CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20943

MEDICAL REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)
MEDICAL OFFICER'S REVIEW

NDA 20,943 / 000
Name of Drug : VERAPAMIL PM (verapamil hydrochloride)
Sponsor : Elan Pharmaceutical Research Corp.
Type of Submission : ORIGINAL
Date of Submissions: Original 12/23/97
Amendments: 2/03/98, 2/12, 2/12, 2/20, 2/24, 2/26, 2/27, 3/03, 3/04,3/19, 3/26/98
3/31/98
Date of Review completed : 4/02/98
Reviewer : Sughok K. Chun, M.D. /S/ 4/03/98

This NDA is being submitted under the provisions of Section 505(b)(2), with a reference to the well established pre-clinical data from the immediate release commercial products as well as the sponsor's own previous NDA
The list and authorization letters for reference to the Dug Master File from 24 companies are submitted.

GENERAL INFORMATION

Name of Drug

Generic : Verapamil HCl (extended-release capsules, controlled-onset)
Trade : **Verapamil PM**

Chemical Name: Benzenacetonirile, α- (3,4-dimethoxyphenyl)ethyl]methylamino]
propyl]3,4-dimethoxy-α-(1-methylethyl)-,monohydrochloride,(±)-.
$C_{27}H_{38}N_2O_4.HCl$ M.W.= 491.07

Pharmacological Category : calcium ion influx inhibitor (slow channel blocker)
Dosage Form : 100mg, 200mg, and 300mg hard gelatin capsules
Route of administration : Oral
Related Drugs : Verapamil, Verelan® SR, Cardizem® CD
Indication : Treatment of hypertension

Resume

Verapamil is a calcium ion influx inhibitor and immediate release tablets (Isoptin® by Knoll, Calan® by G.D. Searle, NDA 18,593) has been approved on 3/8/1982 for the treatment of angina, PSVT & AFib/AFlutter, and hypertension (HTS); and slow release tablets were approved for the treatment of HTS (Isoptin® SR by Knoll, Calan® SR by Searle; NDA 19,152) on 12/16/1986 ; Elan (NDA

Verapamil PM formulation, hard gelatin pellet filled capsules, has been designed to initiate the release of verapamil 4 - 5 hrs after ingestion. This delay is introduced by the level of non-enteric release-controlled polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the GI tract comes into contact with polymer coated beads, the water soluble polymer slowly dissolves and drug diffuses through the pores in the coating. The water insoluble polymer continues to

act as a barrier, maintaining the controlled release of the drug. The rate of release is essentially independent of pH, posture, food, and GI motility.

Verapamil PM(VerPM) has a unique delivery system, designed for bedtime dosing, incorporating a 4 to 5 hr delay in drug delivery, resulting in a maximum plasma conc. (Cmax) of verapamil in the morning hours.

Chemistry, Manufacturing and Controls : Refer to the chemistry review.

Clinical Pharmacology : Refer to the pharmacology review.

Pharmacokinetics (PK) and metabolism : Refer to the PK review.

VerPM achieved a plasma profile consistent with night-time dosing at either single-dose or steady-state, with a distinct 4 to 6 hour lag, followed by a steady rise in plasma concentration.

Following single-dose or steady-state night-time administration of VerPM 200mg, the relative bioavailability was approx 70% compared to divided doses of Isoptin® (total daily dose of 240mg). This is equivalent to a dose-normalized relative bioavailability of approx 85%. Administration of VerPM 200mg in the morning resulted in a relative bioavailability of 90% compared to divided doses of Isoptin® (240mg), which corresponds to a relative dose-normalized bioavailability of 108%.

Following steady-state dosing of VerPM 200mg once-daily at night for 5 days, the relative verapamil bioavailability was 69% compared to Isoptin® 80mg Q8h for 5 days (83% dose normalized). Cmax was reduced by a factor of 1.6 for VerPM and peak-to-trough fluctuations were reduced.

Food had no impact on the extent of absorption of VerPM. Food had a modest impact on the rate of metabolism of VerPM reflected primarily in the norverapamil peak levels, with a lesser impact on the R-verapamil peak levels. The degree and stereoselectivity of verapamil metabolism was in the same range for VerPM and Isoptin®. Although some evidence of lack of proportionality of doses was observed for VerPM, in particular for the lower doses (100mg, 200mg) compared to the higher doses (300mg, 400mg), this non-linearity was enantiomer specific, with the R-enantiomer showing the greatest degree of non-linearity (S-enantiomer has greater pharmacologic activity).

The drug release phase of VerPM is prolonged with Cmax occurring approx 11 hrs after administration, Cmax were approx half the Cmax of Isopin®. Cmin occur approx 4 hrs after bedtime dosing while subject is sleeping. Css is achieved by the 3rd or 4th day of dosing. In healthy volunteers, following administration of VerPM (200 mg/day), mean Cmax of R isomer was 77.8 ng/ml and S isomer was 16.8 ng/ml; AUC (0-24 hr) of the R isomer was 1037 ng.h /ml and 195 ng.h /ml for the S isomer

In general, bioavailability of verapamil is higher and half life is longer in elderly (>65 yrs) subjects. Lean body weight also affects its PK inversely. It was not possible to observe a gender difference in the clinical trials of VerPM due to a small sample size.

