the most part mild. Edema is clearly the result of vasodilation as is the frequently experienced headache. There is no evidence of fluid retention. The not infrequent palpitations (subjective awareness of heartbeat) appear to result from the increased cardiac output attendant on reduced systemic vascular resistance. Tachycardia was described rarely and a small statistically significant increase in pulse is of little or no clinical significance. The drug appears to be entirely safe in the range studied. It can be recommended that the drug should be instituted in small doses and not increased for at least 2-3 weeks is given so as to establish the efficacy of the lowest dose.

#### Study #302

The study is a multicenter trial conducted by Harold Escovitz of Valhalla, N.Y. Center A,, Nathaniel Winter of Kansas City, Missouri, Center C, James B. Knochel, Center B and Remainder Kumar of Dallas Texas, Center D, Warren Davison, Torance, California.

1. Objective: To evaluate the safety and efficacy of 2.5-10 mg b.i.d. doses of PN 200 in hypertension.

2. Design: The study was a randomized parallel group placebo controlled double blind dose titration trial.



TABLE 7  
IN 200-110 STUDY NO. 302  
MEAN DAILY DBP (mm Hg)  
VALID PATIENTS RECEIVING IN 200-110

	Week 1	Week 2	Week 3	Week 4
N	26	25	27*	26***
Mean	11.04	9.44	11.10	12.00
S.D.	0.30	2.21	0.24	0.03
Min.	4.00	3.00	5.00	4.00
Max.	5.00	14.20	24.50**	20.00

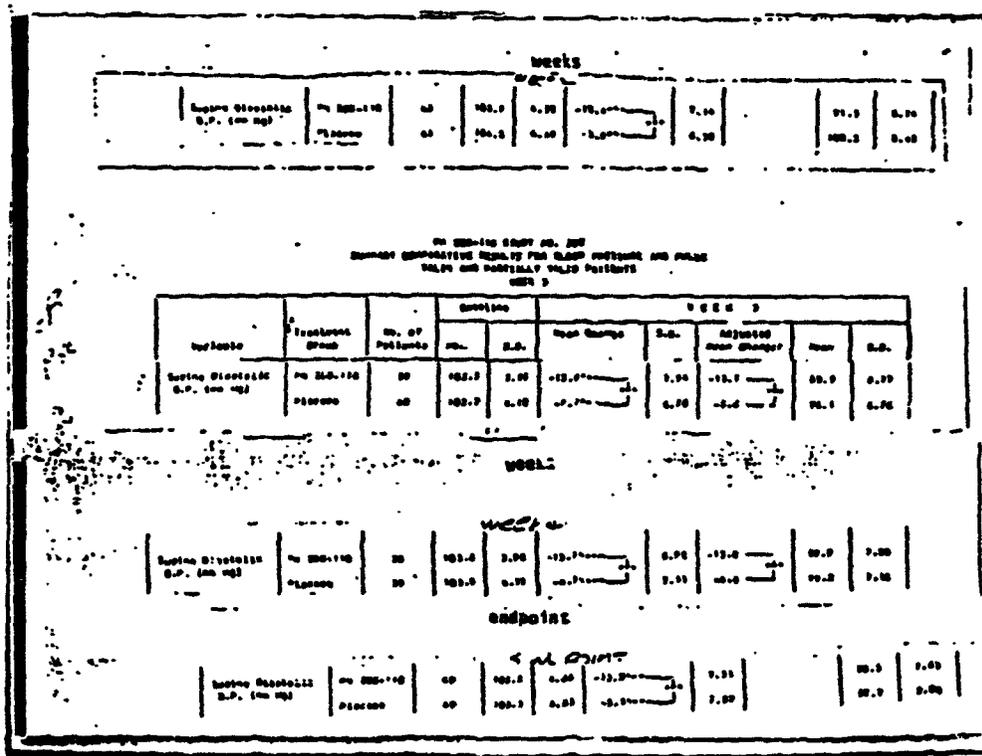
\*Patient No. 258 returned only one of ten bottles at the Week 3 visit.  
\*\*Patient No. 255 was prescribed to receive 12.5 mg/day (5 mg in AM, 7.5 in PM) but consumed 20.5 mg/day based upon return capsule count.  
\*\*\*Patients Nos. 252 and 262 did not return their IN 200-110 medication at the Week 4 visit.

TABLE 8  
IN 200-110 STUDY NO. 302  
MEAN DAILY DBP (mm Hg)  
VALID AND PARTIALLY VALID  
PATIENTS RECEIVING IN 200-110

	Week 1	Week 2	Week 3	Week 4
N	24*	23	26**	26***
Mean	9.20	8.03	11.20	12.00
S.D.	0.20	2.27	0.17	0.03
Min.	4.00	3.00	5.00	4.00
Max.	5.00	14.20	24.50***	20.00

\*Patient No. 246 did not return the IN 200-110 medication at the Week 3 visit.  
\*\*Patient No. 255 consumed only one of ten bottles at the Week 3 visit.  
\*\*\*Patient No. 255 was prescribed to receive 12.5 mg/day (5 mg in AM, 7.5 in PM) but consumed 20.5 mg/day based upon return capsule count.  
\*\*\*\*Patients Nos. 252 and 262 did not return their IN 200-110 medication at the Week 4 visit.

A statistically significant difference from placebo was apparent with the 1st week of active treatment. Response of DBP is shown in the table. Similar change occurred in systolic pressure and there was a small but statistically significant rise in pulse rate.



BEST COPY AVAILABLE

The data are displayed in the curves for systolic BPs, pulse and standing BPs.

Figure 1  
 PH 200-110 STUDY 2302  
 Supine Systolic BP  
 Change from Baseline for All Valid Patients  
 (n=77)

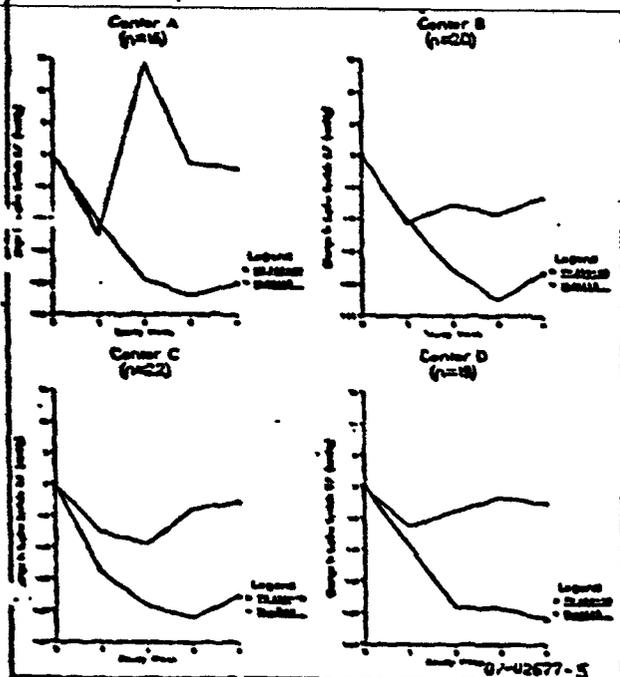
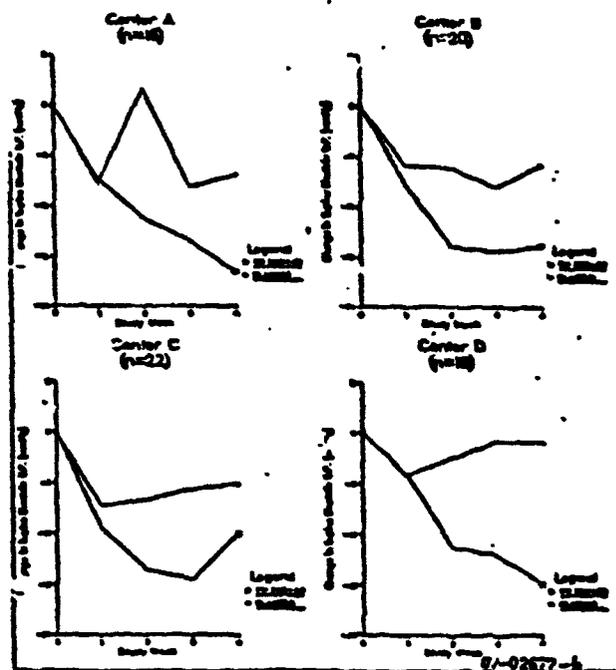


Figure 2  
 PH 200-110 STUDY 2302  
 Supine Diastolic BP  
 Change from Baseline for All Valid Patients  
 (n=77)



The difference between placebo and drug was maintained between weeks 3 and 4. Fall in blood pressure in response to treatment without respect to doses shown in the tables in the curves.

