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.

TABLE 8

TABLE 9

PN 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
		PN 200-110	Propranolol	PN 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	0.584
	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

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 10

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 11

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	11.78
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	7.90

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

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

TABLE 12

TABLE 13
FH 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)	FH 200-110	37	147.9	17.17	-18.4***	-14.3***	-16.2***	-18.2***	-17.3*** (d)	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)	FH 200 110	37	101.9	5.35	-14.1*** (d)	-15.6*** (d)	-16.1*** (d)	-16.1*** (d)	-15.4*** (d)	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.)	FH 200-110	37	78.6	10.79	3.2(*) (d)	3.0(*) (d)	6.4** (d)	3.9(*) (d)	4.1** (d)	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	6.34

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

TABLE 14
PN 200-110 STUDY NO. 304

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	21.29
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	-9.0	93.3	10.05
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	-12.0	63.1	8.76

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

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

TABLE 15

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 intial 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	Seborrnea 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.

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
Propranolol	201	Heart	SEM 2/6 along left sternal border (not noted on initial physical exam but was recorded pre-study)*
	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	Atrial gallop-lower left sternal border
			2, 4, 6, 8	Grade II/VI systolic murmur, lower left sternal border
	155	Extremities	1, 2, 4, 6, 8, 10	Bipedal pitting edema to knee - 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

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, 6, 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

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
		Dyspnea Paroxysmal	1	Shortness of breath - wheezing
		Pulmonary Findings	1	Non-cardiac bronchospasm
	352	Other	8	Diarrhea
	356	Cough	1, 2	
		Dyspnea Exertion	2	Bronchitis past week - lung field clear

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
yspnea 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) 213 (10) 302 (1)		7/36	0/35
Abdomen	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) 307 (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

TABLE 33
(Continued)

PN 200-110 STUDY NO. 302

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110 (Continued)	415	Nasal Dryness Energy Decrease	4 - Mild 4 - Mild		
	418	Weight Gain Coordination, Diff/ Loss	4 - Moderate 2 - Mild	3 - Mild	
Placebo	105	Chest Pain	2 - Moderate	4 - Moderate	
	107	Palpitation	4 - Mild		
	113	Flatulence	4 - Moderate		
	115	Tinnitus	1 - Mild	4 - Mild	
	152	Dizziness	-3 - Mild		
	154	Constipation	2 - Mild		
	158	URI Coughing Headache	-2 - Mild 2 - Mild -3 - Moderate	-1 - Mild 3 - Mild	
	159	Back Ache/Pain, etc. Chest Pain	4 - Moderate -2 - Mild		
	202	Edema Cramps Leg/Feet Tingling	1 - Mild -2 - Mild -2 - Mild	4 - Mild	
	204	Dry Mouth	2 - Mild		
	205	Diarrhea Dizziness	3 - Mild 2 - Mild	4 - Mild	

*Presented only if there is a multiple occurrence.

**Presented only if different from information recorded under first or last occurrence.

TABLE 33
(Continued)

PN 200-110 STUDY NO. 302

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
Placebo (Continued)	252	Headache Hyperdipsia (Thirsty)	1 - Mild 3 - Mild		
	254	Dizziness	-1 - Mild	3 - Mild	
	257	Throat Pain/Numb/Ache, etc. Headache	-2 - Mild 2 - Mild		
	302	Joint Pain Numbness	4 - Mild -2 - Moderate	4 - Moderate	
	304	Back Ache/Pain, etc. Nasal Congestion	-2 - Moderate -1 - Mild	1 - Moderate	
	306	URI with Cough Chest Pain Headache	-2 - Moderate -3 - Mild 3 - Moderate		
	307	Coughing Headache	1 - Mild -3 - Mild	2 - Mild 4 - Moderate	-1 - Moderate
	312	Headache	-1 - Mild		
	313	Dizziness Chest Pain	2 - Mild 2 - Mild	3 - Mild	
	315	Cold Throat Discomfort Fatigue	-1 - Mild -3 - Mild -1 - Mild	2 - Mild 2 - Mild	
	352	Dizziness	-1 - Mild		
	356	Dizziness Dry Mouth	1 - Mild -3 - Mild	2 - Mild	
	357	Nausea Vomiting Headache	2 - Moderate 2 - Moderate 1 - Mild		

resented only if there is a multiple occurrence.

**Presented only if different from information recorded under first or last occurrence.

TABLE 33
(Continued)

PN 200-110 STUDY NO. 302

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
Placebo (Continued)	359	Arthritis	-2 - Mild	4 - Mild	
		Chest Pain	-3 - Mild		
		Edema	2 - Mild	4 - Mild	
		Diarrhea	3 - Mild		
		Nausea	3 - Mild		
		Dizziness	-3 - Moderate	2 - Mild	
		Drowsy	1 - Mild	4 - Mild	
		Fatigue	-1 - Mild	1 - Mild	
		Headache	2 - Mild	4 - Mild	
	361	Cold	-1 - Mild		
		Teeth Ache, Pain, etc.	3 - Moderate	4 - Moderate	
		Dizziness	4 - Mild		
		Drowsy	2 - Moderate	4 - Mild	
		Headache	-1 - Mild		
		Nervousness	2 - Moderate	4 - Mild	
	403	Weight Gain	-3 - Moderate	-2 - Moderate	
		Rash	-1 - Mild	2 - Mild	
		Impotence	3 - Mild	4 - Mild	
		Many Dreams	3 - Mild	4 - Mild	
		Headache	-1 - Mild		
	409	Weight Gain	-3 - Moderate	-2 - Moderate	
	414	Backache/Pain, etc.	3 - Moderate	4 - Mild	
		Coughing	4 - Mild		
		Dizziness	2 - Mild		
		Headache	1 - Mild		
	416	Headache	4 - Mild		
	417	Abdominal Discomfort	1 - Moderate		
		Nervousness	1 - Severe		
		Shakiness, Shaking	1 - Severe		
		Hyperhidrosis	1 - Severe		

*Presented only if there is a multiple occurrence.

**Presented only if different from information recorded under first or last occurrence.

TABLE 34
PN 200-110 STUDY NO. 302
COMPARATIVE ADVERSE REACTION FREQUENCIES ADJUSTED FOR BASELINE EFFECTS

Body System Adverse Reaction	Week 1		Week 2		Week 3		Week 4		Entire Study Period*	
	PN 200-110 (n = 49)	Placebo (n = 49)	PN 200-110 (n = 49)	Placebo (n = 48)	PN 200-110 (n = 42)	Placebo (n = 45)	PN 200-110 (n = 42)	Placebo (n = 45)	PN 200-110 (n = 49)	Placebo (n = 49)
Miscellaneous										
Teeth Ache, Pain, etc.						1 (2.2)		1 (2.2)		1 (2.0)
Weight Gain					1 (2.4)		1 (2.4)		2 (4.1)	
Skin										
Mouth Sores/Ulcers					1 (2.4)		1 (2.4)		1 (2.0)	
Rash					1 (2.4)				1 (2.0)	
Muscle-Skeletal										
Backache/Pain						1 (2.2)		2 (4.4)		2 (4.1)
Arm/Leg Heavy/Tired					1 (2.4)				1 (2.0)	
Joint Pain								1 (2.2)		1 (2.0)
Legs Ache/Pain							1 (2.4)		1 (2.0)	
Respiratory										
Chest Congestion					1 (2.4)				1 (2.0)	
Coughing		1 (2.0)	2 (4.1)	2 (4.2)		1 (2.2)		1 (2.2)	2 (4.1)	3 (6.1)
Nasal Dryness							1 (2.4)		1 (2.0)	
Cardiovascular										
Chest Pain				2 (4.2)		1 (2.2)	1 (2.4)	1 (2.2)	1 (2.0)	2 (4.1)
Dyspnea			1 (2.0)						1 (2.0)	
Edema		1 (2.0)		2 (4.2)	3 (7.1)	2 (4.4)	3 (7.1)	2 (4.4)	4 (8.2)	2 (4.1)
Palpitations	1 (2.0)		1 (2.0)		1 (2.4)		2 (4.8)	1 (2.2)	2 (4.1)	1 (2.0)
Tachycardia					1 (2.4)				1 (2.0)	
Gastrointestinal										
Abdominal Discomfort		1 (2.0)	3 (6.1)						3 (6.1)	1 (2.0)
Constipation	2 (4.1)			1 (2.1)			1 (2.4)		3 (6.1)	1 (2.0)
Diarrhea						2 (4.4)		1 (2.2)		2 (4.1)
Flatulence								1 (2.2)		1 (2.0)
Nausea	1 (2.0)			1 (2.1)		1 (2.2)	1 (2.4)		2 (4.1)	2 (4.1)
Stools, Loose	1 (2.0)		1 (2.0)						1 (2.0)	
Vomiting				1 (2.1)						1 (2.0)
Urogenital										
Diuresis	1 (2.0)								1 (2.0)	
Impotence						1 (2.2)		1 (2.2)		1 (2.0)
Nocturia			1 (2.0)						1 (2.0)	
Polluduria					1 (2.0)				1 (2.0)	
Central Nervous System										
Coordination, Diff/Loss			1 (2.0)		1 (2.4)				1 (2.0)	
Dizziness		1 (2.0)		4 (8.3)	1 (2.4)		3 (7.1)	1 (2.2)	4 (8.2)	5 (10.2)
Energy Decrease							1 (2.4)		1 (2.0)	
Drowsy		1 (2.0)		2 (4.2)		2 (4.4)		2 (4.4)		2 (4.1)
Headache	3 (6.1)	3 (6.1)	5 (10.2)	2 (4.2)	4 (9.5)	1 (2.2)	5 (11.9)	2 (4.4)	9 (18.4)	7 (14.3)
Many Dreams	1 (2.0)		1 (2.0)			1 (2.2)		1 (2.2)	1 (2.0)	1 (2.0)
Nervousness,		1 (2.0)		1 (2.1)		1 (2.2)		1 (2.2)		2 (4.1)
Shakiness, Shaking		1 (2.0)								1 (2.0)
Tinnitus		1 (2.0)		1 (2.1)		1 (2.2)		1 (2.2)		1 (2.0)
Autonomic Nervous System										
Flushing					1 (2.4)		1 (2.4)		1 (2.0)	
Dry Mouth				1 (2.1)						1 (2.0)
Hyperhidrosis		1 (2.0)	1 (2.0)		1 (2.4)				1 (2.0)	1 (2.0)
Hyperdipsia						1 (2.2)				1 (2.0)
Visual Disturbance							1 (2.4)		1 (2.0)	

*p>.10 for each adverse reaction for comparing PN 200-110 to placebo (Fisher's Exact Test).