Consumption of high fat meals just before the morning dosing had no effect on the extent of absorption from VerPM. The rate of absorption was not affected by whether the subjects were supine 2 hrs after night-time dosing or non-supine for 4 hrs following morning dosing.

CLINICAL STUDIES

The result of two pivotal, phase III, randomized, parallel group, placebo-controlled studies: **study VER-0596-001-US** 200mg vs. placebo (placb) and **study VER-0596-002-US** VerPM 100mg, 200mg, 300mg, and 400mg vs. placb for 8 weeks are submitted.

Other than the difference in dosing, these studies were identical in design. Identical features applicable to both studies are described below, followed by a separate discussion of the results for each study. The study information is shown in Table 1.

Table 1
Controlled Clinical Trials
Verapamil PM
NDA #20-943

Protocol #	Completion Status (Start/Stop Dates)	Full Report Vol. Pg.	Data Listings Vol. Pg.	Study Design	Treatment/ Dose	# Entered Each Treatment	Age Range (Mean)	% M/F B/W/O
VER-0596-001	Complete (10/28/96-6/18/97)	35 019	51 001 thru 63 465	DB, randomized, PBO controlled, parallel group	Verapamil PM 200 mg	71	30-74 (52)	69/31 7/83/10
					Placebo	66	31-99 (53)	61/39 29/62/9
VER-0596-002	Complete (10/29/96-6/15/97)	38 001	64 001 thru 90 335	DB, randomized, PBO controlled, parallel group	Verapamil PM 100 mg	53	34-78 (53)	72/28 11/85/4
					Verapamil PM 200 mg	58	34-77 (53)	64/36 14/79/7
					Verapamil PM 300 mg	58	29-77 (54)	67/33 9/86/5
					Verapamil PM 400 mg	58	31-84 (52)	64/36 9/91/0
					Placebo	51	25-81 (55)	53/47 12/90/8

Objectives

The primary efficacy objective was to evaluate the magnitude of reduction in the mean DBP at trough (6pm to 10pm) as recorded by ambulatory BP monitoring (ABPM) at baseline (BL) and at the end of 8 week treatment in pts treated with VerPM and with placb.

The secondary efficacy variables include the mean reduction of DBP, SBP and HR in the 24 hr and during the morning 'accelerated phase' of BP rise (6am to 12noon) as recorded by ABPM, and the reduction in the mean seated DBP, SBP and HR from BL to end of treatment at trough and peak by manual BP measurement (MBPM).

The safety objective was to evaluated VerPM by assessing adverse events(AEs), ECG recordings, and clinical laboratory values.

Study Design

Both studies employed a multicenter, parallel group, randomized, double-blind, placebo (placb) controlled study in pts (age $\geq$ 18 yrs) with mild to moderate essential HTN. During a 2- to 4-week single-blind lead-in period (**Phase A**) all patients (pts) received placb. Pts became eligible for randomization to **Phase B** when at $\geq$ 2 subsequent Phase A study visits, they exhibited seated(se)SBP <200 mmHg and seDBP $\geq$ 95 and $\leq$ 114 mmHg by MBPM, with a subsequent mean daytime (8am to 4pm) DBP $\geq$ 90 and $\leq$ 114 mmHg by ABPM.

The study medication was taken once daily, between 9pm to 11pm for 8 weeks.

Statistical Criteria for Evaluation

Intent-to-Treat Patients : Pts who received at least 1 dose of d/b medication, and had BL (qualifying phase A visit) and Final or Early Termination Visit BP measurements. Two modified intent-to-treat populations were defined, one for pts with acceptable ABPM readings (ABPM-intent-to-treat) and one for pts with MBPM readings (MBPM-intent-to-treat).

Efficacy-Evaluable pts : Pts who had completed at least 7 days of d/b medication, and have BL and Final or Early Termination Visit BP measurements: ABPM-efficacy-evaluable and MBPM-efficacy-evaluable.

Statistical Methodology : Statistical analyses were performed using SAS® statistical analysis software, were based upon the pooled data from the individual study centers. Unless otherwise noted, all tests of hypotheses were two-sided and at least at the 5% level of significance. No adjustments were made for the Type 1 error rate (alpha) for multiple significance tests.

Continuous variables were summarized by descriptive statistics (number, mean, standard deviation, minimum, and maximum). Primary and secondary efficacy variables were analyzed using an analysis of covariance model with BL value as covariant, and treatment group as factor in the models. Response rates were analyzed by chi-square test.

Safety assessments included physical examination (PE), ECG, laboratory testing, vital signs, at the Final Visit vs. BL and adverse event (AE) reporting.

CLINICAL STUDY VER-0596-001-US : A double-blind, randomized, multicenter trial evaluating the magnitude of blood pressure reduction with Verelan®PM 200mg when compared to placebo in patients with mild to moderated essential hypertension. Volume 1.35

Objectives and Study Design ; see above.

Number of pts (planned and analyzed) / Disposition :

Sample size estimates were based on the difference in the reduction of BP between placb and VerPM 200mg. With 94 total pts (47 per treatment arm), the power to detect a 5 mmHg difference between the two treatment arms would be 85%, assuming two-sides hypothesis testing and a Type 1 error rate of 5%.

