

TABLE 8
PN 200-110 STUDY NO. 304
AVERAGE DAILY DOSE (mg) BY STUDY WEEK
VALID AND PARTIALLY VALID PATIENTS

Treatment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
PN 200-110										
N	42	41 [†]	42	40	40	40	39 [†]	40	37	36 [†]
Mean	4.9	4.9	8.1	8.8	10.2	10.5	11.9	11.7	11.8	11.8
S.D.	0.46	0.41	2.46	2.45	3.72	3.88	5.20	5.17	4.94	5.00
Min	3.2	3.8	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
Propranolol										
N	42	42	41	38	37	36	32	31	31	31
Mean	120.1	122.8	197.6	201.0	266.9	279.9	334.9	328.3	337.7	329.5
S.D.	9.63	21.64	76.97	60.28	105.53	99.59	142.96	142.16	149.97	145.94
Min	100.0	100.0	100.0	97.5	105.0	102.9	111.4	111.4	111.4	97.5
Max	160.0	240.0	480.0	308.6	531.4	420.0	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.

N. 11107C

0272

TABLE 8

TABLE 9
 FN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR TREATMENT X INVESTIGATOR,
 TREATMENT X TIME, AND TREATMENT X TIME X INVESTIGATOR
 INTERACTIONS FOR THE PLATEAU PERIOD - VALID PATIENTS

Variable	Investigator	Baseline Mean (Sample Size)		Mean Change From Baseline		Treatment X Investigator Interaction	Treatment X Time Interaction	Treatment X Time X Investigator Interaction
		FN 200-110	Propranolol	FN 200-110	Propranolol	p-value	p-value	p-value
Sitting Systolic B.P. (mm Hg)	A	140.2 (13)	142.0 (11)	-14.12	-13.34	0.065(*)	0.512	0.531
	B	161.2 (13)	163.6 (11)	-24.19	-7.57			
	C	141.3 (11)	145.1 (9)	-12.84	-13.00			
Sitting Diastolic B.P. (mm Hg)	A	104.5 (13)	102.9 (11)	-18.23	-10.16	0.212	0.817	0.316
	B	100.1 (13)	100.8 (11)	-14.44	-7.18			
	C	101.2 (11)	100.2 (9)	-13.33	-13.11			
Sitting Pulse (beats/min)	A	81.4 (13)	76.3 (11)	5.04	-10.65	0.904	0.254	0.504
	B	76.8 (13)	76.6 (11)	3.98	-11.77			
	C	77.4 (11)	72.3 (9)	3.25	-10.46			

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

0273

TABLE 9

TABLE 10
PN 200-110 STUDY NO. 304

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

Variable	Treatment Group	No. of Patients	Baseline		Week 1		Adjusted Mean Change ⁺	Treatment Period	
			Mean	S.D.	Mean Change	S.D.		Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	42	149.8	18.51	-9.3***	14.70		140.5	15.40
	Propranolol	42	153.7	19.25	-7.0**	13.25		146.8	19.49
Sitting Diastolic B.P. (mm Hg)	PN 200-110	42	101.9	5.09	-8.8***	7.96	-9.0	93.2	7.92
	Propranolol	42	102.7	5.86	-6.7***	9.12	-6.5	96.0	9.15
Sitting Pulse (per min.)	PN 200-110	42	77.5	11.52	3.5*	9.81	4.0		12.08
	Propranolol	42	74.7	8.09	-8.0***	8.89	-8.5		9.18

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

⁺Adjusted means presented only when the analysis of covariance assumptions were met.

TABLE 11
PN 200-110 STUDY NO. 304

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

Variable	Treatment Group	No. of Patients	Baseline		Week 2		Adjusted Mean Change [†]	Treatment period	
			Mean	S.D.	Mean Change	S.D.		Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	42	149.8	18.51	-10.5***	12.65	-11.2	139.4	14.81
	Propranolol	42	153.7	19.25	-7.9**	16.59	-7.1	145.9	19.91
Sitting Diastolic B.P. (mm Hg)	PN 200-110	42	101.9	5.09	-8.9***	7.81	-9.1	93.1	8.17
	Propranolol	42	102.7	5.86	-7.8***	10.97	-7.6	94.9	10.52
Sitting Pulse (per min.)	PN 200-110	42	77.5	11.52	2.7	10.68	3.3	80.2	11.32
	Propranolol	42	74.7	8.09	-8.0***	7.81	-8.5	66.7	9.26

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

[†]Adjusted means presented only when the analysis of covariance assumptions were met.

TABLE 12
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
WEEKS 1-6 - VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint (Weeks 1-6)		Adjusted Mean Change [†]	Treatment Period	
			Mean	S.D.	Mean Change	S.D.		Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	42	149.8	18.51	-18.9***	13.82		130.9	12.58
	Propranolol	42	153.7	19.25	-9.7***	16.15		144.0	25.75
Sitting Diastolic B.P. (mm Hg)	PN 200-110	42	101.9	5.09	-15.7***	9.10	-15.9	86.2	8.22
	Propranolol	42	102.7	5.86	-9.0***	11.21		-8.8	93.7
Sitting Pulse (per min.)	PN 200-110	42	77.5	11.52	3.4*	8.56	3.8	80.9	12.05
	Propranolol	42	74.7	8.09	-12.3***	6.71		-12.7	62.3

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

[†]Adjusted means presented only when the analysis of covariance assumptions were met.

01-114887

TABLE 13
 PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR VITAL SIGNS - OVER THE PLATEAU PERIOD (WEEKS 7-10) - VALID PATIENTS

Variable	Treatment Group	No. of Patients	Baseline		Mean Change At				Mean Over Weeks 7-10		Treatment Period	
			Mean	S.D.	Week 7	Week 8	Week 9	Week 10	Mean Change	S.D.	Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	37	147.9	17.17	-18.4***	-16.3***	-16.2***	-18.2***	-17.3***	15.25	134.1	9.74
	Propranolol	31	150.5	18.15	-9.8***	-10.6***	-11.4***	-12.9***	-11.2***	11.45	141.6	17.53
Sitting Diastolic B.P. (mm Hg)	PN 200 110	37	101.9	5.35	-14.1***	-15.6***	-16.1***	-16.1***	-15.4***	7.42	89.6	5.04
	Propranolol	31	101.4	5.43	-9.5***	-9.7***	-10.8***	-9.8***	-10.0***	8.51	93.4	6.08
Sitting Pulse (per min.)	PN 200-110	37	78.6	10.79	3.2(*)	3.0(*)	6.4**	3.9(*)	4.1**	8.92	81.9	9.55
	Propranolol	31	75.2	8.77	-10.0***	-10.8***	-11.3***	-11.8***	-11.0***	7.10	66.4	6.37

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

TABLE 14
PN 200-110 STUDY NO. 30A

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
ENDPOINT OVER PLATEAU PERIOD (WEEKS 7-10)

VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint		Adjusted Mean Change*	Treatment Period	
			Mean	S.D.	Mean Change	S.D.		Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	40	150.0	18.85	-18.5***	16.77		131.5	14.77
	Propranolol	32	151.0	18.06	-13.3***	13.60		137.8	18.91
Sitting Diastolic B.P. (mm Hg)	PN 200-110	40	101.9	5.20	-16.1***	8.18	-16.1	85.8	7.29
	Propranolol	32	101.7	5.67	-10.2***	8.57	-10.2	91.6	7.87
Sitting Pulse (per min.)	PN 200-110	40	77.7	11.42	5.2*	12.41	5.8	83.0	12.87
	Propranolol	32	74.9	8.78	-11.8***	6.71	-12.5	63.1	8.15

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

Adjusted means presented only when the analysis of covariance assumptions were met.

TABLE 15
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
ALL PATIENTS - ALL WEEKS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint		Adjusted Mean Change [†]	Treatment Period	
			Mean	S.D.	Mean Change	S.D.		Mean	S.D.
Sitting Systolic B.P. (mm Hg)	PN 200-110	46	149.7	17.71	-18.6***	15.96		131.2	13.49
	Propranolol	43	153.7	19.02	-11.7***			15.09	142.1
Sitting Diastolic B.P. (mm Hg)	PN 200-110	46	101.6	5.10	-15.6***	8.16	-15.8	86.0	7.08
	Propranolol	43	102.6	5.82	-9.2***			9.53	93.3
Sitting Pulse (per min.)	PN 200-110	46	76.6	11.47	5.3**	12.15	5.7	81.9	12.90
	Propranolol	43	74.7	8.00	-11.6***			7.71	63.1

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

[†]Adjusted means presented only when the analysis of covariance assumptions are met.

TABLE 16

PN 200-110 STUDY NO. 304

NEWLY-OCCURRING PHYSICAL EXAM ABNORMALITIES

Treatment Group	Patient No.	Variable	Abnormality
PN 200-110	101	Eyes	Tiny bubbles on anterior lens
	103	Heart	Pounding sound: - Grade II systolic murmur, left sternal border
		Abdomen	Bruit over aorta
	108	Heart	Grade II soft systolic murmur, left sternal border (not noted on initial physical exam)*
		Extremities	2 ⁺ edema both legs
	109	Extremities	Trace to 1 ⁺ edema
	112	Eyes	Grade II A/V = 1/2, increased light reflex (not noted on initial physical exam)*
	155	Skin	Seborrhea around nose and ear (not noted on initial physical exam)*
		Rectal	Prostrate enlarged 3X (Week -4 exam not done)
		Extremities	3 ⁺ edema on ankles
	157	Heart	Loud Grade II-III blowing systolic murmur at apex
	213	Heart	Tachycardia possibly drug related
	253	Extremities	Trace pedal edema - bilaterally
	302	Eyes	O.U. arcus senilis (not noted on initial physical exam)*
		Lungs	Increased A.P. chest diameter (not noted on initial physical exam)*
		Back	Kyphosis (not noted on initial physical exam)*

*Coded as a pre-existing abnormality.