Figure 7

PN 200-110 STUDY #302
Supine Systolic BP
Change from Baseline for All Valid Patients
(n=77)

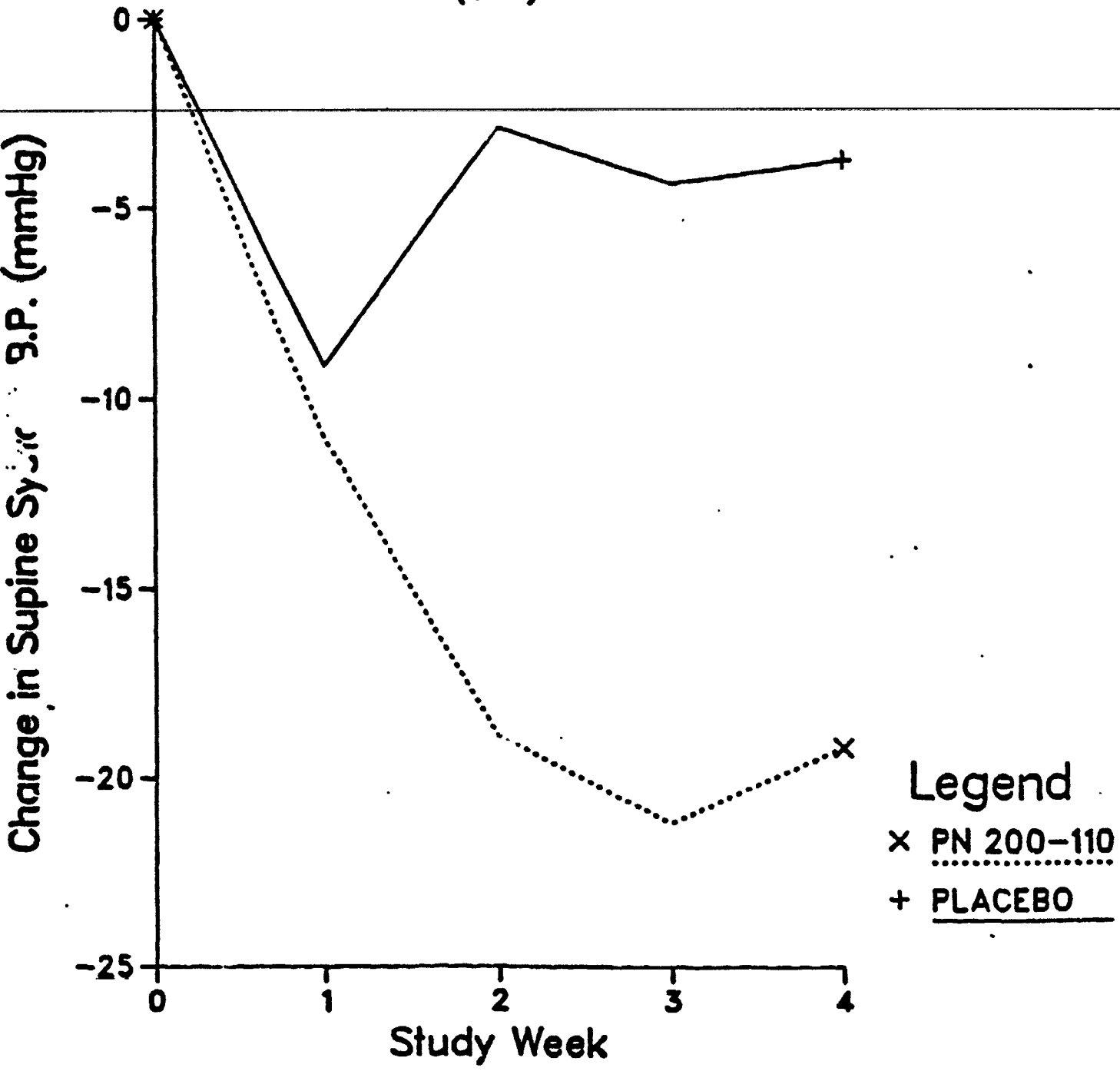


Figure 8

PN 200-110 STUDY #302
Supine Diastolic BP
Change from Baseline for All Valid Patients
(n=77)

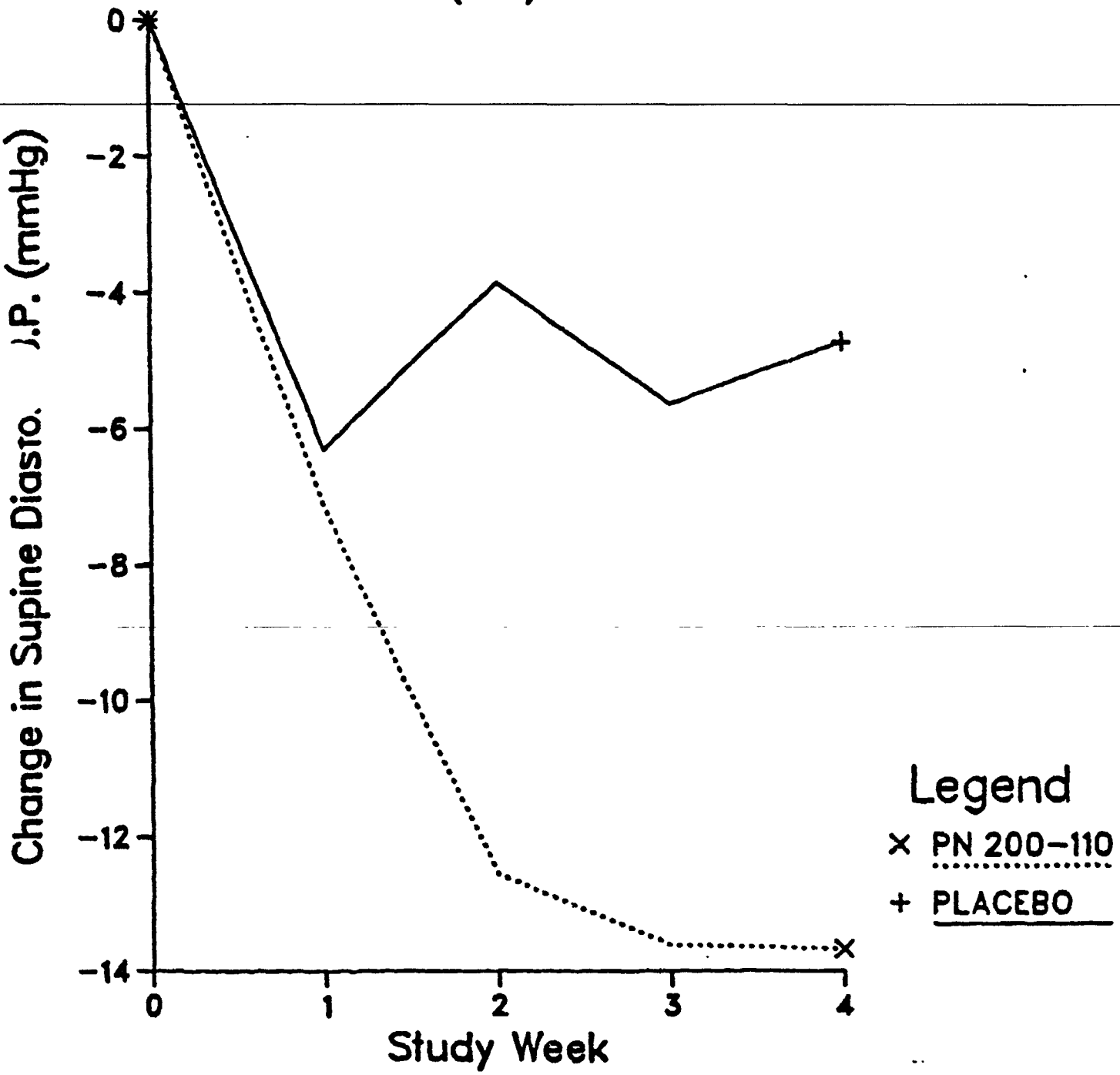


Figure 9

PN 200-110 STUDY #302
Supine Pulse Rate
Change from Baseline for All Valid Patients
(n=77)

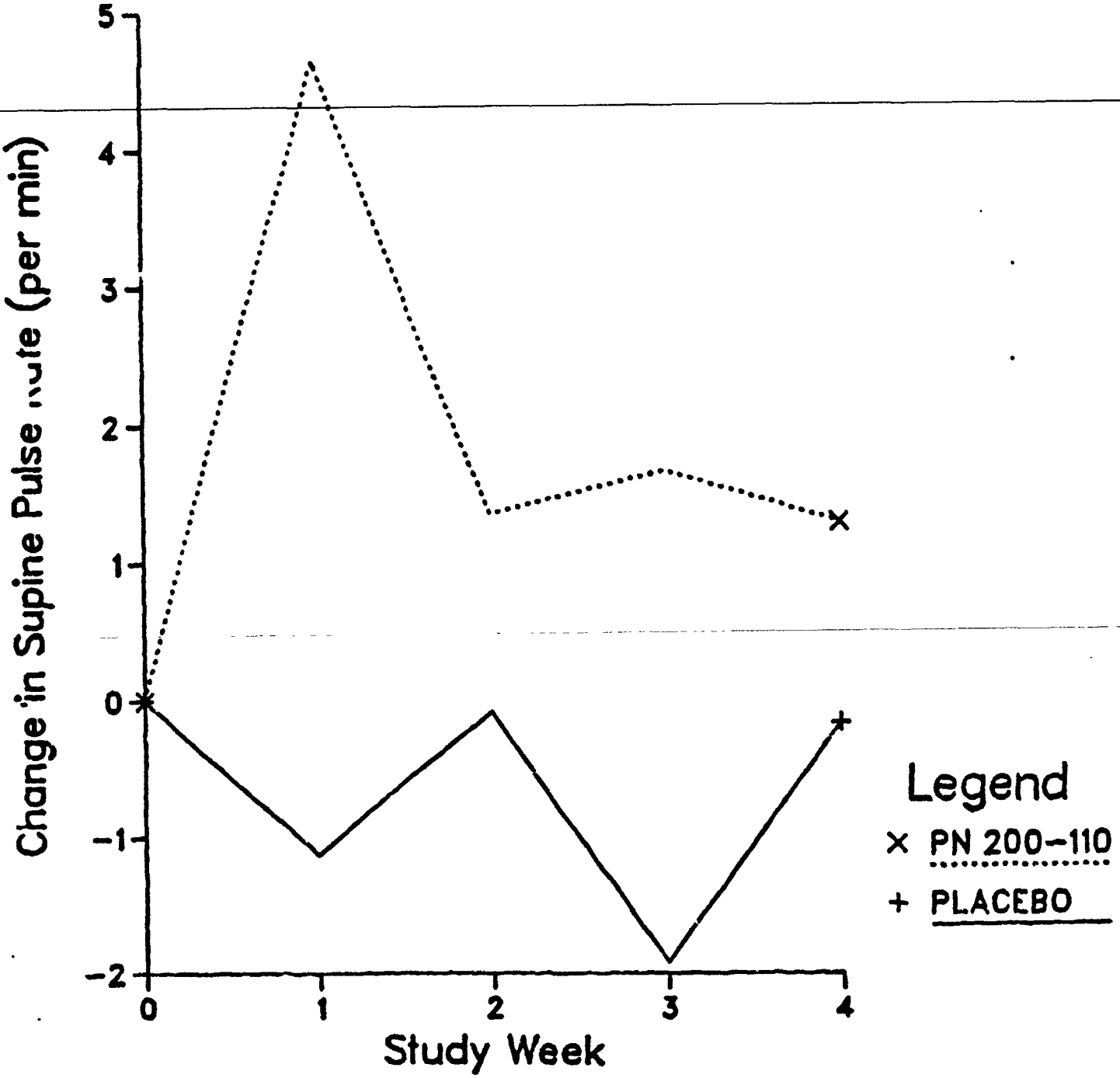


Figure 10

PN 200-110 STUDY #302
Standing Systolic BP
Change from Baseline for All Valid Patients
(n=77)

