TABLE 18

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR BLOOD PRESSURE AND PULSE

ALL PATIENTS

ENDPOINT OF ENTIRE STUDY PERIOD (WEEKS 1-10) VS. BASELINE

			Baseline				Adjusted	Treatment Period	
Variable	Treatment Group	N	Mean	S.D.	Mean Change	S.D.	Mean Change†	Mean	S.D.
Sitting Systolic BP (mm Hg)	PN 200-110	48	148.2	15.87	-16.6***	18.11	-16.6	131.6	18.04
	HCTZ	50	148.3	13.42	-18.6***	12.70	-18.5	129.7	13.87
Sitting Diastolic BP (mm Hg)	PN 200-110	48	100.2	4.24	-16.7***	10.34		83.5	10.33
	HCTZ	50	100.2	4.67	-12.6***	6.68		87.6	8.06
Sitting Pulse (per min)	PN 200-110	48	75.5	10.28	4.5**	10.17	4.9**	80.0	12.52
	HCTZ	50	72.7	8.63	-0.3	8.11	-0.8	72.4	9.08

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

TABLE 30

PN 200-110 STUDY NO. 303

LISTING OF NEWLY-OCCURRING PHYSICAL EXAMINATION ABNORMALITIES BY PATIENT AND TREATMENT GROUP (N=98)

Patient #	Treatment Group	Body System	Specific Abnormality
112	PN 200-110	Ears, Nose, Throat	Infection in right ear canal - resolving
112	PN 200-110	Heart	Aortic systolic murmur - Grade II/VI
112	PN 200-110	Lymph Nodes	Regional nodes enlarged around right ear
112	PN 200-110	Extremities	Discomfort in right ankle; no physical findings
116	PN 200-110	Ears, Nose, Throat	Coryza - 3 days
116	PN 200-110	Lungs	Wheeze
207	PN 200-110	Extremities	Ankle edema - started after 12 days of PN 200-110 treatment
238	PN 200-110	Lungs	Decreased breath sounds right lower lobe; History of COPD and emphysema
239	PN 200-110	Skin	Subcutaneous nodules left upper extremities; Neurofibroma
252	PN 200-110	Heart	Systolic ejection murmur - Grade II/VI
346	PN 200-110	Heart	Systolic ejection murmur - Grade I/VI; left sternal border
339	PN 200-110	Lungs	Scattered rhonchi
103	HCTZ	Skin	Senile keratosis
103	HCTZ	Abdomen	Tenderness over aorta and right upper quadrant
108	HCTZ	Extremities	Marked swelling of right leg/thigh; slight swelling of left leg; thrombophlebitis
108	HCTZ	Neurological	Weakness in Right Babinski (Babinski's Syndrome)
111	HCTZ	Ears, Nose, Throat	Rhinitis (cold for 3 days)
151	HCTZ	Heart	Systolic murmur
203	HCTZ	Lungs	Bibasilar end inspiratory rales initially observed at baseline visit (Week 1)
208	HCTZ	Heart	Positive S_4 Gallop
211	HCTZ	Heart	Systolic ejection murmur - Grade I/VI
319	HCTZ	Skin	Left supraorbital cystic sore
330	HCTZ	Heart	Documented supraventricular tachycardia

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TABLE 21

PN 200-110 STUDY NO. 303
CARDIOVASCULAR EXAMINATION
NEWLY OCCURRING ABNORMALITIES† BY BODY SYSTEM

Body System	Patient Number		# of Patients (%) with Newly Occurring Abnormalities	
	PN 200-110	HCTZ	PN 200-110 (n=48)	HCTZ (n=50)
Chest Pain on Exertion		274†† 311	0 (0)	2 (4)
Chest Pain at Rest	338	311	1 (2)	1 (2)
Dyspnea on Exertion		330	0 (0)	1 (2)
Dyspnea Sitting	239 329		2 (4)	0 (0)
Dyspnea Supine	239		1 (2)	0 (0)
Dyspnea Parox. Noct.	239		1 (2)	0 (0)
Cough	204 205 210 238	203 206 Nasal congestion 214 315	4 (8)	4 (8)
Palpitations	109 204 213 308 312 338	201 302 330	6 (12)	3 (6)
Neck Exam	112 Lymph node	211 Lymph node	1 (2)	1 (2)
Pulmonary Findings	238 Decreased breath sounds (See PE) 335 Scattered rhonchi		2 (4)	0 (0)

†Defined as an abnormality reported during double-blind treatment that was not present at any of the pre double-blind visits or an abnormality that was deteriorating.
††Abnormal at baseline and deteriorating.

TABLE 21 (Continued)

PN 200 110 STUDY NO. 303

CARDIOVASCULAR EXAMINATION
NEWLY OCCURRING ABNORMALITIES† BY BODY SYSTEM

Body System	Patient Number		# of Patients (%) with Newly Occurring Abnormalities	
	PN 200-110	HCTZ	PN 200-110 (n=48)	HCTZ (n=50)
Heart Exam	112 ASM 2/6	208 S_4	8 (16)	8 (16)
	202 S_4	211 SEM 2/6		
	308 SEM 2/6	219 Irreg. S_1 + S_2		
	310 S_4	233 S_4		
	312 Irreg. rhythm	251 Irreg. rate		
	316 SEM 1/6 LSB	311 Occas. ectopic beat		
	322 SEM 1/6	320 SEM 2/6		
	332 SEM 1/6	330 Ectopic beat		
Abdominal Exam		103 Tenderness over aorta; and right lower quadrant (Wk. 10)	0 (0)	1 (2)
Extremities	207 Edema		8 (16)	2 (4)
	308 Edema	108 Leg/thigh swelling-thrombophlebitis		
	313 Swollen toe (broken foot)	114 Osteoarthritis left knee		
	318 Edema			
	322 Edema			
	332 Leg edema			
	334 Edema			
	335 Pedal edema			
Any Body System			22/48 (49)	19/50 (38)

†Defined as an abnormality reported during double-blind treatment that was not present at any of the pre double-blind visits or an abnormality that was deteriorating.

††Abnormal at baseline and deteriorating.

TABLE 23
PN 200-110 STUDY NO. 303

ECG EXAMINATION
NEWLY-OCCURRING ABNORMALITIES

Abnormality†	Patient Number		# of Patients with Newly Occurring Abnormalities/ # of Patients Normal at Initial Visit	
	PN 200-110	HCTZ	PN 200-110 (%)	HCTZ (%)
Rhythm	104 119 204 230 238 239 301 312 319 335 338	237 274 333 342	11/45 (24.4%)	4/43 (9.3%)
Interpretation of ECG	106 119 202 213 238 273 312 316 329 334 335 338 339	228 307 309 311 325 333	13/28 (46.4%)	6/29 (20.7%)
New Code	104 204 205 213 230 232 234 235 239 252 301 319	122 157 203 209 211 229 236 237 240 274 324 337	12/48 (25.0%)	12/50 (24.0%)
Any New Abnormality			24/48 (50.0%)	19/50 (38.0%)

†Defined as in Table 24.

TABLE 24

PN 200-110 STUDY NO. 303

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=98)

Patient #	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
104	PN 200-110	1	90/94	New Code (2)	Sinus tachycardia (HR=108)
104	PN 200-110	4, 5, 7, 8, 10	90/94	Rhythm	Sinus tachycardia (HR=104, 108, 108 110, 104)
106	PN 200-110	4		Overall	ST segment changes; T-wave inversion
119	PN 200-110	4	77/88	Rhythm	Sinus tachycardia (HR=110)
		1		Overall	Minor ST segment changes; sinus tachycardia (HR=100)
202	PN 200-110	8, 10		Overall	Non-specific T-wave changes; low or isoelectric T (8)
204	PN 200-110	5		New Code (46)	Abnormal non-specific ST-T changes
204	PN 200-110	1, 4, 5		Rhythm	One PVC (1, 4); atrial fibrillation (5)
205	PN 200-110	1, 5, 8		New Code (46)	Non-specific ST-T wave changes
213	PN 200-110	8, 10		New Code (46, 47)	Elevated V_1-V_5, early repolarization (8); non-specific T-wave changes (10)
230	PN 200-110	4, 5, 9, 10	91/67	Rhythm	Sinus bradycardia [HR=55 (Wk. 4) and 49 (Wk. 10)]; normal sinus arrhythmia (5); sinus tachycardia [HR=107 (Wk. 9)]
230	PN 200-110	1		New Code (47)	Prolonged qt or tu fusion; consider myocardial disease, electrolyte imbalance or drug effect
232	PN 200-110	2, 8, 10		New Code (35, 43,46)	Incomplete right bundle branch block (2); septal myocardial infarction, age indeterminate (2, 8); non-specific ST segment abnormality (10)
234	PN 200-100	4,8,10		New Code (47)	T-wave abnormality, consider inferior ischemia
235	PN 200-110	5, 6, 9		New Code (47, 4)	Non-specific intranvecus conduction delay (5, 6); occasional PAC (9)
238	PN 200-110	4, 10	61/66	Rhythm	Sinus bradycardia [HR=56 (Wk. 4)]; marked sinus arrhythmia (10)
238	PN 200-110	8, 10		Overall	Right atrial enlargement, rightward axis ST-wave elevation (10); non-specific T-wave abnormality (10)
239	PN 200-110	1, 8		New Code (46, 37)	Occasional premature supraventricular complexes (1), probable left ventricular hypertrophy (8)
239	PN 200-110	4	73/70	Rhythm	Sinus bradycardia (HR=57)
252	PN 200-110	5, 7		New Code (32, 37)	Left ventricular hypertrophy (5), left bundle branch block (7), left axis deviation (7)
273	PN 200-110	1, 4, 5		Overall	Non-specific intraventricular conduction delay (1), old inferior infarction (4, 5), occasional premature ectopic complexes (5)
301	PN 200-110	1		New Code (47)	LAA
301	PN 200-110	4	64/64	Rhythm	Sinus bradycardia (HR=56)
312	PN 200-110	1		Rhythm	Bigeminal rhythm
312	PN 200-110	1		Overall	Bigeminal rhythm
316	PN 200-110	4		Overall	Non-specific ST- and T-wave changes

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 24 (Continued)

PN 200-110 STUDY NO. 303

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=9[illegible])

Patient #	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
319	PN 200-110	8	60/60	New Code (3)	Sinus bradycardia (HR=57)
319	PN 200-110	9	60/60	Rhythm	Sinus bradycardia (HR=56)
329	PN 200-110	1, 4		Overall	Poor R-wave V1-3 (1); non-specific ST and T-wave changes (1); non-specific T-wave flattening diffuse (4)
334	PN 200-110	5		Overall	Left anterior hemiblock
335	PN 200-110	10	88/100	Rhythm	Sinus tachycardia (HR=100), one PVC
335	PN 200-110	10		Overall	Sinus tachycardia, one PVC
338	PN 200-110	1	90/88	Rhythm	Sinus tachycardia (HR=106)
338	PN 200-110	10		Overall	Poor R-wave progression V_1-V_4, non-specific ST-T changes
339	PN 200-110	8		Overall	Left atrial abnormality, poor R-progression, non-specific ST-T changes
122	BCTZ	8		New Code (4, 17)	Premature atrial contraction - bigeminal
157	BCTZ	9		New Code (45)	Minor ST segment and T-wave changes
203	BCTZ	1		New Code (47)	Prominent U-waves, compatible with hypokalemia
209	BCTZ	7		New Code (47)	Early repolarization
211	BCTZ	4, 8		New Code (3)	Sinus bradycardia (HR=54, 59)
228	BCTZ	1		Overall	Inferior MI-age indeterminate
229	BCTZ	3, 5		New Code (43)	Septal myocardial infarction, age indeterminate
236	BCTZ	1, 5, 8		New Code (1, 14, 27)	Sinus arrhythmia (1); left anterior fascicular block; frequent PVC's (8)
237	BCTZ	1, 4	70/62	Rhythm	Sinus bradycardia (HR=54, 55)
237	BCTZ	10		New Code (47)	Non-specific intraventricular conduction delay
240	BCTZ	4		New Code (47)	Non-specific ST and T-wave abnormality
274	BCTZ	5	60/65	Rhythm	Sinus bradycardia (HR=58)
274	BCTZ	1,4		New Code (1, 47)	Arrhythmia (1)
307	BCTZ	8		Overall	Poor R-wave prog V_1-V_3
309	BCTZ	4		Overall	Isolated APC's; left ventricular hypertrophy; non-specific ST-T wave changes
311	BCTZ	4, 5, 8	65/72	Overall	Right bundle branch block, left anterior hemiblock, LVH (5, 8); APC's; sinus bradycardia [HR=56 (Wk. 8)]
324	BCTZ	1		New Code (47)	RSR
325	BCTZ	10		Overall	Micro Q-waves V_2-V_3; suggests old septal multiple infarct
333	BCTZ	6		Rhythm	First degree AV block
333	BCTZ	6		Overall	Q3R suggest inferior wall myocardial infarction; LVH voltage
337	BCTZ	8, 10		New Code (47)	Left atrial abnormality
342	BCTZ	8	62/65	Rhythm	Sinus bradycardia (HR=58)

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 25
PN 200-110 STUDY NO. 301

SUMMARY OF COMPARATIVE RESULTS
FOR ECG VARIABLES

Variable	Treatment Group	COMPLETERS ONLY†							ALL PATIENTS††				
		No. of Patients	Baseline		Titration Period		Plateau Period		No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.
Atrial Rate (per min.)	PN 200-110	38	74.7	11.61	3.71**	7.99	1.75	7.70	47	74.3	11.04	2.02	9.85
	HCTZ	37	69.6	7.83	3.14*	7.96	1.68	8.27	47	70.3	9.53	-1.00	10.00
Ventricular Rate (per min.)	PN 200-110	38	74.7	11.61	3.71**	7.99	1.75	7.70	47	74.3	11.04	3.04(*) (δ)	11.83
	HCTZ	37	69.6	7.83	3.14*	7.96	1.68	8.27	47	70.3	9.53	-1.00 (δ)	10.00
P-R Interval (sec.)	PN 200-110	38	0.159	0.026	0.001	0.017	0.000	0.018	47	0.159	0.025	0.000	0.021
	HCTZ	37	0.166	0.025	0.004	0.015	0.000	0.016	47	0.164	0.024	0.003	0.023
QRS Duration (sec.)	PN 200-110	38	0.081	0.016	0.001	0.009	0.001	0.011	47	0.079	0.015	-0.001	0.014
	HCTZ	37	0.079	0.017	0.004*	0.011	0.003	0.010	47	0.079	0.016	0.000	0.011
Q-T Interval (sec.)	PN 200-110	38	0.367	0.035	0.000	0.025	-0.002 (δ)	0.024	47	0.368	0.034	-0.005	0.029
	HCTZ	37	0.378	0.031	0.007	0.033	0.000 (δ)	0.025	47	0.376	0.030	-0.001	0.031

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

†Patient Nos. 302 (HCTZ group; no baseline evaluation) and 342 (HCTZ group; no titration period evaluation) are omitted.
††Patient Nos. 323 (PN 200-110 treatment group; no post-baseline evaluations) and 208, 251 and 302 (all in the HCTZ group; no baseline evaluations) are omitted.