BEST POSSIBLE COPY

Figure 3  
PN 200-110 STUDY 2002  
Sitting Pulse Rate  
Change from Baseline for All Valid Patients (n=97)

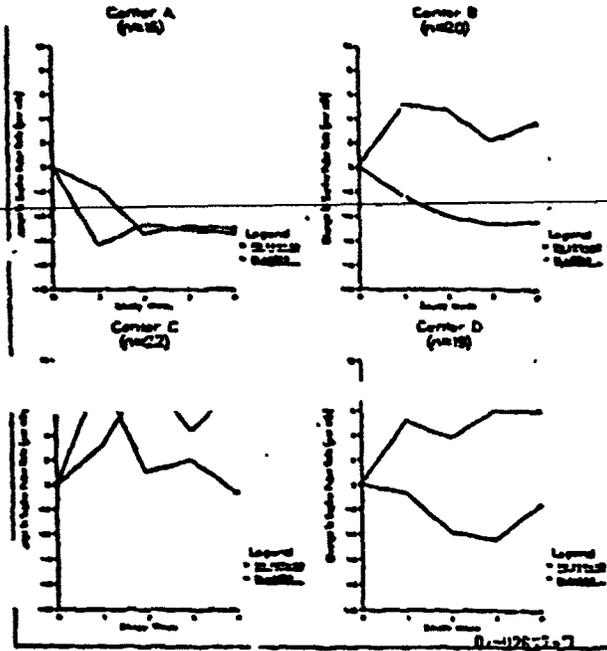


Figure 4  
PN 200-110 STUDY 2002  
Standing Systolic BP  
Change from Baseline for All Valid Patients (n=97)

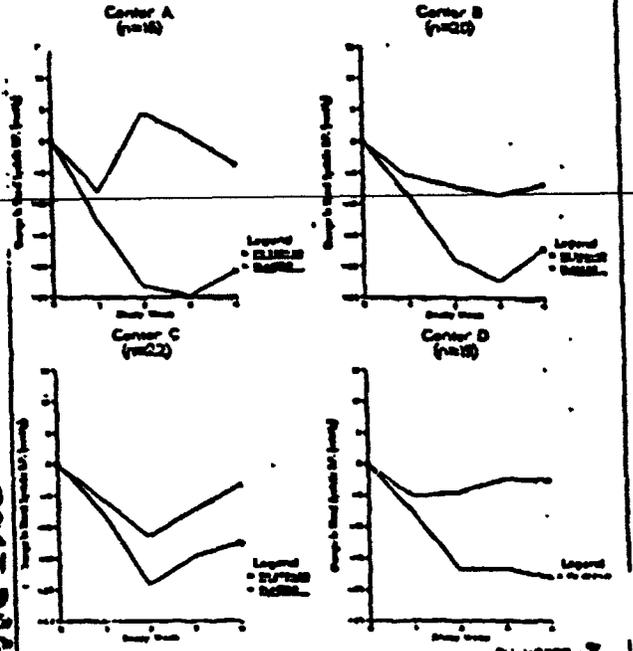


Figure 5  
PN 200-110 STUDY 2002  
Standing Diastolic BP  
Change from Baseline for All Valid Patients (n=97)

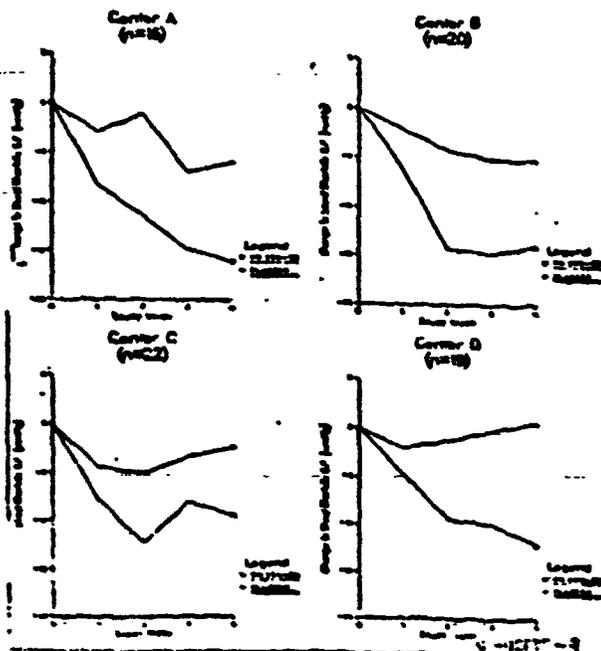
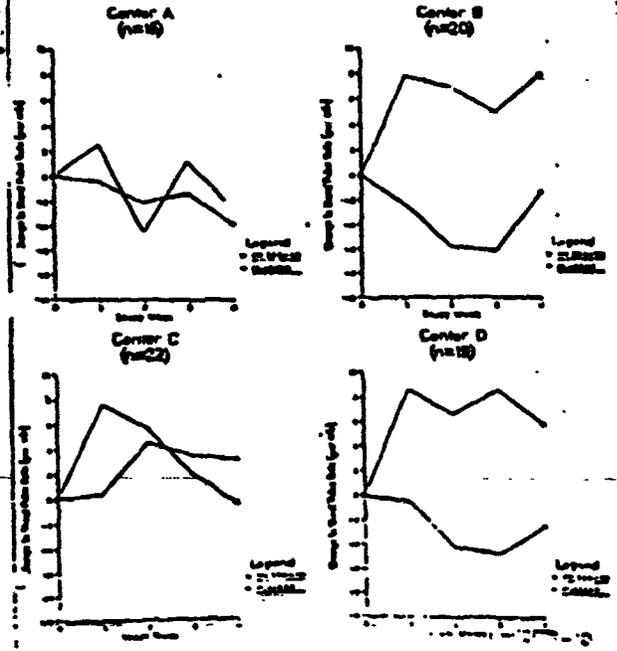
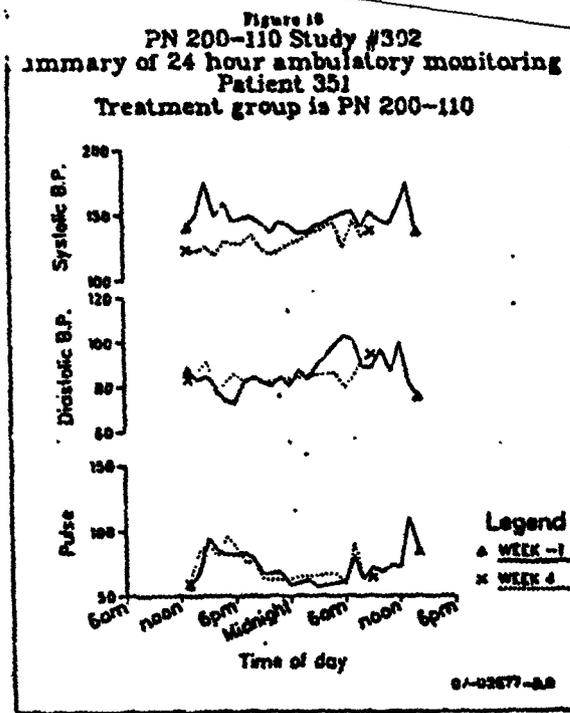
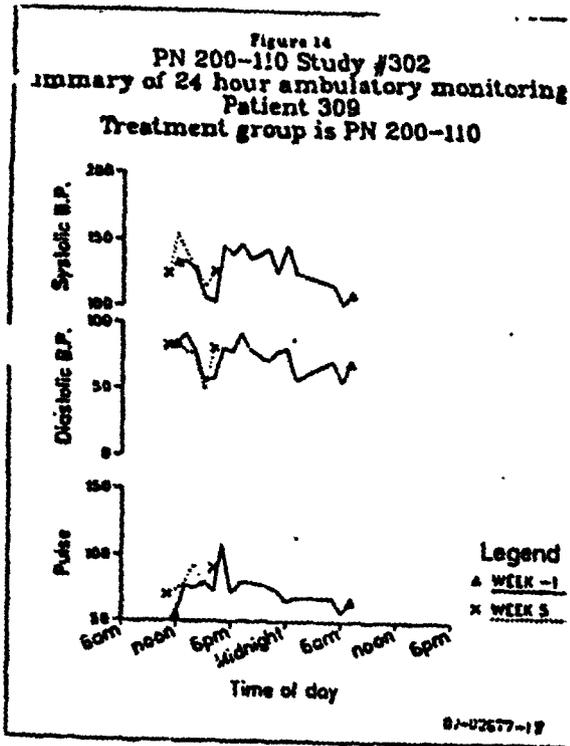


Figure 6  
PN 200-110 STUDY 2002  
Standing Pulse Rate  
Change from Baseline for All Valid Patients (n=97)



ESTABLISHED

Continuous blood pressure were made in a few patients and presented without comment.



Mean Change from Baseline - Supine  
Diastolic Blood Pressure+ (mm Hg)

Treatment Group	N	Week 1	N	Week 2
PN 200-110	45	-6.7***	43	-12.4***
Placebo	42	-6.4***	41	-3.9***

Treatment Group	N	Week 3	N	Week 4
PN 200-110	39	-13.6***	38	-13.7***
Placebo	40	-5.7***	39	-4.7***

All Patient Endpoint Analysis

Treatment Group	N	
PN 200-110	49	-13.0***
Placebo	49	-5.5***

Categorical Responses - Valid Patients - Week 4

Treatment Group	Total N	Number of Patients (%)			
		Category*			
		1	2	3	4
PN 200-110	38	25(66)	8(21)	1(3)	4(11)
Placebo	39	2(5)	8(21)	10(26)	19(49)

\*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.

5. **Safety:** The explanation for the 12 dropouts is given in the table. The statistically significant rise in pulse is of no clinical significance. Side effects such as headache, flushing, edema, due to vasodilation are of little consequence.

Reason	PN 200-110 Group		Placebo Group	
	Pat. #	No. of Pats. (% Total N=49)	Pat. #	No. of Pats. (% Total N=49)
Lost to follow-up	101 161	2 (4%)	312	1 (2%)
Reaction	110 160 411	3 (6%)	417	1 (2%)
Uncooperative/ Noncompliant	156	1 (2%)	257	1 (2%)
Ineffectiveness of Study Drug	360	1 (2%)	356	1 (2%)
Other (expired-MI)	308	1 (2%)	---	
Total		8/49 (16%)		4/49 (8%)

A total of 12 patients (12.2%) were discontinued following randomization into the double-blind study. Of these, 8 patients received PN 200-110 and 4 patients received placebo. Only 3 PN 200-110 treated patients were discontinued due to adverse reactions. One PN 200-110 treated patient (No. 308) died of myocardial infarction which was confirmed by autopsy report and considered by the investigator not to be drug related. Only one patient in each of the treatment groups was discontinued because of ineffectiveness.

The most frequent ADRs are headaches, edema, abdominal discomfort, and constipation. Side effects such as headache, flushing, edema, due to vasodilation are of little consequence. There was no evidence of hepatotoxicity. Symptoms were generally mild to moderate and tended to occur more frequently at higher doses.

Number of Patients Reporting at Least One  
Newly-Occurring Adverse Reaction

Week of Study	Treatment Group*			
	PN 200-110	(%)	Placebo	(%)
Week 1	8/49	(16)	9/49	(18)
Week 2	13/49	(27)	15/48	(31)
Week 3	13/42	(31)	11/45	(24)
Week 4	17/42	(40)	13/45	(29)
Weeks 1-4	25/49	(51)	24/49	(49)

A consistent increase in pulse is too small an effect to be of clinical significance in a healthy population of individuals with slightly increased blood pressure.