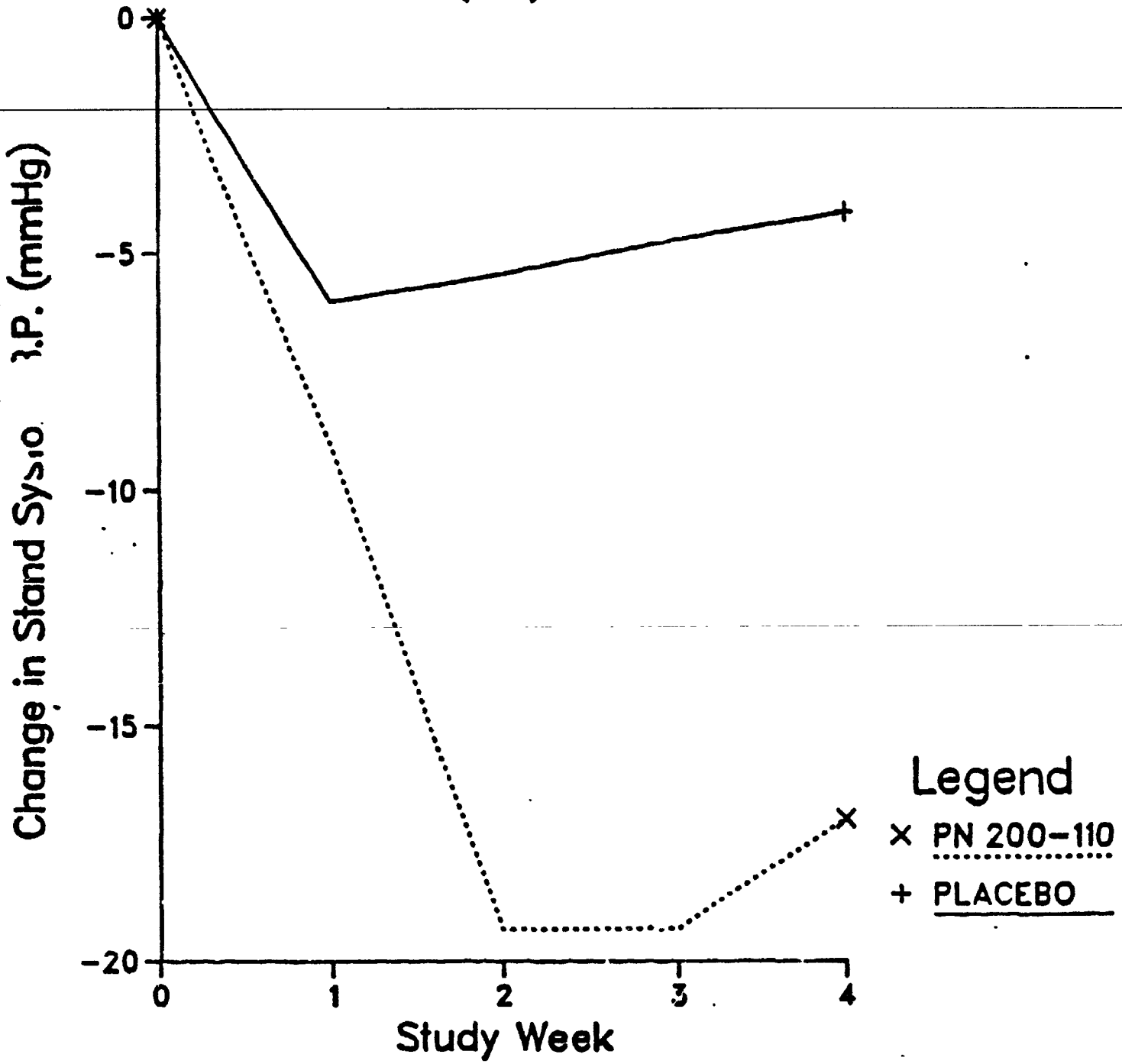


Figure 11

PN 200-110 STUDY #302
Standing Diastolic BP
Change from Baseline for All Valid Patients
(n=77)

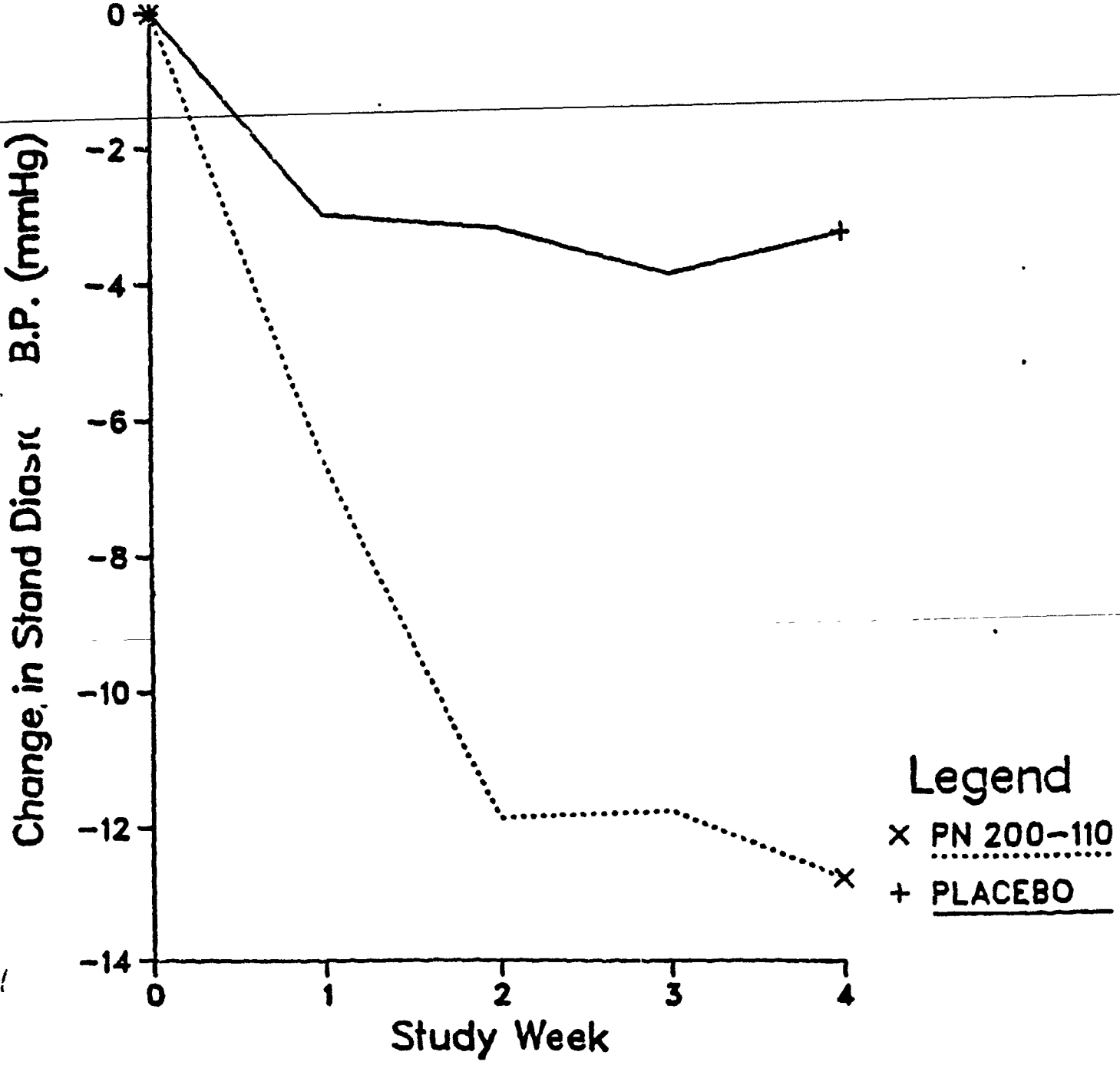


Figure 12

PN 200-110 STUDY #302
Standing Pulse Rate
Change from Baseline for All Valid Patients
(n=77)

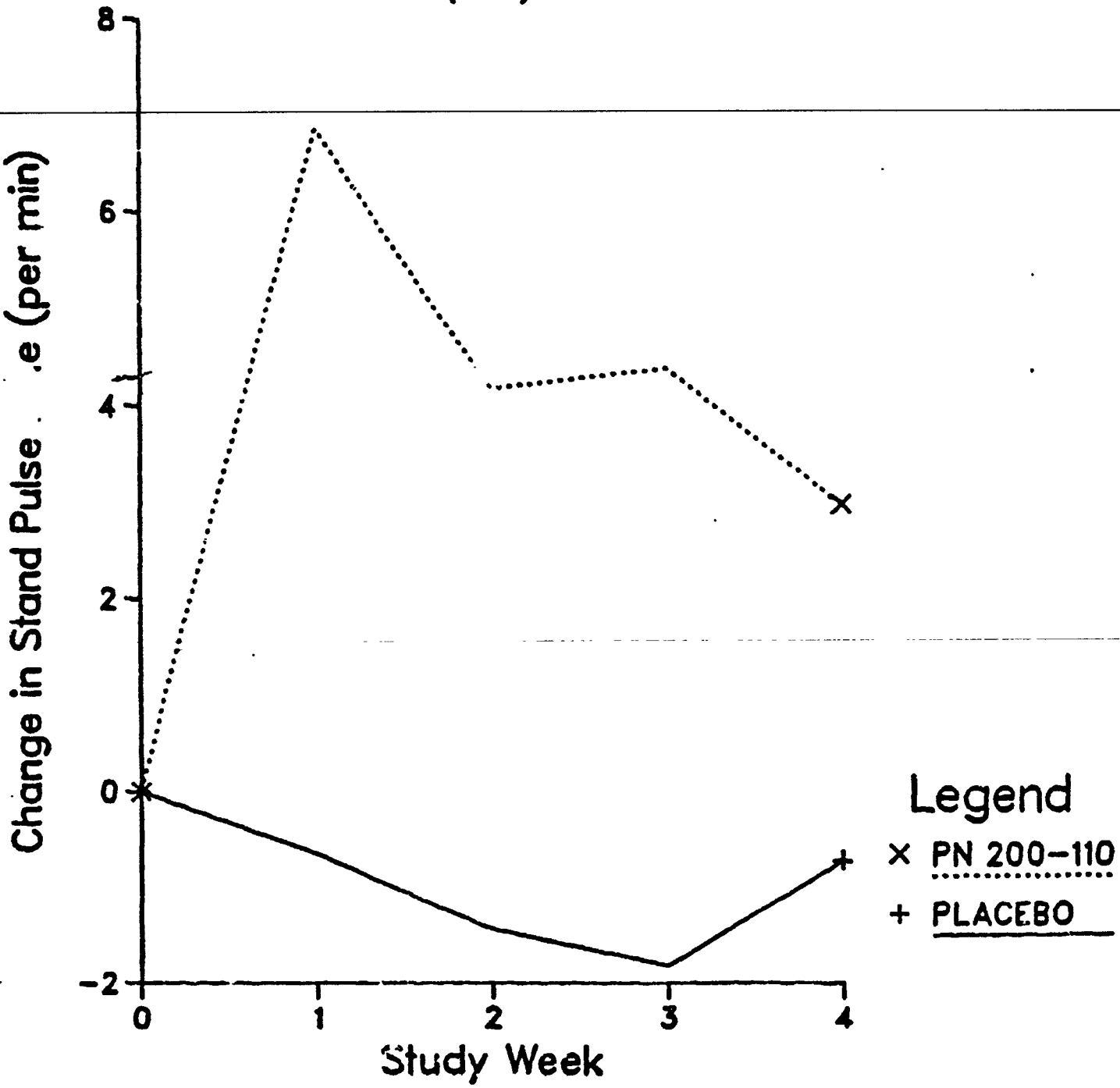


Figure 13

PN 200-110 Study #302
..nmary of 24 hour ambulatory monitoring
Patient 301
Treatment group is PN 200-110