286 pts from 13 study sites entered the placb run-in Phase A segment. Of these, 137 pts met eligibility criteria and progressed to the randomized Phase B segment : placb 66, VerPM 200mg 71. 116 pts completed the study. Reasons not to randomized to phase B and discontinuation (D/C) during Phase B are shown Tables 01-1A and 01-1B.

Table 01-1A: Reasons for Discontinuation during Phase A treatment (not to randomized to Phase B)

Reasons to Discontinue	Number (%)
Fails to meet study criteria	122 (82%)
BP increased	4 (3%)
Withdrew consent	12 (8%)
Lost to follow-up	1 (1%)
Investigators/sponsors decision	5 (3%)
Adverse Event	5 (3%)
Other	1 (1%)
Total	149 (100%)

Table 01-1B: Reasons Premature Discontinuation during Phase B (placebo n= 11 / 66 ; Verapamil PM 200mg n=10 / 71)

Inv.#/	Pt.#	Rx group	Age/sex	RxDay	Reasons
101	1009	placb	55 / m	21	uncontrolled BP
	1357	placb	52 / f	70	unsuccessful ABPM
102	1037	VerPM	44 / m	12	stopped to take Rx
	1047	VerPM	47 / m	12	AE : rash, dyspnea
103	1071	VerPM	45 / f	42	AE : rash/itching
	1076	placb	51 / m	16	AE : rash, face edema, dyspnea ? due to allergic to turkey
	1101	placb	72 / m	56	refused to wear the ABPM
	1388	placb	63 / m	6	BP uncontrolled
104	1112	placb	64 / m	6	AE : hosp for vascular anomaly
105	1142	placb	64 / m	30	out of town
	1155	VerPM	54 / m	54	refused to wear ABPM
106	1199	VerPM	56 / f	66	refused to wear ABPM
	1426	VerPM	42 / m	54	BP uncontrolled
110	1316	placb	44 / m	17	BP uncontrolled
	1327	VerPM	50 / f	20	lost to follow-up
	1338	VerPM	66 / m	45	AE : acute psychosis
111	1294	VerPM	55 / m	26	AE : dizziness, headache, angina accidental injury
	1302	placb	55 / f	76	lost to follow-up
114	1026	VerPM	57 / m	25	AE : generalized edema
	1027	placb	66 / m	49	AE : asthma
	1031	placb	61 / m	6	do not want to continue Rx

Discontinuation of the study during the Phase B due to AE were placb 3 / 66(4.5%), VerPM 5 / 71(7.0%) pts.

Of the 137 pts enrolled in Phase B of this study, 136 (99.3%) were included in the safety population and 116 (84.7%) pts were included in the ABPM intent-to-treat population. Two pts who d/ced prior to completion of receiving 8 wks study drug (pt# 01009 on placb at 3 wks;

pt# 01426 on VerPM 200mg at 7 wks due to uncontrolled HTN) had final ABPM and they were included in the efficacy evaluation.

All pts who met the intent-to-treat criteria also met the efficacy-evaluable criteria for both ABPM and MBPM, 116 and 120 pts respectively. The 1 pt (#1327) not included in the safety population was randomized to VerPM group and attended clinic for the B-0 visit but did not return for subsequent visits and was lost to follow-up.

Demographic and Baseline Characteristics

The demographic, BL characteristics, and BL S/D BP were similar between treatment group except race of population. (more blacks in the placb group).

EFFICACY RESULTS:

Primary Efficacy :

Mean S/D BP and HR by ABPM at trough (6pm to 10pm) : Table 01-2 and Figure 01-1.

Table 01-2 Blood Pressure Recorded by ABPM and Heart Rate at Trough; Mean Values and Change From Baseline

	Placebo (N = 85)			Verelan PM (N = 61)				
Measurement	Baseline	Final	Change	Baseline	Final	Change	p-value*	95% C.I.**
Diastolic BP (mmHg) Mean (S.D.) Minimum Maximum	95.9 (8.67) 76 111	96.9 (8.80) 77 115	+1.0 (9.19) -25 19	98.1 (9.14) 76 122	94.9 (8.61) 72 116	-3.1 (9.26) -25 22	0.047	-7.6 to -0.8
Systolic BP (mmHg) Mean (S.D.) Minimum Maximum	155.5 (15.99) 124 193	157.6 (15.74) 129 193	+2.0 (12.86) -48 27	154.9 (14.94) 132 192	151.0 (15.01) 122 192	-3.9 (13.64) -40 27	0.007	-10.8 to -1.0
Heart Rate (beats/min) Mean (S.D.) Minimum Maximum	83.2 (11.78) 50 112	84.9 (13.37) 59 129	+1.6 (10.03) -32 39	83.5 (12.99) 56 119	80.0 (11.78) 60 103	-3.4 (11.21) -33 30	0.007	ND

Abstracted from Statistical Tables 17A and 17B
*p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment
**C.I. for change from baseline to final for treatment minus change from baseline to final for placebo

Figure 01-1 :Mean (±1 SE) ABPM Diastolic and Systolic Blood Pressure at Trough at Baseline and Final Visit by treatment group

Mean (± 1 SE) ABPM Diastolic Blood Pressure at Trough (6 – 10 pm) at Baseline and Final Visit by Treatment Group