0280

0;-01884

TABLE 16 (Continued)

PN 200-110 STUDY NO. 304

NEWLY-OCCURRING PHYSICAL EXAM ABNORMALITIES

Treatment Group	Patient No.	Variable	Abnormality
PN 200-110 (Continued)	304	Extremities	1+ edema both lower extremities
	305	Ears, Nose, Throat	Chronic otitis - perforation (not noted on initial physical exam)*
	319	Abdomen	Old right lower quadrant surgical scar (not noted on initial physical exam)*
	354	Ears, Nose, Throat	White papillary excrescence in left canal obscuring TM
	357	Extremities	Trace pedal edema
	201	Heart	SEM 2/6 along left sternal border (not noted on initial physical exam but was recorded pre-study)*
Propranolol	254	Lymph Nodes	Submandibular lymph nodes palpable, non-tender**
		Extremities	Swelling, tenderness around knees, ankles, wrists, both elbow joints - limitation of movement on both shoulders**
	311	Eyes	Old TM scars (not noted on initial physical exam)*
	315	Extremities	Knee surgery scar (not noted on initial physical exam)*

*Coded as a pre-existing abnormality.

**Coded as new non-drug related abnormality at Week 4 and Week 10.

07-01885

TABLE 17
PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CARDIOVASCULAR ABNORMALITIES

Treatment Group	Patient No.	Variable	Week(s) of Occurrence	Abnormality
PN 200-110	101	Other	10	Ophthalmologic - "Tiny bubbles" on anterior lens OD - normal variation
	103	Heart	10	Murmur
		Abdomen	10	Abdominal bruit
	106	Abdomen	4	Tenderness to palpation
		Other	4	Vaginal discharge/abdominal cramping
	108	Cough	4	Cough productive of clear sputum
		Palpitations	4	Jittery - 1 1/2 hour palpitations
		Heart	6, 8, 10	Grade III/VI systolic murmur - left sternal border to apex
		Abdomen	6, 8, 10	Abdominal bruit
		Extremities	1, 2, 4, 6, 8, 10	Non-pitting ankle/leg edema
	109	Palpitations	1	5 minutes of palpitations
	112	Heart	1, 2	Grade II/VI systolic murmur, lower left sternal border to apex
		Pulmonary Findings	1	Fine rales - left lung base
	113	Extremities	1, 2, 4, 6, 8, 10	Pitting bipedal edema to lower 1/3 tibia
	115	Palpitations	1	Had palpitation after first dose of study drug - resolved spontaneously
	118	Heart	1, 2, 4, 6, 8	Atrial gallop-lower left sternal border Grade II/VI systolic murmur, lower left sternal border
	155	Extremities	1, 2, 4, 6, 8, 10	Bipedal pitting edema to knees - increased from 1+ on Week 1 to 4+ on Week

07-01887

TABLE 17 (Continued)
 PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CARDIOVASCULAR ABNORMALITIES

Treatment Group	Patient No.	Variable	Week(s) of Occurrence	Abnormality
PN 200-110 (Continued)	157	Pulmonary Findings	8	Bibasilar end, expiratory wheeze
	160	Heart	6	Grade II/VI systolic murmur, lower left sternal border
		Extremities	2, 4	Trace non-pitting bipedal edema
	202	Extremities	4	Slight increase in pre-existing edema
	205	Other	1, 2, 4	Symptoms of URI-improving at Week 4
	207	Extremities	10	2 mm pitting edema; noted pre-study and on initial physical exam. Not noted at Week 4 and subsequent CV evaluations. However, was noted on final physical exam.
	210	Chest Pain Exertional	2	One angina episode in last week
		Orthopnea	1	Pillow orthopnea
	212	Cough	2	Cough secondary to URI
	213	Heart Exam	10	Tachycardia (Heart Rate = 120)
	216	Chest Pain Exertional	8	Deterioration of angina
		Dyspnea Exertion	8	Deteriorating dyspnea on exertion
	217	Other	8	Rattling in throat - 1 Week
	224	Other	2	Dizziness lasting 30 minutes resolves spontaneously on sitting
	253	Other	2, 4	Mild headaches

07-01888
 0283

TABLE 17 (Continued)
 PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CARDIOVASCULAR ABNORMALITIES

Treatment Group	Patient No.	Variable	Week(s) of Occurrence	Abnormality
PN 200-110 (Continued)	255	Extremities	1, 2, 4, 6, 8, 10	Pedal edema
	302	Heart Exam	1	Irregular beats - left axis deviation - non-diagnostic ST T-wave changes, occasional premature nodal beats
	304	Abdomen	10	Trace 1° edema with vasodilated skin
	305	Extremities	1, 2, 4	Slight non-pitting ankle edema
		Other	10	Earache
		Other	10	Perforation right tympanic membrane
	309	Cough	2	Mild cough-secondary to sinus drainage
	316	Palpitations	1, 2, 4, 5, 8, 10	Mild palpitations
	319	Palpitations	4, 6	Palpitation 30 minutes after taking medication - lasts about 90 minutes
	355	Palpitations	1, 2	Palpitations start one hour post-dose - lasts several hours
Other		1, 2	Appears flushed from neck up	
Propranolol	104	Extremities	1	Slight pedal edema
		Other	1	Clouded sensorium - 5 days
	107	Extremities	8	Trace pedal edema bilaterally
	116	Extremities	4, 6	Trace pitting bilateral edema to lower 1/3 tibia
117	Abdomen	6	Abdominal bruit	

TABLE 17 (Continued)
 PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CARDIOVASCULAR ABNORMALITIES

Treatment Group	Patient No.	Variable	Week(s) of Occurrence	Abnormality
Propranolol (Continued)	152	Palpitations	8	3 minutes of palpitations while sitting
		Extremities	6	Trace bilateral edema - foot/leg
	153	Extremities	1, 2, 4	Trace pitting edema bilaterally over tibia
		Other	4	Gout attack - previous history of gout
	158	Pulmonary Findings	4, 6	Rales in lungs - left and right base and upper lobes
	159	Extremities	4	Trace pitting edema to mid tibia
	209	Dyspnea Exertion	2	Mild shortness of breath (5-7 minutes) resolves spontaneously
		Dyspnea Sitting	1, 2	Mild shortness of breath lasting 5 minutes each (multiple episodes)
		Dyspnea Supine	1, 2	Mild shortness of breath lasting 5 minutes each (multiple episodes)
		Other	2	Chest Pain - tightness of chest; mainly subcostal region
	211	Dyspnea Exertion	4	2 blocks for past week - possibly due to uncontrolled blood pressure
	214	Dyspnea Exertion	2, 4, 6, 7	3 blocks - improving
		Extremities	2	Trace edema
		Other	4, 6	URI - Ringing in ears (possibly due to Tylenol) - resolved
215	Other	1	Mild lower back spasm	
301	Palpitations	4	2-3x/week - after eating - less than 1 minute	
	Other	1, 2	Mild chest discomfort after eating	

0285

07-01690

TABLE 17 (Continued)
 PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CARDIOVASCULAR ABNORMALITIES

Treatment Group	Patient No.	Variable	Week(s) of Occurrence	Abnormality
Propranolol (Continued)	306	Cough	1	Dry cough related to resolving URI
	311	Dyspnea Exertion	1	Shortness of breath - wheezing
		Dyspnea Sitting	1	Shortness of breath - wheezing
		Dyspnea Supine	1	Shortness of breath - wheezing
	352	Dyspnea Paroxysmal	1	Shortness of breath - wheezing
		Pulmonary Findings	1	Non-cardiac bronchospasm
		Other	8	Diarrhea
	356	Cough	1, 2	Bronchitis past week - lung field clear
		Dyspnea Exertion	2	

0286
 0:-01891

TABLE 18
 PN 200-110 STUDY NO. 304
 CARDIOVASCULAR EXAMINATION
 NEWLY-OCCURRING ABNORMALITIES*

Abnormality	Patient Number (Weeks of Occurrence)		No. of Patients With Newly-Occurring Abnormality/No. of Patients Normal at Initial Visit	
	PN 200-110	Propranolol	PN 200-110	Propranolol
Chest Pain Exertion	210 (2) 216 (8)		2/43	0/40
Dyspnea Exertion	216 (8)	209 (2) 211 (4) 214 (2,4,6,7) 311 (1) 356 (2)	1/38	5/40
Orthopnea	210 (1)		1/44	0/43
Dyspnea Sitting		209 (1,2) 311 (1)	0/46	2/43
Dyspnea Supine		209 (1,2) 311 (1)	0/45	2/43
Dyspnea Paroxysmal		311 (1)	0/45	1/42
Cough	108 (4) 212 (2) 309 (2)	306 (1) 356 (1,2)	3/43	2/41
Palpitations	108 (4) 109 (1) 115 (1) 316 (1,2,4,6,8,10) 319 (4,6) 355 (1,2)	152 (8) 301 (4)	6/45	2/43
Pulmonary Findings	112 (1) 157 (8)	158 (4,6) 311 (1)	2/44	2/41

*Defined as an abnormality reported during the double-blind phase that was not present during the placebo washout or an abnormality (reported during the placebo phase) that worsened during the double-blind phase of the trial.

TABLE 18 (Continued)
 PN 200-110 STUDY NO. 304

CARDIOVASCULAR EXAMINATION
 NEWLY-OCCURRING ABNORMALITIES*

Abnormality	Patient Number (Weeks of Occurrence)		No. of Patients With Newly-Occurring Abnormality/No. of Patients Normal at Initial Visit	
	PN 200-110	Propranolol	PN 200-110	Propranolol
Heart Examination*	103 (10) 108 (6,8,10) 112 (1,2) 118 (1,2,4,6,8) 160 (6)		7/36	0/35
Abdomen	213 (10) 302 (1) 103 (10) 106 (4) 108 (6,8,10) 304 (10)	117 (6)	4/42	1/39
Extremities	108 (1,2,4,6,8,10) 113 (1,2,4,6,8,10) 155 (1,2,4,6,8,10) 160 (2,4) 202 (4) 207 (10) 255 (1,2,4,6,8,10) 305 (1,2,4)	104 (1) 107 (8) 116 (4,6) 152 (6) 153 (1,2,4) 159 (4) 214 (2)	8/28	7/38
Other	101 (10) 106 (4) 205 (1,2,4) 217 (8) 224 (2) 253 (2,4) 305 (10) 355 (1,2)	104 (1) 153 (4) 209 (2) 214 (4,6) 215 (4) 301 (1,2) 352 (8)	8/43	7/42
Total Number of Patients With at Least One Newly- Occurring Abnormality/ No. of Patients**	30/46	17/43		

*Defined as an abnormality reported during the double-blind phase that was not present during the placebo washout or an abnormality (reported during the placebo phase) that worsened during the double-blind phase of the trial.