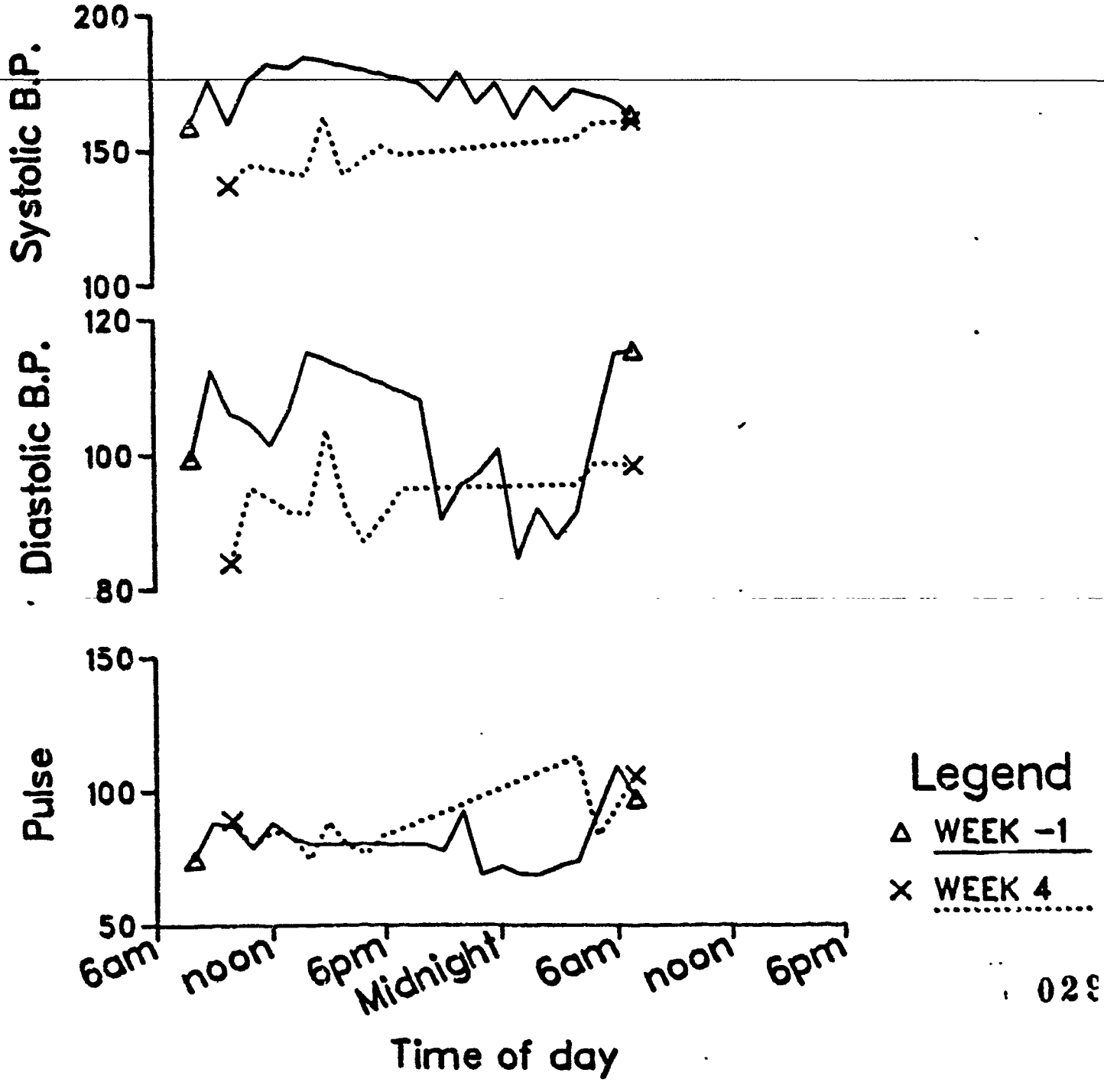
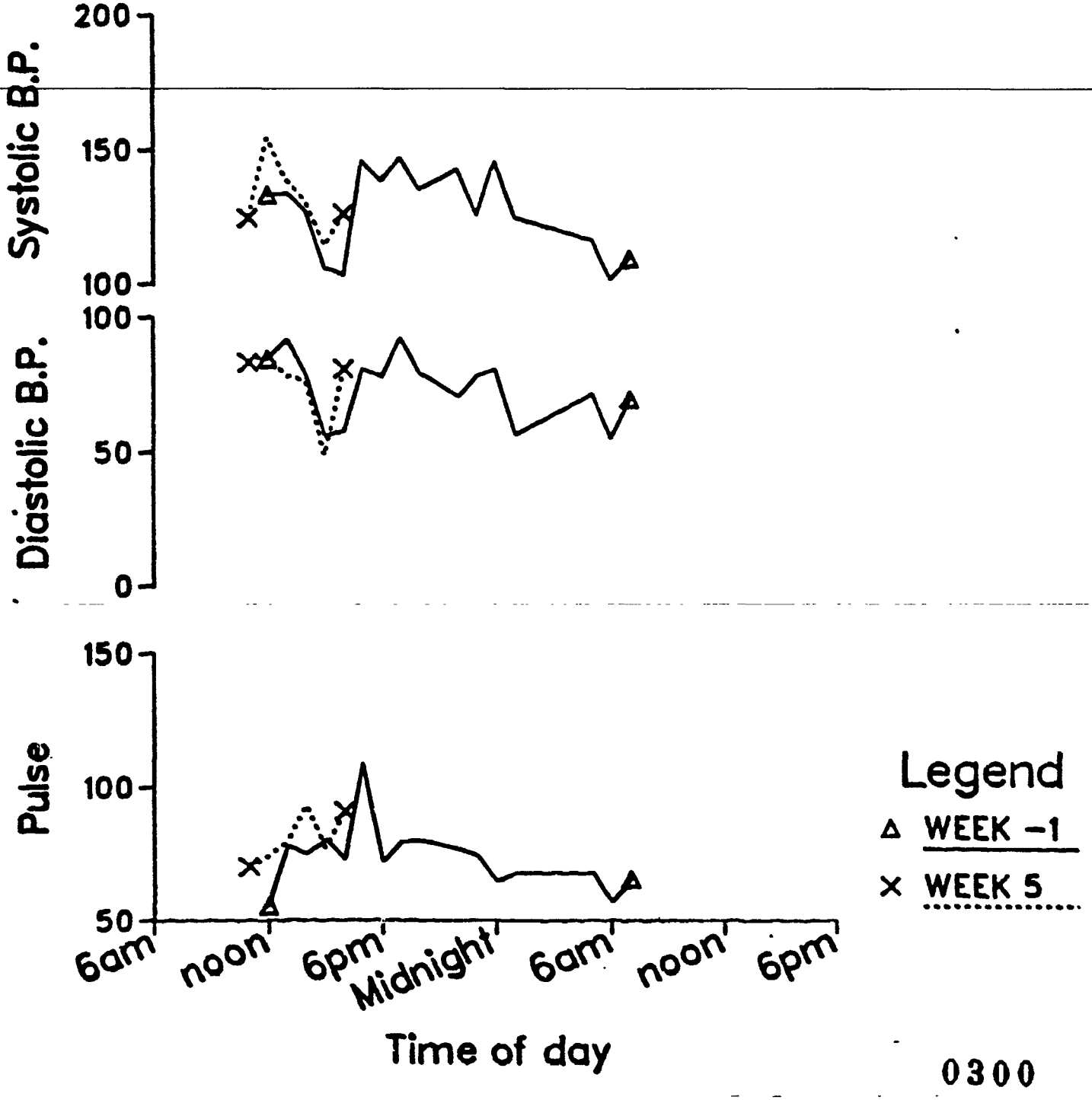


Figure 14

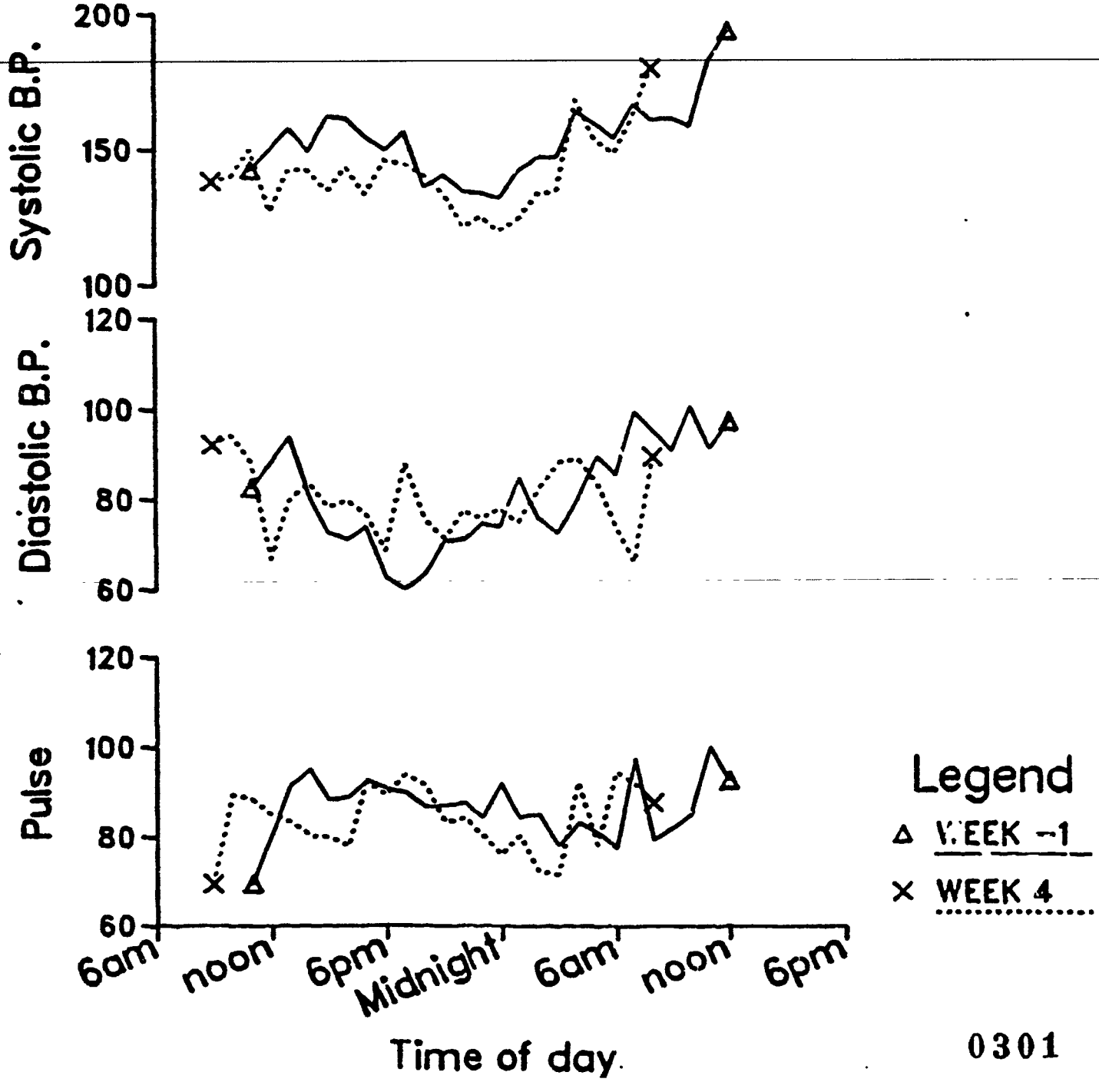
PN 200–110 Study #302
mmary of 24 hour ambulatory monitoring
Patient 309
Treatment group is PN 200–110



0300

Figure 15

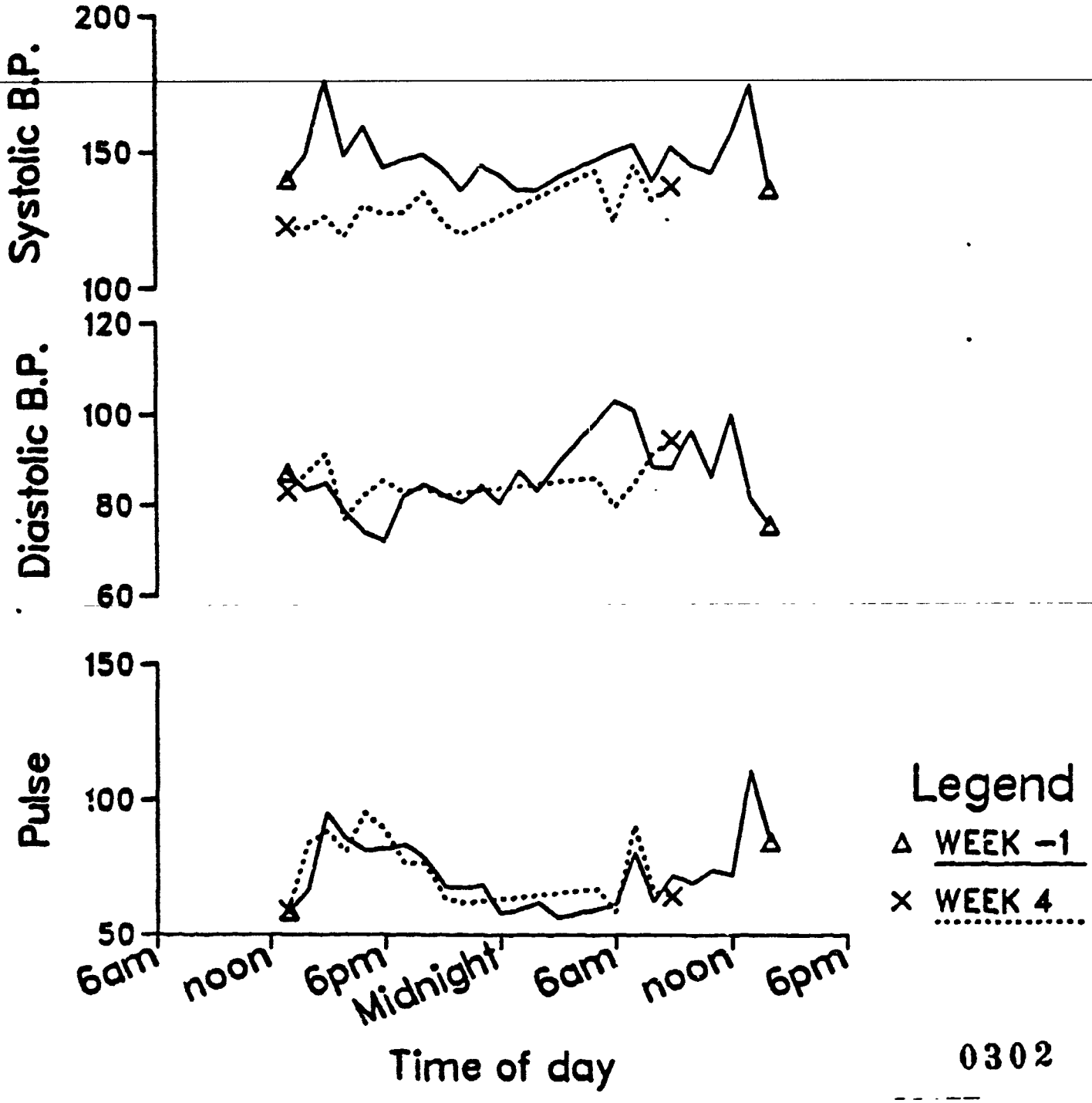
PN 200–110 Study #302
Summary of 24 hour ambulatory monitoring
Patient 311
Treatment group is PN 200–110