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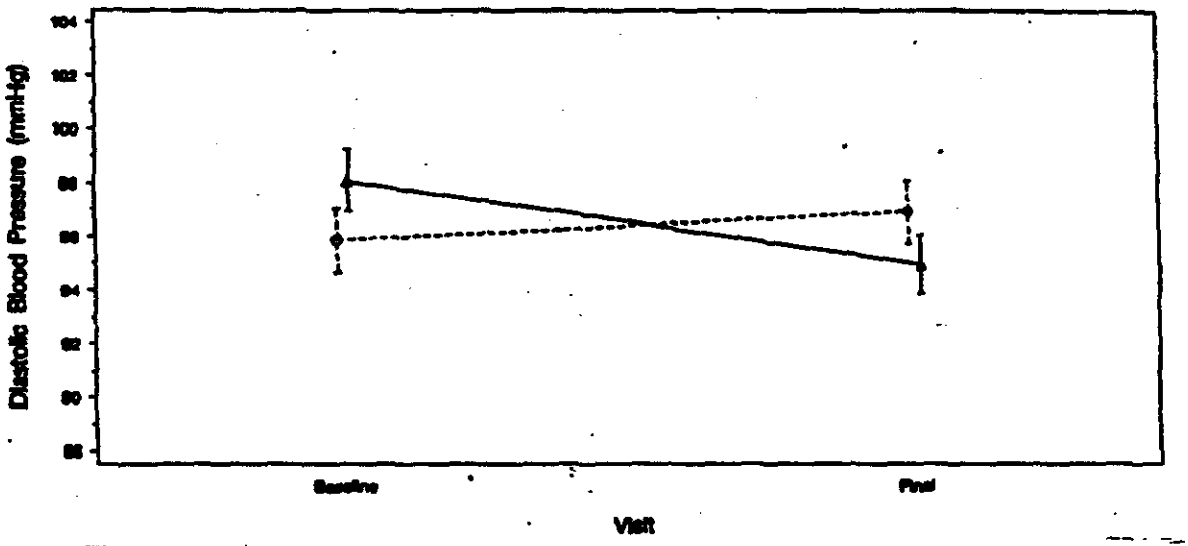
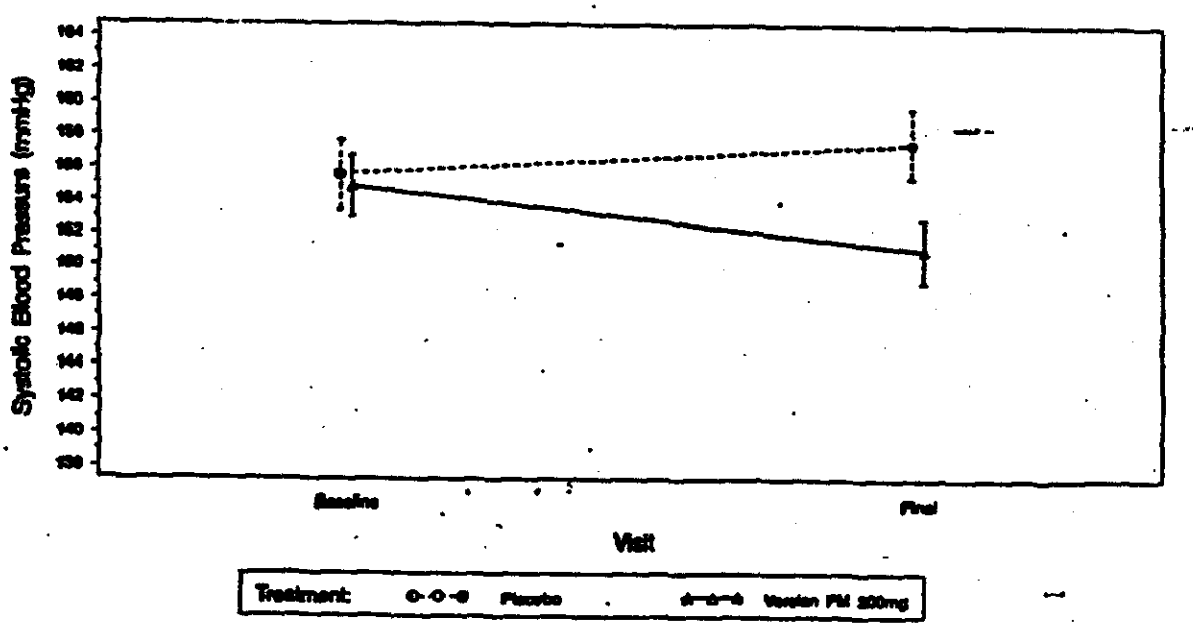


Mean (± 1 SE) ABPM Systolic Blood Pressure at Trough (6 – 10 pm) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



At BL the mean DBP were similar across the two treatment groups. At Final Visit, VerPM group had a statistically (stat.) significant mean change of -3.1 mmHg compared with +1.0 mmHg from BL for placb group (p=0.047). The placb-subtracted mean change (net-effect) in DBP for VerPM 200mg was -4.2 mmHg; the 95% confidence interval (C.I.) -7.6 to -0.8.

The net reduction of SBP with VerPM treatment (5.9 mmHg) from BL was stat. significant (p=0.007) and net reduction of HR 5.0 bpm with VerPM was stat. significant (p=0.007).

Secondary Efficacy Variables

- **Seated BP by Manually measured at Trough (7pm ± 1 hour) :** Table 01-3 and Figure 01-2 .