**Fisher's = .0113

**Chi-square = .0153

07-01893

0288

BEST POSSIBLE COPY

Protocol 305

Title

The Multicenter Evaluation of the Safety and Efficacy of PN 200-110 in the Treatment of Hypertension Compared to Prazosin

Investigators

Russel Greenway McAllister, Jr, M.D.
Veterans Admin Medical Center
Lexington, Kentucky

Arthur A. Sasahara, M.D.
Veterans Admin Medical Center
Brockton, West Roxbury, MA

Udho Thadani, M.D.
Oklahoma University Health
Sciences Center
Oklahoma City, Oklahoma

Dates of Study: September 10, 1984, to June 13, 1986.

Objective

To determine the blood pressure lowering effect on PN 200-110 (PN), 2.5 - 10.0 mg bid, compared to prazosin 2 - 8 mg bid in patients with mild or moderate essential hypertension during a ten week period

Design

This was a multicenter, randomized, double blind, prazosin controlled, parallel group study.

Population

Outpatients, 18 years and older, with a diagnosis of benign essential hypertension were selected for the study. For entry into the double blind phase, a sitting diastolic blood pressure (SDBP) of > 95 mm Hg at two consecutive visits was required.

Exclusion criteria included placebo responders (continuous reduction in SDBP at each visit during a placebo without period) and a > 10 mm Hg decrease in SDBP within 2 weeks of entry into the study.

Study Methods

Study Plan

There was a preliminary 3 to 5 week placebo washout period during which time all previous antihypertensives were withdrawn. Sitting blood pressure was evaluated weekly and patients with a SDBP > 95 mm Hg at two consecutive visits were enrolled in the double blind phase of the study. Patients were randomized to one of the two test drugs and stratified as for previous studies, i.e. SDBP > 95 but < 105 mm Hg and SDBP > 105 mm Hg. Medications were administered twice daily for 10 weeks as per Table 1. Initial doses were 2.5 mg bid PN for 2 weeks or prazosin 1 mg bid for 1 week and 2 mg bid for week 2. If patients could not tolerate dosage at week 2, they were withdrawn from the trial.

If the average SDBP > 90 mm Hg at end of week 2, dose was increased to 5 mg bid PN or 4 mg prazosin bid for weeks 3 and 4. Similarly, dose was increased for weeks 5 and 6 to 7.5 mg PN or 6 mg prazosin bid and weeks 7 and 8 to 10 mg PN or 8 mg prazosin bid. If the SDBP was < 90 mm Hg at end of any two week period, dose was kept at previous level and not increased. If at any time SDBP was > 110 mm Hg, dose could be increased earlier than the two week interval. From week 7, dose was not to be changed, except to decrease for ADRs, if necessary. At end of 10 weeks, patient either entered open label long term study or was given appropriate medication.

Evaluations

Table 2 presents evaluation schedule. Special tests were performed for investigators' interests. Center B evaluated effects of study drugs on plasma level of several vasoactive hormones. Center C performed echocardiography and exercise tolerance testing (ETT). The latter was performed as a symptom limited test of angina. However, it should be noted that angina, except infrequent angina, was not a selection criteria for entry.

Results

A total of 83 patients entered double blind phase; center A contributed 20%, B 52% and C 28% of total. There were 41 randomized to PN and 42 to prazosin. A total of 10 patients were partially withdrawn from the study.

PN
PZA

The mean age was 54.9 years (25 - 75); 87% were white, 12% black and 1% other; 94% were males. There were no statistically significant differences between groups for any demographic characteristic. The mean dose for valid patients is shown in Table 7. Over 75% of valid patients were maintained at 2.5 - 5.0 mg bid PN and 50% prazosin at 12 - 16 mg daily.

Interactions

Table 8 summarizes results for valid patients from analysis of interactions as well as efficacy results on investigator x treatment basis for each variable for weeks 7 - 10. There was a significant treatment x investigator interaction for sitting systolic blood pressure. In center C, prazosin group showed a slightly greater decrease from baseline than PN group, whereas in the other two centers PN had a greater decrease than did prazosin.

Efficacy

As in other studies, analyses were done within and between groups as well as categorical analysis.

Weeks 1 - 6

Tables 9 and 10 summarize results from first two weeks of active therapy, with patients receiving lowest doses. Both drugs caused statistically significant reductions from baseline for all blood pressure variables and increases in pulse rates. PN caused greater decreases in blood pressure with the differences in systolic pressures being statistically significant between groups. The reductions in SDBP were 10.4 mm Hg and 9.0 mm Hg for PN and prazosin respectively at week 1 and 10.5 and 9.6 mm Hg respectively by week 2. Endpoints similar to those given are given in Table 11 with SDBP reductions of 10.4 (PN) and 10.3 mm Hg (prazosin), the between group difference being borderline statistically significant ($p < 0.10$).

Weeks 7 - 10

Table 12 summarizes results during the last two weeks of the study. SDBP was reduced by 10.4 mm Hg (PN) and 10.3 mm Hg (prazosin), the between group difference being borderline statistically significant ($p < 0.10$).

	n =	1		2		3		4	
PN	30	13	43%	12	40%	4	13%	1	3%
Prazosin	33	8	24%	15	45%	8	24%	2	6%

For week 10, the results were similar with 77% PN being category 1 and 2 compared to 72% prazosin. PN had 83% with a SDBP < 90 mm Hg compared to 64% prazosin.

Endpoint Analysis

Table 13 presents these results for all patients, irrespective of validity. Both groups caused statistically significant reductions in blood pressure with PN having the greater reductions.

Results are presented graphically in figures 1 - 6.

Vasoactive Hormones, Center B

Results are shown in Table 14. Measurements were made at baseline and at week 10. There was a statistically significant difference in PRA for prazosin but there were no between group statistical differences.. The mean change in PGE2 levels showed a large increase (61.47 pg/ml) for prazosin while PN was unchanged (0.28).

Echocardiography and ETT

This was done at center C only and results are shown in Table 15. There were no statistical differences between groups for any variable. Table 16 presents ETT data. Except for week 5, total exercise increased for PN but not for prazosin. It should be remembered, however, that prazosin is not recommended for treatment of angina while calcium antagonists are standard systemic and diastolic blood pressures decreased progressively with time, with greater decrements in diastolic pressure occurring with PN and in systolic with prazosin.

Safety

There were no major side effects in any of the patients.

Clinical Laboratories

Samples were analyzed at three separate laboratories. Table 23 presents hematology results. There was a statistically significant increase in WBC in center B. Hemoglobin was decreased with prazosin in centers B and C. Table 24 presents urinalysis results and Table 25 chemistries. Statistically significant changes occurred for prazosin for glucose and chloride and with PN for SGPT. Tables 26 - 28 list newly occurring test results. The number of patients with most frequent occurring abnormalities were:

	PN	Prazosin
Glucose	6	2
Total Bilirubin	1	4
SGOT	7	0 **
SGPT	8	2 *

* and ** p , 0.05 and < 0.01 compared to prazosin.

Individual cases discussed in the report.

Dropouts

These were listed in Table 4. There were 10 withdrawn in PN group and 9 with prazosin. Six PN withdrew due to ADRs compared to 5 prazosin. The reasons in PN group were headache, edema, nausea/vomiting, flushing, macula eye hemorrhage; the other PN withdrawals were unrelated to drug. Prazosin reasons were headache, gi upset, tachycardia, flushing/palpitations, increased heart rate/short of breath. One prazosin was withdrawn due to insufficient response.

Adverse Reactions

There were 23/41 (56%) PN and 31/42 (74%) prazosin with at least one new ADR. Table 32 lists ADRs by patient and Table 33 by body system. The most commonly reported events were;

ADR	PN n = 41	Prazosin n = 42
Joint Pain	3	0
Edema	7	0
Abdominal	2	1

after the first week with even low dose 5 mg daily and this improved as dose was increased. There were no significant changes in ECGs or laboratory data. ADRs occurred in 56% PN compared to 74% prazosin patients.

Reviewer;s Comments

- 1 This study has same problems as before regarding timing of blood pressure measuremets, original number patients enrolled etc
 - 2 ETT results should be ignored as prazosin is not an antianginal drug
 3. The study demonstates that PN is an effective antihypertensive and better than prazosin.
-

TABLE
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 ⁺⁺		Plateau Period Weeks 7 & 8 Weeks 9 & 10	
PN 200-110 group	One, Pcb ⁺ 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	5 mg	5 mg	5-10 mg	5-15 mg	5-20 mg	5-20 mg
Prazosin group	One, Pcb cap bid	One, 1 mg Prz ⁺⁺ cap bid	One, 2 mg Prz cap bid	One or two, 2 mg Prz cap(s) bid	One, two or three 2 mg Prz cap(s) bid	One, two, three, or four 2 mg Prz cap(s) bid	One, two, three or four 2 mg Prz cap(s) bid
	Total Dose/Day	2 mg	4 mg	4-8 mg	4-12 mg	4-16 mg	4-16 mg

← Single-Blind →

← Double-Blind →

cb = Placebo

rz = 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.