0301

Figure 16

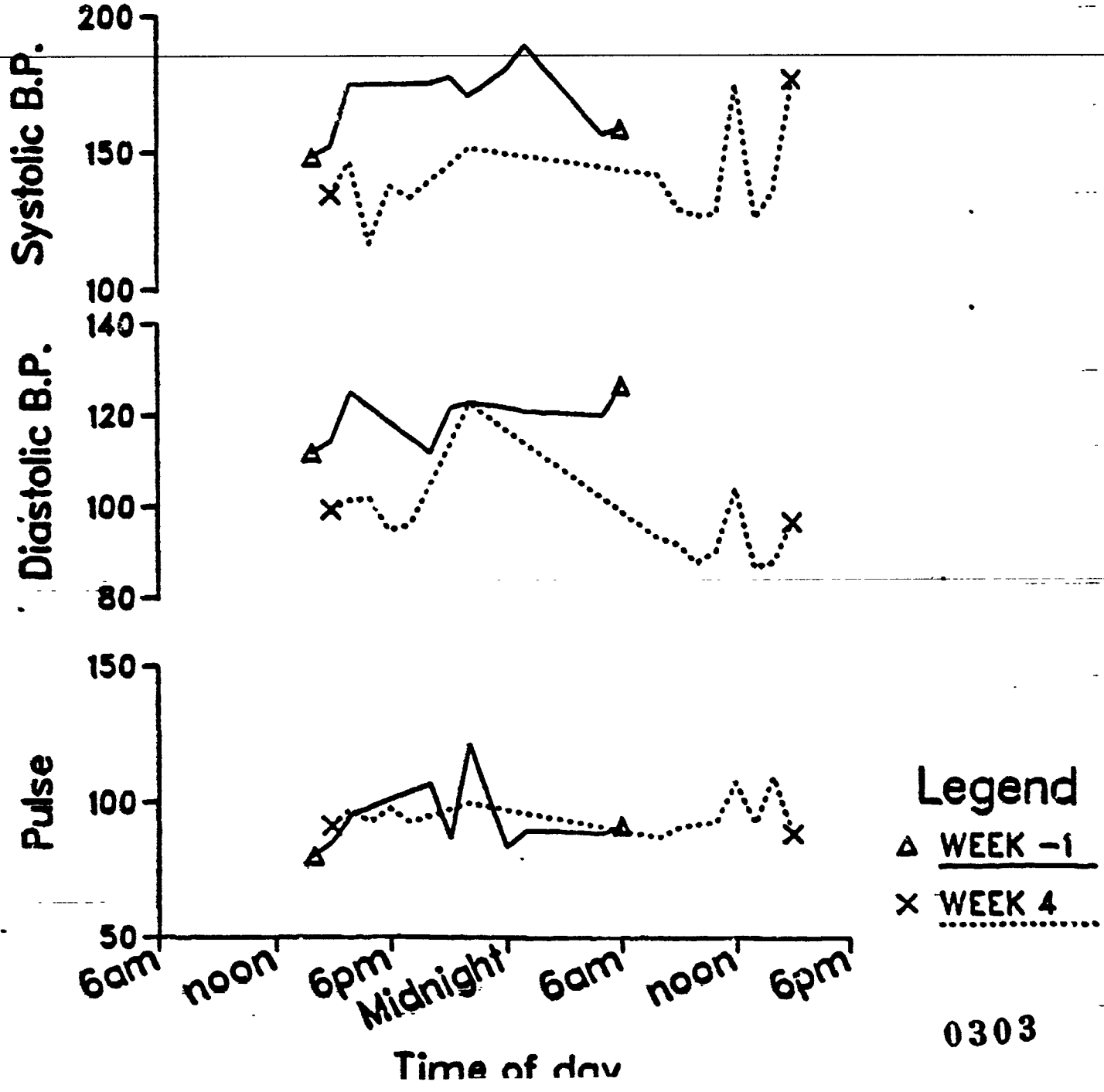
PN 200–110 Study #302
nmary of 24 hour ambulatory monitoring
Patient 351
Treatment group is PN 200–110



0302

Figure 17

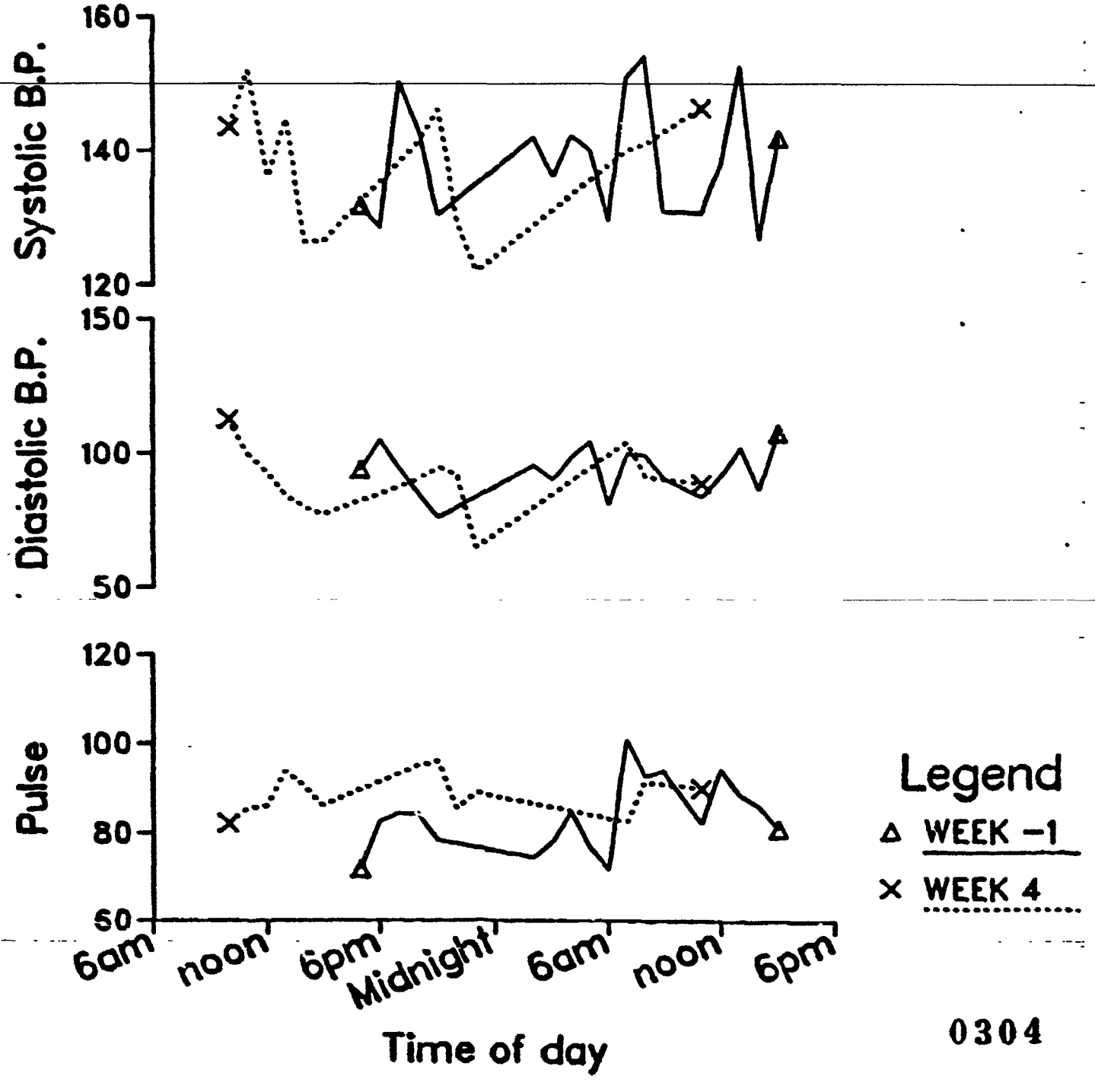
PN 200–110 Study #302
Summary of 24 hour ambulatory monitoring
Patient 355
Treatment group is PN 200–110



0303

Figure 18

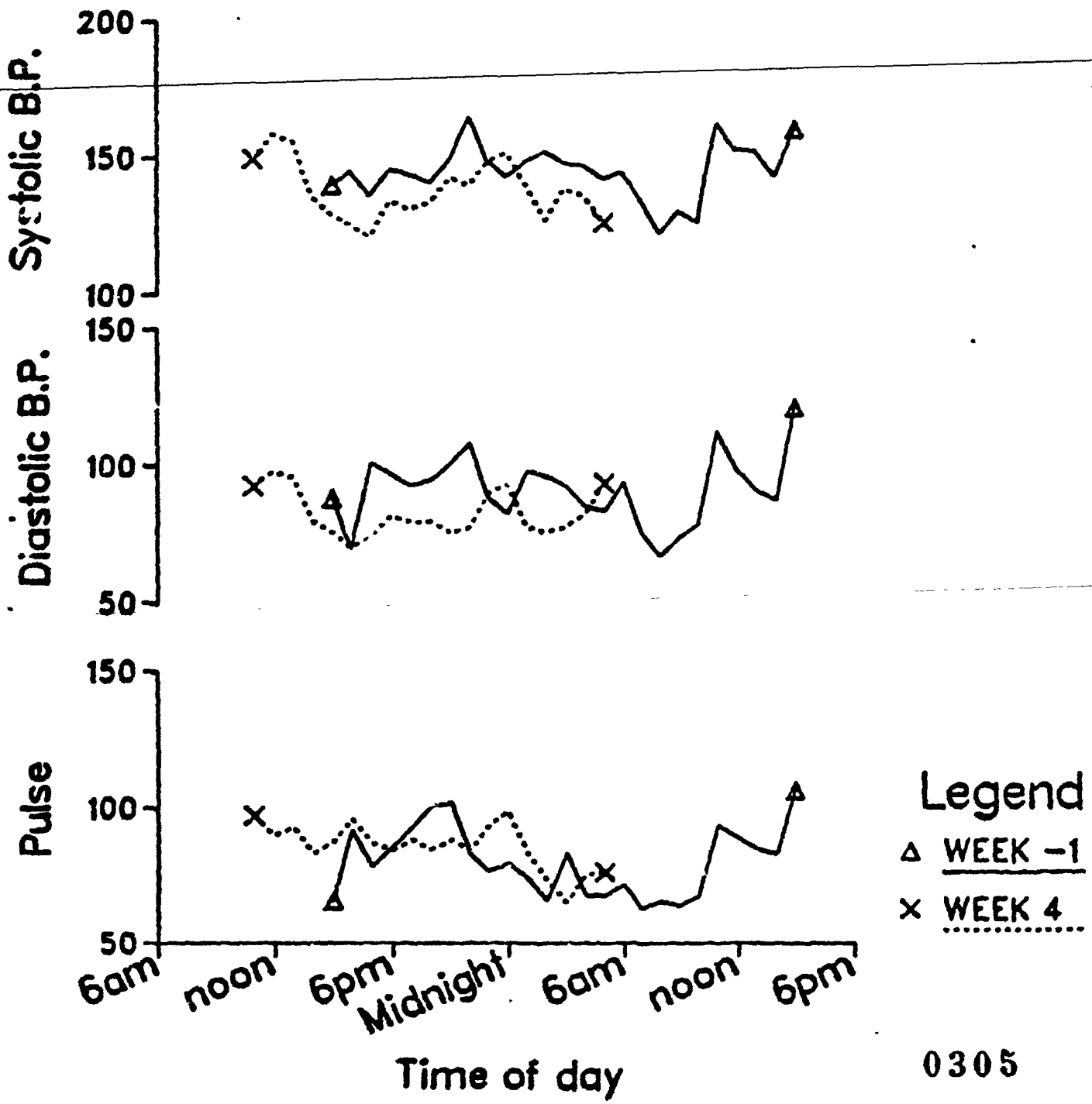
PN 200–110 Study #302
..nmary of 24 hour ambulatory monitoring
Patient 310
Treatment group is Placebo