6. Conclusion: PN-200 is safely tolerated in doses of 5-20 mg/day and is more effective than placebo in reducing moderately elevated blood pressure.

Study #303

Multicenter evaluation of the drug PN-200 conducted by Walter Kirkendall Center at Houston, Texas, Hermes A. Contos, Center B, Richmond, VA, and Paul Samuels, Center C at Manhasset, N.Y.

1. Objective: Evaluation of the safety and efficacy of PN-200 in the treatment of hypertension compared to Hydrochlorothiazide.
2. Design: Double-blind randomized active drug controlled parallel group study.

3. Materials and Methods: Ninety-eight patients classified as mild or moderate hypertensives with a mean age of 54 were randomized after a 3 week placebo washout into a group receiving PN-200 and a group receiving HCTZ. Sixty four percent were male and approximately 50% in each group were black. Patients were distributed approximately equally over the 3 treatment centers. Beginning with 5 mg the dose of PN-200 was titrated to a maximum of 20 mg and the dose of HCTZ similarly adjusted from 25-100 mg per day depending on the blood pressure. Safety was monitored by physical examination and clinical laboratory tests as described elsewhere.

Forty-eight patients were randomized to the PN-200 group, 50 to the HCTZ group and given medications as shown in the dosage schedule.

## DOSAGE SCHEDULE

Treatment Group	Placebo Washout Weeks -3,-2,-1	Active Treatment*	
		Titration Period** Weeks 1, 2, 3, & 4	Plateau Period Weeks 5, 6, 7, 8, 9 & 10
PN 200-110 Group	One, Pcb* cap bid  Total Dose/Day	One, 5.0 mg PN 200-110 cap bid  10 mg	One or two 5.0 mg PN 200-110 cap(s) bid 10-20 mg
HCTZ** Group	One, Pcb* cap bid  Total Dose/Day	One, 25 mg HCTZ cap bid 50 mg	One or two 25 mg HCTZ cap(s) bid 50-100 mg

← Single Blind →

← Double-Blind →

\*Pcb = Placebo

\*\*HCTZ = Hydrochlorothiazide

\*Dose was administered a.c. before breakfast and supper.

\*\*The dose was increased by one capsule bid (i.e., 5 mg PN 200-110 bid or 25 mg HCTZ bid) if the average sitting diastolic blood pressure was >90 mm Hg at the Week 4 evaluation, or at end of weeks 2 or 3 if the average sitting diastolic blood pressure was >110 mm Hg or posed a hazardous state to the patient.

Dosages were titrated during the first 4 weeks and kept constant thereafter for the remaining 5 weeks. Seventy two percent of the patients remained on the lower dose of PN-200 and 68% of the patients on the HCTZ remained on the lower dose of that drug. The pooling of the data was considered justified despite an interaction as shown between the centers in changes from the baseline diastolic blood pressure. Evaluations of profile in response to medication and plasma Renin activity were carried out at Centers A and C and Center.

4. Results: Week by week comparisons of the two drugs is tabulated.

Mean Change from Baseline - (No. of Patients)  
Sitting Diastolic Blood Pressure (mm Hg)

Treatment Group	Week of Study			
	1	2	3	4
PN 200-110	-12.5*** (45)	-15.9*** (43)	-16.3*** (44)	-16.8*** (42)
HCTZ	-10.1*** (47)	-10.0*** (46)	-12.2*** (46)	-13.4*** (45)

Mean Change From Baseline  
Sitting Diastolic Blood Pressure (mm Hg)  
Plateau Period

Treatment Group	N	Average Over Weeks 5-10	N Endpoint
PN 200-110	36	-16.9***	
HCTZ	37	-13.8***	-2.9***

Both study drugs caused significant reductions in blood pressure during the plateau period with

The categorical responses show a slight superiority of PN 200 over HCTZ.

Treatment Group	Total N	Number of Patients (N) Category*			
		1	2	3	4
PN 200-110	36	26(72)	3(8)	5(14)	2(6)
HCTZ	37	17(46)	11(30)	7(19)	2(5)

The mean dose is given in the table.

MEAN DAILY DOSE (MG)  
VALID PATIENTS

WEEK	PN 200-110					HCTZ				
	N	Mean	S.D.	Min.	Max.	N	Mean	S.D.	Min.	Max.
Week 1	36	9.9*	0.49	8.37	12.10	37	47.90	3.10	42.00	50.33
Week 2	35*	9.75	1.17	5.00	11.03	37	40.53	4.00	26.00	47.00
Week 3	36	9.95	0.47	8.37	10.03	37	54.62	13.47	42.00	100.00
Week 4	36	9.00	0.99	7.70	12.37	37	33.43	10.01	20.00	100.00
Week 5	34	11.90	3.90	8.37	20.00	37	39.31	20.00	25.71	100.00
Week 6	36	11.45	4.02	7.00	20.71	37	61.00	19.37	42.00	100.00
Week 7	36	12.13	4.00	8.00	20.71	37	60.32	20.01	46.03	100.00
Week 8	35**	12.15	4.20	3.00†	20.00	37	60.59	21.61	35.71††	100.00
Week 9	36	12.30	4.30	3.00†	20.00	37	61.40	22.40	35.00††	100.00
	36	12.25	4.30	3.71†	21.25	37	59.03	21.32	35.00††	100.00
Weeks 9-10	36	12.05	3.90	8.00	20.11	37	60.13	19.91	41.10	100.00

\*Patient #232 missed the Week 2 visit.  
\*\*Patient #230 missed the Week 4 visit.

†The investigator reduced the dose regimen for Patient No. 129 to 1 capsule qd due to an adverse reaction (fatigue).  
††The investigator reduced the dose regimen for Patient No. 110 to 1 capsule qd due to an adverse reaction (nausea/vomiting).

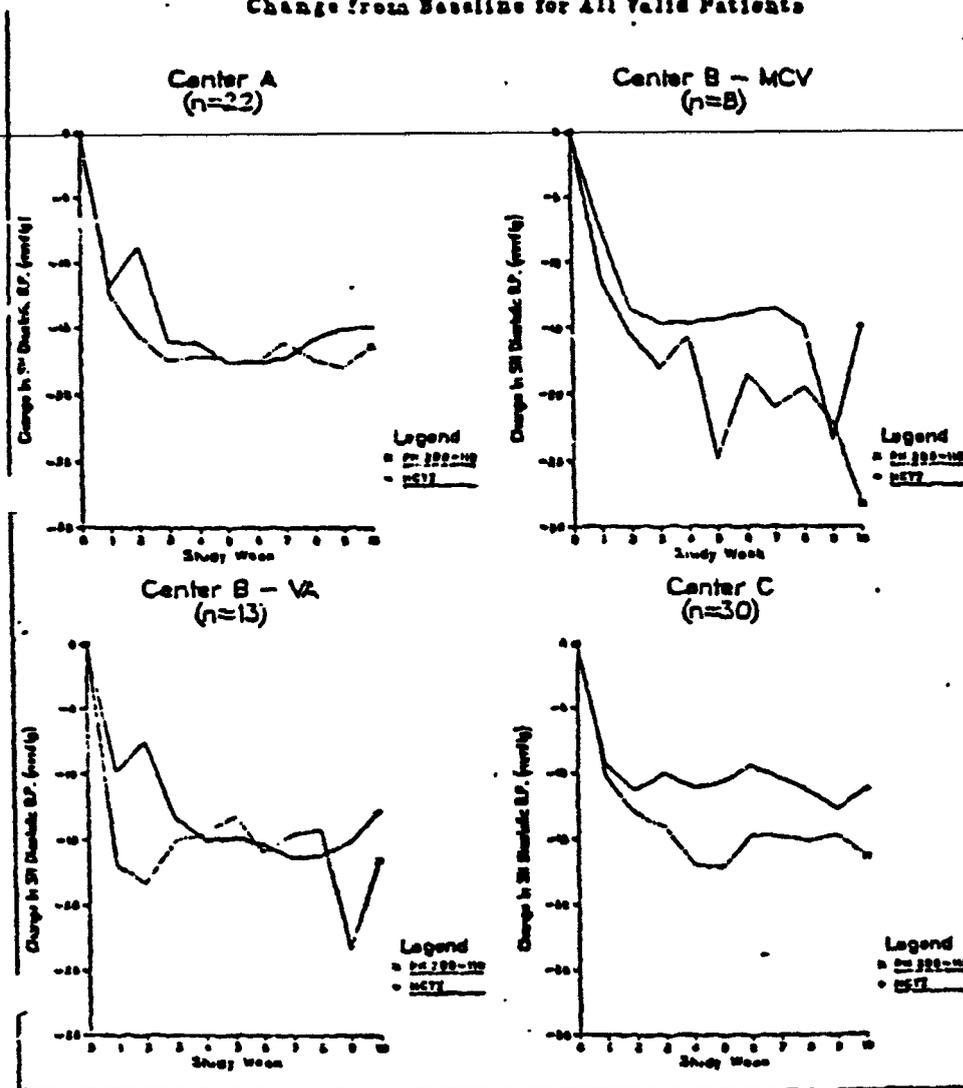
Summary of Dose Titration  
Valid Patients  
No. of Patients Titrated to High Dose

Titrated End of Study Week	PN 200-110 Group	HCTZ Group
2	0	4
3	0	1
4	9	4
6	1	0
7	0	1
8	0	2
Total	10/36 (28%)	12/37 (32%)

Ten (10) patients treated with PN 200-110 and 12 patients treated with HCTZ were titrated to the high dose during the study. Over 72% of the patients in the PN 200-110 treatment group and 68% of the patients in the HCTZ group were maintained at the low dose of the respective study drugs (i.e. 1 capsule bid) for the duration of the double-blind active treatment period. At the end of study Weeks 1, 5, and 9, no patient had the dose of study drug increased.