0383

TABLE 1

TABLE 2
 PH 200-110 STUDY NO. 325
 PLAN CHART

	Initial Visit	END OF WEEK													12 Follow-up Evaluation
		Single-Blind			Double-Blind: Active Treatment Period										
		Plasma Period			Titration Period						Plasma Period				
		-3	-2	-1 Time 0	1	2	3	4	5	6	7	8	9	10 Final Evaluation	
Background Information OF BK, PH	X														
Physical Exam OF PE	X													X ¹⁰	
Cardiovascular Evaluation OF CV	X			X	X	X		X		X		X		X ¹⁰	
Patient Inclusion/Exclusion Criteria OF IE				X											
Blood Pressure; Vital signs OF VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁰	
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) OF LAB	X			X	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰
ECG Evaluation OF ECG	X			X			X			X				X ¹⁰	
Chest X-ray OF CX	X ¹⁰													X ¹⁰	
Ophthalmologic Examination OF OP				X ¹⁰										X ¹⁰	
Concomitant Medication OF CM	X	- AS REQUIRED -													
Concomitant OF CM	X	- AS REQUIRED -													
Medication Check OF MC		X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁰	
Adverse Reaction OF AR		X	X	X	X	X	X	X	X	X	X	X	X	X ¹⁰	
End of Study Information OF ES														X ¹⁰	
Blood Sample for Vasoreactive Hormone Determinations OF OH ¹			X ¹⁰	X									X ¹⁰	X	
Exercise Tolerance Test OF ET ²				X		X		X		X		X			
Echocardiographic Study OF ² OH				X ²⁰										X ²⁰	

¹⁰Or upon discontinuation from the study.
 While a chest X-ray performed at the initial visit was preferable, an X-ray obtained within six (6) months prior to the patient entering the trial may have served as baseline for the study and was not repeated at the initial visit provided that the chest X-ray was normal or according to the investigator's judgment any abnormalities were considered minor or not clinically relevant and a clinical condition requiring a chest x-ray had not occurred during this interval.
¹ophthalmologic examination was performed any time during the washout period but as close as possible to the week -1, Time 0 visit.
²Center C only
 Additional blood samples may have been obtained at Week -2 and Week 9 for better documentation of the reproducibility of measured values.
²⁰Center C only
²⁰Echocardiograms may have been performed 1-3 days prior to the above cited visits.
¹Liver function tests only (SGOT, SGPT, alkaline phosphatase, LDH and total bilirubin) - Initiated Oct./Nov. 1986.

TABLE 4

PN 200-110 STUDY NO. 305

REASONS FOR PARTIAL VALIDITY FOR EFFICACY ANALYSIS

Treatment Group	Patient	Valid Thru Week	Reason Week Discontinued
PN 200-110	106	1	(Week 1) <u>ADR</u> - Headache, flushing, nausea/vomiting
	115	6	(Week 6) <u>ADR</u> - Edema
	202	9	(Week 10) <u>ADR</u> - Macula hemorrhage: eye
Prazosin	205	8	(Week 8) <u>ADR</u> - Headache
	252	1	(Week 1) <u>Unrelated Illness</u> - Chest pain*
	258	2	(Week 2) <u>Unrelated Illness</u> - Pulmonary edema
	314	5	(Week 5) <u>Other</u> - Lost to follow
	317	7	(Week 7) <u>ADR/Study Drug Ineffective</u> - Blurred vision, edema, fatigue, ear pressure
	352	4	(Week 4) <u>Uncooperative</u>
	353	5	(Week 5) <u>ADR</u> - Headache
	109	1	(Week 1) <u>Other</u> - Study interferes
	116	4	(Week 5) <u>Other</u> - Lost to follow
	207	8	(Week 8) <u>Study Drug Ineffective</u>
	217	4	(Week 5) <u>Unrelated Illness</u> - Headache
	255	1	(Week 1) <u>ADR</u> - GI upset
	307	3	(Week 3) <u>ADR</u> - Increased HR/pulse, aching legs, shortness of breath
316	5	(Week 5) <u>ADR</u> - 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 3 (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 <80% compliant during the active treatment period. At the Week 1 and Week 2 clinic visits, the last dose of medication was taken the evening

TABLE 5

PN 200-110 STUDY NO. 305

NUMBER OF PATIENTS BY EFFICACY ANALYSES 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	35	7	1	43
C	8	4	0	8	2	1	16	6	1	23
	30	10	1	33	7	2	63	17	3	83

0386

Table 5

TABL

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	9.54	9.38	9.46
S.D.	0.26	0.24	2.83	2.65	4.14	3.98	5.21	5.35	5.37	5.36
Min	4.29	4.29	4.82	4.64	4.29	4.38	4.29	4.64	4.64	4.38
Max	5.42	5.36	14.64	14.29	16.88	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	1.98	3.92	6.13	6.45	7.81	7.99	9.48	9.52	9.48	9.39
S.D.	0.10	0.16	2.01	2.04	3.29	3.46	4.59	4.60	4.58	4.45
Min	1.57	3.43	3.71	3.75	2.86	3.56	3.43	3.43	3.56	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 6, Patient No. 110 missing data for Week 9.

0387

Table 7

TAB.

PN 200-110 STUDY NO. 305

Summary Comparative Results for Treatment X Investigator
Treatment X Time, and Treatment X Time X Investigator Interaction for
the Plateau Period - Valid Patients

Variable	Investigator	Baseline Mean (Sample Size)		Mean Change from Baseline		Treatment X Investigator Interaction	Treatment X Time Interaction	Treatment X Time X Investigator Interaction
		PN 200-110	Prazosin	PN 200-110	Prazosin	p-value	p-value	p-value
Sitting Systolic B.P. (mmHg)	A	155.8 (6)	156.8 (6)	-24.86	-3.75	0.0385	0.4629	0.6505
	B	149.3 (16)	153.7 (19)	-18.17	-7.62			
	C	145.1 (8)	150.8 (8)	-7.56	-12.63			
Sitting Diastolic B.P. (mmHg)	A	100.3 (6)	101.8 (6)	-16.44	-9.29	0.1900	0.4991	0.3964
	B	101.3 (16)	102.1 (19)	-17.13	-13.10			
	C	100.3 (8)	103.5 (8)	-11.91	-14.06			
Sitting Pulse (per min.)	A	77.5 (6)	72.2 (6)	-0.29	0.52	0.7048	0.0663	0.6992
	B	76.8 (16)	82.4 (19)	0.91	1.76			
	C	75.8 (8)	90.7 (8)	4.70	1.56			
Standing Systolic B.P. (mmHg)	A	153.5 (6)	157.0 (6)	-29.25	-7.71	0.3573	0.8513	0.6324
	B	148.0 (16)	150.5 (19)	-15.46	-4.38			
	C	151.5 (8)	153.6 (8)	-11.19	-10.28			
Standing Diastolic B.P. (mmHg)	A	104.7 (6)	100.2 (6)	-22.88	-8.25	0.0992	0.6269	0.7179
	B	102.3 (16)	100.4 (19)	-17.23	-11.99			
	C	103.0 (8)	104.5 (8)	-8.81	-10.09			
Standing Pulse (per min.)	A	81.7 (6)	71.2 (6)	1.86	6.33	0.9922	0.0623	0.1297
	B	83.0 (16)	85.8 (19)	1.08	4.05			
	C	79.1 (8)	93.1 (8)	6.23	8.97			

Table 8

3880

TABLE 14
PN 200-110 STUDY NO. 305
SUMMARY COMPARATIVE RESULTS
FOR VASOACTIVE HORMONES - CENTER B

Variable	Treatment Group	No. of Patients	Baseline		Week 10	
			Mean	S.D.	Mean Change	S.D.
Plasma Renin Activity (ng/ml/hr)	PN 200-110	15	1.5	1.02	0.39	0.87
	Prazosin	19	1.4	1.25	0.65**	0.89
Angiotensin-II (pg/ml)	PN 200-110	16	31.6	8.07	0.38	6.83
	Prazosin	19	30.7	6.41	2.79(*)	6.52
Aldosterone (ng/dl)	PN 200-110	14	14.6	9.10	-0.21	7.38
	Prazosin	19	21.9	12.21	-0.11	10.79
Cortisol (ng/dl)	PN 200-110	10	17.3	4.35	-0.10	6.74
	Prazosin	14	20.6	8.19	-0.79	11.92
Prostacyclin 6-Keto-PGF _{1α} (pg/ml)	PN 200-110	18	51.0	28.92	-2.61	22.92
	Prazosin	19	45.5	37.16	3.79	19.42
Prostaglandin PGE ₂ -M (pg/ml)	PN 200-110	18	88.4	57.58	0.28	66.19
	Prazosin	19	90.9	80.64	61.47(*)	150.71

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

TABLE 15

PN 200-110 STUDY NO. 305

SUMMARY OF ECHOCARDIOGRAPHIC DATA

CENTER C ONLY

COMPLETED PATIENTS ONLY

Variable	Treatment Group	No. of Patients	Baseline		Mean Change	S.D.
			Mean	S.D.		
Aortic Root (cm)	PN 200-110	6	3.38	0.26	-0.08	0.15
	Prazosin	7	3.30	0.26	-0.04	0.19
Left Atrial Diameter Systole (mm)	PN 200-110	6	3.68	0.57	0.12	0.17
	Prazosin	7	3.71	0.70	-0.09	0.47
Right Ventricular Diameter (cm)	PN 200-110	6	2.02	0.63	0.43	0.67
	Prazosin	7	2.11	0.80	-0.20	0.74
Left Ventricular Internal Diameter Diastole (cm)	PN 200-110	6	4.92	0.61	0.07	0.31
	Prazosin	7	4.96	0.19	0.04	0.42
Left Ventricular Internal Diameter Systole (cm)	PN 200-110	6	3.10	0.41	-0.25	0.60
	Prazosin	7	3.14	0.66	0.04	0.55
Minor Axis Shortening (pct)	PN 200-110	6	35.67	3.98	7.17	10.98
	Prazosin	7	37.71	8.64	-2.71	6.87
Posterior Wall Thickness (cm)	PN 200-110	6	1.13	0.29	-0.10	0.14
	Prazosin	7	1.04	0.20	0.03	0.16
Septal Wall Thickness (cm)	PN 200-110	6	1.03	0.27	0.05	0.08
	Prazosin	7	1.17	0.31	0.01	0.12