0304

Figure 19

PN 200–110 Study #302
Summary of 24 hour ambulatory monitoring
Patient 313
Treatment group is Placebo



0305

Figure 20

PN 200–110 Study #302
.nmary of 24 hour ambulatory monitoring
Patient 352
Treatment group is Placebo

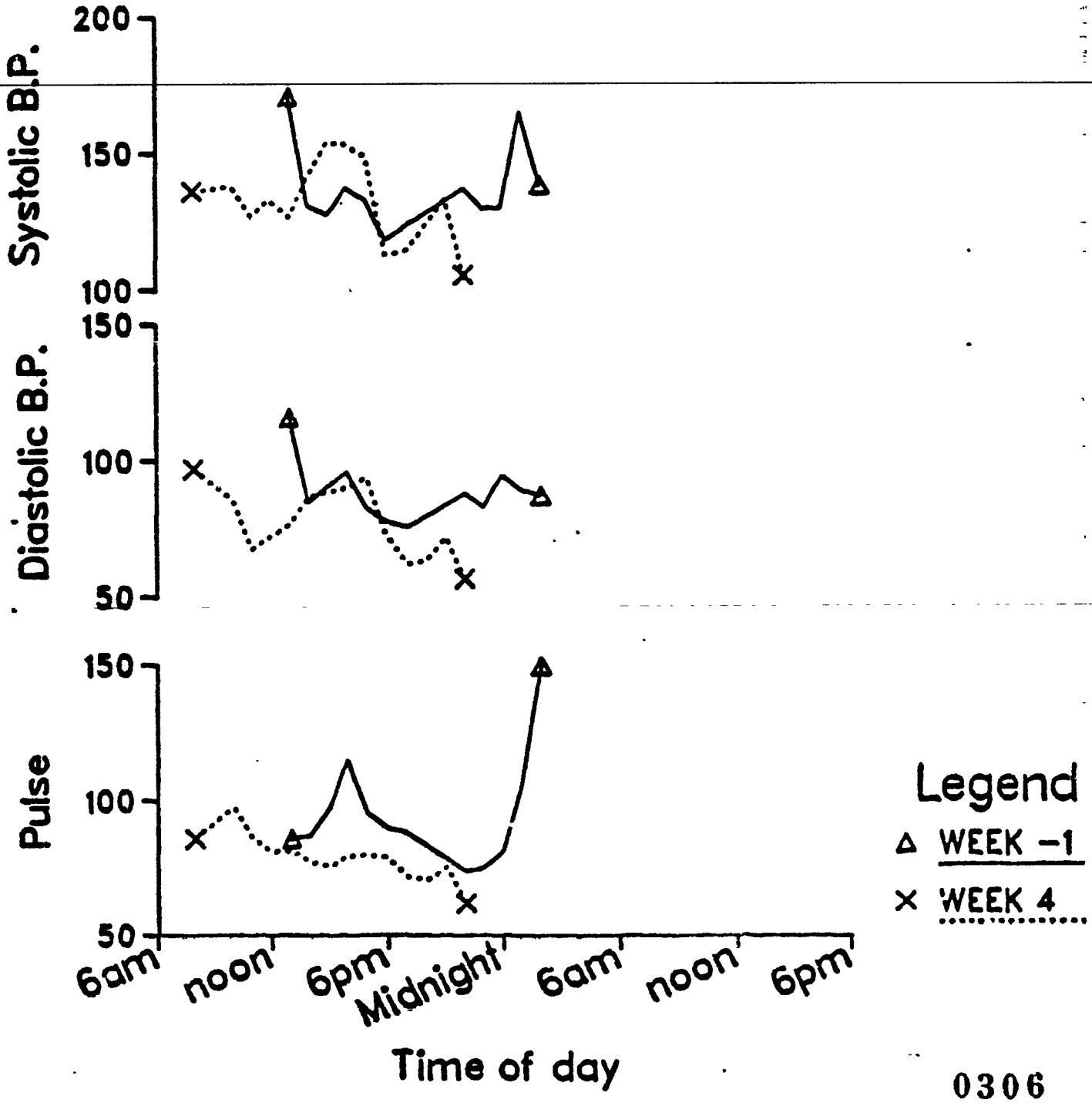
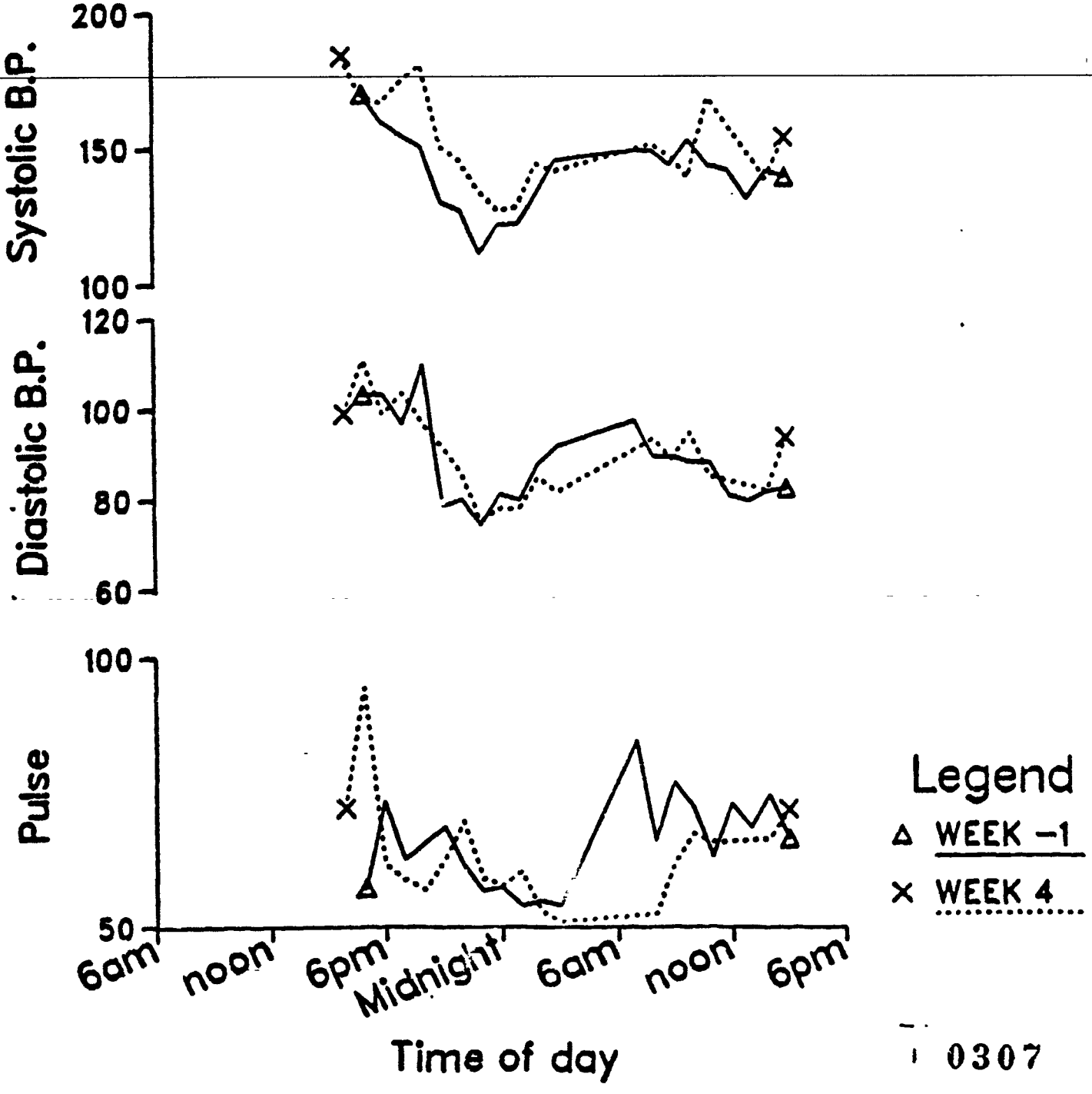


Figure 21

PN 200–110 Study #302
Summary of 24 hour ambulatory monitoring
Patient 353
Treatment group is Placebo



Protocol 303

Title

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

Investigators

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Dates of Study: May 23, 1984 to April 16, 1986.

Objective

To evaluate the safety and blood pressure lowering effect of PN 200-110 (PN) 5 - 10 mg bid, compared to hydrochlorothiazide (HCT) 25 - 50 mg bid, in patients with mild or moderate essential hypertension during a ten week period.

Design

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

Population

Outpatients of either sex, 18 years and older, with a diagnosis of benign essential hypertension were eligible for the study. For entry into the double blind period, patients were required to have a sitting diastolic blood pressure (SDBP) of > 95 mm Hg at end of placebo washout period.

Patients entered the 3 - 5 week placebo washout period, during which all previous antihypertensives were withdrawn. Sitting blood pressures were evaluated and, to qualify for study, patients were required to have a SDBP > 95 mm Hg on any two consecutive visits during this period. Placebo responders, defined as a continuous reduction in SDBP for each evaluation day of this period and a > 10 mm Hg decrease at end of period, and severe hypertensives SDBP > 120 mm Hg on two consecutive evaluation days, were excluded.

After completion of placebo period, qualified patients were randomized to either PN or HCT. Patients were stratified to groups > 95 - < 105 mm Hg and > 105 mm Hg. Medication was given as per schedule in Table 1; PN 5 mg bid or HCT 25 mg bid for 4 weeks. If average SDBP was > 90 mm Hg at end of week 4 or was > 110 mm Hg at end of week 2 or 3, dose was increased to PN 10 mg bid or HCT 50 mg bid for remainder of study (6 weeks). From week 5, the dose remained unchanged unless SDBP was more than 105 mm Hg, in which case dose was increased but could not excced PN 10 mg bid or HCT 50 mg bid. Dose could be reduced in case of ADR.

Evaluations

Table 2 presents evaluation schedule. Patients were seen weekly and vital signs recorded. Special examinations performed for investigator's interest included plasma lipid profiles at Centers A and C and plasma renin activity and plasma aldosterone at Center A.

Results

A total of 98 patients entered double blind phase with Center A contributing 29%, Center B (two sites in Richmond) 31% and Center C 41% of total. A total of 48 patients were randomized to PN and 50 to HCT. There were 73 (36 PN and 37 HCT) completing the study and considered completely valid for analysis. An additional 19 were partially valid and 6 were invalid for analyses. Four (two in each group) completed the study but were not valid as they had not satisfied entry criteria for blood pressure or compliance. Table 4 lists reasons for declaring patients invalid. Table 5 summarizes, by center, number of valid, partially valid and invalid patients. The [illegible]

[redacted]

The mean age of the patients was 53.9 years (24 - 74); 50 were male (54%); 40 (43%) were white, 48 (52%) black, 1 oriental and 3 "other". Mean duration of hypertension was 10.2 years. There was no statistically significant differences between the two treatment groups. Center C consisted of 77% white while other two centers were mainly black. Table 7 summarizes patient distribution by last week of study completed.