Response of diastolic B.P. to the two drugs is displayed graphically.

Figure 2  
PN 200-110 Study #303  
Sitting Diastolic BP  
Change from Baseline for All Valid Patients



The mean dose indicates the vast majority of the patients were controlled. All responded favorably to smaller doses. Only 10 patients receiving PN 200 required higher doses and 12 with HCTZ were titrated at a higher dose. Statistically significant change shown with both drugs is shown in the following tables and the time course of response is displayed in the curves showing change in the seated systolic and diastolic, seated and standing systolic and diastolic blood pressures.

5. Safety: There were 11 dropouts from the PN-200 treated group and 11 from the hydrochlorothiazide group. Most of the patients left the study for reasons unrelated to the medication. One patient receiving the PN 200 developed atrial fibrillation and another left because of palpitation. Alterations in blood chemistry were prominent in the HCTZ group and were related to the known effects of the medication. One patient developed abnormal creatinine and decrease in platelets which were thought to be related to HCTZ and resulted in discontinuation from the study. A single case of headache was considered unrelated to medication in the PN-200-200 group in a patient who had been non-compliant. Most of the symptoms were the same as those encountered in other studies and were not severe. There were no serious cardiovascular side effects other than those noted.

6. Conclusion: Both PN and HCTZ exerted a statistically significant effect on lowering blood pressure compared with baseline levels. There was a slight statistically greater effect exerted by PN-200 than by the diuretic in this study. Both drugs were safely tolerated and the dose response indicated the advisability of instituting treatment with small doses of PN 200.

#### Study #304

This multicenter study was conducted by Dr Karl Engleman (Center A) Philadelphia, PA; F. Gilbert McMann (Center B), New Orleans, LA; And Gerald R. Mitchell and Edward B Nelson (Center C, Houston, TX).

1. Objective: To measure the efficacy of PN 200 in mild essential hypertension compared to Propranolol.

2. Design: The study of 10 weeks duration was designed as a double blind propranolol controlled study.

3. Materials and Methods: Eighty-nine patients were randomized after 3 weeks washout. A total number of 89 entered the study, 46 to the PN-200 group, 43 to the propranolol group, 65% black, 50% white in both groups. The dosage schedules are as tabulated.

Inclusion and exclusion criteria were modified to exclude patients with bronchial asthma who were likely to be at undue risk from propranolol. Blood pressures were measured weekly and in 5 patients, at the end of the study, blood pressure was monitored for a 24 hour period. Safety was carefully monitored by the usual clinical and laboratory methods. Special test at Center B included echocardiograph and at Center C the ambulatory blood pressure was carried out over a 24 hour period.

NDA 19-546

DOSE SCHEDULE

Treatment Group	Placebo Run-in Weeks -3, -2, -1	Active Treatment*					Optional Tapering Off
		Titration Period			Plateau Period††		
		Weeks 1 & 2	Weeks 3 & 4	Weeks 5 & 6	Weeks 7 & 8	Weeks 9 & 10	
PA 200-110 Group	Tab. bid	2.5 mg PM 200-110 bid	2.5 mg or 5 mg PM 200-110 bid	2.5 mg, 5 mg or 7.5 mg PM 200-110 bid	2.5 mg, 5 mg 7.5 mg or 10 mg PM 200-110 bid	Taper off	
	Total Daily Dose	5 mg	5-10 mg	5-15 mg	5-20 mg		
Propranolol Group	Pcb bid	60 mg Ppnl <sup>†††</sup> bid	60 mg or 120 mg Ppnl bid	60 mg, 120 mg or 180 mg Ppnl bid	60 mg, 120 mg, 180 mg or 240 mg Ppnl bid	Taper off	
	Total Daily Dose	120 mg	120-240 mg	120-360 mg	120-480 mg		

← Single → ← Double-Blind →

\*Pcb = Placebo  
 †††Ppnl = Propranolol  
 †Dose of the study drugs was administered bid before breakfast and supper, and at least 30 minutes before the blood pressure was recorded.  
 ††The dose was increased by one capsule (2.5 mg PM 200-110 or 60 mg propranolol) bid at bi-weekly intervals if the sitting diastolic blood pressure was >90 mm Hg at the clinic evaluation. The dose may have been increased any time the average supine diastolic was >110 mm Hg.  
 †††Beginning with Week 7, the dose of the study drugs remained unchanged. However, the dose was reduced in a stepwise manner to a lower level in case of an adverse reaction. At no time was the prescribed dose of the study drug to be less than 2.5 mg PM 200-110 bid or 60 mg propranolol bid or to exceed 10 mg PM 200-110 bid or 240 mg propranolol bid.

Deviation from schedule is indicated by mean dose calculated in the usual manner.

AVERAGE DAILY DOSE (mg) BY STUDY WEEK FOR VALID PATIENTS

Treatment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
<b>PN 200-110</b>										
N	31	36+	37	37	37	37	36+	37	37	36+
Mean	4.9	4.9	8.3	8.8	10.3	10.7		11.8	11.8	11.8
S.D.	0.45	0.39	2.43	2.43	3.60	3.92	2	5.13	4.94	5.00
Min	3.2	3.0	4.3	4.6	4.3	4.7	4.6	4.3	4.7	5.0
Max	5.8	6.1	11.4	14.4	17.5	18.9	22.5	20.0	20.0	20.0
<b>Propranolol</b>										
N	31	31	31	31	31	31	31	31	31	31
Mean	118.5	121.9	195.2	197.4	255.2	271.0	332.0	328.3	337.7	329.5
S.D.	6.98	11.84	79.05	61.98	106.83	102.57	144.82	142.16	149.97	145.94
Min	102.9	110.0	100.0	102.9	105.0	102.9	111.4	111.4	111.4	97.5
Max	137.1	180.0	480.0	308.6	531.4	411.4	480.0	480.0	574.3	480.0

\*Patient No. 312 failed to return the medication bottles for Weeks 2, 7 and 10 so his average daily dose could not be determined for these time periods.

4. Results: There was a significant change in blood pressure from the first week in both groups, by the second week the PN was shown to exert a greater effect on lowering blood pressure and this difference was maintained throughout the study as shown in the truncated tables.

Mean Change from Baseline - Sitting Diastolic Blood Pressure† (mm Hg)

Treatment Group	N	Week 1	Week 2
PN 200-110	42	-8.8***	-8.9***
Propranolol	42	-6.7***	-7.8***

Treatment Group	N	Endpoint for Weeks 1-6
PN 200-110	42	-15.7***
Propranolol	42	-9.0***

Treatment Group	N	Average Over Weeks 7-10	N	Endpoint
PN 200-110	37	-15.4***	40	-16.1***
Propranolol	31	-10.0***	32	-10.2***

\*\*\*p < .001

By categorical analysis, in the PN-200 treated group, 80% showed at least 10 mm/hg fall in blood pressure in the sitting diastolic blood pressure. Forty one percent reached category 1. These figures are shown in the table below for the valid patients. No mention is made of stratification of patients to the various groups by severity of blood pressure at the outset of the study.

---

**Categorical Responses - Valid Patients - Week 10**

Treatment Group	Total N	Number of Patients (%)			
		1	2	3	4
PN 200-110	37	16(43)	13(35)	6(16)	2(5)
Propranolol	31	6(19)	6(19)	10(32)	9(29)

p=0.007

**Categorical Responses - Valid Patients -  
Plateau Period - (Week 7-10)**

Treatment Group	Total N	Number of Patients (%)			
		1	2	3	4
PN 200-110	37	15(41)	16(43)	3(8)	3(8)
Propranolol	31	6(19)		7(23)	10(32)

p=.067

Comparison of the effects of the two drugs on blood pressure over the course of the study shown in Figure 1 and the 24 hour monitoring is displayed in Figures 4-9 in 5 patients.

Figure 2

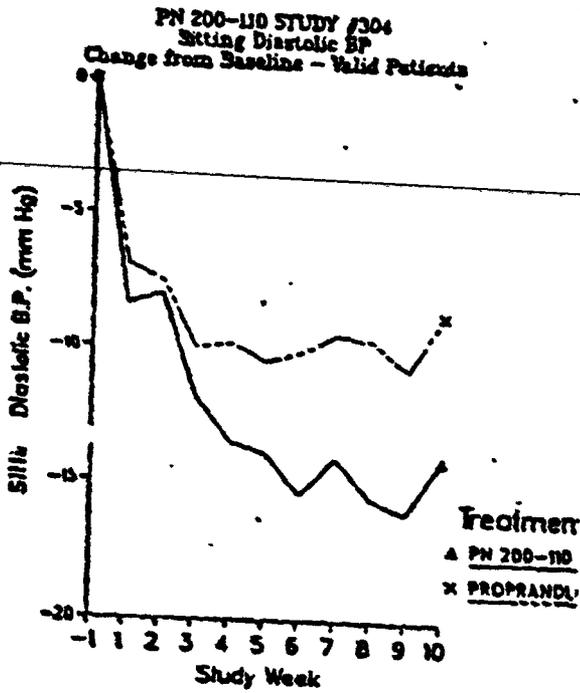


Figure 3

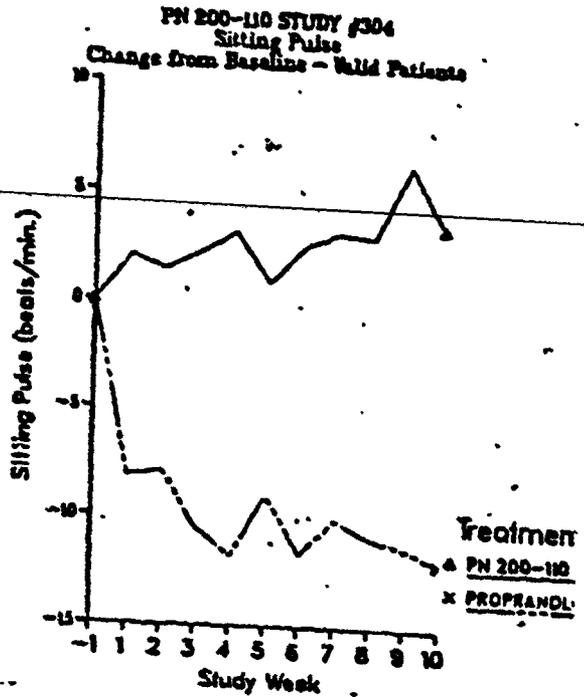


FIGURE 4  
PN 200-110 Study #304  
Summary of 24 Hour Ambulatory Monitoring  
Patient 305  
Treatment Group is PN 200-110