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SUMMARY OF CONFIRMATIVE RESULTS FOR HEMATOLOGY LAB DATA
CENTER A - RIDGE BIOMEDICAL, DUBLIN, OHIO

Variable (Normal Range)	Treatment Group	COMPLETERS DAT* No. of Patients	Baseline Mean	Baseline S.D.	Titration Period Mean Change	Titration Period S.D.	Plateau Period Mean Change	Plateau Period S.D.	ALL PATIENTS* No. of Patients	Baseline Mean	Baseline S.D.	Endpoint Mean Change	Endpoint S.D.
Hemoglobin gm/dl (14-18)	PN 200-110	10	13.3	1.53	0.09	0.52	0.08	0.83	13	12.4	1.73	-0.01	1.13
	HCTZ	12	13.8	1.78	0.39(*)	0.62	0.83	0.54	14	13.8	1.66	-0.06	0.54
Hematocrit % (42-52)	PN 200-110	10	41.1	4.38	0.30	2.06	0.20	2.87	13	40.9	3.84	0.08	3.48
	HCTZ	12	41.4	5.21	1.50*	2.20	0.50	2.28	14	41.4	4.80	0.21	2.75
WBC x 10^3 cu mm (4-11)	PN 200-110	10	6.5	2.10	1.51*	2.01	1.08(*)	1.72	13	6.2	1.97	0.95(*)	1.63
	HCTZ	12	5.7	1.21	0.36	0.92	0.75	0.87	14	5.7	1.14	0.32	1.05
Bands % (0-7)	PN 200-110***	7	0.0	0.00	0.00	0.00	0.00	0.00	10	0.0	0.00	0.00	0.00
	HCTZ****	9	0.0	0.00	0.00	0.00	0.06	0.17	11	0.0	0.00	0.00	0.00
Neutrophils % (40-75)	PN 200-110	10	54.2	8.66	1.50	11.87	1.10	12.46	13	53.5	7.92	0.77	11.20
	HCTZ	12	59.6	8.79	0.50	4.38	1.71	5.29	14	57.1	10.54	2.39	7.49
Lymphocytes % (15-47)	PN 200-110	10	34.2	7.07	-1.00	11.40	-0.60	11.41	13	33.8	7.24	-0.46	10.22
	HCTZ	12	31.7	7.13	-0.17	3.91	-1.67	4.19	14	32.5	7.83	-1.14	4.90
Monocyte % (0-8)	PN 200-110	10	5.7	2.00	0.20	1.55	0.00	1.29	13	5.5	1.81	-0.08	1.44
	HCTZ	12	5.4	1.38	0.25	1.14	0.13	1.91	14	5.5	1.51	-0.21	2.39
Eosinophils % (0-8)	PN 200-110	10	4.0	4.35	-0.80	2.04	-0.65	2.50	13	3.4	3.95	-0.23	2.01
	HCTZ	12	2.4	1.38	-0.33	0.78	0.13	1.82	14	2.4	1.28	-0.14	1.46
Basophils % (0-1)	PN 200-110	10	0.7	0.48	-0.10	0.57	0.05	0.50	13	0.7	0.48	-0.08	0.49
	HCTZ	12	0.7	0.49	-0.08	0.67	-0.04	0.66	14	0.6	0.50	-0.07	0.73

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

*Patient No. 156 (PN 200-110 treatment group) is not included due to no evaluation during the titration period.

**Patient No. 138 (PN 200-110 treatment group) is not included due to no post-baseline lab evaluations.

***Patient Nos. 107, 109 and 114 (PN 200-110 treatment group) are not included due to no baseline data.

****Patient Nos. 105, 115 and 117 (HCTZ treatment group) are not included due to no baseline data.

Table 27

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TABLE 27 (Continued)

PN 200-110 STUDY NO. 302
SUMMARY OF COMPARATIVE RESULTS FOR HEMATOLOGY LAB DATA
CENTER 8 (VA) - RICHMOND VA MEDICAL CENTER, RICHMOND, VA

Variable (Normal Range)	Treatment Group	COMPLETERS ONLY							ALL PATIENTS				
		No. of Patients	Baseline		Titration Period		Plateau Period		No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.
Hemoglobin g/dl (12-18)	PN 200-110	7	14.7	0.89	-0.27	0.88	-0.42*	0.37	7	14.7	0.89	-0.54**	0.36
	HCTZ	6	15.0	1.25	0.05	0.79	0.27	0.94	8	15.0	1.12	0.03	1.05
Hematocrit % (37-52)	PN 200-110	7	45.1	2.67	-1.29	2.69	-1.93**	1.17	7	45.1	2.67	-2.29**	1.11
	HCTZ	6	45.0	3.69	0.50	3.15	1.00	3.21	8	45.1	3.23	0.13	3.68
WBC x 10^3 cu mm (5-11)	PN 200-110	7	7.3	3.70	0.31	1.07	0.50(*)	0.66	7	7.3	3.70	0.66	1.01
	HCTZ	6	5.7	1.36	0.27	0.75	0.80**	0.46	8	5.8	1.19	0.71(*)	0.98
Bands % (3-5)	PN 200-110	7	3.1	4.30	-1.14	4.53	-1.57	4.07	7	3.1	4.30	-1.86	3.67
	HCTZ	6	2.0	1.27	0.17	1.60	-0.58	2.08	8	1.6	1.30	0.50	2.78
Neutrophils % (58-73)	PN 200-110	7	54.7	10.56	0.86	15.63	-0.50	9.42	7	54.7	10.56	0.86	11.30
	HCTZ	6	55.8	5.85	2.83	9.70	-0.33	5.71	8	54.6	5.66	-0.75	5.87
Lymphocytes % (25-30)	PN 200-110	7	31.9	11.58	-0.57	10.71	-1.29	8.77	7	31.9	11.58	-3.71	13.41
	HCTZ	6	33.3	3.39	-4.17	12.11	1.83	5.14	8	33.1	4.39	1.00	4.54
Monocytes % (3-7)	PN 200-110	7	6.7	2.93	0.14	5.84	1.64	4.19	7	6.7	2.93	0.86	4.85
	HCTZ	6	8.0	4.15	-2.33	5.54	-1.17	3.06	8	7.9	3.60	-1.00	3.93
Eosinophils % (1-7)	PN 200-110*	6	2.3	1.51	1.83	3.25	0.33	1.47	6	2.3	1.51	-0.17	1.17
	HCTZ	6	2.5	2.07	-1.00	2.53	-0.42	0.74	8	2.3	1.83	0.25	1.83
Basophils % (0-1)	PN 200-110*	6	1.2	1.33	-0.99	1.52	-0.83	1.75	6	1.2	1.33	-0.83	1.72
	HCTZ	6	0.5	0.84	-0.17	0.75	0.17	1.51	8	0.5	0.76	0.13	1.13

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

†Veterans Administration Hospital

*Patient No. 29 is not included due to no baseline data

TABLE 27 (Continued)

PN 200-110 STUDY NO. 303
SUMMARY OF COMPARATIVE RESULTS FOR HEMATOLOGY LAB DATA
CENTER B (MCV) - ROCHE BIOMEDICAL, RICHMOND, VA

Variable (Normal Range)	Treatment Group	COMPLETERS ONLY*						ALL PATIENTS**				
		No. of Patients	Baseline		Titration Period		Plateau Period		No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.
Hemoglobin gm/dl (13.9-18)	PN 200-110	4	16.1	0.77	-0.60	1.10	-0.55	1.16	7	15.4	1.05	-0.19	0.96
	HCTZ	4	14.6	2.05	-0.68(*)	0.38	-0.85	0.86	7	15.0	1.67	-0.39	1.33
Hematocrit % (39-55)	PN 200-110	4	47.5	2.38	-1.75	2.22	-1.50	2.74	7	45.6	2.99	-0.86	2.61
	HCTZ	4	44.8	6.85	-2.25(*)	1.71	-3.00(*)	2.38	7	45.4	5.38	-1.71	4.39
WBC x 10^3 cu mm (4-10.5)	PN 200-110	4	6.1	0.10	0.18	1.15	0.53	1.21	7	6.6	0.99	-0.07	1.08
	HCTZ	4	6.0	0.73	-0.13	0.73	-0.18	0.55	7	6.5	0.84	-0.14	0.68
Bands % (0-5)	PN 200-110***	3	0.0	0.00	0.00	0.00	0.00	0.00	6	0.0	0.00	0.00	0.00
	HCTZ	4	0.0	0.00	0.00	0.00	0.00	0.00	7	0.0	0.00	0.00	0.00
Neutrophils % (45-75)	PN 200-110	4	57.8	8.54	-3.75	5.38	-0.88	7.73	7	61.7	8.67	-2.14	6.69
	HCTZ	4	51.5	4.12	2.50	5.32	-1.63	3.33	7	54.0	8.35	-2.00	5.77
Lymphocytes % (20-45)	PN 200-110	4	32.3	9.29	1.75	4.79	1.25	6.40	7	28.3	9.05	2.29	6.10
	HCTZ	4	39.3	4.11	-1.75	5.38	2.25	4.70	7	36.7	7.25	1.86	7.43
Monocytes % (0-10)	PN 200-110	4	5.0	1.41	0.25	0.96	-0.38	1.11	7	5.1	1.07	-0.43	0.79
	HCTZ	4	4.5	2.08	-0.25	1.71	-0.75	0.96	7	5.0	1.83	-0.43	1.51
Eosinophils % (0-6)	PN 200-110	4	3.8	2.06	-0.25	1.50	-0.25	1.26	7	3.3	1.70	0.43	1.51
	HCTZ	4	3.3	2.06	-0.50	1.92	-0.13	1.44	7	2.9	1.77	0.57	1.40
Basophils % (0-2)	PN 200-110	4	0.8	0.50	0.00	0.82	0.00	0.82	7	1.0	0.58	-0.29	0.76
	HCTZ	4	0.8	0.50	0.25	0.50	0.13	0.25	7	0.9	0.38	-0.14	0.38

(*)p<.10, *p<.05, **p<.01, ***p<.001
Medical College of Virginia
*Patient Nos. 205 (PN 200-110 treatment group) and 206 (HCTZ treatment group) .
**Patient No. 208 (HCTZ treatment group) is not included due to no baseline da
***Patient No. 202 (PN 200-110 treatment group) is not included due to no basel
cluded due to no evaluations during the titration period.