(*) p<0.10, * p<0.05, ** p<0.01, *** p<0.001

TABLE 16
 PN 200-110 STUDY NO. 305
 EXERCISE TOLERANCE TEST AT DIPPOINT OF EXERCISE
 CENTER C ONLY

Variable	Treatment	Week 2		Week 4		Week 6		Week 8		Week 10						
		N	Baseline	Mean Change	N	Baseline	N	Baseline	N	Baseline	N	Baseline				
			Mean			Mean		Mean		Mean		Mean				
Exercise Duration (sec.)	PN 200-110	6	500.8	22.5	5	536.4	24.4	4	488.0	-55.3	3	467.7	41.7(*)	3	467.7	33.3
	Prazosin	4	512.8	4.5	4	512.8	3.0	4	512.8	4.5	4	512.8	-15.0	4	512.8	-4.5
Standing Heart Rate (per min.)	PN 200-110	6	165.3	-3.0	5	168.4	-1.2	4	157.5	-4.5	3	147.7	10.0	3	147.7	12.3*
	Prazosin	4	161.8	7.0	4	161.8	1.0	4	161.8	1.0	4	161.8	-5.8	4	161.8	2.5
Standing Systolic B.P. (mm Hg)	PN 200-110	6	218.3	-11.3	5	228.0	-32.8*	4	241.0	-19.5	3	228.0	-33.3	3	228.0	-34.0**
	Prazosin	4	213.0	-15.5	4	213.0	-33.0	4	213.0	-35.0	4	213.0	-35.5*	4	213.0	-57.5(*)
Standing Diastolic B.P. (mm Hg)	PN 200-110	6	110.3	-8.0(*)	5	110.4	-12.6	4	113.0	4.5	3	114.0	-14.0(*)	3	114.0	-24.7(*)
	Prazosin	4	96.0	-6.5	4	96.0	-3.5	4	96.0	-8.5	4	96.0	-13.5*	4	96.0	-11.0
ST Segment Change	PN 200-110	6	0.17	-0.05	5	0.20	-0.16	4	0.25	-0.13	3	0.00	0.07	3	0.00	0.10
	Prazosin	4	0.40	-0.20	4	0.40	-0.20	4	0.40	-0.35	4	0.40	-0.28	4	0.40	-0

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

Table 16

4004

TABLE 9

PN 200-110 STUDY NO. 305

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

Variable	Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted† Mean Change	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic B.P. (mmHg)	PN 200-110	39††	151.8	14.96	-11.4***	13.36	-11.7	140.3	19.55
	Prazosin	40	154.2	13.24	-5.1*	12.91	-4.8	149.2	14.36
Sitting Diastolic B.P. (mmHg)	PN 200-110	39	102.2	5.97	-10.4***	8.61	-10.4	91.8	9.79
	Prazosin	40	102.4	5.27	-9.0***	6.23	-8.9	93.4	6.20
Sitting Pulse (per min.)	PN 200-110	39	76.7	11.66	4.1*	12.21	3.1	80.8	12.88
	Prazosin	40	82.3	12.51	3.4*	8.16	4.3	85.7	12.03
Standing Systolic B.P. (mmHg)	PN 200-110	39	153.2	15.61	-13.5***	13.99	-13.3	139.6	17.63
	Prazosin	40	151.8	14.71	-2.2	11.90	-2.4	149.6	16.13
Standing Diastolic B.P. (mmHg)	PN 200-110	39	104.0	6.09	-9.2***	8.24		94.8	9.57
	Prazosin	40	101.7	6.20	-7.1***	7.21		94.7	8.61
Standing Pulse (per min.)	PN 200-110	39	82.1	13.35	3.3(*)	11.20		85.4	15.02
	Prazosin	40	84.7	12.81	7.1***	9.81		91.8	15.57

0392

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

†Pre only when analysis of covariance assumption met.
††Pat n. 111 missing Week 1 evaluation.

TABLE 10

PN 200-110 STUDY NO. 305

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

Variable	Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted† Mean Change	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic B.P. (mmHg)	PN 200-110	38	150.1	14.30	-12.3***	14.24	-12.8	137.8	16.80
	Prazosin	38	153.6	13.28	-8.8**	15.62	-8.2	144.8	17.19
Sitting Diastolic B.P. (mmHg)	PN 200-110	38	101.7	5.80	-10.6***	8.41	-10.7	91.1	9.03
	Prazosin	38	102.2	5.35	-9.5***	8.27	-9.4	92.7	8.46
Sitting Pulse (per min.)	PN 200-110	38	77.0	11.71	4.6*	11.72	3.5	81.6	13.35
	Prazosin	38	83.0	12.26	5.9***	10.00	7.0	88.9	11.40
Standing Systolic B.P. (mmHg)	PN 200-110	38	151.7	16.17	-14.8***	13.77	-14.9	136.9	17.40
	Prazosin	38	152.1	14.98	-6.9*	16.24	-6.9	145.2	18.19
Standing Diastolic B.P. (mmHg)	PN 200-110	38	103.8	6.12	-10.3***	7.94		93.5	9.80
	Prazosin	38	101.7	6.36	-8.8***	9.54		92.9	10.31
Standing Pulse (per min.)	PN 200-110	38	82.1	13.56	4.5**	10.02	4.2	86.6	15.61
	Prazosin	38	85.1	12.86	8.5***	12.24	8.8	93.6	14.25

01-03193

†Presented only when analysis of covariance assumptions were met.

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

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
 VALID AND PARTIALLY VALID PATIENTS - ENDPOINT ANALYSIS FOR WEEKS 1 THRU 6 (TITRATION PERIOD)

Variable	Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted Mean Change	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic B.P. (mmHg)	PN 200-110	40	151.3	15.03	-16.4***	15.60	-16.9	132.9	16.82
	Prazosin	40	154.2	13.24	-8.6***	14.07	-8.0	145.7	16.69
Sitting Diastolic B.P. (mmHg)	PN 200-110	40	102.1	5.93	-14.3***	10.77	-14.4	87.8	9.91
	Prazosin	40	102.4	5.27	-10.5***	7.72	-10.7	91.5	7.47
Sitting Pulse (per min.)	PN 200-110	40	76.8	11.51	3.7(*)	12.01	2.4	80.4	12.86
	Prazosin	40	82.3	12.51	2.6	12.06	3.9	84.9	12.46
Standing Systolic B.P. (mmHg)	PN 200-110	40	152.8	16.59	-17.4***	16.98	-17.1	135.4	17.49
	Prazosin	40	151.8	14.71	-8.2**	15.86	-8.4	143.6	16.44
Standing Diastolic B.P. (mmHg)	PN 200-110	40	103.9	6.05	-13.8***	12.11	-13.2	90.1	11.44
	Prazosin	40	101.7	6.20	-9.9***	8.54	-10.5	91.9	8.50
Standing Pulse (per min.)	PN 200-110	40	81.9	13.28	4.7*	11.74	4.4	86.6	16.58
	Prazosin	40	84.7	12.81	5.2*	12.80	5.6	89.9	13.98

†Presented only when analysis of covariance assumptions were met.

(*)p<0.10. *p<0.05, **p<0.01, ***p<0.001

07-05194

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
VALID PATIENTS - WEEKS 7 THRU 10 (PLATEAU PERIOD)

Variable	Treatment Group	No. of Patients	Baseline		Mean Change at Week				Mean of Weeks (7-10)	S.D.
			Mean	S.D.	7	8	9*	10		
Sitting Systolic B.P. (mmHg)	PN 200-110	30	149.5	15.36	-17.5***	-17.5***	-14.6***	-15.6***	-16.7***	13.65
	Prazosin	33	153.6	17.05	-7.5**	-8.4**	-7.1**	-9.5***	-8.1***	10.95
Sitting Diastolic B.P. (mmHg)	PN 200-110	30	100.9	5.02	-14.0***	-17.1***	-15.1***	-15.6***	-15.6***	6.62
	Prazosin	33	102.4	5.51	-12.7***	-12.9***	-12.0***	-13.0***	-12.6***	5.81
Sitting Pulse (per min.)	PN 200-110	30	76.7	11.28	3.0	2.8	2.1	-0.6	1.7	9.61
	Prazosin	33	82.6	12.90	0.2	0.9	1.5	3.3(*)	1.5	7.27
Standing Systolic B.P. (mmHg)	PN 200-110	30	150.1	17.07	-16.2***	-10.6***	-14.3***	-17.7***	-17.1***	14.11
	Prazosin	33	152.5	15.06	-6.9*	-5.6*	-5.3	-7.9*	-6.4*	15.31
Standing Diastolic B.P. (mmHg)	PN 200-110	30	103.0	6.00	-14.9***	-17.2***	-14.5***	-17.0***	-16.1***	8.81
	Prazosin	33	101.3	6.51	-11.6***	-10.6***	-9.8***	-11.3***	-10.8***	7.71
Standing Pulse (per min.)	PN 200-110	30	81.7	14.26	4.2(*)	3.8(*)	1.7	1.1	2.6	9.71
	Prazosin	33	84.9	13.38	4.6*	5.5**	6.5***	6.1**	5.7***	7.21

(*)p<0.10, *p<0.05, **p<0.01, ***p<0.001

*Patient No. 110 (PN 200-110) had no study data recorded for Week 9 visit.

01-03195

PN 200-110 STUDY NO. 305

SUMMARY COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE
ALL PATIENTS - ENDPOINT ANALYSIS OF WEEKS 1 THRU 10

Variable	Treatment Group	No. of Patients	Baseline		Mean Change	S.D.	Adjusted† Mean Change	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic B.P. (mmHg)	PN 200-110	41	151.8	15.09	-14.9***	16.84	-15.2	136.8	17.65
	Prazosin	42	153.5	13.67	-8.2***	12.49	-7.9	145.3	16.92
Sitting Diastolic B.P. (mmHg)	PN 200-110	41	102.1	5.86	-15.0***	10.10	-15.0	87.2	8.31
	Prazosin	42	102.2	5.23	-11.2***	8.32	-11.2	91.0	7.7
Sitting Pulse (per min.)	PN 200-110	41	76.8	11.38	2.2	12.26	1.5	79.0	13.01
	Prazosin	42	82.1	12.22	3.0(*)	11.42	3.7	85.1	15.71
Standing Systolic B.P. (mmHg)	PN 200-110	41	153.1	16.49	-18.8***	14.53	-18.4	134.2	16.01
	Prazosin	42	151.3	14.54	-6.9*	19.32	-7.3	144.3	19.41
Standing Diastolic B.P. (mmHg)	PN 200-110	41	103.9	5.97	-15.8***	10.96	-15.2	88.1	10.31
	Prazosin	42	101.7	6.22	-9.8***	9.46	-10.5	91.9	9.5
Standing Pulse (per min.)	PN 200-110	41	81.9	13.12	3.2(*)	11.39		85.1	16.0
	Prazosin	42	85.1	12.63	6.0**	11.45		91.1	17.3

†Presented only when analysis of covariance assumptions were met.