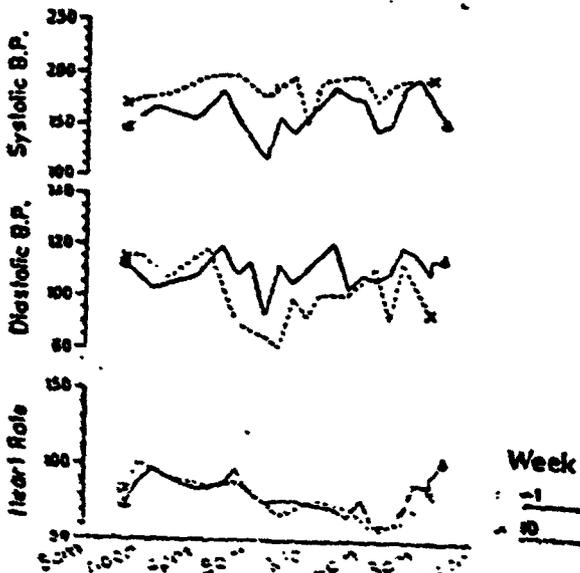
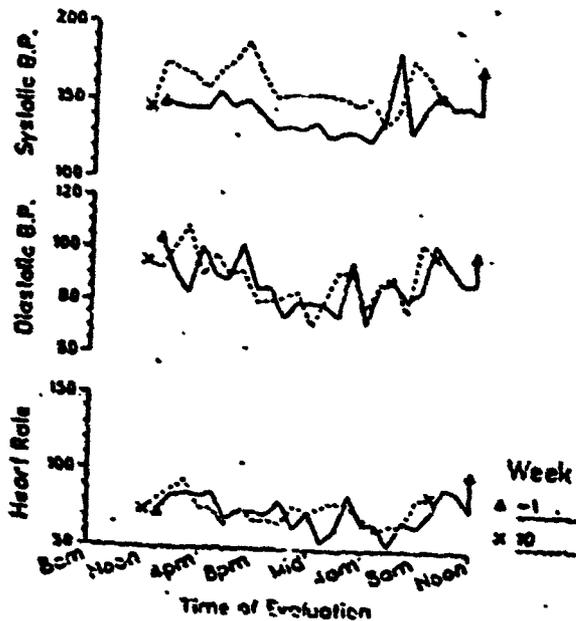
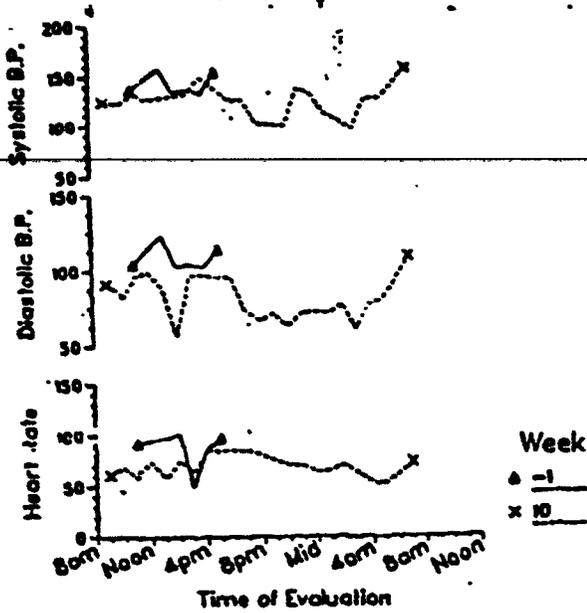


FIGURE 5  
PN 200-110 Study #304  
Summary of 24 Hour Ambulatory Monitoring  
Patient 308  
Treatment Group is PN 200-110

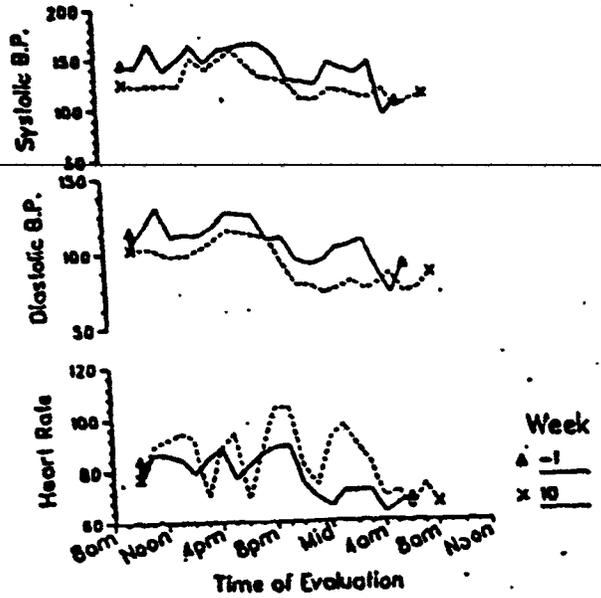


NDA 19-546

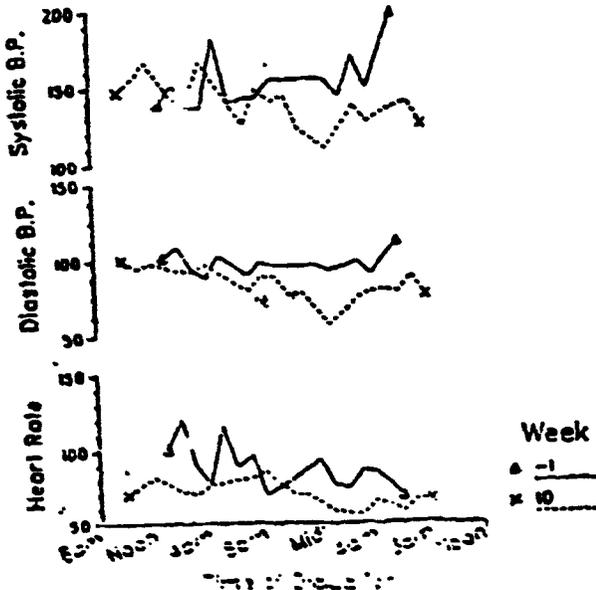
**FIGURE 6**  
 PN 200-110 Study #304  
 Summary of 24 Hour Ambulatory Monitoring  
 Patient 318  
 Treatment Group is PN 200-110



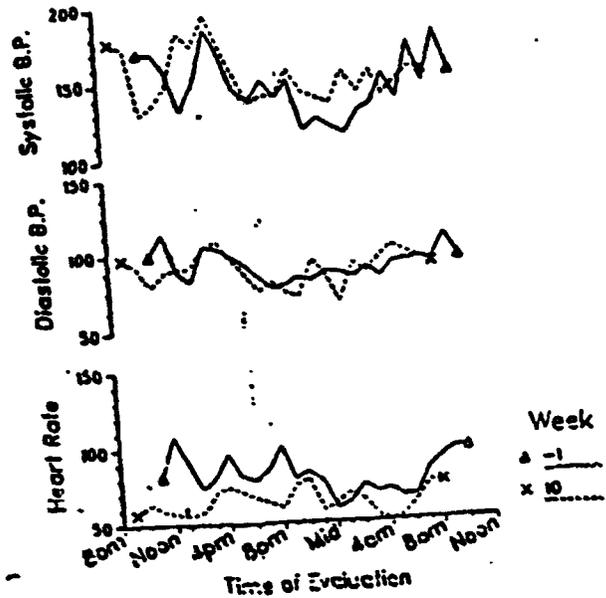
**FIGURE 7**  
 PN 200-110 Study #304  
 Summary of 24 Hour Ambulatory Monitoring  
 Patient 351  
 Treatment Group is PN 200-110



**FIGURE 8**  
 PN 200-110 Study #304  
 Summary of 24 Hour Ambulatory Monitoring  
 Patient 301  
 Treatment Group is Propranolol



**FIGURE 9**  
 PN 200-110 Study #304  
 Summary of 24 Hour Ambulatory Monitoring  
 Patient 306  
 Treatment Group is Propranolol



5. **Safety:** Five patients from the PN group and 12 from the propranolol group were eliminated. The adverse symptoms are compared in the table. Hyperglycemia was encountered in both groups. This has been found in several patients in the PN-200 study groups but has resulted in no serious difficulty. Most of the symptoms described have been mild well tolerated and have not resulted, as a rule, in elimination from the study.

**Most Frequently Reported Newly-Occurring Adverse Reactions**

Adverse Reaction	PN 200-110 Group (N=46) No. of Pts. (%)	Propranolol Group (N=43) No. of Pts. (%)
Edema	8 (17.4%)	3 (7.0%)
Palpitations	5 (10.9%)	0 (*)
Abdominal Discomfort	3 (6.5%)	6 (14%)
Diarrhea	4 (8.7%)	4 (9.3%)
Dizziness	4 (8.7%)	2 (4.7%)
Fatigue	2 (4.3%)	7 (16.3%) (*)
Headache	13 (28.3%)	6 (14%)
Flushing	5 (10.9%)	0 (*)
Visual Disturbance	0	3 (7%)

(\*)  $p < 0.10$  between-group differences

The vast majority of adverse reactions in the PN 200-110 treated group were considered by the investigator to be mild or moderate in severity, and were transient in nature. Severe headaches were reported on one occasion each for two patients (Nos. 103 and 355). One case of severe dizziness was noted for patient No. 151, and one case of severe toothache (Patient No. 154). These were the only instances that an adverse reaction was considered severe during the double-blind administration of PN 200-110.