Table 27 (cont)

TABLE 27 (Continued)

PN 200-110 STUDY NO. 303
SUMMARY OF COMPARATIVE ANALYSIS FOR HEMATOLOGY LAB DATA
CENTER C - NORTHSHORE MEDICAL CENTER, NORTHSHORE, NY

Variable (Normal Range)	Treatment Group	COMPLETERS ONLY*							ALL PATIENTS**				
		No. of Patients	Baseline		Titration Period		Plateau Period		No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.
Hemoglobin gm/dl (11-18.2)	PN 200-110	14	14.7	1.70	0.14	0.65	-0.09	0.80	17	14.6	1.70	-0.12	0.84
	HCTZ	15	14.7	1.26	0.61* (1)	0.80	0.35	0.92	19	15.0	1.28	0.28	0.95
Hematocrit % (33-52)	PN 200-110	14	43.9	4.80	0.36	2.37	0.04	2.16	17	42.8	4.95	0.29	2.31
	HCTZ	15	43.8	3.30	1.73*	2.40	0.80	3.18	19	44.8	3.99	0.93	3.39
WBC x 10^3 cu mm (3.9-10.9)	PN 200-110	14	6.5	2.29	0.08	1.46	-0.22	1.64	17	6.3	2.17	0.02	1.81
	HCTZ	15	7.1	2.68	0.03	1.75	0.22	1.50	19	7.2	2.44	-0.20	1.69
Bands % (1-5)	PN 200-110	14	0.0	0.00	0.43	1.60	0.11	0.40	17	0.0	0.00	0.06	0.24
	HCTZ	15	0.0	0.00	0.00	0.00	0.03	0.13	18***	0.0	0.00	0.00	0.00
Neutrophils % (47-75)	PN 200-110	14	56.1	7.13	0.36	6.31	-2.08	6.65	17	56.6	7.25	-2.18	6.28
	HCTZ	15	60.0	11.69	-0.60	7.13	-2.87	10.96	19	59.7	11.09	-2.21	9.16
Lymphocytes % (18-46)	PN 200-110	14	33.6	8.00	-0.64	6.65	2.04(*)	6.09	17	32.8	7.84	2.06	5.21
	HCTZ	15	31.0	11.36	0.47	5.54	2.73	10.65	19	31.2	10.48	1.90	9.13
Monocytes % (2-11)	PN 200-110	14	5.8	2.01	0.36	2.01	0.43	1.87	17	6.1	2.08	0.82 (1)	2.63
	HCTZ	15	5.7	1.80	0.20	1.66	0.20	1.88	18***	5.6	1.72	0.17 (1)	1.63
Eosinophils % (0-6)	PN 200-110	14	4.0	2.54	-0.57	1.56	-0.49	1.52	17	3.7	2.62	-0.67	1.94
	HCTZ	15	2.6	0.91	0.20	1.21	-0.03	1.46	18***	2.8	1.34	0.56	1.35
Basophils % (0-2)	PN 200-110	14	0.7	0.61	0.07	0.62	-0.04	0.75	17	0.8	0.56	-0.29	0.77
	HCTZ	15	0.7	0.46	-0.07	0.46	-0.07	0.26	19	0.7	0.48	0.00	0.33

(*)p<.10, *p<.05, **p<.01, ***p<.001
*Patient No. 337 (HCTZ treatment group) is not included due to no evaluations during the titration period.
**Patient Nos. 312, 323 and 341 (PN 200-110 treatment group) and Patient No. 340 (HCTZ treatment group) are not included due to no post-baseline lab evaluations performed
***Patient No. 304 (HCTZ treatment group) is not included due to no post-baseline evaluations.

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Table 27 (cont

TABLE 28

PN 200-110 STUDY NO. 303

SUMMARY OF COMPARATIVE RESULTS FOR URINALYSIS LAB DATA
CENTER A - ROCHE BIOMEDICAL, DUBLIN, OHIO

Variable (Normal Range)	Treatment Group	COMPLETERS ONLY							ALL PATIENTS*				
		No. of Patients	Baseline		Titration Period		Plateau Period		No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.		Mean	S.D.	Mean Change	S.D.
Specific Gravity (1.016-1.022)	PN 200-110	11	1.020	0.006	-0.007	0.005	0.000	0.005	13	1.019	0.006	0.000	0.006
	HCTZ	12	1.020	0.005	0.001	0.009	0.000	0.004	14	1.020	0.005	-0.001	0.005
pH (5-6)	PN 200-110	11	5.0	0.00	0.18	0.41	0.18 (δ)	0.32	13	5.0	0.00	0.00 (δ)	0.00
	HCTZ	12	5.2	0.58	0.17	0.58	0.46**	0.45	14	5.1	0.54	0.50**	0.52

(δ)p<.10, *p<.05, **p<.01, ***p<.001

*Patient No. 118 (PN 200-110 treatment group) is not included due to no post-baseline lab evaluations performed.

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Table 28

Protocol 304

Title

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

Investigators

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Dates of Study: June 1, 1984 to June 14, 1986.

Objective

To evaluate the efficacy and safety of PN 200-110 (PN), 2.5 - 10.0 mg bid, in the treatment of hypertension compared to propranolol 60 - 240 mg bid.

Design

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

Patient Population

Outpatients of either sex, over the age of 18 years, with benign essential hypertension were selected for this study. Each patient entered a preliminary 3 week placebo washout period, during which all previous antihypertensives were withdrawn and blood pressure was evaluated each week. In order to qualify for the double blind period, patients were to have an average [illegible] blood pressure [illegible]

medications, bradycardia, AV block > 1st degree, alcohol or drug abuse in previous 2 years, diabetes mellitus requiring insulin therapy, bronchial asthma, COPD or respiratory allergy, pregnant or lactating females.

Medications

Identically appearing capsules of either 2.5 mg PN or 60 mg propranolol were supplied. Study design and dosing schedule is shown in Table 1. For first three weeks, all patients received placebo bid. Doses of all study drugs were administered bid and at least 30 minutes prior to blood pressure being measured. Patients who satisfied entry criteria were stratified as in previous studies and randomized to PN or propranolol.

Initial dose of drugs were 2.5 mg bid (PN) or propranolol 60 mg bid. This was given during weeks 1 and 2. If SDBP > 90 mm Hg at this time, dose was increased to 5 mg bid or 120 mg bid respectively for weeks 3 and 4. Similarly, doses were increased for weeks 5 and 6 to 7.5 mg bid or 180 mg bid and for weeks 7 and 8, dose was 10 mg bid or 240 mg bid respectively. If average SDBP was < 90 mm Hg at end of weeks 2, 4 or 6 dose remained unchanged for next 2 weeks and, if then necessary was increased as described. If at any time SDBP > 110 mm Hg, dose could be increased after one week instead of two. From week 7, dose remained constant unless a reduction was required due to adverse reaction. At end of 10 weeks, medication was tapered.

Evaluations

Evaluations were done weekly as per Table 2. Method of recording blood pressures and pulse rate described in report. At Center B, left ventricular function was determined using echocardiography at weeks -1 and 10. At Center C, ambulatory blood pressure determinations were done over 24 hour periods at week -1 and week 10

Results.

A total of 89 patients were randomized to double blind phase. Of these, 68 were completely valid for analysis, 16 partially valid and 5 invalid.

The mean age of the patients was 50.7 years (19 - 76); 29 (33%) were white, 58 (65%) wwre black, 1 oriental and 1 other. There were 44 males and 45 females. Mean duration of hypertension was 11 years. With exception of body weight (higher in PN group), there were no statistically significant differences between groups.

Table 7 presents mean dose, by week for all valid patients and Table 8 presents similar data for partially valid group. During fixed dose period, mean dose was 12 mg PN and 332 mg propranolol. Table 9 summarizes data from analysis of interactions as well as efficacy results on investigator x treatment basis for each efficacy variable for weeks 7 - 10. There was a marginally ($p=0.065$) treatment x investigator interaction for sitting systolic blood pressure. Center B had greater decrease in PN group and less increase in propranolol group than other two centers.

Efficacy

Efficacy data were examined both between and within groups as well as by categorizing as in previous studies.

Weeks 1 - 2.

Tables 10 and 11 summarize data for this period with patients on lowest dose medication. PN reduced SDBP from baseline by 8.8 mm Hg week 1 and by 8.9 mm Hg week 2; the respective reductions for propranolol were 6.7 and 7.8 mm Hg. Reductions by both drugs were statistically significant from baseline but not between groups. The differences in pulse rate were statistically significant between groups with PN causing an increase in rate and propranolol a decrease.

Weeks 1 - 6 (Titration)

Table 12 presents these data for valid and partially valid patients. The reductions for both groups are statistically significant from baseline for all variables as well as being statistically significant between groups. The PN group reduced SDBP by 15.7 mm Hg compared to 9.0 mm Hg with propranolol. The increment in decrease over [illegible] significant with PN than with propranol[illegible] pulse rate.

[illegible]

Categorical Responses, as defined below, for valid patients at week 10 were:

	n =	1	2	3	4
PN	37	16 (43%)	13 (35%)	6 (16%)	2 (5%)
Propr	31	6 (19%)	6 (19%)	10 (32%)	9 (29%)

Category 1: SDBP < 85 mm Hg; 2: > 10 mm Hg but still > 85 mm Hg; 3: > 5 but < 10 mm Hg; 4: < 5 mm Hg or increase.

Over 80% (31/37) PN group had at least 10 mm Hg reduction in SDBP and 41% (15/37) had a decresae < 85 mm Hg over weeks 7 - 10. For propranolol, the figures were 19% and 26% respectively. PN was significantly more effective than propranolol.

Number of valid patients titrated to each dose level at week 10 was:

Group	n =	1	2	3	4
PN	37	8 22%	13 35%	10 27%	6 16%
Propr	31	7 23%	4 13%	8 26%	12 39%

Level 1; 5 mg PN or 120 mg propr; 2: 10 mg or 240 mg; 3: 15 mg or 360 mg; 4: 20 mg or 480 mg.

Only 16% PN received highest dose compared to 39% propranolol

All Patients - Endpoint Analysis

Table 15 summarizes results from analysis including all patients regardless of validity. These results are similar to those seen in Tables 13 and 14.

Figures 1 - 3 display all results for valid patients graphically.

Safety

Table 16 lists specific newly occurring abnormalities in physical examination. There were 15 abnormalities for PN and 4 with propranolol. Tables 17 and 18 list newly occurring cardiovascular abnormalities. These occurred in 30 PN and 17 propr patients. One PN was withdrawn due to increased angina and shortness of breath. One propranolol [illegible]

Clinical Laboratory Data

Tables 25 - 30 present data for laboratory changes. (Tables 25 and 26 hematology; 27 and 28 urine, 29 and 30 chemistry). The only statistically significant changes occurred in chemistries. The main parameters affected were inorganic phosphorous, BUN, uric acid, glucose, alkaline phosphatase, potassium and creatinine. The difference between groups for alkaline phosphatase was significant. The results were not clinically significant. Alkaline phosphatase was the most frequently occurring change for PN.

Adverse Reactions

Table 4 listed patients who withdrew and their reasons. Tables 37 and 38 list ADRs by patient and body system. Overall from weeks 1 - 10, 83% PN and 65% propranolol reported at least one newly occurring abnormality.. At week 2, the difference between groups was statistically significant (PN 28% vs propranolol 9%). The difference over the 10 weeks was marginally significant $p < .10$. The most frequent reported PN ADRs were in the central nervous and cardiovascular systems. In propranolol it was central nervous and gastrointestinal systems. The most frequently reported events are shown below:

ADR	PN n=46		Propranolol n = 43.	
Edema	8	17%	3	7%
Palpitations	5	11%	0	*
Abdominal Discomfort	3	7%	6	14%
Diarrhea	4	9%	4	9%
Dizziness	4	9%	2	5%
Fatigue	2	4%	7	16% *
Headache	13	28%	6	14%
Flushing	5	11%	0	*

* Between group differences $p < 0.10$

Echocardiography

Table 39 summarizes data from center B for echocardiographic results [illegible] statistically significant observed [illegible] volume [illegible] systolic [illegible]

Ambulatory [illegible]

[illegible]

[redacted]

Discussion

Both drugs significantly reduced blood pressures from baseline but the reductions with PN were significantly greater than with propranolol. About 67% propranolol patients were black and this group does not respond as well to beta blockers as do whites. it is possible, therefore, that patient selection may have influenced results in propranol group. There were more ADRs with PN but not serious events requiring withdrawal from study.