Table 01-3 Seated Blood Pressure, Measured Manually and Heart Rate at Trough; Mean Values and Change From Baseline

	Placebo (N =58)			Verelan PM (N = 63)				
Measurement	Baseline	Final	Change	Baseline	Final	Change	p-value*	95% C.I**.
Diastolic BP (mmHg)								
Mean (S.D.)	101.2 (6.24)	98.1 (8.55)	-3.0 (8.43)	101.6 (6.10)	94.4 (8.08)	-7.3 (9.59)	0.012	-7.6 to -1.0
Minimum	78	82	-22	89	79	-24		
Maximum	113	121	29	114	115	26		
Systolic BP (mmHg)								
Mean (S.D.)	156.0 (15.73)	153.6 (15.07)	-2.1 (14.36)	154.0 (13.78)	147.6 (13.34)	-6.7 (14.28)	0.020	-9.9 to 0.7
Minimum	121	128	-43	123	129	-31		
Maximum	187	187	28	189	180	36		
Heart Rate (beats/min)								
Mean (S.D.)	77.4 (11.02)	76.1 (9.75)	-1.2 (11.12)	78.2 (9.86)	76.4 (9.06)	-2.2 (7.46)	0.740	ND
Minimum	52	66	-22	57	57	-20		
Maximum	104	104	39	103	96	18		

Abstracted from Statistical Tables 20A. and 20B

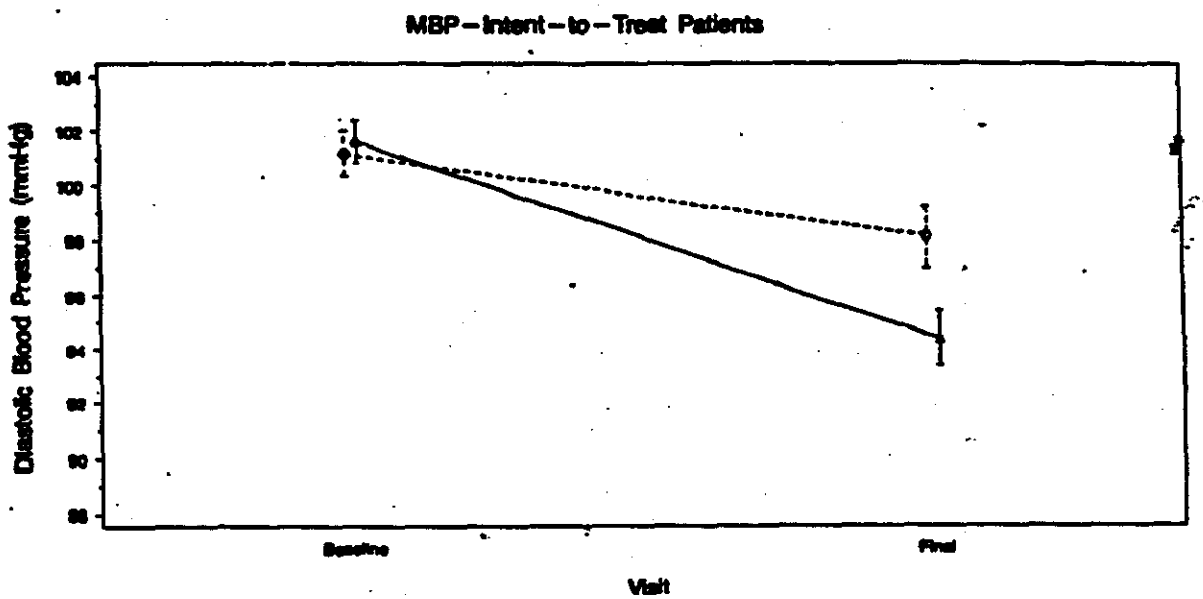
* p-value for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