6. Conclusion: Both drugs are shown to be effective in reduction of mild hypertension. The seeming superiority of PN over propranolol may be attributable in part to the relatively high proportion of blacks in whom propranolol is less effective in reducing hypertension than in white patients with a similar disorder. Both drugs are safety tolerated. The side effects due to PN-200 are in general mild. The aggravated hyperglycemia encountered from time to time is not fully explained by the known pharmacological effects of the drug. Other side effects are readily explained.

Study #305

This multicenter evaluation was conducted at Center A by Russell McCalaster, Lexington, Kentucky, Center B by Arthur Sasahara, West Roxbury, Massachusetts, and Center C by Udho Thadeni, Oklahoma City, Oklahoma.

1. Objective: Comparison of safety and efficacy of PN-200 to Prazosin in mild hypertension

2. Design: Double-blind prazosin controlled, randomized parallel group trial. The treatment plan is given in Table 1.

TABLE 1  
PN 200-110 STUDY NO. 305  
DOSAGE SCHEDULE

Treatment Group	Placebo Washout Weeks -3, -2, -1	Active Treatment*					
		Week 1	Week 2**	Titration Period Weeks 3 & 4**		Platform Period Weeks 5 & 6**	
PN 200-110 Group	One, Pch <sup>o</sup> cap bid	One, 2.5 mg PN 200-110 cap bid	One, 2.5 mg PN 200-110 cap bid	One or two, 2.5 mg PN 200-110 cap(s) bid	One, two or three 2.5 mg PN 200-110 cap(s) bid	One, two, three, or four 2.5 mg PN 200-110 cap(s) bid	One, two, three or four 2.5 mg PN 200-110 cap(s) bid
		Total Dose/Day	2.5 mg	2.5 mg	2.5-10 mg	2.5-15 mg	2.5-20 mg
Prazosin Group	One, Pch cap bid	One, 1 mg Pz <sup>o</sup> cap bid	One, 2 mg Pz cap bid	One or two, 2 mg Pz cap(s) bid	One, two or three 2 mg Pz cap(s) bid	One, two, three, or four 2 mg Pz cap(s) bid	One, two, three or four 2 mg Pz cap(s) bid
		Total Dose/Day	1 mg	2 mg	2-4 mg	2-12 mg	2-16 mg

← Single Blind →      ← Double-Blind →

<sup>o</sup>Pch = Placebo  
<sup>o</sup>Pz = Prazosin  
 \*Dose was administered a.c. before breakfast and supper. First doses of placebo and active drugs were taken at bedtime.  
 \*\*The dose was increased by one capsule bid if the sitting diastolic blood pressure was >90 mm Hg at bi-weekly intervals or was >110 mm Hg after one week of treatment at the lower dose, or in the opinion of the investigator posed a hazardous state to the patient.

3. Materials and Methods: Eighty-three(83) patients entering the study were randomized, 41 into PN 200 and 42 into the Prazosin group. Seventy-eight(78) percent of the patients were men. Patients were selected according to the established criteria for inclusion and exclusion. Center B contributed 52%, Center A 20%, and Center C 28%. Measurement of vasoactive hormones were conducted at Center B. Safety measures were subjected to the same observations as noted elsewhere. Sixty-three(63) patients were considered valid at the completion of the study. The two groups were similar with respect to the background characteristics examined. Cross centers for comparison of blood pressures was justified by the analysis of variance and covariance with repeated measurements of blood pressure response. Having considered the matter of interaction, the data were evaluated for efficacy by two means. First, the analysis of covariance was applied to the 2 groups for comparison at 5 time points: weeks 1,2 at the end of the titration period, week 6, at the end of 7 to 10 weeks for the valid patients, and for all patients at the end of 10 weeks. Results were also subjected to the categorical analysis as followed in the previous studies.

TABLE 7  
 PN 200-110 STUDY NO. 305  
 DESCRIPTIVE STATISTICS FOR MEAN DAILY DOSE (IN MG)  
 VALID PATIENTS

TREATMENT - PN 200-110 (N=30)										
	Week 1*	Week 2	Week 3	Week 4	Week 5	Week 6*	Week 7	Week 8	Week 9*	Week 10
Mean	4.92	4.95	7.33	7.49	8.34	8.28	9.18	9.34	9.38	9.46
S.D.	0.26	0.24	2.03	2.03	4.14	3.98	3.21	3.39	3.37	3.36
Min	4.29	4.29	4.02	4.44	4.29	4.38	4.29	4.44	4.64	4.38
Max	5.42	5.36	14.64	14.29	16.00	15.00	20.00	20.00	20.00	20.00

TREATMENT - PRAZOSIN (N=33)										
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
Mean	1.50	3.92	4.13	4.49	7.81	7.99	9.48	9.32	9.48	9.39
S.D.	0.10	0.16	2.01	2.04	3.29	3.46	4.39	4.68	4.38	4.43
Min	1.37	3.43	3.71	3.73	2.06	3.36	3.43	3.43	3.36	3.71
Max	2.29	4.00	8.00	8.67	12.00	12.00	17.14	16.00	16.00	16.00

\*Calculated on returned medication count and number of capsules consumed.

\*\*N=29; Patient No. 111 missing data for Weeks 1 and 4, Patient No. 110 missing data for Week 9.

4. Results: Both drugs showed a statistically significant effect on blood pressure at the end of week 1. At this time, in week 2, the two drugs were approximately equally effective. At the end of week 1 to 6 there was very little change. At the end of the study there was a distinct statistically significant superiority of PN 200 over Prazosin. The categorical analysis showed that 13 of the 43 patients of the PN group reached category 1 and only 1 in group 4, whereas 8 of the Prazosin group made category 1, 2 were in category 4. Summary of the categorical analysis is given in the table below. Comparison of PN and Prazosin over the course of the study is shown graphically.

**Categorical Analysis - Valid Patients**  
**Change From Baseline - Plateau Period (Weeks 7-10)**

Treatment Group	Total N	Number of Patients (#)			
		Category*			
		1	2	3	4
PN 200	30	13 (43)	12 (40)	4 (13)	1 (3)
Prazosin	33	8 (24)	15 (45)	8 (24)	2 (6)

\*Category 1: Sitting diastolic <85 mm Hg with at least a 10 mm Hg decrease; Category 2: >10 mm Hg decrease, but still >85 mm Hg; Category 3: >5-<10 mm Hg decrease; and Category 4: <5 mm Hg decrease or an increase.

PN 200 appears to be superior to Prazosin in monotherapy of hypertension.

5. Safety: There were 20 dropouts. Summary of classification to validity is found in Table 5.

TABLE 5  
 PN 200-110 STUDY NO. 305  
 NUMBER OF PATIENTS BY EFFICACY ANALYSIS CLASSIFICATION

Investigator	PN 200-110			Prazosin			Total			Total
	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	
A	6	2	0	6	2	1	12	4	1	17
B	16	4	1	19	3	0	32	7	1	43
C	0	0	0	0	2	1	14	6	1	23
	22	6	1	25	7	2	63	17	3	85

NDA 19-546

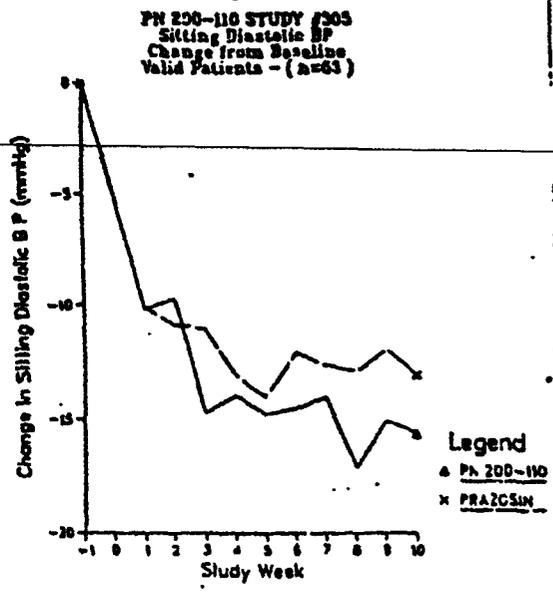
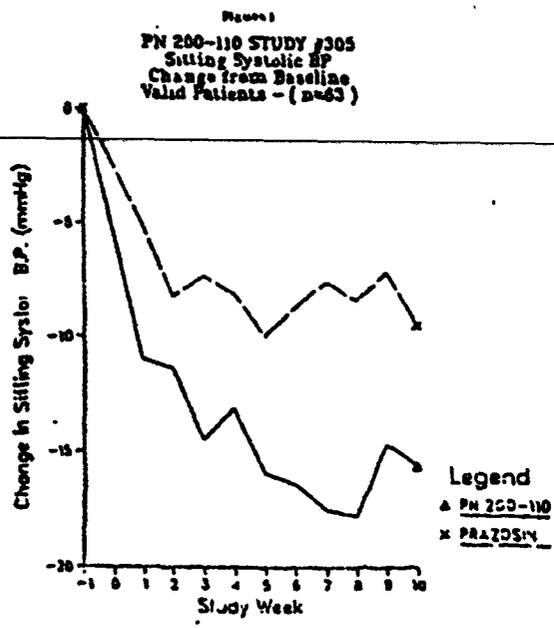


Figure 3  
 PN 200-110 STUDY #305  
 Sitting Pulse Rate  
 Change from Baseline  
 Valid Patients - (n=63)

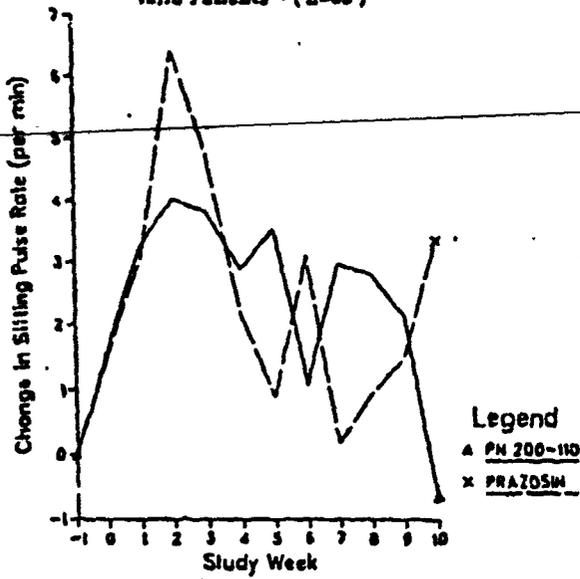


Figure 4  
 PN 200-110 STUDY #305  
 Standing Systolic B.P.  
 Change from Baseline  
 Valid Patients - (n=63)