Mean daily dose of study drugs is shown in Table 8. Over fixed dose period (weeks 5 - 10), mean dose was 12.1 mg PN and 60.1 mg HCT. Dose was reduced for two patients during this period due to ADRs, fatigue (PN) and palpitations (HCT). Ten PN and 12 HCT were titrated to high dose during the study. Over 72% PN and 68% HCT were maintained on low dose for duration of active phase. Table 9 lists dose for partially valid patients.

Interactions

Table 10 summarizes statistical significance of interactions from analysis of efficacy variables. It also displays efficacy results by investigator and treatment for weeks 5 - 10. There was a statistically significant treatment x time x investigator interaction for sitting diastolic blood pressure. Table 11 gives the per-timepoint analysis for this variable. None of the treatment x investigator interactions showed statistical significance for this analysis at any week.

Efficacy

Blood pressure data from all 98 patients were analyzed; 73 were valid patients and 19 partially valid. The data from 6, considered invalid, were included in all-patient endpoint analysis. Analyses were done within and between groups as well as by categorizing as previously discussed in prior summaries.

Titration Weeks 1 - 4:

Tables 12 - 15 summarize results for weeks 1, 2, 3 and 4 of active treatment for valid and partially valid groups. SDBP results are summarized below.

Group

Fixed Dose Weeks 5 - 10

Tables 16 and 17 summarize results for this period for valid patients and valid plus partially valid respectively. Results of SDBP for valid patients was - 16.9 mm Hg (PN) and - 13.8 mm Hg (HCT). For endpoint analysis, the reductions were - 17.7 (PN) and - 12.9 mm Hg (HCT). Both drugs caused statistically significant reductions in SDBP compared to baseline with between group differences also being statistically significant.

The mean increase in pulse rates were 2 - 4 bpm for PN and was statistically significant from baseline and from HCT. Categorical analysis for valid patients is shown below.

Group	n =	Number (%) Patients			
		1	2	3	4
PN	36	26 (72%)	3 (8%)	5 (14%)	2 (6%)
Placebo	37	17 (46%)	11 (30%)	7 (19%)	2 (5%)

Approximately 80% of PN and 76% HCT had at least a 10 mm Hg decrease in SDBP; but, 72% PN versus 46% HCT had a mean SDBP < 85 mm Hg over this period. Sponsor maintains that this shows PN to be more efective than HCT when used as monotherapy. The results are reasonably consistent across centers, except center C had fewer category 1 patients than the other centers. About 89% PN and 86% HCT had a mean SDBP < 90 mm Hg.

All Patients - Endpoint Analysis.

Table 18 summarizes results for endpoint analyses for all patients, irrespective of validity.

Graphic Display - Valid Patients

Figures 1 - 3 present changes from baseline, by center while figures 4 - 6 display mean changes from baseline for all valid patients. As may be seen, there is a reduction in blood pressure after one week but full effect is not seen until the second week and then remains reasonably consistent [illegible]

There were no clinically significant changes in x-ray examinations. ECG changes are shown in Tables 23 - 25. There was a higher incidence of newly occurring abnormalities with PN than with HCT (50% v 38%). The most frequently reported events were sinus tachycardia, sinus bradycardia, sinus arrhythmia and ST and/ or T wave changes. PN patients exhibiting sinus tachycadia during the study, had a heart rate based on 88 - 100 bpm during placebo period. Those with bradycardia had a rate of 60 - 70 during placebo phase. Except for one patient (49 bpm), rate was at least 55 bpm. One PN was withdrawn due to atrial fibrillation. One PN had bigeminal rhythm at end of first week and was withdrawn due to palpitations.

Clinical Laboratory Tests

Table 27 presents results by center for hematology variables. Even though some of the results were statistically significant, they were not regarded as clinically significant. Table 28 presents urinalysis results and Table 29 chemistry. Variables that showed statistically significant mean changes from baseline in more than one center are: calcium, BUN, uric Acid, total protein, albumin,cholesterol, alkaline phosphatase, potassium, chloride and CO2. The changes normally expected from HCT were seen in this study. Changes by patient over time are presented in Tables 30, 32 and 34. There were no serious changes in SGOT or SGPT. Elevated alkaline phosphatase was recorded in 5 PN and 1 HCT patient. Blood glucose increased in 7 PN and 6 HCT patients.

Dropouts

Table 4 listed patients withdrawn from the study. A total of 10 PN and 11 HCT withdrew during active phase. PN had 7 withdrawals due to ADRs: 3 headaches, 1 myalgia/edema, 1 each atrial fibrillation, ankle edema, dizziness and palpitations. Five HCT withdrew. One PN who completed the study died of unknown causes 2 weeks later.

Special Evaluations.

Table 39 [illegible] from Center A for [illegible]

Week	PN	%	HCT	%
1	10/48	21	16/50	32
2	10/46	22	14/48	29
3	15/46	33	10/48	21
4	15/45	33	11/47	23
5	10/43	23	12/47	26
6	12/43	28	7/45	16
7	3/40	8	8/43	19
8	7/39	18	8/42	19
9	7/39	18	8/41	20
10	4/37	11	6/39	15
Weeks 1 - 10	33/48	69	38/50	76

There were no statistically significant differences between groups. Table 42 lists ADR by patient. The ADRs listed as severe were (PN): diarrhea, vomiting, headache, pollakuria, gout, inflamed eyes, dizziness. For HCT, the severe reactions were: flu, weakness, urinary infection, increased platelets, hypokalemia, backache and fatigue. Headaches were reported as severe in 3 PN patients, 2 requiring withdrawal from study. Table 43 presents comparative data after adjustment for baseline.

The most commonly reported events were headache, dizziness, palpitations, edema and abdominal discomfort. There was a statistically significant difference for edema compared to HCT. Two of nine edema patients were discontinued from the study. Weakness and chest pain were more frequent with HCT and abdominal discomfort with PN.

Discussioon

Both study drugs caused significant reductions in blood pressure after one week treatment with further reductions as study progressed. The reductions with PN were greater than with HCT.

Reviewer's Comments

1. Comments similar to previous studies. What were results if analysed according to stratification?

TABLE 1

PN 200-110 STUDY NO. 303

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 200-100 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.

TABLE 2

PH 200-110 STUDY NO. 303

FLOW CHART

Evaluation	Initial Visit	END OF WEEK													
		Single-Blind			Double-Blind: Active Treatment Period										
		Placebo Washout			Titration Period				Plateau Period						
	-4	-3	-2	-1 Time 0	1	2	3	4	5	6	7	8	9	10 Final Evaluations	12 Follow-up Evaluation
Background Information CRF BK, PH*	X														
Physical Exam CRF PE	X													X*	
Cardiovascular Evaluation CRF CV	X			X	X		X**	X	X	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*	
Laboratory Evaluation (incl. urinalysis, CBC, blood chem.) CRF LAB	X			X	X[1]	X[1]	X[1]	X	X[1]	X[1]	X	X[1]	X[1]	X*	X[1]
ECG Evaluation CRF ECG	X			X	X		X**	X	X	X**	X**	X	X**	X*	
Chest X-Ray CRF CX	X†													X*	
Ophthalmologic Examination OP				X††										X*	
Concomitant Medication CRF CM	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	X*	
Lipoprotein Profile CRF LP Center A				X				X						X	
Center C	X	X	X	X		X		X		X		X		X	
PRA, plasma aldosterone and 24 Hour Urine CRF LAB-3 Center A				X				X						X	
End of Study Information CRF ES														X*	

*Or upon discontinuation from the study.

†A chest X-ray obtained within six (6) months prior to the patient entering the trail 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 abnormality was considered minor and not clinically relevant and a clinical condition requiring a chest X-ray had not occurred during this interval. Otherwise, an X-ray was obtained.

††The ophthalmologic examination was performed any time during the washout period but as close as possible to the Week -1, Time 0 visit.

**Evaluation completed only if dose was increased during the present interval.

[1] Liver function tests only: LDH, total bilirubin, SGOT, SGPT, alkaline phosphatase, initiated during October and November 1984 study was in progress.

[2] case report form identifiers.

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TABLE 4

PN 200-110 STUDY NO. 303

REASONS FOR DECLARATION OF PARTIAL VALIDITY
OR INVALIDITY FOR EFFICACY ANALYSES

Treatment Group	Patient No.	Valid Through Week	Week Discontinued	Reason for Discontinuation
		- PARTIALLY VALID -		
PN 200-110	106	5	6	Headache - unrelated illness: Headache disappeared 3 wks. before stopping med. Pt. discontinued at patient's request, and was put on Fiorinal® for migraine by private physician.
	118	3	3	Uncooperative
	152	8	8	Uncooperative
	204	5	6	Adverse Reaction - atrial fibrillation
	207	3	4	Adverse Reaction - ankle edema
	308	6	6	Patient left country
	312	1	1	Adverse Reaction - palpi .tions
	334	4	9	Adverse Reaction - myalgia and edema (patient took HCTZ during Week 5).
	341	3	4	Adverse Reaction - dizziness
		- PARTIALLY VALID -		
HCTZ	120	4	6	Uncooperative
	208	8	8	Abnormal labs SGOT increased (Screening - within normal limits) SGPT increased (Week 1)
	209	7	7	Study drug not effective
	228	8	9	Adverse Reaction - abnormal labs - BUN, Creatinine, Platelets increased (possibly related to diuretic therapy,
	251	3	3	Study drug not effective
	274	6	6	Chest Pain - unrelated illness Patient entered with stable exertional chest pain, which increased and persisted after discontinuing HCTZ
	304	6	6	Patient left town
	309	5	5	Patient required prostate surgery
	324	8	9	Adverse Reaction - myalgia
	340	1	1	Patient left town

TABLE 4 (Continued)

PN 200-110 STUDY NO. 303

REASONS FOR DECLARATION OF PARTIAL VALIDITY
OR INVALIDITY FOR EFFICACY ANALYSES

Treatment Group	Patient No.	Valid Through Week	Week Discontinued	Reason for Discontinuation
		- INVALID -		
PN 200-110	205	Invalid	-	Completed study but non-compliant (79% compliant)
	323	Invalid	1	Adverse Reaction - headache and only 57% compliant for Week 1
	338	Invalid	-	Completed study but did not satisfy blood pressure entry requirements
		- INVALID -		
HCTZ	103	Invalid	-	Completed study but did not satisfy blood pressure entry requirements
	105	Invalid	1	Adverse Reaction - nausea/ weakness and was only 42% compliant during Week 1
	[illegible]	Invalid	-	Completed study but was non-compliant (78% of doses taken)

TABLE 5

PN 200-110 STUDY NO. 303

DISTRIBUTION OF PATIENTS BY EFFICACY ANALYSES CLASSIFICATION AND CENTER

Investigator	Treatment Group						Total			Total
	PN 200-110			HCTZ						
	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	
A	11	3	0	11	1	2	22	4	2	28
B(MCV)*	4	2	1	4	3	1	8	5	2	15
B(VA)*	7	0	0	6	2	0	13	2	0	15
C	14	4	2	16	4	0	30	8	2	40
Total	36	9	3	37	10	3	73	19	6	98

*MCV - Medical College of Virginia
VA - McGuire VA Hospital

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TABLE 7

PN 200-110 STUDY NO. 303

DISTRIBUTION OF PATIENTS BY STUDY WEEKS COMPLETED

Center	Treatment Group	Last Study Week Completed										Total
		1	2	3	4	5	6	7	8	9	10	
A	PN 200-110	0	0	1	0	0	1	0	1	0	11	14
	HCTZ	1	0	0	0	0	1	0	0	0	12	14
B(MCV)+	PN 200-110	0	0	0	1	0	1	0	0	0	5	7
	HCTZ	0	0	1	0	0	0	1	1	0	5	8
B(VA)+	PN 200-110	0	0	0	0	0	0	0	0	0	7	7
	HCTZ	0	0	0	0	0	1	0	0	1	6	8
C	PN 200-110	2	0	0	1	0	1	0	0	2	14++	20
	HCTZ	1	0	0	0	1	1	0	0	1	16	20
Total	PN 200-110	2	0	1	2	0	3	0	1	1	38	48
	HCTZ	2	0	1	0	1	3	1	1	2	39	50

+Center B: MCV - Medical College of Virginia
VA - McGuire VA Hospital

++Patient No. 319 completed the trial, but no study data was obtained at the final evaluation visit (Week 10). The patient was considered a completely valid patient for analysis.