** C.I. for change from baseline to final for treatment minus change from baseline to final for placebo

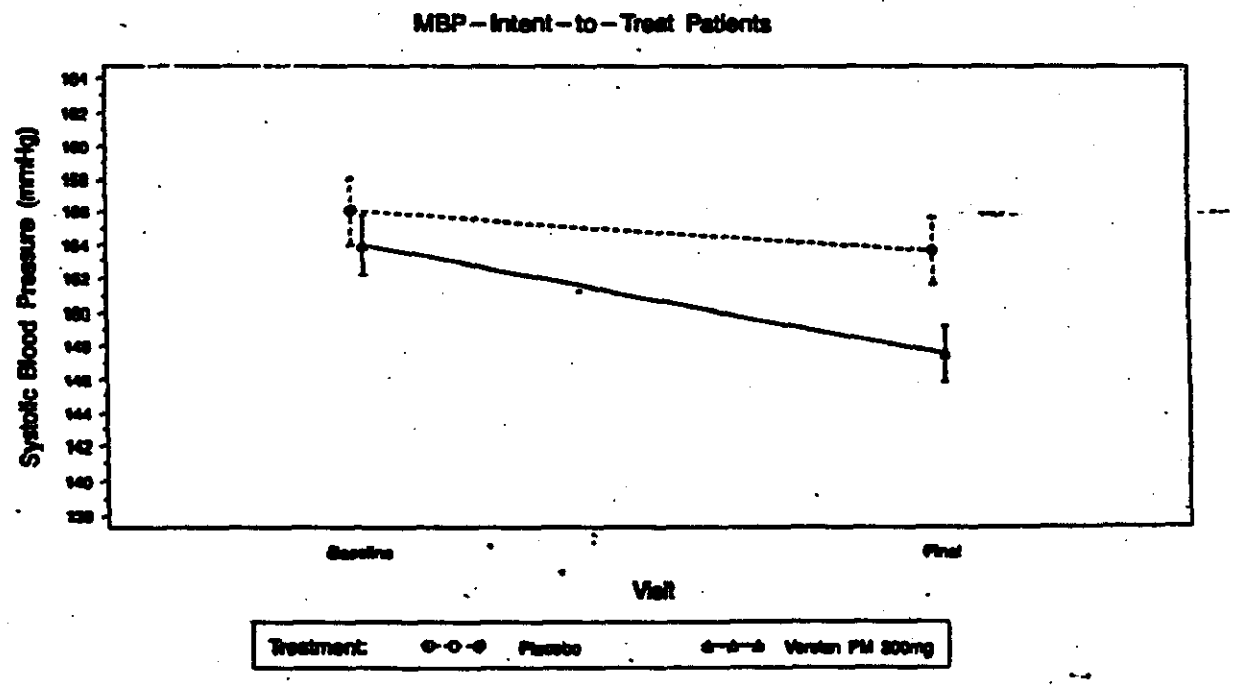
There was no difference of MBPM or HR between the groups at BL. Mean seS / D BP changes at Final Visit were stat. significant (DBP p=0.012; SBP p=0.020) : VerPM 200mg -6.7 / -7.3 vs. placb -2.1 / -3.0 mmHg (net-effect : S / D BP = -4.6 / -4.0 mmHg).

The net reduction of mean HR with VerPM treatment (1.0 bpm) from BL was not stat. significant (p=0.740).

Figure 01-2:
Mean (± 1 SE) Seated Manual Diastolic Blood Pressure at Trough (7 pm ± 1 hour) at Baseline and Final Visit by Treatment Group



Mean (± 1 SE) Seated Manual Systolic Blood Pressure at Trough (7 pm ± 1 hour) at Baseline and Final Visit by Treatment Group



- **24-Hour ABPM and HR (10pm to 10pm next day) :** Table 01-4 and Figure 01-3

Table 01-4 24-Hour Blood Pressure Recorded by ABPM and Heart Rate; Mean Values and Change From Baseline

	Placebo (N=65)			Verelan PM (N=61)			
Measurement	**Baseline**	**Final**	**Change**	**Baseline**	**Final**	**Change**	**p-value***
Diastolic BP (mmHg)							
Mean (S.D.)	93.0 (6.52)	93.6 (7.57)	+0.6 (5.94)	94.2 (5.35)	91.2 (6.67)	-3.0 (5.42)	0.002
Minimum	79	78	-20	80	78	-17	
Maximum	105	108	11	107	108	18	
Systolic BP (mmHg)							
Mean (S.D.)	149.8 (13.92)	151.1 (15.08)	+1.3 (8.99)	149.2 (10.88)	145.3 (11.43)	-3.9 (8.92)	0.001
Minimum	120	124	-30	127	126	-33	
Maximum	182	187	16	173	176	30	
Heart Rate (beats/min)							
Mean (S.D.)	79.8 (10.21)	79.7 (11.03)	-0.1 (6.66)	79.4 (10.76)	76.2 (9.49)	-3.2 (5.92)	0.005
Minimum	57	57	-20	58	57	-27	
Maximum	100	100	18	109	95	10	

Abstracted from Statistical Table 19
* p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

The mean change in S / D BP at the Final Visit with VerPM 200mg vs. placb was stat. significant (DBP p=0.002; SBP p=0.001); VerPM -3.9 / -3.0 vs. placb +1.3 / +0.6 mmHg (net-effect : S / D BP = -5.2 / -3.6 mmHg).

The decrease of HR at Final Visit with VerPM (3.1 bpm) was stat. significant (p=0.005).

Figure 01-3

Mean (± 1 SE) 24 Hour (10 pm – 10 pm) ABPM Diastolic Blood Pressure at Baseline and Final Visit by Treatment Group