Reviewer's Comments

1. This study shows PN to be more effective than propranolol in treatment of hypertensives. However, as the majority of propranolol patients were black, this could have influenced results

2. Similar comments as previous study with regard to timing of blood pressure measurements

3. PN has a higher incidence of ADRs but more propranolol patients were withdrawn due to ADRs.

[redacted]

TABLE 19
PN 200-110 STUDY NO. 304

NEWLY-OCCURRING CHEST X-RAY ABNORMALITIES

Treatment Group	Patient No.	Week	Abnormality
PN 200-110	108	10	Mild cardiomegaly
	115	10	Prominent ascending aortic segment unchanged since Week -4
	322	10	Slight left ventricular configuration - Linear atelectase or fibrosis, left lung base
Propranolol	117	10	Heart is slightly enlarged with a left ventricular configuration - may have increased since Week -4 - lungs are negative
	251	10	Borderline enlargement of cardiac shadow

TABLE 20

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
109	PN 200-110	10	55/57	Rhythm	Sinus bradycardia (HR=54)
		4, 8		New Code (36)	Left atrial hypertrophy
118		4		New Code (43)	Rule out old inferior myocardial infarction
154		2		Overall	Borderline left ventricular hypertrophy, left atrial hypertrophy
155		2, 4, 6, 8, 10		New Code (47)	Lateral ischemia
202		2		New Code (47)	Left axis deviation
207		2, 4, 6, 8, 10		New Code (47)	Probable biventricular hypertrophy; possible hypertrophic cardiomyopathy (2, 4, 6)
210		4, 6, 8, 9		New Code (37)	Probable left ventricular hypertrophy with strain
213		10	90/82	Rhythm	Sinus tachycardia (HR=120)
		10		Overall	Borderline long PR interval, borderline prominent P waves persist
217		10	62/58	New Code (2)	Sinus tachycardia (HR=102)
220		4, 6, 8, 10		New Code (22, 27, 47)	Mild 1° AV block (6, 8, 10); left anterior hemiblock (6); P waves compatible with atrial overload
253		4, 6, 8, 10		Overall	Short PR interval (4); prominent U waves, consider electrolyte abnormality (6, 8); increase of non-specific ST-T abnormalities(10)

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20 (CONTINUED)

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
~~255~~	~~PN 200-110~~ (cont'd)	~~6, 10~~		~~New Code (46)~~	~~Slight increase in ST-T wave abnormalities (6); slight improvement in ST-T wave abnormalities (10)~~
302		10 4, 6, 10		Rhythm New Code (27, 47)	Frequent premature beats Left anterior hemiblock (6, 10); increased P wave V1, QTC upper limit of normal
304		2, 4, 6, 8, 10		New Code (46, 47)	T waves more prominent (2); non-specific ST-T wave changes (6, 8, 10); left atrial abnormality (4)
305		6, 8, 10		New Code (1, 43, 47)	Sinus arrhythmia (6); possible old anterior myocardial infarction (6); QSV1-V2 (6, 8); V6-3 nodal beats (6) baseline artifact (8); J point elevation (8, 10); nodal beat with pulse V5 (10)
~~308~~		4 8		Rhythm New Code (47)	Sinus arrhythmia Poor R wave progression vs lead placement
312		2, 4		New Code (47)	Early repolarization
314		2, 6, 8		New Code (37, 47)	Probable left ventricular hypertrophy (6); axis shift (2); compared to Week 6, loss of T waves in lateral leads (8)
316		4		Rhythm	Sinus arrhythmia

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20 (CONTINUED)

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
316 (cont'd)	PN 200-110 (cont'd)	1,2,4,6, 8, 10		Overall	Loss of T waves in lateral leads (1); non-specific ST-T wave changes (2, 4, 6, 8, 10)
318		4, 8	75/95	New Code (1, 3)	Sinus arrhythmia (8); sinus arrhythmia with bradycardia (4)
319		6, 10		New Code (46)	Non-specific ST-T wave changes
322		4		New Code (47)	Left axis deviation
323		4, 8, 10 6		Rhythm New Code (47)	Sinus arrhythmia Slight left axis shift
351		2, 10		Rhythm	Sinus arrhythmia
354		6 2, 4, 6, 8	82/75	Rhythm Overall	Sinus arrhythmia Sinus tachycardia (HR=94,100) (2, 8); non-specific ST-T wave abnormalities
355		2, 4, 6, 8, 10		New Code (37, 46)	Left ventricular hypertrophy; non-specific ST-T wave changes (6, 8)
357		2, 4, 10		New Code (46)	Non-specific ST-T wave changes
110	Propranolol	2, 4, 6, 8, 10	71/64	Overall	Left ventricular hypertrophy (2, 4, 8, 10); left atrial hypertrophy (4, 6); left axis deviation (8, 10); sinus bradycardia (HR=58) (10); V5, V6 more abnormal than Week 6 (10)
152		2, 6, 8, 10		New Code (36, 47)	Left atrial hypertrophy (8); greater ischemia T wave change than Week-1 (2, 6, 8, 10)

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20 (CONTINUED)

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
158	Propranolol (cont'd)	2, 6		Overall	Premature ventricular beats (2); atrial hypertrophy (6)
159		2		Overall	Inverted T waves
201		10		New Code (46)	Minor non-specific ST-T wave segment sagging
203		4	84/68	Rhythm	Sinus bradycardia (HR=54)
206		2, 3, 10	64/65	Rhythm	Accelerated left atrial rhythm (2); sinus bradycardia (HR=48,54) (3, 10) sinus arrhythmia (3, 10)
		2		Overall	Non-specific ST-T changes
		10		New Code (37)	Mild left ventricular hypertrophy possible
208		2, 4	60/60	Rhythm	Sinus bradycardia (HR=50,55); sinus arrhythmia
209		6, 10	75/78	Rhythm	Sinus bradycardia (HR=56,54); sinus arrhythmia
214		4		Rhythm	Sinus arrhythmia
		6, 7		New Code (13, 14, 47)	Single, probably supraventricular, premature beat with aberration (7) occasional premature ventricular beats (6); possible chronic coronary disease, possible small inferior myocardial infarction scar (7)
215		6, 8, 10	65/68	Rhythm	Sinus bradycardia (HR=58,55,55)

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20 (CONTINUED)

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
218	Propranolol (cont'd)	4, 6, 10	82/82	Rhythm	Sinus bradycardia (HR=58,56,54); sinus arrhythmia
		2, 4, 6, 8, 10		New Code (22, 37, 47)	1° AV heart block (4, 6, 8, 10); probable left ventricular hypertrophy with strain; inverted T waves could possibly represent ischemia (6, 8)
219		6, 8, 10		Overall	Mild 1° AV block (6); mild prolongation of the PR interval, minor ST-T wave changes.
223		8, 10		New Code (46)	Minor ST-T wave changes (8); improved at Week 10
251		4	74/70	New Code (3)	Sinus bradycardia (HR=56)
254		4, 6, 8, 10		New Code (47)	Borderline prominent P waves, probable mild atrial overload
306		2, 8, 10	65/75	New Code (2, 46, 47)	Sinus bradycardia (HR=55,56,55); non-specific T wave changes, left atrial abnormality (2); short PR (10)
307		2, 4, 6, 8, 10	67/65	New Code (3, 46, 47)	Sinus bradycardia (HR=56,57,56) (2, 6, 8); ST-T wave changes (4, 6, 8, 10); early repolarization (4)
310		8, 10 2	69/64	Rhythm New Code (3)	Sinus bradycardia (HR=59,54) Sinus bradycardia (HR=59)

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20 (CONTINUED)

PN 200-110 STUDY NO. 304

LISTING OF NEWLY-OCCURRING ECG ABNORMALITIES BY PATIENT AND TREATMENT GROUP
(N=89)

Patient No.	Treatment Group	Week(s) Observed	Heart Rate at Week -4/ Week -1 (Beats/Min)	Type of Abnormality*	Specific Abnormality (Weeks - All if Blank)
315	Propranolol (cont'd)	4, 8, 9	64/64	Rhythm	Sinus arrhythmia (4); sinus bradycardia (HR=58,57) (8, 9)
		4, 8, 9		Overall	Incomplete right bundle branch block (4); sinus bradycardia (8, 9)
		5		New Code (3)	Sinus bradycardia (HR=51)
320		6		Rhythm	Sinus arrhythmia.
		2, 4, 6, 8, 10	76/70	Overall	Non-specific ST-T wave changes (2, 6, 10); early repolarization (4); sinus bradycardia (HR=58) (10); left ventricular hypertrophy by voltage (10)
324		2, 4, 6, 8, 10		New Code (1, 22, 46, 47)	Sinus arrhythmia (4); borderline 1° AV block (8, 10); non-specific ST-T wave changes (2, 4, 6, 8); early repolarization (2, 8)
352		2, 4	71/65	New Code (3, 43, 47)	Sinus bradycardia (HR=57) (4); old lateral myocardial infarction (2); Qs complex in V1 (4)
353		3	75/63	New Code (3)	Sinus bradycardia (HR=58)
356		2, 4		New Code (22)	Borderline 1° AV block

*Rhythm = Rhythm coded as normal at baseline, abnormal during the double-blind period.
Overall = Overall interpretation coded as normal at baseline, abnormal during the double-blind period.
New Code = Code which does not occur during baseline and does occur during the double-blind period at an evaluation with at least one of the following: 1) abnormal rhythm, 2) abnormal overall interpretation, or 3) significant difference from previous ECG.

TABLE 20A

PN 200-110 STUDY NO. 304

ECG EXAMINATION
NEWLY-OCCURRING ABNORMALITIES+

Abnormality	Patient Number		No. of Patients With Newly-Occurring /BN/# Of Patients Normal At Baseline (%)		P-Value From Fisher's Exact Test
	PN 200-110	Propranolol	PN 200-110	Propranolol	
Rhythm	109 316 213 323 302 351 308 354	203 215 206 218 208 310 209 315 214 320	8/31 (26)	10/33 (30)	0.78
Overall Interpretation of ECG	154 316 213 354 253	110 219 158 315 159 320 206	5/14 (36)	7/21 (33)	1.00
New Code	109 305 118 308 155 312 202 314 207 318 210 319 217 322 220 323 255 355 302 357 304	152 306 201 307 206 310 214 315 218 324 223 352 251 353 254 356	21/46** (46)	16/43** (37)	0.52
Number of Patients With at Least One Newly-Occurring Abnormality/ Number of Patients	27/46 (59)	25/43 (58)			1.00

+Defined as per Table 20

++Total number of patients

TABLE 21
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR ECG DATA

COMPLETED PATIENTS ONLY

Variable	Treatment Group	No. of Patients	Baseline		Mean Change					Mean Over Weeks 2-10	
			Mean	S.D.	Week 2	Week 4	Week 6	Week 8	Week 10	Mean Change	S.D.
Ventricular Rate* (per min.)	PN 200-110	39	71.7	11.94	2.23	2.33	3.87*	3.38(*)	4.74**	3.27*	8.95
	Propranolol	28	69.6	9.60	-8.43***	-9.32***	-11.54***	-10.39***	-11.71***	-10.28***	7.99
P-R Interval (sec.)	PN 200-110	39	0.156	0.021	0.000	-0.002	0.000	0.003	-0.002	0.000	0.014
	Propranolol	28	0.161	0.018	0.004	0.001	0.002	0.006	0.003	0.003	0.019
QRS Duration (sec.)	PN 200-110	39	0.080	0.011	-0.001	0.001	0.002	0.003	-0.001	0.001	0.009
	Propranolol	28	0.081	0.011	-0.001	-0.001	-0.001	-0.001	-0.002	-0.001	0.011
Q-T Interval (sec.)	PN 200-110	39	0.378	0.024	-0.009**	-0.009(*)	-0.010*	-0.012*	-0.012**	-0.010**	0.020
	Propranolol	28	0.380	0.027	0.011*	0.009(*)	0.023***	0.019***	0.013(*)	0.015**	0.023

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

*On the ventricular rate was analyzed as the atrial rate was equal to the ventricular rate.

TABLE 21

TABLE 22
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR ECG DATA

ALL PATIENTS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Ventricular Rate+ (per min.)	PN 200-110	46	71.1	12.37	4.93* ***	14.89
	Propranolol	41	68.8	8.96	-11.05*** ***	8.85
P-R Interval (sec.)	PN 200-110	46	0.156	0.020	-0.001 *	0.015
	Propranolol	41	0.161	0.020	0.006(*) *	0.020
QRS Duration (sec.)	PN 200-110	46	0.080	0.010	-0.001	0.013
	Propranolol	41	0.082	0.012	-0.002	0.011
Q-T Interval (sec.)	PN 200-110	46	0.378	0.027	-0.014** ***	0.029
	Propranolol	41	0.383	0.027	0.017*** ***	0.031

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

+Only the ventricular rate was analyzed as the atrial rate was equal to the ventricular rate.

TABLE

PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR HEMATOLOGY LABORATORY DATA

COMPLETED PATIENTS ONLY

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 4		Week 6		Week 10		Mean Over Weeks 4-10	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.
Hemoglobin gm/dl (11.9-17.6)	PN 200-110	40	14.6	1.51	0.04	0.97	0.08	0.70	0.0	0.86	0.04	0.71
	Propranolol	29	14.3	1.56	0.00	0.59	-0.12	0.76	0.03	0.92	0.01	0.68
Hematocrit % (37-54)	PN 200-110	40	44.4	4.16	0.21	3.24	0.14	2 54	-0.30	3.18	0.02	2.51
	Propranolol	29	43.5	4.10	0.17	1.89	-0.09	2.49	0.69	2.43	0.26	1.89
WBC x 10^3 cu mm (3.9-11.4)	PN 200-110	40	6.4	1.30	0.09	1.14	0.18	1.11	0.09	1.39	0.12	0.97
	Propranolol	29	6.12	1.47	0.25	1.06	0.30*	0.76	0.27	1.33	0.27	0.90
Neutrophils % (42-81)	PN 200-110	34	55.7	9.15	1.15	6.97	1.21	6.63	1.00	9.06	1.12	6.44
	Propranolol	28	55.3	12.22	-0.61	10.58	0.64	10.12	-0.04	12.35	0.00	10.46
Lymphocytes % (10-47)	PN 200-110	39	35.0	9.65	-1.48	6.42	-1.76	7.13	-1.90	7.91	-1.72(*)	6.01
	Propranolol	29	35.5	12.24	-0.24	12.81	-0.97	10.48	-0.69	12.30	-0.63	11.39
Monocytes % (0-10)	PN 200-110	39	6.5	1.97	0.13	2.22	0.33	2.02	0.72(*)	2.52	0.39	1.71
	Propranolol	29	6.2	2.19	0.31	2.80	0.35	2.74	0.97(*)	2.63	0.54	2.15
Eosinophils % (0-8)	PN 200-110	39	2.4	1.89	0.15	1.50	0.13	1.36	-0.10	1.41	0.06	1.26
	Propranolol	29	2.5	1.53	0.93	4.07	0.00	1.31	-0.10	1.97	0.28	2.05
Basophils % (0-2)	PN 200-110	39	0.5	0.60	0.13	1.03	0.03	0.81	0.10	0.94	0.09	0.76
	Propranolol	29	0.7	0.63	0.14	0.69	0.07	0.65	0.10	0.77	0.10	0.59