TAL
PN 200-110 STUDY NO. 303

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	9.99	0.65	8.57	12.14	37	49.98	3.18	42.86	58.33
Week 2	35*	9.73	1.17	5.00	11.43	37	49.53	4.84	36.84	67.86
Week 3	36	9.95	0.47	8.57	10.83	37	54.62	13.87	42.86	100.00
Week 4	36	9.88	0.93	7.19	13.57	37	53.42	14.61	32.1	100.00
Week 5	36	11.98	3.90	8.57	20.00	37	59.31	20.84	35.71	100.00
Week 6	36	11.65	4.02	7.86	20.71	37	61.00	19.57	42.86	100.00
Week 7	36	12.13	4.00	8.00	20.71	37	60.52	20.01	46.43	100.00
Week 8	35**	12.15	4.20	5.00†	20.00	37	60.59	21.61	35.71††	100.00
Week 9	36	12.30	4.50	5.00†	20.00	37	61.40	22.49	25.00††	100.00
Week 10	36	12.25	4.34	5.71†	21.25	37	59.83	21.32	25.00††	100.00
Weeks 5-10	36	12.05	3.90	8.88	20.11	37	60.13	19.91	41.18	100.00

*Patient #252 missed the Week 2 visit.
**Patient #230 missed the Week 8 visit.

†The investigator reduced the dose regimen for Patient No. 329 to 1 capsule qd due to an adverse reaction (fatigue).
††The investigator reduced the dose regimen for Patient No. 330 to 1 capsule qd due to an adverse reaction (palpitations).

Table 8

TABLE 9

PN 200-110 STUDY NO. 303

MEAN DAILY DOSE (MG)
VALID AND PARTIALLY VALID PATIENTS

WEEK	PN 200-110					HCTZ				
	N	Mean	S.D.	Min.	Max.	N	Mean	S.D.	Min.	Max.
Week 1	45	9.85	0.85	7.14	12.14	47	49.73	3.69	34.09	58.33
Week 2	43*	9.62	1.29	5.00	11.43	46	49.54	4.62	36.84	67.86
Week 3	44	10.02	1.75	5.71	20.00	46	55.64	15.06	38.89	100.00
Week 4	42	10.13	1.78	7.19	20.00	45	53.92	15.12	32.14	100.00
Week 5	40	11.98	3.82	8.57	20.00	44	62.28	22.73	35.71	100.00
Week 6	38	11.58	3.92	7.86	20.71	43	62.62	20.92	42.86	103.57
Week 7	37	12.07	3.96	8.00	20.71	41	60.86	20.42	37.50	100.00
Week 8	36**	12.13	4.14	5.00†	20.00	40	61.05	21.42	35.71††	100.00
Week 9	36	12.30	4.50	5.00†	20.00	37	61.40	22.49	25.00††	100.00
Week 10	36	12.25	4.34	5.71†	21.25	37	59.83	21.32	25.00††	100.00
Weeks 5-10	40	12.05	3.81	8.88	20.11	44	62.62	21.39	41.18	100.00

*Patient No. 252 missed the Week 2 visit.
**Patient No. 230 missed the Week 8 visit.

†The investigator reduced the dose regimen for Patient No. 329 to 1 capsule qd due to an adverse reaction (fatigue).
†The investigator reduced the dose regimen for Patient No. 330 to 1 capsule qd due to an adverse reaction (palpitations).

PN 200-110 STUDY NO. 303
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
		PN 200-110	HCTZ	PN 200-110	HCTZ	p-value	p-value	p-value
Sitting Systolic B.P. (mm Hg)	A	146.5 (11)	149.6 (11)	-16.52	-23.45	0.21	0.93	0.63
	B (MCV)*	156.6 (4)	163.0 (4)	-29.02	-29.46			
	B (VA)*	150.7 (7)	150.5 (6)	-11.30	-25.08			
	C	140.2 (14)	144.1 (16)	-18.85	-15.30			
Sitting Diastolic B.P. (mm Hg)	A	100.1 (11)	101.6 (11)	-17.12	-16.39	0.29	0.61	0.01
	B (MCV)*	102.5 (4)	100.1 (4)	-22.33	-15.81			
	B (VA)*	101.4 (7)	98.3 (6)	-16.58	-15.11			
	C	98.0 (14)	98.1 (16)	-15.36	-10.98			
Sitting Pulse (beats/min)	A	77.2 (11)	70.0 (11)	5.18	6.64	0.66	0.10	0.98
	B (MCV)*	85.5 (4)	75.6 (4)	-1.13	-3.42			
	B (VA)*	73.1 (7)	70.2 (6)	5.56	0.82			
	C	72.9 (14)	72.9 (16)	0.11	0.46			

*MCV - Medical College of Virginia
VA - McGuire VA Hospital

Table 10

TABLE 11

FH 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR SITTING DIASTOLIC BLOOD PRESSURE
VALID PATIENTS
PER TIME POINT ANALYSIS DURING THE PLATEAU PERIOD

Investigator	Baseline Mean (Sample Size)		Mean Change from Baseline at:											
			Week 5		Week 6		Week 7		Week 8		Week 9		Week 10	
	FH 200-110	HCTZ	FH 200-110	HCTZ	FH 200-110	HCTZ	FH 200-110	HCTZ	FH 200-110	HCTZ	FH 200-110	HCTZ	FH 200-110	HCTZ
A	100.1 (11)	101.6 (11)	-17.27	-17.64	-17.55	-17.64	-16.09	-17.27	-17.45	-15.82	-18.00	-15.09	-16.36	-14.91
B (HCV)	102.5 (4)	100.1 (6)	-24.75	-14.38	-18.50	-13.88	-21.00	-13.50	-19.50	-14.88	-22.00	-23.38	-20.25	-14.88
B (VA)	101.4 (7)	98.3 (6)	-13.14	-14.83	-15.93	-15.33	-14.57	-16.33	-14.17*	-16.17	-23.29	-15.17	-16.57	-12.83
C	98.0 (14)	98.1 (16)	-17.18	-10.75	-14.68	-9.47	-14.79	-10.38	-15.14	-11.38	-14.64	-12.72	-16.31**	-11.19
Total	99.8 (36)	99.4 (37)	-17.26	-13.89	-16.22	-13.32	-15.83	-13.73	-16.20	-13.89	-18.17	-14.97	-17.74	-12.96
p-Value for:														
Treatment Effect			0.057		0.076		0.252		0.143		0.048		0.009	
Investigator Effect			0.308		0.035		0.494		0.241		0.005		0.085	
Treatment x Investigator Interaction			0.091		0.504		0.239		0.600		0.419		0.299	

*n=6 **n=15

Table 11

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TABLE 12

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

WEEK 1 - VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	N	Baseline Mean	Baseline S.D.	Mean Change	S.D.	Adjusted Mean Change†	Treatment Period Mean	Treatment Period S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	45	147.9	16.35	-14.1***	16.09	-14.6	133.8	12.03
	HCTZ	47	149.6	12.75	-16.1***	13.66	-15.6	133.5	14.39
Sitting Diastolic BP (mm Hg)	PN 200-110	45	100.5	4.21	-12.5***	7.95		88.0	8.41
	HCTZ	47	100.4	4.70	-10.1***	7.40		90.3	9.03
Sitting Pulse (per min)	PN 200-110	45	75.2	10.46	4.7***	8.78	4.9	79.9	12.14
	HCTZ	47	72.7	8.69	3.4**	7.77	3.2	76.1	10.71

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

TABLE 13

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

WEEK 2 - VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	N	Baseline		Mean Change	S.D.	Adjusted Mean Change†	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	43*	146.8	15.68	-17.3***	14.28	-18.2	129.5	11.08
	HCTZ	46	149.8	12.79	-16.3***	14.22	-15.4	133.6	14.29
Sitting Diastolic BP (mm Hg)	PN 200-110	43*	100.3	4.23	-15.9***	7.63		84.4	7.49
	HCTZ	46	100.4	4.76	-10.0***	7.33		90.4	9.24
Sitting Pulse (per min)	PN 200-110	43*	79.2	10.59	4.3**	8.82	4.7 (*)	79.6	11.83
	HCTZ	46	72.5	8.88	1.7	8.77	1.3	74.2	10.15

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

†Results presented only when analysis of covariance assumptions were met.

*Patient #252 did not have a Week 2 visit.

TABLE 14

PM 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

WEEK 3 - VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	N	Baseline		Mean Change	S.D.	Adjusted Mean Change†	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	44	147.5	16.43	-17.2***	17.51		130.5	9.73
	HCTZ	46	149.8	12.79	-18.5***	11.87		131.4	12.96
Sitting Diastolic BP (mm Hg)	PN 200-110	44	100.5	4.24	-16.3***	9.63		84.2	9.60
	HCTZ	46	100.4	4.76	-12.2***	6.16		88.2	7.87
Sitting Pulse (per min)	PN 200-110	44	75.4	10.52	5.1**	10.32	5.8 (*)	80.5	11.56
	HCTZ	46	72.5	8.88	3.1*	8.01	2.4	75.6	6.98

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

TABLE 15

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

WEEK 4 - VALID AND PARTIALLY VALID PATIENTS

Variable	Treatment Group	N	Baseline		Mean Change	S.D.	Adjusted Mean Change†	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	42	147.8	16.81	-19.0***	17.15	-19.5	128.8	12.54
	HCTZ	45	149.4	12.67	-20.1***	14.16	-19.5	129.4	13.59
Sitting Diastolic BP (mm Hg)	PN 200-110	42	100.4	4.32	-16.8***	8.87		83.6	9.34
	HCTZ	45	100.0	4.18	-13.4***	5.49		86.6	6.35
Sitting Pulse (per min)	PN 200-110	42	75.4	10.74	4.2**	7.70	4.6 (*)	79.5	11.62
	HCTZ	45	72.4	8.94	2.0	8.82	1.5	74.3	9.43

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

TABLE 16

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

VALID PATIENTS

PLATEAU PERIOD (WEEKS 5-10) MEAN VS. BASELINE

Variable	Treatment Group	N	Baseline		Mean Change	S.D.	Adjusted Mean Change†	Treatment Period	
			Mean	S.D.				Mean	S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	36	146.0	15.76	-17.8***	15.09	-18.7	128.2	11.11
	HCTZ	37	148.8	12.84	-20.8***	11.13	-19.9	128.C	10.21
Sitting Diastolic BP (mm Hg)	PN 200-110	36	99.8	4.02	-16.9***	6.35		82.9	5.54
	HCTZ	37	99.4	3.35	-13.8***	5.21		85.6	5.94
Sitting ulse (per min)	PN 200-110	36	75.6	11.21	2.6(*)	7.76	3.2	78.2	10.83
	HCTZ	37	71.9	7.79	1.9(*)	6.73	1.3	73.c	6.74

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

TABLE 17

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

VALID AND PARTIALLY VALID PATIENTS

ENDPOINT OF PLATEAU PERIOD (WEEKS 5-10)

Variable	Treatment Group	N	Baseline Mean	Baseline S.D.	Mean Change	S.D.	Adjusted Mean Change†	Treatment Period Mean	Treatment Period S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	40	148.0	17.19	-18.7***	17.02	-19.2	129.3	12.84
	HCTZ	44	149.4	12.82	-19.1***	13.01	-18.7	130.4	13.24
Sitting Diastolic BP (mm Hg)	PN 200-110	40	100.4	4.34	-17.7***	8.75	-17.6	82.7	8.07
	HCTZ	44	100.0	4.22	-12.9***	6.85	-13.0	87.1	7.62
Sitting Pulse (per min)	PN 200-110	40	75.6	10.67	4.2*	10.46	4.6	79.8	13.45
	HCTZ	44	72.4	9.04	-0.5	8.36	-0.9	71.9	9.42

(•)p<.10, *p<.05, **p<.01, ***p<.001
†Results presented only when analysis of covariance assumptions were met.