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

01-01196

TABLE 18
PN 200-110 STUDY NO. 305

CARDIOVASCULAR EVALUATION
NEWLY-OCCURRING ABNORMALITIES

Treatment	Patient	Week	Variable	Abnormality	
PN 200-110	102	2	Other	Mild bitemporal headache	
		6	Other	Left knee pain; old problem exacerbated	
		8	Other	Knee pain improved	
		10	Other	Knee pain stable	
	104	6	Other	Fractured left clavicle	
		8	Other	Clavicle stable	
	106	1	Other	Severe migraine type headache - condition deteriorating	
					108
	2	Other	Insomnia improved		
	115	4	Extremities	Two days history of bilateral pedal edema; increasing in day and decreasing at night, 2+ at exam	
					6
	205	6	Chest pain at rest	One episode of sub-sternal chest pain	
	312	8	Other	Shoulder - related to old injury 8 yrs. ago	
	317	6	2	Other	Nosebleed
			6	Chest Pain	Stated chest pain occurred under right arm to RUQ-possibly related to back injury (old)
			7	Extremities	Slight edema ankles

0420

01-02201

TABLE 18 (Continued)
 PN 200-110 STUDY NO. 305

CARDIOVASCULAR EVALUATION
 NEWLY-OCCURRING ABNORMALITIES

Treatment	Patient	Week	Variable	Abnormality
Prazosin (Con't)	307	2	Dyspnea exertion	Has developed occasional shortness of breath on exertion
	310	4	Cough Other	Related to hay fever Hay fever
	311	8	Other	Leg pain - injured right leg on 3/21/86 - felt at that time it was not significant
	316	2	Othe Palpitation	Knee pain Palpitations occurred once for about 15 min.
		4	Palpitation	Feels flutters in chest approximately 2 times a day

0421

0.-02204

TABLE 18 (Continued)
 PN 200-110 STUDY NO. 305

CARDIOVASCULAR EVALUATION
 NEWLY-OCCURRING ABNORMALITIES

Treatment	Patient	Week	Variable	Abnormality
PN 200-110 (Con't)	355	2	Other	Lower back pain - difficulty getting around
		4	Other	Lower back pain - stable
		6	Other	Lower back pain - improving
		8	Other	Lower back pain - stable
Prazosin	103	10	Extremities Extremities	Swelling in hands - 1+ Hands and feet 1+ edema - patient was taken off diuretic to begin study-retains fluid
		8	Other	States heart pounds occasionally when nervousness occurs
		10	Other	Heart pounds not as noticeable
		2	Other	Cold with chills, cough, fever, aching muscles
		6	Other	One to two seconds of dizziness
	105	8	Heart examination Other	Intermittent S ₄ - atrial gallop Head cold for 2 days
		1	Other	Pre-existing abnormalities: headache stable to increased; edema stable
		2	Other	Headache deteriorating; edema stable
		4	Other	Headache; edema stable
		6	Other	Headache stable; edema improved
8	Other	Headache; edema improved; new abnormality - constipation		

Exclusion criteria were secondary or malignant hypertension; angina; MI in previous 6 months; arrhythmias; investigational drug in prior 4 weeks; medications or diseases that could interfere with study drug evaluation; CHF; bradycardia; AV block > 1st degree; diabetes mellitus requiring insulin therapy; bronchial asthma or COPD or respiratory allergy; alcohol or drug abuse; pregnant or lactating females; certain specified medications.

Medications

Identically appearing capsules of either PN 2.5 mg or propranolol 60 mg were supplied. HCT was supplied as Esidrex. Dosage is summarized in Table 1. Medication was to be taken twice daily, before breakfast and before evening meal.

Study Plan

After completing the run-in period, qualified patients entered double blind active period and were randomized to either PN or propranolol (both in addition to HCT). As for previous protocols, patients were stratified as per their blood pressures. Initial dose of drugs were 2.5 mg PN or 60 mg propranolol bid for two weeks. If average SDBP > 90 mm Hg, doses were increased to 5 mg bid or 120 mg bid respectively for weeks 3 and 4. Similarly, dose was increased every two weeks if necessary to 7.5 mg bid or 180 mg bid (weeks 5 and 6), then 10 mg or 240 mg bid for weeks 7 and 8. If SDBP < 90 mm Hg at end of weeks 2, 4 or 6, dose was not increased for next two week period. If SDBP increased above 90 mm Hg, dose could then be increased as above. If, at any time, SDBP > 110 mm Hg, dose could be increased after one week instead of the specified two weeks. From week 7, dose could not be increased and at no time could dose exceed PN 10 mg bid or propranolol 240 mg bid. Evaluations were carried out as per schedule in Table 2.

Results

A total of 78 patients were randomized to double blind phase, 40 PN and 38 propranolol. Of these, 62 (33 PN and 29 propranolol) were regarded as completely valid and 16 were partially valid. Centers A and B contributed 26 and 27 patients and D 22 patients. Table 3 presents a summary of the results of the study.

Mean dose is summarized in Table 7 and 8. PN dose at weeks 7 - 10 averaged 13 mg daily and propranolol 257 mg daily. The average dose of HCT was 50 mg daily; 4 PN and 7 propranolol patients received 100 mg HCT daily.

Interactions

Table 9 summarizes analysis of interactions for valid patients. It also shows efficacy results by investigator for weeks 7 - 10. No interaction for pulse or blood pressures was statistically significant.

Efficacy

Efficacy was evaluated as in previous studies, within and between groups and categorized by reductions in blood pressure.

Weeks 1 - 2.

Table 10 and 11 presents data for weeks 1 and 2 for valid patients. After one week, both groups had equivalent and statistically significant reductions in blood pressure from baseline. At week 2, propranolol had slightly greater decreases than with PN, but these differences were not statistically significant. The differences in pulse rate were significant with propranolol causing a decrease and PN an increase. The reductions in SDBP at these times were:

	<u>n =</u>	<u>Week 1</u>	<u>n =</u>	<u>Week 2</u>
PN	40	- 10.1	40	- 10.2
Propr	38	- 10.0	36	- 12.9

Weeks 3 and 4

Results were similar to first two weeks and are seen in Tables 12 and 13. Both drugs caused statistically significant reductions in blood pressure with no between group differences, except for pulse rate. SDBP reductions were:

	<u>n =</u>	<u>Week 3</u>	<u>n =</u>	<u>Week 4</u>
PN	38	- 10.1	38	- 10.2
Propr	36	- 10.0	36	- 12.9

Fixed Dose Weeks 7 - 10

Tables 16 and 17 present data for valid and "all" patients. Both drugs demonstrated clinically and statistically significant reductions in blood pressure compared to baseline with no statistically significant differences between groups. Reductions in SDBP for this period were 15.1 mm Hg (PN) and 15.5 mm Hg (propranolol). The differences in pulse rate were significant between groups (3 - 4 bpm increase PN and 14 - 20 bpm decrease propranolol).

Categorical analysis for weeks 7 - 10, using same criteria as in previous studies:

		1		2		3		4	
PN	n = 33	8	24%	21	64%	4	12%	0	0%
Propr	n = 29	8	28%	16	55%	4	14%	1	3%

At least 10 mm Hg reduction was seen in 88% PN and 83% propranolol patients. Sixty nine (69%) percent propranolol and 55% PN had a SDBP < 90 mm Hg at weeks 7 - 10.

Prescribed daily dose for valid patients over weeks 7 - 10 was:

Daily Dose PN n = 33			Daily Dose propranolol n = 29		
5 mg	10	30%	120 mg	10	34%
10 mg	4	12%	180 mg	1	3%
15 mg	9	27%	240 mg	7	24%
20 mg	10	30%	360 mg	6	21%
			480 mg	5	17%

All Patients - Endpoint Analysis

Table 19 summarizes data for endpoint analyses for all patients. Results are the same as seen in previous tables.

Data are displayed graphically in figures 1 - 6.

Safety

ECG changes are shown in Table 22A and 23. Twenty one PN and 24 propranolol group had new events reported. One in each group were discontinued from the study, tachycardia and bradycardia respectively. Sinus tachycardia was more frequent with PN and sinus bradycardia with propranolol. The tachycardia was in a range of 100 - 110 bpm, an increase of 10 - 20 bpm over baseline. The bradycardia rates were in 40s with a decrease of 25 - 30 bpm over baseline.

Clinical Laboratory Tests

Table 27 summarizes per time point data for patients with completed data weeks 6 and 10. The changes observed were not clinically significant. Table 28 lists newly occurring abnormal test, by patient. The changes were not considered clinically relevant. Table 29 compares incidence of new events across both groups.

Dropouts

Table 4 listed all drop outs. Five PN discontinued due to ADRs: 2 for tachycardia; urticaria and rash/edema; GI reflux; headaches, short of breath and palpitations. Four propranolol discontinued for ADRs, 3 for therapy failure and one MI.

Adverse Reactions

Summarized in Table 30 by patient and 31 by body system. The number of patients reporting at least one new event is shown in following table.

Week	PN	%	Propranolol	%
1	10/40	25	7/38	18
2	5/40	13	3/38	8
3	11/39	28	3/38	8
4	4/37	11	5/37	14
5	9/37	24	6/35	17
6	5/36	14	6/33	18
7	4/35	11	3/32	9
8	5/35	14	1/30	3
9	5/35	14	1/30	3
10	5/35	14	1/30	3

Discussion

The addition of PN to HCT resulted in both clinically and statistically significant reductions in blood pressure from baseline at all time points. There were no statistical differences between PN and propranolol for blood pressure but there were differences for heart rates. Even though PN had a higher incidence of ADRs 73% versus 45%, the events were not serious.

Reviewer's comments.

- 1 It is presumed that dose of HCT was not changed during study.

- 2 Same comments as before regarding timing, stratification etc
- 3 PN appears to be as effective as propranolol when combined with HCT. Protocol 304 showed PN to be more effective than propranolol but this could have been due to the high % of blacks. In this study there are also a high % blacks but patients were receiving HCT in addition to beta blocker. Would the results have been the same if the population had been white ?