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

TABLE 25

TABLE 26
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR HEMATOLOGY LABORATORY DATA
ALL PATIENTS

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Hemoglobin gm/dl (11.9-17.6)	PN 200-110	45	14.5	1.50	-0.03	0.86
	Propranolol	39	14.2	1.57	0.25	1.00
Hematocrit % (37-54)	PN 200-110	45	44.1	4.06	-0.33	3.06
	Propranolol	39	43.4	4.05	0.66	2.72
WBC x 10^3 cu.mm (3.9-11.4)	PN 200-110	45	6.3	1.32	0.08	1.32
	Propranolol	39	6.3	1.57	0.31	1.55
Neutrophils % (42-81)	PN 200-110	42	56.4	8.97	0.83	8.45
	Propranolol	39	56.6	10.90	-1.05	11.93
Lymphocytes % (10-47)	PN 200-110	44	34.8	9.31	-1.77	7.83
	Propranolol	39	34.3	11.15	0.18	12.69
Monocytes % (0-10)	PN 200-110	44	6.3	2.03	0.82(*)	2.71
	Propranolol	39	6.2	2.17	0.74	2.96
Eosinophils % (0-8)	PN 200-110	44	2.4	1.93	-0.21	1.81
	Propranolol	39	2.3	1.42	-0.05	1.76
Basophils % (0-2)	PN 200-110	44	0.6	0.63	0.02	0.95
	Propranolol	39	0.7	0.61	0.10	0.75

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

TABLE 27
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR URINALYSIS LABORATORY DATA

COMPLETED PATIENTS ONLY

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 4		Week 6		Week 10		Mean Over Weeks 4-10	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.
Specific Gravity (1.001-1.035)	PN 200-110	38	1.023	0.006	0.001	0.008	-0.001	0.007	-0.001	0.006	0.000	0.005
	Propranolol	27	1.023	0.007	-0.001	0.006	-0.001	0.008	-0.001	0.007	-0.001	0.006
pH (5-7)	PN 200-110	38	5.3	0.63	-0.05	0.73	-0.13	0.62	0.00	0.74	-0.06	0.61
	Propranolol	27	5.3	0.56	-0.19	0.62	-0.11	0.70	-0.30*	0.61	-0.20(*)	0.59

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

TABLE 27

TABLE 28
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR URINALYSIS LABORATORY DATA

ALL PATIENTS

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Specific Gravity (1.001-1.035)	PN 200-110	45	1.022	0.006	-0.001	0.006
	Propranolol	40	1.022	0.007	0.000	0.007
pH (5-7)	PN 200-110	45	5.3	0.60	0.04	0.74
	Propranolol	40	5.3	0.57	-0.20*	0.61

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

TABLE 29

PN 200-110 NO. 3[illegible]

SUMMARY COMPARATIVE RESULTS FOR C[illegible] ORATORY DATA

COMPLETED PATIENTS ONLY

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 4		Week 6		Week 10		Mean Over Weeks 4-10	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.
Calcium mg/dl (8.8-10.5)	PN 200-110	37	9.6	0.39	0.05 (t)	0.41	0.01 (t)	0.36	0.04	0.40	0.03	0.31
	Propranolol	28	9.6	0.38	-0.11(*)	0.35	-0.16*	0.43	0.08	0.47	-0.07	0.35
Inorganic Phosphorus mg/dl (2.2-4.6)	PN 200-110	37	3.2	0.44	-0.14 (t)	0.64	-0.08 (t)	0.45	-0.08 (t)	0.52	-0.10 (t)	0.46
	Propranolol	28	3.3	0.54	0.30*	0.65	0.18	0.56	0.25*	0.51	0.24*	0.50
BUN mg/dl (6-23)	PN 200-110	37	12.8	4.34	0.19 (t)	3.04	0.22	3.34	0.35 (t)	3.29	0.25 (t)	2.85
	Propranolol	28	12.2	2.82	1.93***	2.76	0.96	3.01	1.86***	3.00	1.58***	2.02
Uric Acid mg/dl (2.2-8.3)	PN 200-110	37	5.3	1.03	0.13	1.11	-0.04 (t)	0.78	-0.15 (t)	0.86	-0.02 (t)	0.74
	Propranolol	28	5.5	1.65	0.46*	0.66	0.64***	0.71	0.42***	0.69	0.51***	0.50
Glucose mg/dl (65-130)	PN 200-110	37	[illegible]33.2	31.61	1.22	25.48	2.30	27.11	5.62	25.71	3.05	23.80
	Propranolol	28	104.7	28.00	4.04	26.93	2.68	25.57	6.79	24.78	4.50	23.30
Total Protein gm/dl (6.4-8.1)	PN 200-110	37	7.3	0.34	0.18**	0.40	0.16*	0.37	0.17*	0.41	0.17**	0.34
	Propranolol	28	7.3	0.35	0.05	0.39	0.04	0.29	0.14*	0.35	0.08	0.28
Albumin gm/dl (3.7-5.0)	PN 200-110	37	4.2	0.31	0.02	0.27	0.01	0.28	0.07	0.28	0.03	0.24
	Propranolol	28	4.2	0.31	0.0	0.22	-0.03	0.27	0.02	0.21	0.00	0.19
Total Bilirubin mg/dl (0.2-1.6)	PN 200-110	41	0.5	0.22	-0.02	0.19	-0.01	0.15	-0.02	0.15	-0.01	0.13
	Propranolol	31	[illegible].5	0.18	-0.01	0.17	0.01	0.18	0.05	0.22	0.02	0.16
Cholesterol mg/dl (130-250)	PN 200-110	37	217.3	36.60	4.38	23.76	5.60	27.57	5.97	26.29	5.32	23.51
	Propranolol	28	224.2	51.10	-1.11	23.82	0.29	22.71	6.75	28.58	1.58	22.41

(•)p<.10, *p<.05, **p<.01, ***p<.001

TABLE 29 (CONTINUED)
PN 200-110

SUMMARY COMPARATIVE RESULTS FOR CLINICAL LABORATORY DATA

COMPLETED PATIENTS ONLY

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Week 4		Week 6		Week 10		Mean Over Weeks 4-10	
			Mean	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.	Mean Change	S.D.
Alkaline Phosphatase IU/L (10-45)	PN 200-110	41	27.4	11.67	2.59*	7.09	3.24*	7.85	3.76**	7.65	3.20**	6.37
	Propranolol	31	29.0	12.94	1.61	6.55	1.58	6.72	1.65	8.12	1.61	5.83
LDH IU/L (110-250)	PN 200-110	41	170.9	21.95	0.07	22.49	2.61	29.45	-1.05	24.86	0.55	22.14
	Propranolol	30	172.0	31.98	-1.93	25.46	1.20	26.00	-2.20	25.39	-0.98	20.86
SGOT IU/L (10-50)	PN 200-110	41	27.0	13.60	-0.76	11.84	0.00	9.03	0.19	15.29	-0.12	10.60
	Propranolol	31	24.4	11.41	-0.26	7.07	-1.32	6.87	0.10	11.06	-0.50	6.00
SGPT IU/L (5-55)	PN 200-110	41	26.2	20.58	-1.83	16.06	-1.34	13.38	-1.15	18.70	-1.44	15.12
	Propranolol	30	21.9	14.05	-1.27	7.52	0.57	10.00	0.33	11.28	-0.12	8.05
Sodium mmol/l (134-143)	PN 200-110	37	139.3	1.96	0.03	2.61	-0.51	3.21	0.11	2.18	-0.13	2.08
	Propranolol	27	138.5	2.77	0.78	3.33	0.07	3.61	0.56	3.42	0.47	3.12
Potassium mmol/l (3.5-5.3)	PN 200-110	37	4.2	0.31	-0.05	0.35	-0.07	0.34	-0.10	0.35	-0.07	0.29
	Propranolol	27	4.3	0.33	0.14***	0.20	0.05	0.32	0.16**	0.24	0.12**	0.19
Chloride mmol/l (96-107)	PN 200-110	37	102.3	2.24	0.00	2.49	-0.81	3.37	-0.27	3.38	-0.36	2.28
	Propranolol	27	102.6	2.47	0.37	4.14	-0.85	2.89	-0.63	3.22	-0.37	2.6
CO_2 mmol/l (25-32)	PN 200-110	33	26.1	3.17	0.22	2.95	-0.27	2.98	0.35	3.44	0.10	2.69
	Propranolol	27	26.7	2.16	-0.10	3.05	0.22	2.99	0.62	3.21	0.25	2.51
Creatinine mg/dl (0.6-1.3)	PN 200-110	37	1.0	0.16	-0.02	0.19	-0.06*	0.14	-0.03	0.18	-0.03*	0.14
	Propranolol	27	1.0	0.13	0.04	0.14	0.05	0.20	0.08**	0.13	0.06*	0.11

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

0358

TABLE 29

TABLE 30
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR CHEMISTRY LABORATORY DATA
ALL PATIENTS

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Calcium mg/dl (8.8-10.5)	PN 200-110	44	9.6	0.37	0.04	0.41
	Propranolol	38	9.6	0.39	0.06	0.45
Inorganic Phosphorus mg/dl (2.2-4.6)	PN 200-110	44	3.2	0.43	-0.06	0.53
	Propranolol	38	3.3	0.53	0.26**	0.51
BUN mg/dl (6-23)	PN 200-110	44	13.0	4.17	0.34	3.23
	Propranolol	38	13.0	4.18	1.66*	4.91
Uric Acid mg/dl (2.2-8.3)	PN 200-110	44	5.3	1.16	-0.20	0.92
	Propranolol	38	5.4	1.48	0.43***	0.67
Glucose mg/dl (65-130)	PN 200-110	44	101.3	30.11	8.46*	26.41
	Propranolol	38	102.6	29.03	8.32*	23.01
Total Protein gm/dl (6.4-8.1)	PN 200-110	44	7.3	0.35	0.15*	0.41
	Propranolol	38	7.3	0.33	0.16**	0.34
Albumin gm/dl (3.7-5.0)	PN 200-110	44	4.2	0.31	0.07	0.28
	Propranolol	38	4.2	0.31	0.01	0.27
Total Bilirubin mg/dl (0.2-1.6)	PN 200-110	46	0.6	0.22	-0.02	0.15
	Propranolol	42	0.5	0.20	0.04	0.21
Cholesterol mg/dl (120-290)	PN 200-110	44	218.5	35.99	4.00	25.65
	Propranolol	38	229.1	50.19	4.29	26.70

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

TABLE 30 (Continued)
PN 200-110 STUDY NO. 304

SUMMARY COMPARATIVE RESULTS FOR CHEMISTRY LABORATORY DATA
ALL PATIENTS

Variable (Normal Range)	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Alkaline Phosphatase IU/L (10-45)	PN 200-110	46	26.4	11.55	4.67***	8.13
	Propranolol	42	29.3	12.30	0.64	7.99
LDH IU/L (110-250)	PN 200-110	46	171.7	23.43	-2.04	24.23
	Propranolol	41	177.0	32.78	-5.85	30.16
SGOT IU/L (10-50)	PN 200-110	46	26.8	12.95	0.30	14.72
	Propranolol	42	24.3	10.15	-0.26	10.04
SGPT IU/L (5-55)	PN 200-110	46	25.7	19.99	-0.17	17.93
	Propranolol	41	22.1	13.31	-0.59	10.21
Sodium mmol/L (134-143)	PN 200-110	44	139.5	2.31	0.07	2.30
	Propranolol	37	139.4	2.77	0.19	3.20
Potassium mmol/L (3.5-5.3)	PN 200-110	44	4.3	0.36	-0.14**	0.36
	Propranolol	37	4.2	0.32	0.15**	0.25
Chloride mmol/L (96-107)	PN 200-110	44	102.4	2.15	-0.18	3.22
	Propranolol	37	102.7	2.54	-1.00	3.67
CO_2 mmol/L (25-32)	PN 200-110	42	26.3	3.08	-0.01	3.43
	Propranolol	37	26.5	2.31	0.88(*)	2.90
Creatinine mg/dl 0.6-1.3)	PN 200-110	44	1.0	0.16	-0.01	0.19
	Propranolol	37	1.0	0.14	0.11***	0.14