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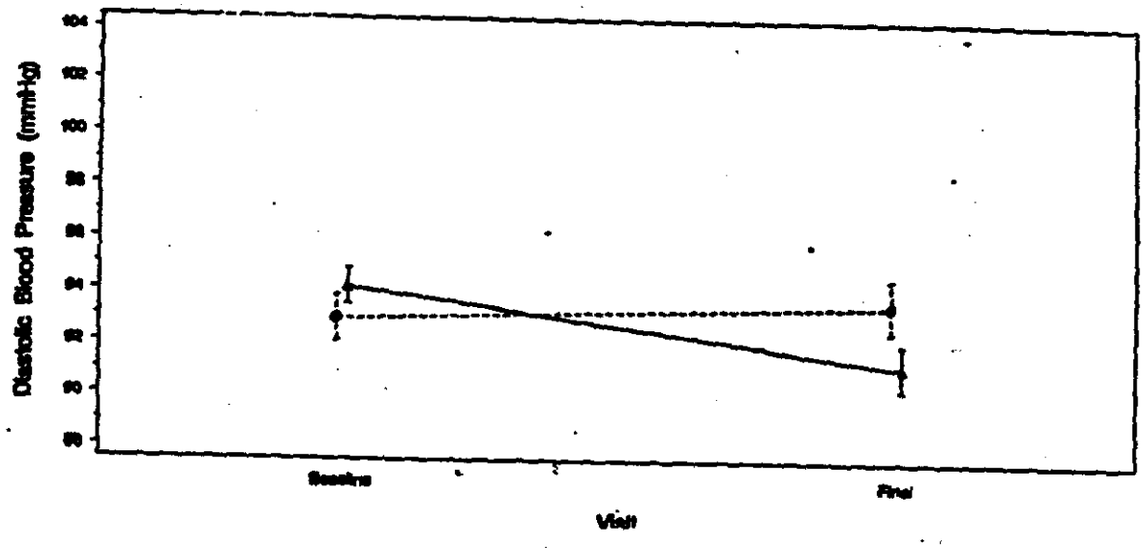
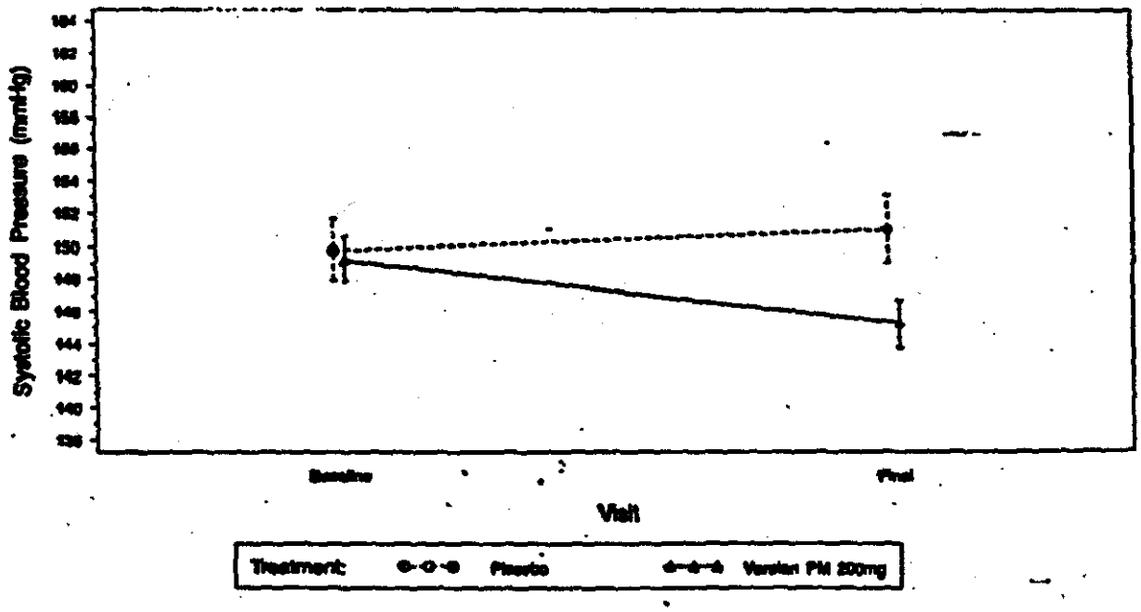


Mean (± 1 SE) 24 Hour (10 pm – 10 pm) ABPM Systolic Blood Pressure at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



- **ABPM and HR during the Accelerated Phase (6am to 12noon)** : Table 01-5 and Figure 01-4

The reduction in mean S / D BP with VerPM 200mg vs. placb was stat. significant (DBP p=0.004; SBP p=0.001) : VerPM -7.2 / -5.4 vs. placb 0 / -1.0 (net-effect S / D BP = -7.2 / -4.4 mmHg).

The reduction in mean HR (2.0 bpm) with VerPM was not stat. significant (p=0.132).

Table 01-5 Blood Pressure Recorded by ABPM and Heart Rate During the Accelerated Phase; Mean Values and Change From Baseline

	Placebo (N=55)			Verelan PM (N=61)			
Measurement	Baseline	Final	Change	Baseline	Final	Change	P-value*
Diastolic BP (mmHg)							
Mean (S.D.)	98.5 (8.17)	97.5 (8.62)	-1.0 (7.40)	100.5 (6.82)	95.1 (7.45)	-5.4 (6.95)	0.004
Minimum	83	80	-23	88	79	-21	
Maximum	117	121	13	115	112	11	
Systolic BP (mmHg)							
Mean (S.D.)	154.1 (15.36)	154.1 (16.45)	0 (11.85)	155.6 (12.35)	148.4 (10.86)	-7.2 (10.40)	0.001
Minimum	126	126	-34	132	125	-43	
Maximum	191	192	24	186	179	19	
Heart Rate (beats/min)							
Mean (S.D.)	81.1 (11.22)	79.4 (11.68)	-1.7 (8.69)	80.9 (10.90)	77.1 (10.06)	-3.7 (7.21)	0.132
Minimum	61	53	-23	59	57	-25	
Maximum	109	106	26	100	102	16	