TABLE OF CONTENTS

	Page
I. INTRODUCTION AND OBJECTIVES.....	1
II. MATERIALS AND METHODS.....	1-14
A. Patients.....	1-5
B. Study Plan.....	5-9
1. Study Medications.....	5
2. Dosage Schedule.....	5-7
3. Evaluations.....	7-9
C. Statistical Methodology.....	9-14
1. Background Information.....	9
2. Mean Dose.....	9
3. Efficacy - Blood Pressure and Pulse.....	9-11
a. Interactions.....	9-10
b. Analysis of Variance/Covariance.....	10-11
c. Categorical Analysis.....	11
4. Safety.....	11-14
a. Physical Examination.....	11
b. Cardiovascular Evaluation.....	12
c. Chest X-Ray.....	12
d. Electrocardiographic Evaluation.....	12
e. Body Weight, Temperature and Respiratory Rate.....	12
f. Clinical Laboratory Tests.....	12-13
g. Adverse Reactions.....	13-14
III. RESULTS.....	14-30
A. Patient Validity.....	14-15
B. General Background Data.....	15
C. Mean Dose.....	15-16
D. Efficacy - Interactions.....	16

FLOW CHART

040A

	Initial Visit -4	END OF WEEK													12 Follow-up Evaluation	
		Single-Blind			Double-Blind: Active Treatment Period											
		Placebo Run-In Period			Titration Period					Plateau Period						
		-3	-2	-1 ⁺ Time 0	1	2	3	4	5	6	7	8	9	10 Final Evaluations		
Background Information CRF BK, PM	X															
Physical Exam CRF PE	X														X*	
Cardiovascular Evaluation CRF CV	X			X	X						X				X*	
Patient Inclusion/Exclusion Criteria CRF IE				X												
Blood Pressure; Vital Signs CRF VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X*	
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) CRF LAB	X			X	X ¹	X ¹	X ¹	X ¹	X ¹	X	X ¹	X ¹	X ¹	X*	X ¹	
ECG Evaluation CRF ECG	X			X	X					X				X*		
Chest X-ray. CRF CX	X ⁺⁺													X ⁺⁺		
Concomitant Medication CRF OM	X	- AS REQUIRED -														
Comment CRF COM	X	- AS REQUIRED -														
Medication Check CRF MC		X	X	X	X	X	X	X	X	X	X	X	X	X*		
Adverse Reaction CRF AR		X	X	X		X	X	X	X	X	X	X	X	X*		
End of Study Information CRF ES														X*		

*Or upon discontinuation from the study.

**An end of study chest X-ray was optional at Centers A, B, and D; Center C did not perform end of study chest X-rays.

⁺These evaluations (Time 0) were performed prior to initiating double-blind active treatment period even if the run-in period was only two weeks in duration.

¹A chest X-ray obtained within six (6) months prior to the patient entering the trial may have served as baseline for the study provided that the chest X-ray was normal or according to the investigator's judgement any abnormalities were considered minor and not clinically relevant and a clinical condition which required a chest X-ray had not occurred during this interval. Otherwise, an X-ray was obtained.

¹L¹ iction tests only: LDH, SGOT, SGPT, alkaline ph... and total bilirubin. These tests were initiated du... ober
 a ber, 1984 as the study was ongoing.

01-03480

7 3 1
PN 200-110 STUDY NO. 307
DOSAGE SCHEDULE

0405

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	
← MAINTAIN CONSTANT DOSE AND DOSAGE SCHEDULE FOR HYDROCHLOROTHIAZIDE (Esidrix®) →							
PN 200-110 Group	Pcb* bid	2.5 mg PN 200-110 bid	2.5 mg or 5 mg PN 200-110 bid	2.5 mg, 5 mg or 7.5 mg PN 200-110 bid	2.5 mg, 5 mg 7.5 mg or 10 mg PN 200-110 bid		Taper off
	Total Daily Dose	5 mg	5-10 mg	5-15 mg	5-20 mg		
← MAINTAIN CONSTANT DOSE AND DOSAGE SCHEDULE FOR HYDROCHLOROTHIAZIDE (Esidrix®) →							
Propranolol Group	Pcb bid	60 mg Ppnl** 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 Blind →

← Double-Blind →

†This period may have been shortened to two weeks if the patient's supine diastolic blood pressure was >110 mm Hg on the first two visits.

*Pcb = Placebo

**Ppnl = Propranolol

††Dose of the study drugs was administered shortly after awakening in the morning and before the evening meal between 5:00-8:00 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 supine 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 dose of the study drug less than 2.5 mg PN 200-110 bid or 60 mg propranolol bid or exceed 5 mg PN 200-110 bid or 240 mg propranolol bid.

01-02479

TABLE 4
PN 200-110 STUDY NO. 307

REASONS FOR PARTIAL VALIDITY FOR EFFICACY ANALYSIS

Patient No.	Treatment Group	Valid Thru Week	Discontinuation Week	Reasons
152	PN 200-110	2	2	Urticaria - Adverse Reaction
157	PN 200-110	3	3	Edema, Rash, GI Reflux - Adverse Reactions
206	PN 200-110	9	9	Subject Relocated
253	PN 200-110	9	10	Tachycardia - Adverse Reaction
302	PN 200-110	2	3	Noncompliant - 50% of Medication Taken in Wk 3
310	PN 200-110	6	6	Headaches, Shortness of Breath, Palpitations, Flushing - Adverse Reactions
314	PN 200-110	5	5	Tachycardia, Chest Pain Adverse Reactions
155	Propranolol	4	4	Study Drug Ineffective
204	Propranolol	8	8	Bradycardia - Adverse Reaction
208	Propranolol	4	5	Myocardial Infarction
312	Propranolol	3	3	Treatment Failure - Study Drug Ineffective
315	Propranolol	7	7	Treatment Failure - Study Drug Ineffective
351	Propranolol	5	5	Lost to Follow-Up
401	Propranolol	3	4	Upset Stomach - Adverse Reaction
406	Propranolol	6	6	Dizziness - Adverse Reaction
451	Propranolol	7	7	Stomach Discomfort - Adverse Reaction/Study Drug Ineffective

TABLE 5
 PN 200-110 STUDY NO. 307

NUMBER OF PATIENTS BY EFFICACY ANALYSIS CLASSIFICATION

Investigator	PN 200-110			Propranolol			Total			Total
	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	
A	8	2	0	9	1	0	17	3	0	20
B	8	2	0	8	2	0	16	4	0	20
C	8	3	0	7	3	0	15	6	0	21
D	9	0	0	5	3	0	14	3	0	17
Total	33	7	0	29	9	0	62	16	0	78

0407

TABLE 5

TABLE 7
PN 200-110 STUDY NO. 307

MEAN DAILY DOSE (IN MG)
VALID PATIENTS ONLY

Weeks 1-5	Treatment		Weeks 6-10	Treatment	
	PN 200-110	Propranolol		PN 200-110	Propranolol
Week 1			Week 6		
N	33	29	N	33	29
Mean	4.86	118.44	Mean	10.47	221.38
S.D.	0.44	7.63	S.D.	4.49	102.70
Min.	3.04	85.71	Min.	4.29	90.00
Max.	5.71	128.57	Max.	20.00	480.00
Week 2			Week 7		
N	33	28*	N	33	29
Mean	4.87	120.88	Mean	13.20	257.74
S.D.	0.50	19.43	S.D.	7.39	132.67
Min.	3.21	90.00	Min.	4.58	107.14
Max.	6.43	205.71	Max.	38.00	540.00
Week 3			Week 8		
N	33	29	N	33	29
Mean	7.32	177.72	Mean	12.50	255.07
S.D.	2.67	78.87	S.D.	6.01	125.13
Min.	4.38	94.26	Min.	4.64	120.00
Max.	13.00	437.14	Max.	22.86	480.00
Week 4			Week 9		
N	33	29	N	33	29
Mean	8.23	177.55	Mean	12.97	257.06
S.D.	2.67	73.27	S.D.	6.22	130.84
Min.	4.64	81.82	Min.	4.32	111.43
Max.	15.00	360.00	Max.	20.00	480.00
Week 5			Week 10		
N	33	29	N	33	29
Mean	10.24	217.64	Mean	12.64	256.65
S.D.	4.44	92.37	S.D.	6.02	129.51
Min.	3.57	109.09	Min.	3.96	115.38
Max.	17.86	420.00	Max.	20.00	480.00

* Patient No. 404 - Week 2 visit was determined to be invalid as the last doses of both the study drug and hydrochlorothiazide were taken four days prior to the Week 2 visit.

N.B. Most patients received a daily dose of 50 mg hydrochlorothiazide. Four PN 200-110 treated patients (Nos. 102, 152, 153, and 353) and seven propranolol treated patients (Nos. 107, 110, 111, 151, 154, 158, and 306) received 100 mg hydrochlorothiazide daily.

TABLE 8
PN 200-110 STUDY NO. 307

MEAN DAILY DOSE (IN MG)
VALID AND PARTIALLY VALID PATIENTS

Weeks 1-5	Treatment		Weeks 6-10	Treatment	
	PN 200-110	Propranolol		PN 200-110	Propranolol
Week 1			Week 6		
N	40	38	N	36	33
Mean	4.89	118.06	Mean	10.87	227.27
S.D.	0.40	10.08	S.D.	4.50	103.57
Min.	3.04	85.71	Min.	4.29	90.00
Max.	5.71	150.00	Max.	20.00	480.00
Week 2			Week 7		
N	40	36*	N	35	32
Mean	5.02	126.37	Mean	13.30	266.38
S.D.	0.93	27.45	S.D.	7.18	132.64
Min.	3.21	90.00	Min.	4.58	107.14
Max.	10.00	240.00	Max.	38.00	340.00
Week 3			Week 8		
N	38	38	N	35	30
Mean	7.67	188.78	Mean	12.65	250.07
S.D.	2.64	84.50	S.D.	5.86	125.97
Min.	4.38	94.29	Min.	4.64	105.00
Max.	13.00	437.14	Max.	22.86	480.00
Week 4			Week 9		
N	37	36	N	35	29
Mean	3.43	188.82	Mean	12.91	257.06
S.D.	2.58	84.16	S.D.	6.06	130.84
Min.	4.64	81.82	Min.	4.32	111.43
Max.	15.00	458.18	Max.	20.00	480.00
Week 5			Week 10		
N	37	34	N	33	29
Mean	10.52	229.50	Mean	12.64	256.63
S.D.	4.33	98.98	S.D.	6.02	129.51
Min.	3.57	109.09	Min.	3.96	115.38
Max.	17.86	420.00	Max.	20.00	480.00

* Patient No. 208 - Week 2 visit was determined to be invalid as the p.m. dose prior to and the a.m. dose of study drug was not taken before the week 2 visit. The last dose of HCTZ was taken 2 days before the week 2 visit.