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

TABLE 37

PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110	101	Abdominal Discomfort	-3 - Mild	-2 - Mild	
		Flushing	-3 - Mild	-2 - Mild	
		Headache	1 - Moderate		
	103	Headache	4 - Severe		
		URI	8 - Moderate	9 - Mild	
	106	Diarrhea	2 - Mild		
		Vaginal Discharge	3 - Mild	6 - Mild	4 - Moderate
		Abdominal Discomfort	4 - Moderate	10 - Moderate	
	108	Hives	-3 - Mild	10 - Moderate	2 - Moderate
		Edema	1 - Mild	10 - Moderate	4 - Moderate
		Viral Syndrome	4 - Moderate	6 - Mild	
		Palpitation	4 - Moderate		
	109	Back, Ache/Pain, etc.	4 - Moderate		
		Edema	5 - Moderate	10 - Moderate	
	112	Pollakiuria	6 - Moderate	7 - Mild	
		Headache	8 - Mild		
		URI	10 - Moderate		
	113	Fatigue	-3 - Mild	10 - Mild	
		Pain/Ache, Misc.	2 - Mild	10 - Mild	
	115	Nasal Congestion	-2 - Mild	-1 - Mild	
		Sneezing	-2 - Mild		
		Headache	1 - Mild	2 - Mild	
		Palpitation	2 - Mild		
		Pruritus	3 - Mild		
		Insomnia	3 - Mild	7 - Mild	
		Back, Ache/Pain, etc.	7 - Moderate	8 - Mild	
	118	Headache	-3 - Mild	7 - Mild	
		Shoulder Pain	1 - Moderate	10 - Mild	
		Pollakiuria	1 - Mild		
		Flushing	1 - Mild	8 - Mild	
		Chest Pain	5 - Mild		
		Heart Flutter	5 - Mild	10 - Mild	

resented only if there is a multiple occurrence.
resented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence+	Worst Occurrence++
PN 200-110 (Continued)	151	Throat, Pain/Numb/ Ache/Discomfort, etc	-2 - Mild	-1 - Mild	
		Numbness	4 - Mild	7 - Mild	
		Rhinitis	4 - Mild	7 - Mild	
		Dizziness	7 - Severe	8 - Mild	
	154	Fatigue	-3 - Mild		
		Headache	-2 - Severe		
		Teeth, Ache/Pain	3 - Moderate	7 - Severe	
	155	Edema	-1 - Mild	10 - Moderate	4 - Moderate
		Nocturia	3 - Mild	10 - Mild	5 - Moderate
		Fatigue	6 - Mild	10 - Mild	
	157	Headache	-3 - Severe		
	160	Throat, Pain/Numb/ Ache/Discomfort, etc	6 - Mild	7 - Mild	
	202	Fatigue	7 - Mild	9 - Mild	
		Dizziness	10 - Mild		
	204	Headache	-1 - Mild		
	205	Throat Discomfort	1 - Mild		
		Sneezing	1 - Mild		
		URI	2 - Mild	5 - Mild	
		Elevated SGPT	4 - Mild	10 - Mild	
		Edema	8 - Mild	10 - Mild	
	207	Hyperhidrosis	2 - Mild	6 - Mild	
	210	Drowsy	-3 - Mild	-1 - Mild	
		Angina	-2 - Moderate	3 - Mild	
		Breath, Short/Diff, etc.	-2 - Severe	1 - Moderate	
		Headache	3 - Mild		

esented only if there is a multiple occurrence.
+presented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110 (Continued)	212	Arthritis Pain	-3 - Moderate	10 - Moderate	
		Breath, Short/Diff, etc.	-3 - Mild	-1 - Mild	
		Headache	1 - Moderate		
		URI	2 - Mild		
		Throat, Dry	6 - Mild	10 - Mild	
		Erytheme (Skin Red Blotching)	6 - Mild	10 - Mild	
		Edema	10 - Moderate		
	213	Headache	8 - Mild		
		Tachycardia	9 - Moderate	10 - Moderate	
		Dizziness	10 - Mild		
	216	Angina	-3 - Mild	8 - Moderate	-1 - Moderate
		Fatigue	-1 - Mild		
		Joint Pain	2 - Mild	4 - Mild	
		Weight Gain	2 - Mild	3 - Mild	
		Retro Sternum Pain	5 - Mild	6 - Mild	
		Breath, Short/Diff, etc.	8 - Moderate		
	217	Chest Pain	-3 - Mild		
		Flu Symptoms	-2 - Moderate		
		Headache	1 - Moderate		
		URI	1 - Mild	2 - Mild	
		Drowsy	7 - Mild		
		Throat Discomfort	8 - Mild		
		Dyspnea	8 - Mild		
	220	Headache	2 - Mild		
	224	Edema	-3 - Mild		
		Headache	-2 - Mild	3 - Mild	
		Breath, Short/Diff, etc.	-1 - Mild	4 - Mild	
		Dizziness	2 - Mild		
	225	Dizziness	-1 - Mild	6 - Mild	
	252	Skin (Misc. Abnormality)	-2 - Mild	-2 - Mild	
		Edema	7 - Mild	9 - Mild	

esented only if there is a multiple occurrence.
+Presented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110 (Continued)	253	Abdominal Discomfort	-3 - Mild	-1 - Mild	
		Lethargy	-1 - Mild		
		Headache	2 - Mild	4 - Mild	
		Joint Pain	3 - Mild		
		URI	6 - Mild		
		Urinary Infected	9 - Mild	10 - Mild	
	255	Headache	-3 - Mild	10 - Mild	
		Diarrhea	3 - Mild		
		Nausea	3 - Mild		
		Edema	6 - Mild		
	302	Hiccups	-3 - Moderate	-2 - Moderate	
	304	Flushing	1 - Mild	10 - Mild	
		Edema	1 - Mild	10 - Mild	
		Legs, Misc. Ache/Pain, etc.	3 - Moderate	8 - Mild	
		Menst. Cramp/Dysmenorrhea	8 - Moderate		
	305	Nasal Congestion	1 - Mild	2 - Mild	
		Joint Pain	1 - Moderate	2 - Moderate	
	308	Headache	-2 - Moderate	5 - Mild	
		Chest Pain	3 - Mild		
		Fever	6 - Moderate		
		Flushing	6 - Mild	7 - Mild	
		Dizziness	6 - Moderate		
		Diarrhea	6 - Moderate		
		Nausea	6 - Moderate		
	309	Nose Running/Rhinorrhea	2 - Mild	3 - Mild	
	312	Throat, Pain/Numb/Ache/Discomfort, etc	7 - Mild		
		Teeth, Ache/Pain, etc	9 - Moderate		
		Chest Pain	10 - Mild		
		Nausea	10 - Moderate		
		Fever	10 - Moderate		
		Headache	10 - Moderate		

0304

*Presented only if there is a multiple occurrence.
**Presented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
PN 200-110 (Continued)	314	Boil on Buttock	3 - Moderate		
		URI	7 - Mild		
		Nasal Congestion	7 - Mild		
	316	Palpitation	1 - Moderate	10 - Mild	
		Throat Discomfort	7 - Mild	10 - Moderate	8 - Moderate
		Coughing	9 - Moderate	10 - Moderate	
	318	Headache	-3 - Moderate	5 - Moderate	
	319	Hand/Feet, Pain/Ache, etc.	-1 - Moderate		
		Edema	-1 - Moderate	2 - Moderate	
		Fight Injuries	2 - Moderate		
		Abdominal Discomfort	2 - Moderate		
		Diarrhea	2 - Moderate		
		Palpitation	3 - Mild	7 - Mild	
		Flushing	3 - Mild		
	322	Pruritus (Leg/Arm, Itch)	-3 - Mild	-2 - Mild	
		Headache	-2 - Mild	5 - Mild	2 - Moderate
		Sinusitis/Sinus Inflam	-1 - Mild	1 - Mild	
	351	Abdominal Discomfort	2 - Mild		
	355	Palpitation	1 - Mild	3 - Mild	2 - Moderate
		Headache	1 - Severe	10 - Moderate	
		Flushing	1 - Moderate	10 - Mild	
	357	Viral Symptoms	-3 - Moderate		
		Headache	-1 - Mild		
		Nasal Congestion	5 - Moderate		
		Edema	6 - Mild	10 - Mild	
Propranolol	102	URI	9 - Mild	10 - Mild	
	104	Headache	-3 - Mild		
		Abdominal Discomfort	-3 - Mild		
		Fogginess	1 - Moderate	3 - Moderate	

esented only if there is a multiple occurrence.
esented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
Propranolol (Continued)	105	Pain/Ache, Misc.	-3 - Moderate	-2 - Moderate	
		Lethargy	4 - Mild	5 - Mild	
		Nose Running/Rhinorrhea	4 - Mild	5 - Mild	
		Joint Pain	4 - Mild	5 - Mild	
	107	Nausea	1 - Mild		
		URI	4 - Mild	10 - Mild	
		Fatigue	5 - Mild	10 - Mild	
		Edema	8 - Mild	10 - Mild	
	110	Many Dreams	-1 - Moderate		
	111	Breath, Short/Diff, etc.	-3 - Mild	-2 - Mild	
		Edema	-3 - Moderate	-2 - Moderate	
		URI	-1 - Moderate	1 - Mild	
		Hay Fever	3 - Mild	10 - Mild	9 - Moderate
		Nausea	5 - Moderate		
		Groin, Pain in	9 - Moderate	10 - Moderate	
	114	Cold Symptoms	5 - Mild	8 - Mild	
	116	Viral Syndrome	-1 - Mild		
	152	Drowsy	4 - Moderate	9 - Mild	
		Headache	8 - Mild		
	153	Pruritus	-2 - Mild	-1 - Mild	
		Edema	1 - Mild	7 - Moderate	
		Gout Attack	4 - Mild		
	156	Headache	3 - Mild		
		Visual Disturbance	3 - Mild		
	158	URI	4 - Moderate	6 - Mild	
	159	Cold	1 - Mild	4 - Mild	
		URI	5 - Moderate	7 - Mild	

*Presented only if there is a multiple occurrence.
**Presented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence*+
Propranolol (Continued)	201	Cold	2 - Mild	3 - Mild	
		Constipation	5 - Mild		
		Rectal Bleeding	5 - Mild		
	203	Arms, Misc. Abnormality	-2 - Mild		
		Headache	-2 - Mild	5 - Mild	
		Dyspnea	-1 - Moderate	1 - Mild	
		Cardiac (Misc. Abnormality)	7 - Severe		
		Cerebral Infarction	7 - Severe		
	206	Bradycardia (Slow Heart Beat)	4 - Mild	10 - Mild	6 - Moderate
	208	Abdominal Discomfort	4 - Mild	6 - Mild	
	209	Breath, Shor./Diff, etc.	1 - Mild	3 - Mild	
		Chest Pain	1 - Mild	3 - Mild	
		Abdominal Discomfort	- Mild	4 - Mild	
		Bradycardia (Slow Heart Beat)	4 - Mild	10 - Mild	
		Headache	10 - Mild		
	211	Edema	3 - Mild		
		Vomiting	4 - Moderate		
		Dyspnea	4 - Mild	5 - Mild	
		Fatigue	6 - Mild		
	214	Headache	-3 - Moderate	7 - Mild	
		Abdominal Discomfort	-3 - Mild	2 - Mild	
		Pollakiuria	-3 - Mild	2 - Mild	
		Dyspnea	2 - Moderate		
		Fatigue	2 - Moderate		
		Ears, Stopped/Popping, etc.	4 - Mild	5 - Mild	
		URI	4 - Mild	5 - Mild	
		Dizziness	5 - Mild	6 - Moderate	
		Epistaxis (Nose Bleed)	5 - Mild		
		Eyes, Spots Before	6 - Moderate		

*Presented only if there is a multiple occurrence.
**Presented only if different from information recorded under first or last occurrence.

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TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
Propranolol (Continued)	215	Throat, Pain/Numb/ Ache/Discomf, etc.	1 - Mild		
		Muscle Spasm	4 - Moderate		
		Cold Symptoms	8 - Mild		
	218	Breath, Short/Diff, etc.	3 - Mild	4 - Mild	
		Diarrhea	7 - Mild	8 - Mild	
	219	Swallowing Difficult/ Dysphagia	-3 - Mild	-1 - Mild	
		URI	-2 - Mild	-1 - Mild	
	221	URI	3 - Mild		
		Teeth, Ache/Pain, etc.	6 - Moderate	7 - Mild	
	223	Headache	-3 - Mild		
	251	Abdominal Discomfor.	7 - Mild		
		Diarrhea	7 - Mild		
	301	Joint Pain	1 - Mild		
		Chest Pain	1 - Mild	2 - Mild	
		Headache	3 - Mild	6 - Mild	
		Diarrhea	10 - Moderate		
	303	Fatigue	3 - Moderate		
		Abdominal Discomfort	3 - Moderate	7 - Moderate	
		Flatulence	3 - Moderate		
		Muscle Pain	3 - Moderate		
		Dizziness	3 - Moderate		
		Headache	6 - Moderate		
	306	URI	-1 - Moderate	5 - Moderate	
	307	Libido Decrease/ Frigidity	4 - Moderate	10 - Moderate	
		Nasal Congestion	9 - Moderate	10 - Moderate	
	310	Stools, Loose	2 - Moderate		

esented only if there is a multiple occurrence.
resented only if different from information recorded under first or last occurrence.

TABLE 37 (Continued)
PN 200-110 STUDY NO. 304

ADVERSE REACTION LISTING

Treatment Group	Patient No.	Adverse Reaction	Week And Severity Of		
			First Occurrence	Last Occurrence*	Worst Occurrence**
Propranolol (Continued)	311	Wheezing	1 - Moderate	2 - Moderate	
		Fatigue	1 - Moderate	2 - Moderate	
		Sinusitis/Sinus Inflam	1 - Moderate	2 - Moderate	
		Visual Disturbance	2 - Mild		
	317	Groin, Pain In	-1 - Mild	2 - Mild	
		Impotence	5 - Moderate	7 - Mild	
		Tingling	5 - Mild	6 - Mild	
		Hands/Feet, Pain/Ache, etc.	6 - Mild	7 - Mild	
	320	Abdominal Discomfort	-3 - Moderate		
		Headache	-3 - Moderate		
	321	Fatigue	1 - Moderate	4 - Moderate	
	324	Headache	-2 - Mild	5 - Mild	4 - Severe
		Abdominal Discomfort	5 - Mild		
	352	Visual Disturbance	2 - Mild	3 - Mild	
		Abdominal Discomfort	7 - Severe		
		Diarrhea	7 - Severe		

*esented only if there is a multiple o currence.
.esented only if different from information recorded under first or last occurrence.