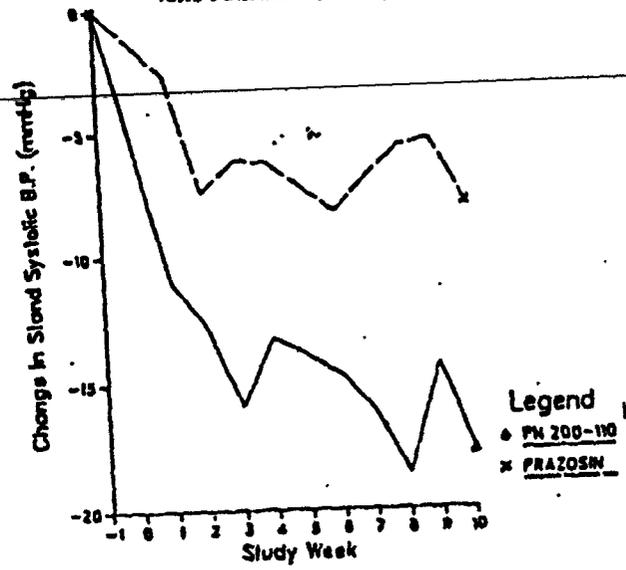


Figure 5  
 PN 200-110 STUDY #305  
 Standing Diastolic B.P.  
 Change from Baseline  
 Valid Patients - (n=63)

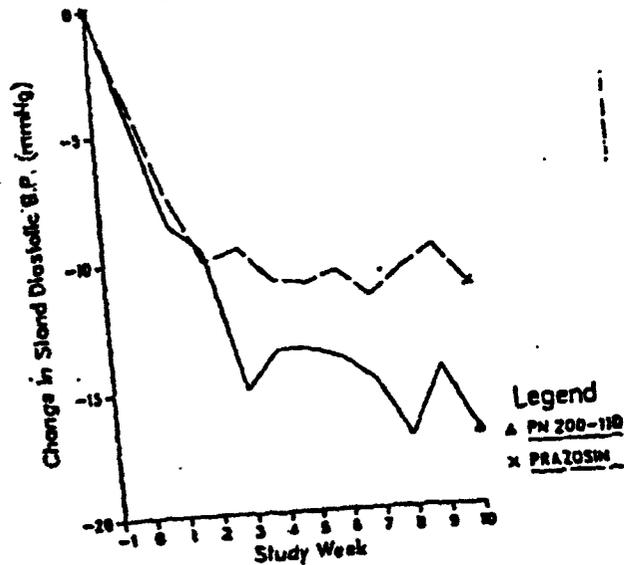
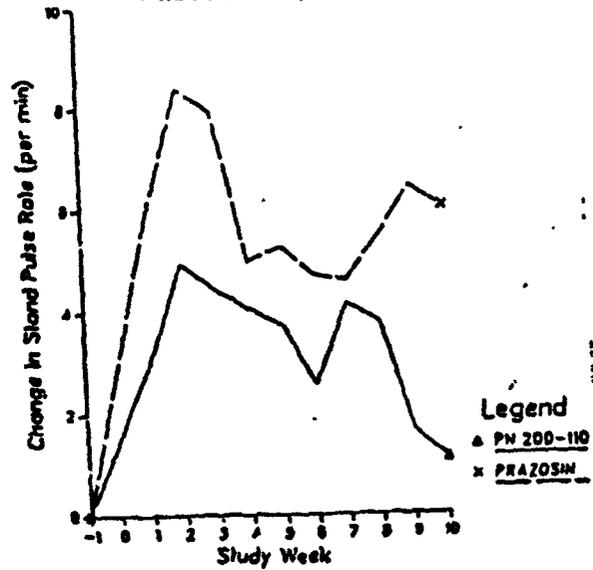


Figure 6  
 PN 200-110 STUDY #305  
 Standing Pulse Rate  
 Change from Baseline  
 Valid Patients - (n=63)



The invalid patients were those that for some reason did not enter the randomization after the washout. Those that were considered partially valid were those that left for some reason after beginning the active treatment. All patients invalid or partially valid were included in the analysis of safety. Six patients were discontinued from the PN group due to adverse reaction and 5 from the prazosin. Twenty percent of the patients receiving PN experienced headache and 16% of those receiving prazosin had headaches. Aside from those 11 leaving from both groups together all other side effects were considered mild or moderate. One patient in the PN group developed backache and impotence. Most frequently reported adverse reactions are shown below:

**REASONS FOR PARTIAL VALIDITY FOR EFFICACY ANALYSIS**

Treatment Group	Patient	Valid Thru Week	Reason Week Discontinued
PN 200-110	106	1	(Week 1) ADR - Headache, flushing, nausea/vomiting
	113	6	(Week 6) ADR - Edema
	202	9	(Week 10) ADR - Macula hemorrhage; eye
	205	8	(Week 8) ADR - Headache
	252	1	(Week 1) Unrelated illness - Chest pain
	258	2	(Week 2) Unrelated illness - Pulmonary edema
	316	3	(Week 3) Other - Lost to follow
	317	7	(Week 7) ADR/Study Drug Ineffective - Blurred vision, edema, fatigue, ear pressure
	352	6	(Week 6) Unrelated illness
	353	3	(Week 3) ADR - Headache
	Prazosin	109	1
115		4	(Week 5) Other - Lost to follow
207		8	(Week 8) Study Drug Ineffective
217		4	(Week 5) Unrelated illness - Headache
355		1	(Week 1) ADR - GI upset
307		3	(Week 3) ADR - Increased BP/pulse, aching legs, shortness of breath
316		3	(Week 3) ADR - Headache

In addition, three (3) patients were considered totally invalid for the efficacy analyses for the reasons described below:

Patient No. 112 - (Prazosin treatment group) Discontinued from the study at Week 2 (ADR - Tachycardia) but did not meet blood pressure entry criteria for advancement to the active treatment phase.

Patient No. 225 - (PN 200-110 treatment group) Completed the study but did not meet the blood pressure entry criteria for advancement to the active treatment phase.

Patient No. 306 - (Prazosin treatment group) Discontinued from study at Week 2 (ADR - Flushing, increased heart rate, throat tightness, and palpitations) and was still receiving drug during the active treatment period. At the Week 1 and Week 2 clinic visits, the last dose of prazosin was given. The patient did not return to the clinic.

Tiny dot hemorrhages occurred in one patient receiving PN 200. These vanished a month after discontinuing treatment. The conclusion that the finding was unrelated to the drug seems entirely reasonable. It is reported in none of the other studies. The lab studies gave special attention to liver function in light of the experience with liver dysfunction amongst volunteers in Study 310. Alkaline phosphatase along with bilirubin were evaluated weekly and two weeks after the study in patients who did not enter the long term open label study. A total of 9 patients treated with PN-200 exhibited elevated SGOT or SGPT during the study. Three exhibited elevation during the placebo washout period. Blood changes in liver function appeared transient and in only one was there an elevation in more than the 2 enzymes during the study. There was nothing to suggest that there was progressive change attributable to drug. ~~No detailed history of alcohol consumption is given.~~ Transient elevation and blood sugar were found as in other studies which presented no clinical problem. There was an increase in pulse rate which is statistically significant though too small to be of clinical importance.

Conclusion: PN 200 is shown by this study to be superior to Prazosin in treatment of benign essential hypertension. Both significantly decreased systolic and diastolic blood pressure from baseline reading. Standing blood pressure response was similar in the two groups. The study shows as do others that the effect on hypertension is not manifest until after a week's treatment.

The drug is safely tolerated in doses given. Safety evaluation indicates that the altered liver function experienced in earlier studies were not encountered.

#### Study #307

This multi-center study was carried out at 4 medical centers: Center A by Dr. Albert Carr of Augusta, Georgia; Center B by Jerry R. Mitchell of Houston, Texas; Center C by Nathaniel Winer of Kansas City, Missouri; Center D by Manual T. Velasquez of Milwaukee, Wisconsin.

1. Objective: To evaluate the safety and efficacy of PN 200 combined with hydrochlorothiazide compared to combination of hydrochlorothiazide and propranolol in the treatment of hypertension.
2. Design: Double blind randomized active drug controlled parallel group trial.
3. Materials and Methods: Seventy-eight patients entered the study which lasted 10 weeks following a 2-3 week placebo run in.

The following table lists all adverse reactions.