Patient No. 404 - Week 2 visit was determined to be invalid as the last doses of both the study drug and hydrochlorothiazide were taken four days prior to the Week 2 visit.

N.B. Most patients received a daily dose of 50 mg hydrochlorothiazide. Four PN 200-110 treated patients (Nos. 102, 152, 153 and 353) and seven propranolol treated patients (Nos. 107, 110, 111, 151, 154, 158 and 306) received 100 mg hydrochlorothiazide daily.

0409-02488

SUMMARY COMPARATIVE RESULTS FOR TREATMENT X INVESTIGATOR, TREATMENT X TIME,
 AND TREATMENT X TIME X INVESTIGATOR INTERACTIONS FOR THE PLATEAU PERIOD - VALID PATIENTS

Variable	Investigator	Baseline Mean (Sample Size)		Mean Change From Baseline		Treatment x Investigator Interaction	Treatment x Time Interaction	Treatment x Time x Investigator Interaction
		PN 200-110	Propranolol	PN 200-110	Propranolol	p-value	p-value	p-value
Supine Systolic B.P. (mmHg)	A	156.0 (8)	161.0 (9)	-28.0	-21.0	0.678	0.643	0.474
	B	152.9 (8)	154.6 (8)	-20.7	-16.7			
	C	144.5 (8)	146.1 (7)	-12.6	-16.9			
	D	153.3 (9)	150.3 (5)	-16.7	-16.5			
Supine Diastolic B.P. (mmHg)	A	105.5 (6)	105.8 (9)	-15.8	-13.4	0.715	0.982	0.787
	B	105.2 (8)	107.4 (8)	-15.9	-17.3			
	C	107.1 (8)	102.7 (7)	-15.7	-16.5			
	D	100.8 (9)	103.6 (5)	-13.2	-15.0			
Supine Pulse (beats/min)	A	73.6 (6)	73.7 (9)	9.5	-14.8	0.073	0.312	0.939
	B	75.5 (8)	79.6 (8)	5.7	-13.0			
	C	92.5 (8)	83.1 (7)	-6.5	-14.3			
	D	71.7 (9)	74.6 (5)	3.1	-11.4			
Standing Systolic B.P. (mmHg)	A	145.8 (8)	151.1 (9)	-26.8	-22.2	0.984	0.787	0.220
	B	147.6 (8)	147.0 (8)	-20.9	-18.2			
	C	138.0 (8)	134.0 (7)	-15.4	-14.4			
	D	153.7 (9)	150.3 (5)	-19.1	-14.4			
Standing Diastolic B.P. (mmHg)	A	100.1 (8)	102.1 (9)	-16.3	-11.3	0.525	0.366	0.252
	B	108.1 (8)	105.5 (8)	-16.9	-15.3			
	C	101.4 (8)	97.6 (7)	-13.0	-13.9			
	D	109.6 (9)	111.4 (5)	-12.4	-14.7			
Standing Pulse (beats/min)	A	81.5 (8)	84.4 (9)	8.8	-21.8	0.088	0.773	0.779
	B	89.1 (8)	89.1 (8)	7.6	-16.5			
	C	101.8 (8)	96.0 (7)	-8.6	-23.4			
	D	84.0 (9)	86.2 (5)	4.4	-18.4			

TABLE 9

TABLE 10
 PN 200-110 STUDY NO. 307

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

Variable	Treatment Group	No. Pts.	Baseline		Mean Change	S.D.	Adjusted Mean Change*	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mmHg)	PN 200-110	40	152.3	21.84	-13.5***	17.44		138.7	15.05
	Propranolol	38	155.8	18.09	-13.6***	13.67		142.3	21.20
Supine Diastolic B.P. (mmHg)	PN 200-110	40	104.8	7.66	-10.1***	7.64		94.7	9.07
	Propranolol	38	105.8	7.58	-10.0***	8.57		95.9	10.97
Supine Pulse (per min.)	PN 200-110	40	79.0	13.43	2.8	10.66	3.2	81.8	10.65
	Propranolol	38	77.5	10.70	-11.4***	11.48	-11.8	66.1	11.25
Standing Systolic B.P. (mmHg)	PN 200-110	40	146.0	20.96	-14.9***	18.29		131.1	15.55
	Propranolol	38	148.0	18.30	-10.7***	12.78		137.3	18.43
Standing Diastolic B.P. (mmHg)	PN 200-110	40	105.0	10.13	-9.6***	11.05	-9.5	95.4	10.54
	Propranolol	38	104.6	9.37	-7.9***	9.62	-7.9	96.8	11.58
Standing Pulse (per min.)	PN 200-110	40	90.1	14.07	2.1	11.57	2.4	92.2	11.68
	Propranolol	38	88.5	12.23	-17.6***	11.62	-18.0	70.9	13.40

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

*Presented only when analysis of covariance assumptions were met.

TABLE 11
PN 200-110 STUDY NO. 307

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

Variable	Treatment Group	No. Pts.	Baseline		Mean Change	S.D.	Adjusted Mean Change*	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mmHg)	PN 200-110	40	152.3	21.84	-13.5***	21.92		138.8	15.61
	Propranolol	36	156.6	18.29	-15.9***	14.07		140.7	19.37
Supine Diastolic B.P. (mmHg)	PN 200-110	40	104.8	7.66	-10.2***	9.38		94.7	10.58
	Propranolol	36	105.9	7.76	-12.9***	9.54		93.0	11.78
Supine Pulse (per min.)	PN 200-110	40	79.0	13.43	3.3(*)	10.55	3.5	82.5	12.06
	Propranolol	36	78.0	10.67	-11.1***	11.38	-11.3	66.9	12.34
Standing Systolic B.P. (mmHg)	PN 200-110	40	146.0	20.96	-13.0***	21.50	-13.5	133.0	18.58
	Propranolol	36	148.3	18.63	-14.5***	15.98	-13.8	133.8	17.84
Standing Diastolic B.P. (mmHg)	PN 200-110	40	105.0	10.13	-10.8***	11.95	-10.7	94.2	11.16
	Propranolol	36	104.7	9.28	-10.4***	11.28	-10.5	94.3	12.99
Standing Pulse (per min.)	PN 200-110	40	90.1	14.07	2.0	11.31	2.3	92.1	11.57
	Propranolol	36	88.9	12.41	-16.0***	12.71	-16.2	73.0	13.84

(*)p<0.10, *p<0.05, **p<0.01, ***p<0.001

*Presented only when analysis of covariance assumptions were met.

TABLE 12
PN 200-110 STUDY NO. 307

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

Variable	Treatment Group	No. Pts.	Baseline		Mean Change	S.D.	Adjusted Mean Change*	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mmHg)	PN 200-110	38	153.0	21.71	-13.9***	16.29		139.1	15.18
	Propranolol	38	155.8	18.09	-16.0***	18.96		139.8	25.70
Supine Diastolic B.P. (mmHg)	PN 200-110	38	104.5	7.50	-10.2***	8.57	-10.4	94.3	8.78
	Propranolol	38	105.8	7.58	-13.4***	10.56	-13.3	92.4	12.85
Supine Pulse (per min.)	PN 200-110	38	78.2	12.48	2.8°	8.54	3.0°	81.0	9.83
	Propranolol	38	77.5	10.70	-12.6***	10.85	-12.8	64.9	12.02
Standing Systolic B.P. (mmHg)	PN 200-110	38	146.4	20.47	-14.3***	18.90		132.1	14.64
	Propranolol	38	148.0	18.30	-15.6***	18.80		132.4	23.87
Standing Diastolic B.P. (mmHg)	PN 200-110	38	104.9	9.66	-10.2***	11.00		94.7	8.45
	Propranolol	38	104.6	9.37	-12.4***	11.88		92.2	14.01
Standing Pulse (per min.)	PN 200-110	38	89.2	12.59	3.3(°)	10.58	3.4°	92.5	11.04
	Propranolol	38	88.5	12.23	-18.3***	11.53	-18.4	70.3	14.82

(*)p<0.10, °p<0.05, **p<0.01, ***p<0.001

*Presented only when analysis of covariance assumptions were met.

TABLE 13
PN 200-110 STUDY NO. 307

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

Variable	Treatment Group	No. Pts.	Baseline		Mean Change	S.D.	Adjusted Mean Change [†]	Treatment Period	
			Mean	S.D.				Mean	S.D.
Supine Systolic B.P. (mmHg)	PN 200-110	37	151.1	18.66	-15.7***	15.96		135.4	13.04
	Propranolol	36	156.0	18.10	-15.5***	14.56		140.5	19.19
Supine Diastolic B.P. (mmHg)	PN 200-110	37	104.2	7.43	-13.4***	6.63		90.8	8.26
	Propranolol	36	106.0	7.72	-14.1***	7.04		91.9	10.05
Supine Pulse (per min.)	PN 200-110	37	78.2	12.65	1.9	9.73	2.1	80.1	10.52
	Propranolol	36	77.2	10.87	-11.9***	11.02	-12.1	65.3	10.62
Standing Systolic B.P. (mmHg)	PN 200-110	37	145.6	20.01	-15.8***	17.74		129.8	12.63
	Propranolol	36	148.4	18.61	-14.8***	14.74		133.5	18.06
Standing Diastolic B.P. (mmHg)	PN 200-110	37	104.9	9.79	-12.4***	9.47		92.6	7.58
	Propranolol	36	104.8	9.29	-11.7***	8.49		93.1	10.64
Standing Pulse (per min.)	PN 200-110	37	89.4	12.74	2.6	10.05	2.9	91.9	9.80
	Propranolol	36	87.9	12.11	-19.3***	9.74	-19.6	68.6	11.71

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

[†]Presented only when analysis of covariance assumptions were met.