TABLE 38
PN 200-110 STUDY NO. 304

COMPARATIVE ADVERSE REACTION FREQUENCIES

Variable	Treatment Group		p-Value From Fisher's Exact Test
	PN 200-110 N=46 (%)	Propranolol N=43 (%)	
Miscellaneous			
Pain/Ache, Misc.	1 (2.2)	0 (0.0)	1.00
Fever (Pyrexia)	2 (4.3)	0 (0.0)	0.49
Teeth/Mouth Pain	2 (4.3)	1 (2.3)	1.00
Throat Discomfort	3 (6.5)	0 (0.0)	0.24
Weight Gain	1 (2.2)	0 (0.0)	1.00
Skin			
Erythema	1 (2.2)	0 (0.0)	1.00
Pruritus	1 (2.2)	0 (0.0)	1.00
Hives	1 (2.2)	0 (0.0)	1.00
Musculo-Skeletal			
Back, Ache/Pain, etc.	2 (4.3)	0 (0.0)	0.49
Chest Pain	1 (2.2)	0 (0.0)	1.00
Muscle Pain	0 (0.0)	1 (2.3)	0.48
Hand/Feet, Pain/Ache, etc.	0 (0.0)	1 (2.3)	0.48
Groin, Pain in	0 (0.0)	1 (2.3)	0.48
Joint Pain	3 (6.5)	2 (4.7)	1.00
Legs, Misc. Ache/Pain, etc.	1 (2.2)	0 (0.0)	1.00
Muscle Spasm	0 (0.0)	1 (2.3)	0.48
Shoulder Pain	1 (2.2)	0 (0.0)	1.00
Respiratory			
Coughing	1 (2.2)	0 (0.0)	1.00
Nose Running/Rhinorrhea	1 (2.2)	1 (2.3)	1.00
Nasal Congestion	3 (6.5)	1 (2.3)	0.62
Sinusitus/Sinus Inflammation	0 (0.0)	1 (2.3)	0.48
Sneezing	1 (2.2)	0 (0.0)	1.00
Throat, Pain/Numb/Ache/ Discomfort, etc.	2 (4.3)	1 (2.3)	1.00
Wheezing	0 (0.0)	1 (2.3)	0.48

TABLE 38 (Continued)
PN 200-110 STUDY NO. 304

COMPARATIVE ADVERSE REACTION FREQUENCIES

Variable	Treatment Group		p-Value From Fisher's Exact Test
	PN 200-110 N=46 (%)	Propranolol N=43 (%)	
Cardiovascular			
Bradycardia	0 (0.0)	2 (4.7)	0.23
Breath, Short/Difficult, etc.	1 (2.2)	2 (4.7)	0.61
Heart Flutter	1 (2.2)	0 (0.0)	1.00
Cardiac (Misc. Abnormality)	0 (0.0)	1 (2.3)	0.48
Cerebral Infarction	0 (0.0)	1 (2.3)	0.48
Chest Pain	2 (4.3)	2 (4.7)	1.00
Dyspnea	1 (2.2)	2 (4.7)	0.61
Edema	8 (17.4)	3 (7.0)	0.20
Retro Sternum Pain	1 (2.2)	0 (0.0)	1.00
Epistaxis	0 (0.0)	1 (2.3)	0.48
Palpitation	5 (10.9)	0 (0.0)	0.06(*)
Tachycardia	1 (2.2)	0 (0.0)	1.00
Gastrointestinal			
Abdominal Discomfort	3 (6.5)	6 (14.0)	0.30
Constipation	0 (0.0)	1 (2.3)	0.48
Diarrhea	4 (8.7)	4 (9.3)	1.00
Flatulence	0 (0.0)	1 (2.3)	0.48
Nausea	3 (6.5)	2 (4.7)	1.00
Rectal Bleeding	0 (0.0)	1 (2.3)	0.48
Stools, Loose	0 (0.0)	1 (2.3)	0.48
Vomiting	0 (0.0)	1 (2.3)	0.48
Urogenital			
Impotence	0 (0.0)	1 (2.3)	0.48
Menstrual Cramps/Dysmenorrhea	1 (2.2)	0 (0.0)	1.00
Nocturia	1 (2.2)	0 (0.0)	1.00
Pollakiuria	2 (4.3)	0 (0.0)	0.49
Urinary Infected	1 (2.2)	0 (0.0)	1.00
Vaginal Discharge	1 (2.2)	0 (0.0)	1.00

(*)p<.10

TABLE 39
PN 200-110 STUDY NO. 304

SUMMARY OF ECHOCARDIOGRAPHIC DATA
CENTER 8 ONLY
COMPLETED PATIENTS ONLY

Variable	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Body Surface Area m^2	PN 200-110	13	1.9	0.17	0.00	0.01
	Propranolol	11	1.9	0.18	0.00	0.03
Ejection Fraction %	PN 200-110	12	0.7	0.10	0.01	0.08
	Propranolol	10	0.8	0.10	0.00	0.07
Fractional Shortening %	PN 200-110	12	36.3	7.38	1.18	6.40
	Propranolol	10	38.0	7.45	-0.03	6.14
Left Ventricular Diastolic Dimension cm	PN 200-110	12	5.0	0.38	-0.22*	0.33
	Propranolol	10	4.8	0.62	-0.01	0.39
Left Ventricular Mass gm	PN 200-110	11	301.6	92.55	1.51	63.35
	Propranolol	10	269.0	74.13	-13.20	41.89
Left Ventricular Mass Index gm/m^2	PN 200-110	11	152.6	39.65	4.18	31.22
	Propranolol	10	142.9	37.74	-7.29	21.75
Left Ventricular Posterior wall Thickness cm	PN 200-110	12	1.2	0.21	0.08	0.20
	Propranolol	10	1.2	0.21	-0.03	0.15
Mean Velocity Circumference Shortening	PN 200-110	5	1.0	0.28	0.10	0.19
	Propranolol	5	1.1	0.25	0.02	0.33
Septal Wall Thickness cm	PN 200-110	11	1.3	0.28	0.09	0.19
	Propranolol	10	1.3	0.19	-0.04	0.18
Cardiac Output	PN 200-110	12	5.3	0.90	-0.25	1.16
	Propranolol	10	5.1	1.92	-0.80(*)	1.26
End Diastolic Volume cc	PN 200-110	12	119.6	21.05	-10.58*	16.30
	Propranolol	10	109.5	32.86	0.08	17.39
End Systolic Volume cc	PN 200-110	12	42.2	16.49	-5.05*	6.89
	Propranolol	10	35.8	14.48	2.42	7.44
Left Ventricular Ejection Time sec	PN 200-110	6	0.4	0.02	0.00	0.02
	Propranolol	6	0.5	0.01	0.46	0.00
Pre-Ejection Period sec	PN 200-110	10	0.1	0.02	0.00	0.03
	Propranolol	9	0.1	0.02	0.11	0.01
Stroke Volume cc	PN 200-110	12	77.3	15.61	-5.33	18.47
	Propranolol	10	73.7	23.91	-2.29	16.68
Systolic Time Interval sec	PN 200-110	6	0.3	0.02	0.01	0.03

TABLE 40
PN 200-110 STUDY NO. 304

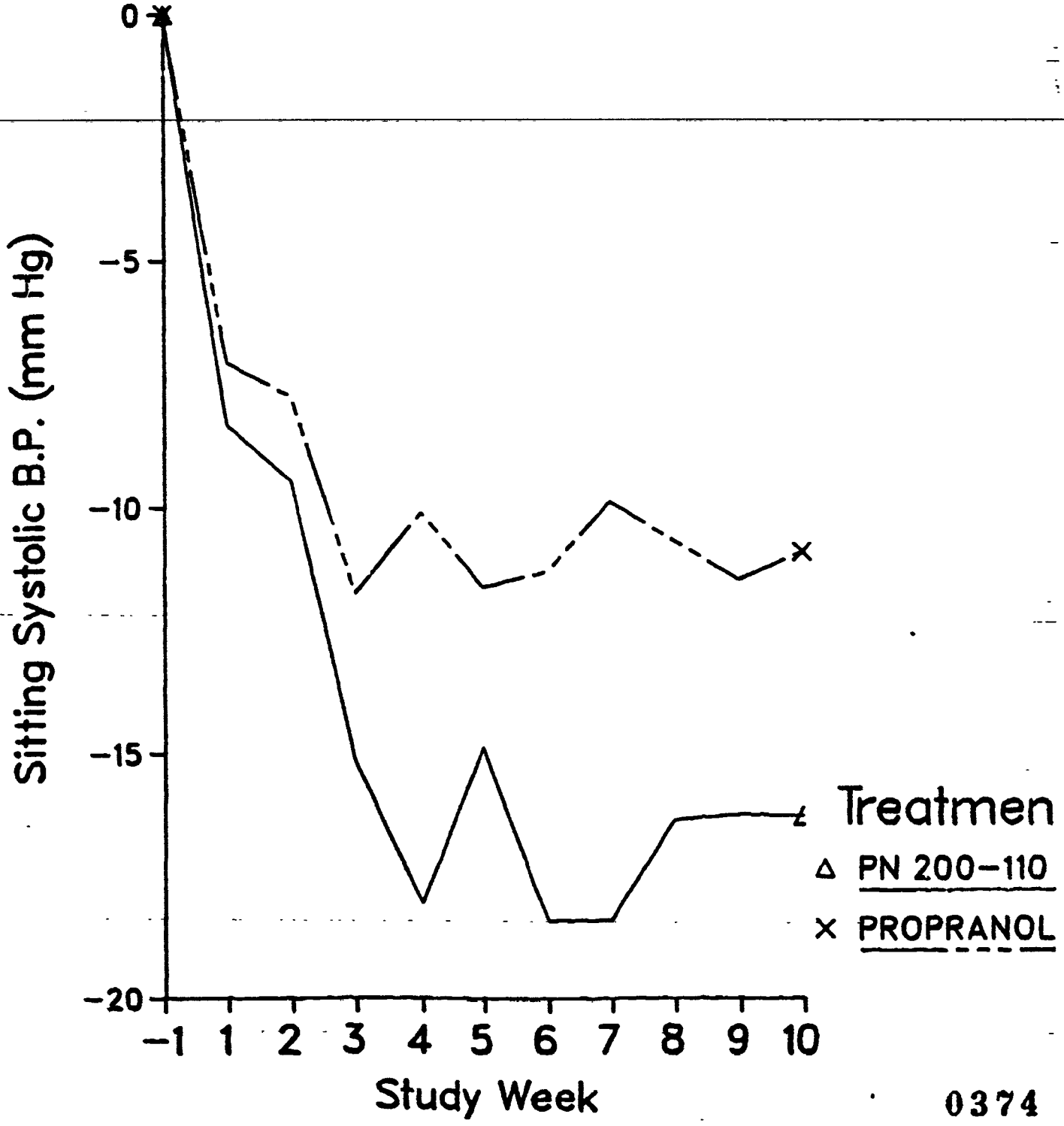
24-HOUR AMBULATORY BLOOD PRESSURE MONITORING

DESCRIPTIVE STATISTICS

Variable	Treatment Group	No. of Patients	Baseline		Endpoint	
			Mean	S.D.	Mean Change	S.D.
Systolic B.P. (mm Hg)	PN 200-110	4	148.1	11.18	0.64	22.08
	PROPRANOLOL	2	152.1	2.08	-4.05	11.30
Diastolic B.P. (mm Hg)	PN 200-110	4	103.7	9.43	-13.01	11.31
	PROPRANOLOL	2	95.1	3.73	-7.67	6.14
Heart Rate (per minute)	PN 200-110	4	80.7	4.56	-5.05	10.03
	PROPRANOLOL	2	86.0	2.88	-17.74	1.66