Treatment Group	Patient	Adverse Reaction	Date and Severity of		
			First Occurrence	Last Occurrence	Last Occurrence
PW 200-130	102	Headache Joint pain	2 - Mild 6 - Mild	10 - Mild	
	104	Edema Fractured clavicle	-1 - Mild 5 - Mild	10 - Mild 9 - Mild	
	106	Headache Vomiting Flushing	-1 - Mild 1 - Moderate 1 - Moderate	1 - Severe	
	108	Insomnia Menstruis Urinary infected	1 - Mild 2 - Mild 4 - Mild	3 - Mild 3 - Mild 5 - Mild	
	110	Cold symptoms	-1 - Mild	1 - Mild	
	111	Headache	7 - Severe		
	113	Headache	-3 - Moderate	-1 - Moderate	
	115	Edema Tachycardia	4 - Moderate 3 - Mild	6 - Severe 4 - Mild	
	202	Retina, hemorrhage (eyes)	10 - Mild		
	203	Coughing Nasal congestion Rhinitis Cramps, muscle Headache Chest pain	-3 - Mild -3 - Mild -1 - Moderate 3 - Moderate 6 - Mild 6 - Mild	-2 - Mild -2 - Mild 1 - Moderate 7 - Moderate 8 - Moderate	
	208	Joint pain	-1 - Severe	2 - Mild	
	213	Irritability Limb decrease/frigidity	2 - Mild 2 - Mild	3 - Mild 3 - Mild	
	216	Joint pain	7 - Moderate	10 - Mild	
	225	Abdominal discomfort	3 - Moderate	4 - Mild	
	228	Headache	-1 - Moderate		
	232	Chest pain	-1 - Moderate	1 - Moderate	
	234	Joint pain	4 - Severe	8 - Moderate	
	236	Stomach, swollen Dizziness	8 - Mild 9 - Mild		
	238	Headache	-3 - Moderate	1 - Mild	
	260	Headache	-3 - Mild	-1 - Mild	
	261	Headache	-1 - Moderate		
	302	Flu symptoms	-3 - Moderate		

The design is sketched in the diagram

PN 200 + HCTZ

N=40

N=78

2-3 wks Randomization

Propranolol + HCTZ

N=30

Pts entering washout had been treated for a least one week with HCTZ and experienced no fall in blood pressure. Sixty-two percent of the 78 patients were black and all over the age of 18. All of essential mild to moderate hypertension randomized after the run in period into 40 receiving PN 200 and 38 receiving propranolol both along with hydrochlorothiazide. The criteria for entrance into the study were as specified with modification at the 2-3 weeks run in was preceded by 2 weeks of treatment with hydrochlorothiazide demonstrating the failure of treatment with this medication. The dose ranged from 2.5 mg to 10 mg PN 200 b.i.d. and 60 mg to 120 mg propranolol b.i.d. The schedule is shown in detail in the table.

Treatment Group	Placebo Run-In Weeks -3, -2, -1*	Active Treatment*					Optional Tapering Off
		Titration Period			Plateau Period†		
		Weeks 1 & 2**	Weeks 3 & 4**	Weeks 5 & 6**	Weeks 7 & 8	Weeks 9 & 10	
PN 200-110 Group	Pcb* bid  Total Daily Dose	2.5 mg PN 200-110 bid  5 mg	2.5 mg or 5 mg PN 200-110 bid  5-10 mg	2.5 mg, 5 mg or 7.5 mg PN 200-110 bid  5-15 mg	2.5 mg, 5 mg 7.5 mg or 10 mg PN 200-110 bid  5-20 mg		Taper off
	MAINTAIN CONSTANT DOSE AND DOSAGE SCHEDULE FOR HYDROCHLOROTHIAZIDE (Esidrix®)						
Propranolol Group	Pcb bid  Total Daily Dose	60 mg Propranolol bid  120 mg	60 mg or 120 mg Propranolol bid  120-240 mg	60 mg, 120 mg or 180 mg Propranolol bid  120-360 mg	60 mg, 120 mg, 180 mg or 240 mg Propranolol bid  120-480 mg		Taper off
	MAINTAIN CONSTANT DOSE AND DOSAGE SCHEDULE FOR HYDROCHLOROTHIAZIDE (Esidrix®)						

(Single-blind) (Double-blind)

\*This period may have been shortened to two weeks if the patient's systolic blood pressure was >110 mm Hg on the first two visits.  
 \*\*Pcb = Placebo  
 \*\*\*Propranolol  
 †Dose of the study drugs was administered shortly after awakening in the morning and before the evening meal between 3:00-6:00 p.m.  
 ‡The dose was increased by one capsule (2.5 mg PN 200-110 or 60 mg propranolol) bid at bi-weekly intervals if the systolic blood pressure was >90 mm Hg at the clinic evaluation. The dose may have been increased any time the average systolic blood pressure was >110 mm Hg.  
 §Beginning with week 7, the dose of the study drugs remained unchanged. However, the dose was reduced in a stepwise manner to a level below the average systolic blood pressure at the end of the study drug less than 2.5 mg PN 200-110 or 60 mg propranolol bid.

4. Results: The comparison of the groups at weekly intervals was assayed by analysis of variance and co-variance. Also, the categorical analysis compared the degree of response of the two drugs. From the first week on, there was a statistically significant fall in blood pressure in both groups. This difference persisted throughout the study and there was a strikingly similar distribution of the categorical response between the two groups. As anticipated there was a marked difference in the pulse. The pulse was higher in the Isradapine group and at times significantly low in the propranolol group. Comparison of the two groups is displayed graphically in Figures 1-6.

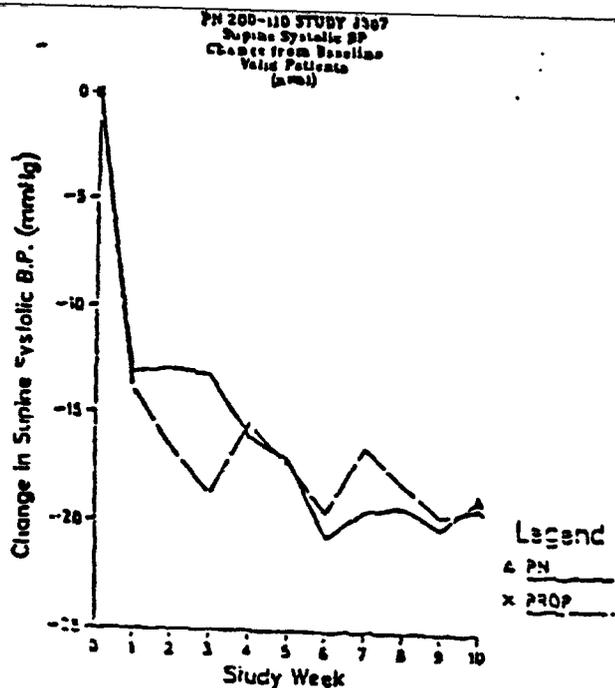


Fig. 1

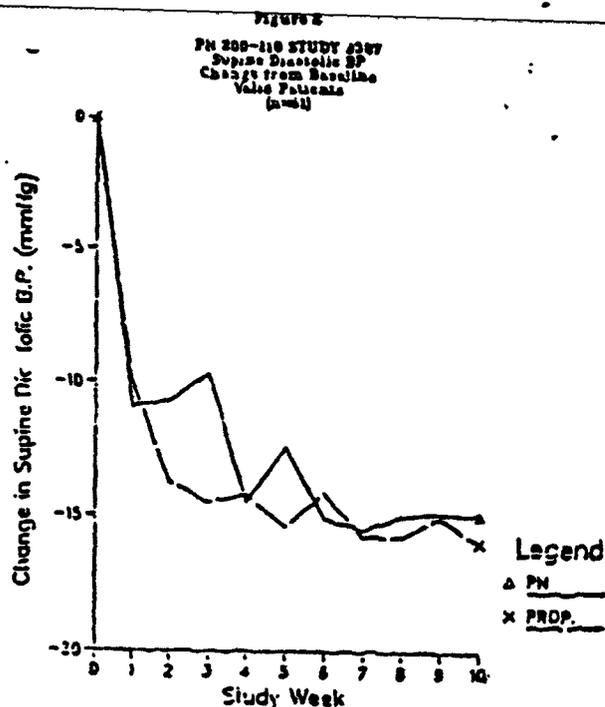


Fig. 2

Blood pressure response is nearly identical.

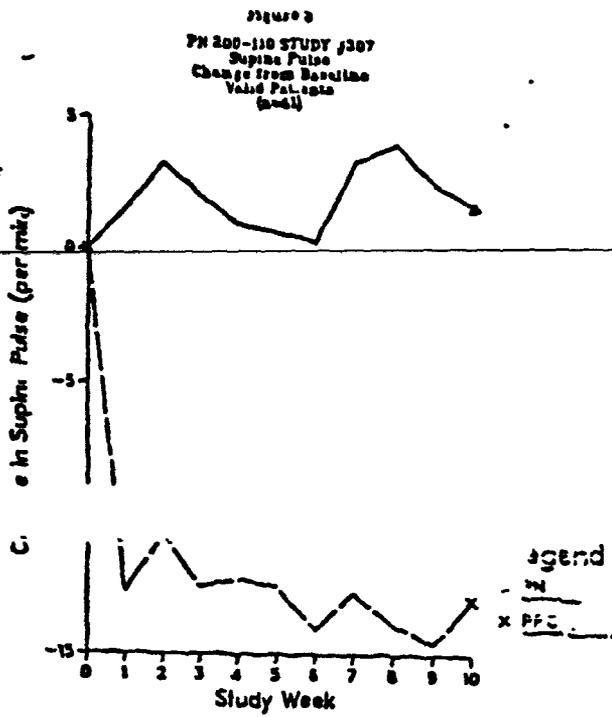


Fig. 3

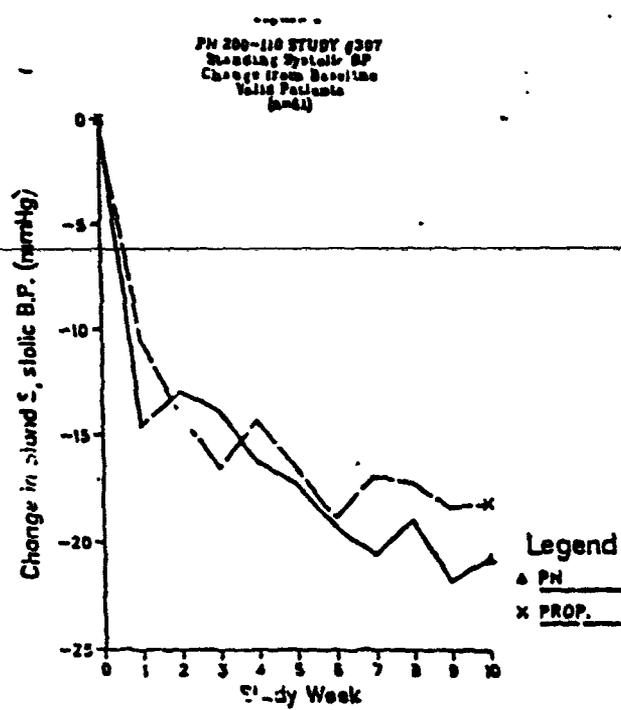


Fig. 4