Figure 1

PN 200–110 STUDY #304
Sitting Systolic BP
Change from Baseline – Valid Patients



0374

Figure 2

PN 200–110 STUDY #304
Sitting Diastolic BP
Change from Baseline – Valid Patients

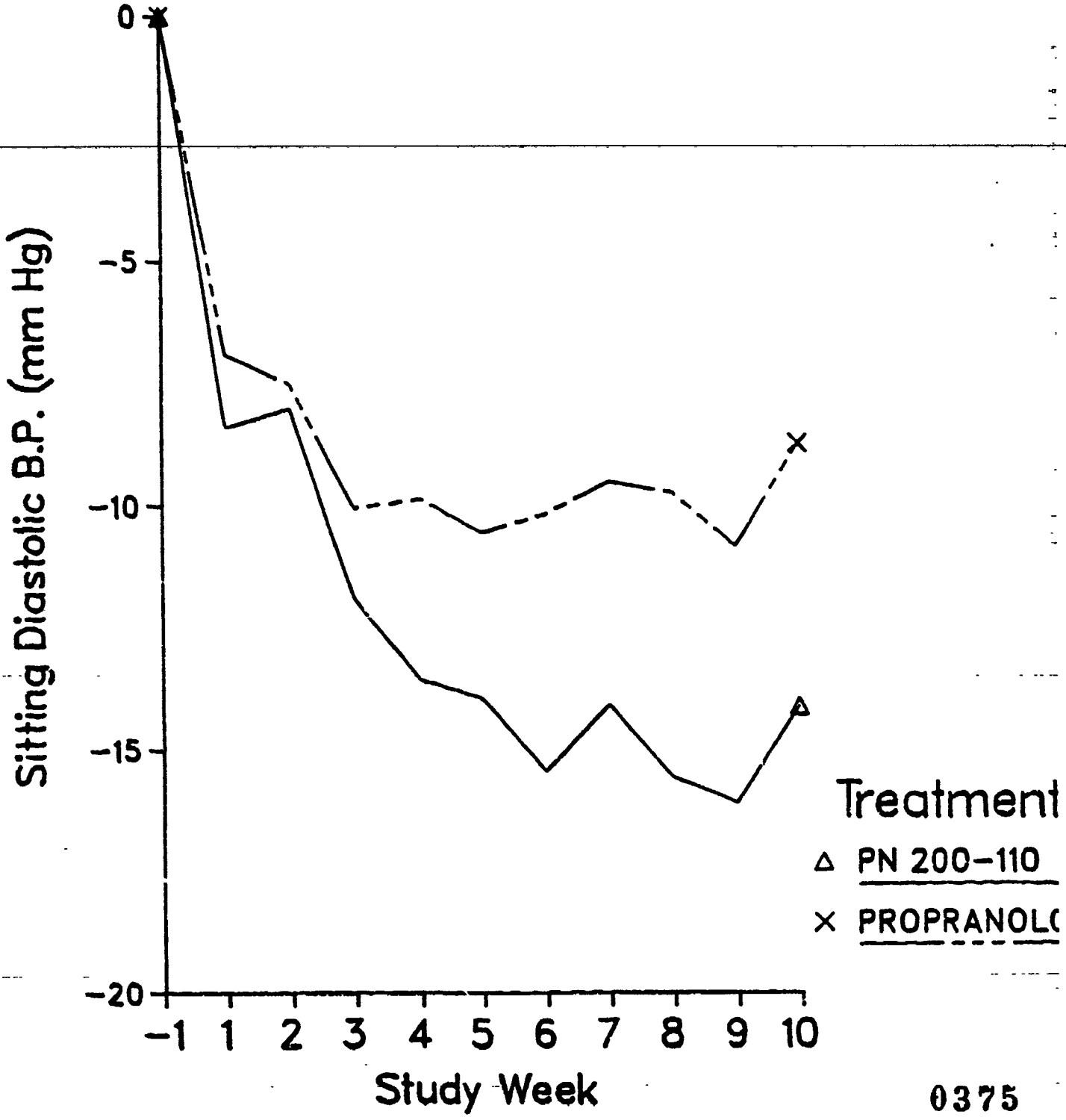


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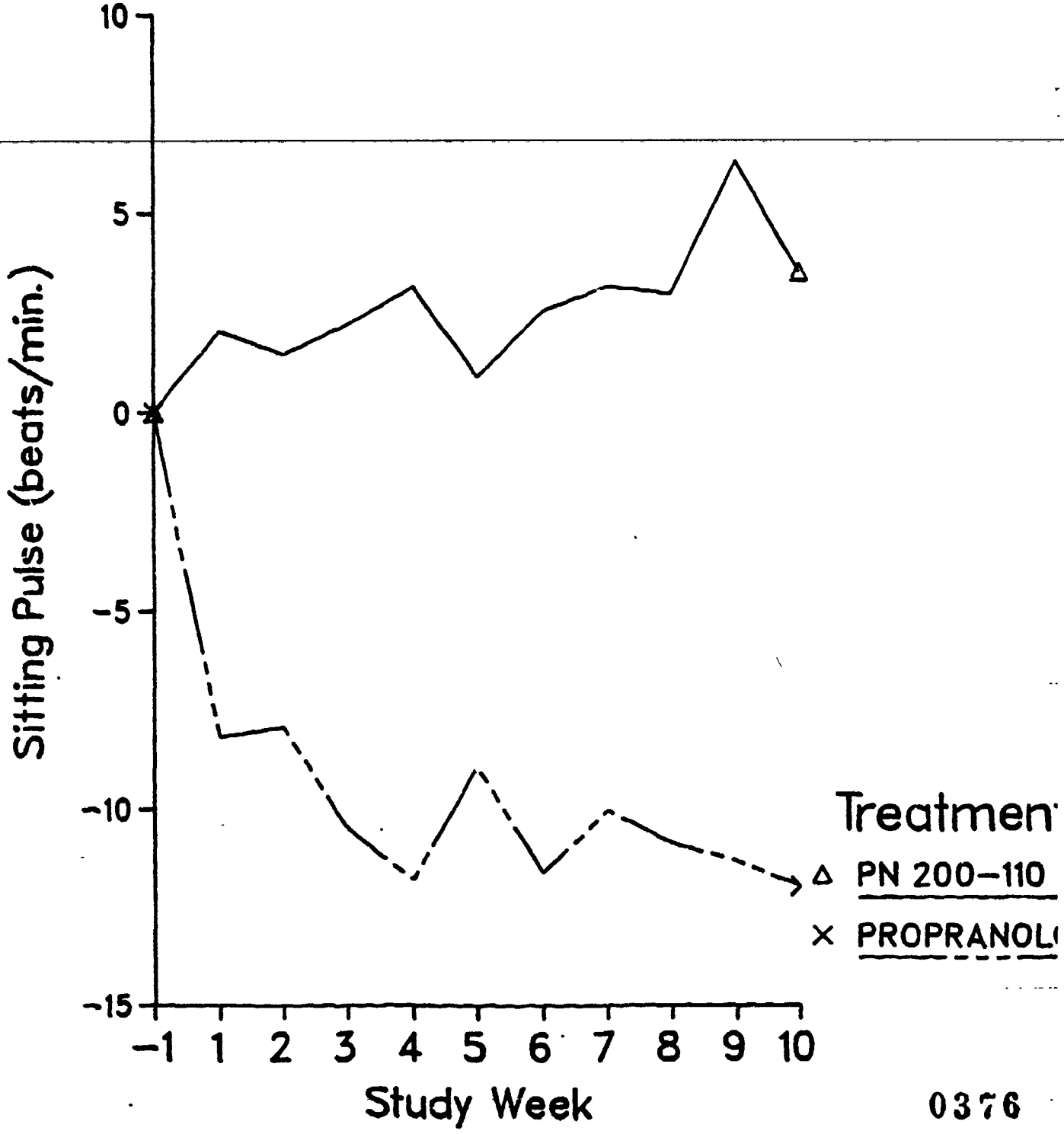
Figure 3

PN 200–110 STUDY #304
Sitting Pulse
Change from Baseline – Valid Patients



TAL
PN 200-110 STUDY NO. 304

DOSAGE SCHEDULE

Treatment Group	Placebo Run-In Weeks -3, -2, -1	Active Treatment*					Optional Tapering Off
		Titration Period			Plateau Period††		
		Weeks 1 & 2++	Weeks 3 & 4++	Weeks 5 & 6++	Weeks 7 & 8	Weeks 9 & 10	
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	→	
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 →					

*Pcb = Placebo

**Ppnl = Propranolol

+Dose of the study drugs was administered bid before breakfast and supper, and at least 30 minutes before the blood pressure was recorded.

++The dose was increased by one capsule (2.5 mg PN 200-110 or 60 mg propranolol) bid at bi-weekly intervals if the sitting diastolic blood pressure was >90 mm Hg at the clinic evaluation. The dose may have been increased any time the average supine diastolic was >110 mm Hg.

††*Beginning with Week 7, the dose of the study drugs remained unchanged.* However, the dose was reduced in a stepwise manner to a lower level in case of an adverse reaction. At no time was the prescribed dose of the study drug to be less than 2.5 mg PN 200-110 bid or 60 mg propranolol bid or to exceed 10 mg PN 200-110 bid or 240 mg propranolol bid.

Table 1

TABLE 2
FM 200-110 STUDY NO. 304

EVALUATION SCHEDULE

Evaluations	Initial Visit	END OF WEEK													
		Single-Blind			Double-Blind: Active Treatment Period										12 Follow-up Evaluation
		Placebo Washout			Titration Period						Plateau Period				
	-4	-3	-2	-1 Time 0	1	2	3	4	5	6	7	8	9	10 Final Evaluations	
Background Information CRF BK, BK-1**	X														
Physical Exam CRF PE	X													X°	
Cardiovascular Evaluation CRF CV	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°	
24-Hour Ambulatory BP and Heart Rate CRF ABP				X[1]										X°[1]	
Laboratory Evaluation [illegible], urinalysis CBC, chem.) CRF LAB	X			X	X°	X°	X°	X	X°	X	X °	X°	X°	X°	X°
[illegible]aluation CRF ECG	X			X		X		X		X		X		X°	
[illegible]ardiogram CRF EC				X[2]										X°[2]	
Chest X-ray CRF CX	X†													X°	
Ophthalmologic Examination CRF 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°	
End of Study Information CRF ES														X	

*Or upon discontinuation from the study.

°Liver function tests only (LDH, SGOT, SGPT, alkaline phosphatase, and total bilirubin) initiated during October/November, 1984.

**Case Report Form identifiers.

†A chest X-ray obtained within six (6) months prior to the patient entering the trial may have served as baseline for the study and was not repeated at the initial visit provided that the chest X-ray was normal and a clinical condition requiring a chest x-ray had not occurred during this interval. Otherwise, a x-ray was obtained.

††The ophthalmologic examination may have been performed any time during the washout period but as close as possible to the week [illegible] 0 visit. The final exam may have been performed within one week of the final evaluations but as close as possible to [illegible]al evaluations.

[illegible]nter C only.

[2]The echocardiogram may have been obtained within 1-4 days prior to the Week -1 and Week 10 clinic visits. This evaluation applies only to Center B.

TABLE 4
PN 200-110 STUDY NO. 304
REASONS FOR PARTIAL VALIDITY OR INVALIDITY FOR EFFICACY ANALYSIS

Patient No.	Treatment Group	Week Discontinued	Valid Thru Week	Reasons
Partially Valid				
204	PN 200-110	4	3	Patient unable to keep appointments
210	PN 200-110	9	8	Uncooperative
216	PN 200-110	8	8	Adverse Reaction - increased angina/shortness of breath
309	PN 200-110	4	3	Emergency Surgery (acute aortic dissection)
354	PN 200-110	8	8	Treatment Failure
104	Propranolol	3	3	Adverse Reaction - clouded sensorium
156	Propranolol	3	3	Treatment Failure
158	Propranolol	6	6	Treatment Failure
203	Propranolol	7	6	Subject expired (cardiac arrest secondary to arrhythmia or myocardial infarction).
208	Propranolol	6	5	Uncooperative and Adverse Reaction - abdominal pain
214	Propranolol	7	6	Treatment Failure
313	Propranolol	2	2	Lost to Follow-Up
321	Propranolol	4	4	Adverse Reaction - Fatigue
352	Propranolol	8	6	Adverse Reaction - Gastro-intestinal
353	Propranolol	3	3	Routine Surgery (vaginal)
356	Propranolol	8	7	Adverse Reaction - Fatigue
Invalid				
109*	PN 200-110	N/A	N/A	Non-qualifying blood pressure during washout (diastolic bp <95 mm Hg at Week -1)
308*	PN 200-110	N/A	N/A	Non-qualifying blood pressure during washout (mean diastolic bp 94 mm Hg at Week -2)
319*	PN 200-110	N/A	N/A	Non-compliant - less than 80% medications taken during active treatment
323*	PN 200-110	N/A	N/A	Non-qualifying blood pressure during washout (mean diastolic bp <95 mm Hg at Week -1)
311	Propranolol	1	N/A	Adverse Reaction - Broncho-spasm. Did not take dose of study medication the day of visit.

02

TABLE 5
PN 200-110 STUDY NO. 304

NUMBER OF PATIENTS BY EFFICACY ANALYSES CLASSIFICATION

Investigator	PN 200-110			Propranolol			Total			TOTAL
	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	Valid	Partially Valid	Invalid	
A	13	0	1	11	3	0	24	3	1	28
B	13	3	0	11	3	0	24	6	0	30
C	11	2	3	9	5	1	20	7	4	31
TOTAL	37	5	4	31	11	1	68	16	5	89

TABLE 7
FN 200-110 STUDY NO. 304

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

Treatment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
FN 200-110										
N	37	36+	37	37	37	37	36+	37	37	36+
Mean	4.9	4.9	8.3	8.8	10.3	10.7	12.0	11.8	11.8	11.8
S.D.	0.45	0.39	2.43	2.43	3.68	3.92	5.22	5.13	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	31	31	31	31	31	31	31	31	31	31
Mean	118.5	121.9	195.2	197.4	255.2	271.0	332.8	326.3	337.7	329.5
S.D.	6.98	11.84	79.05	61.98	106.83	102.57	144.82	142.16	149.97	145.94
Min	102.9	110.0	100.0	102.9	105.0	102.9	111.4	111.4	111.4	97.5
Max	137.1	180.0	480.0	308.6	531.4	411.4	480.0	480.0	574.3	480.0

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