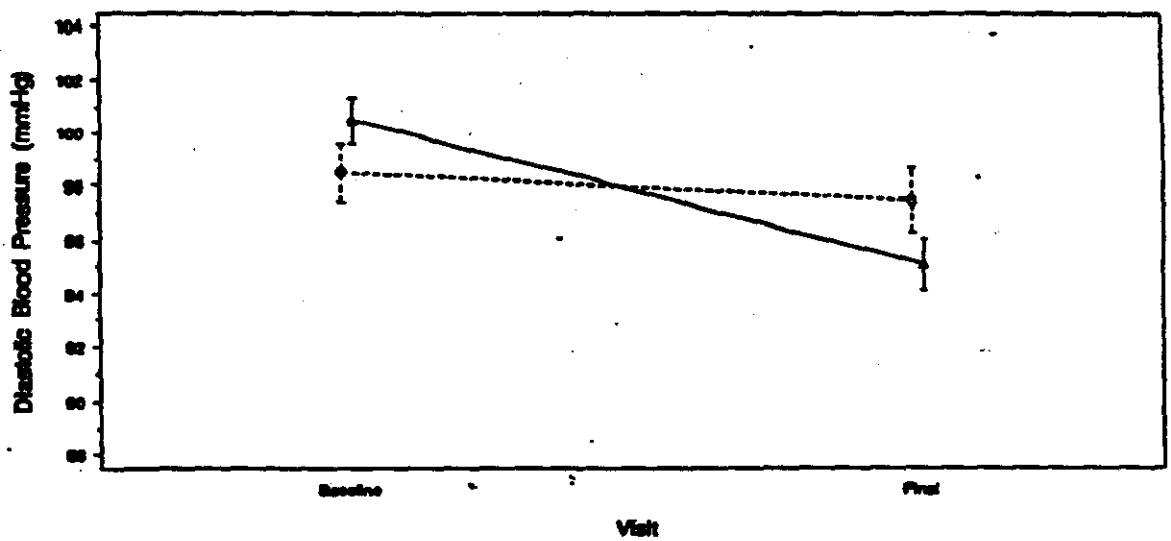
Abstracted from Statistical Table 18

* p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

Figure 01-4

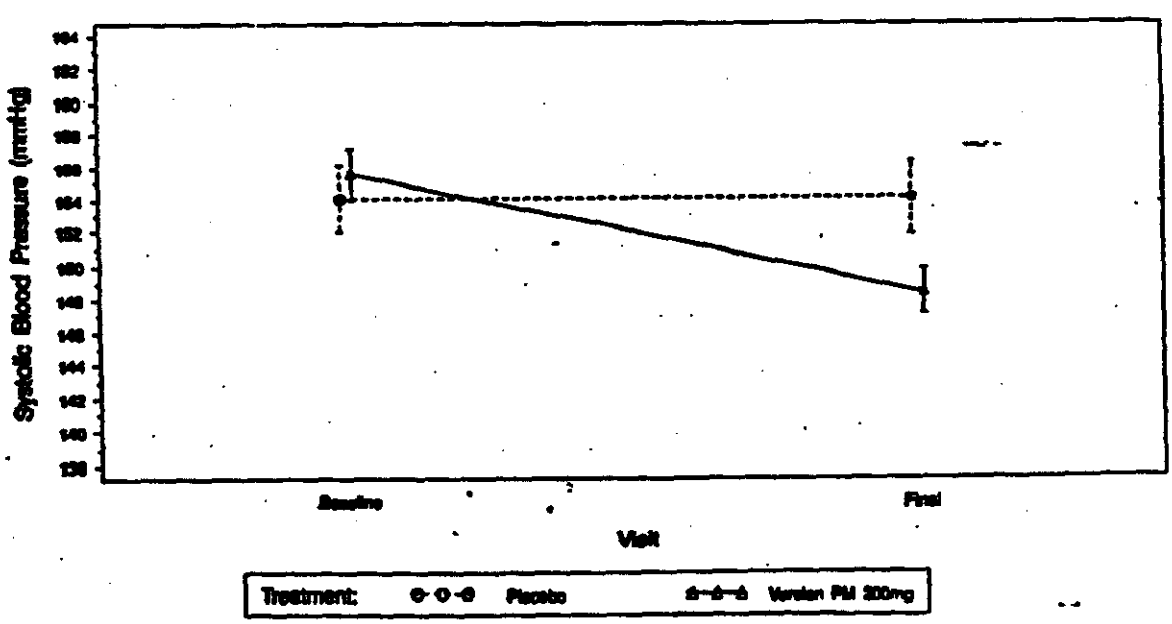
Mean (± 1 SE) ABPM Diastolic Blood Pressure During Accelerated Phase (6 am – 12 noon) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



Mean (± 1 SE) ABPM Systolic Blood Pressure During Accelerated Phase (6 am – 12 noon) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



- **Seated MBPM and HR at Peak (8am ± 1 hour) :** Table 01-6 and Figure 01-5

Table 01-6 Seated Blood Pressure, Measured Manually and Heart Rate at Peak; Mean Values and Change From Baseline

	Placebo (N = 58)			Verelan PM (N = 63)			
Measurement	Baseline	Final	Change	Baseline	Final	Change	p - value*
Diastolic BP (mmHg)							
Mean (S.D.)	101.5 (6.40)	97.4 (7.57)	-4.1 (6.46)	101.3 (6.48)	92.9 (7.94)	-8.4 (8.50)	0.001
Minimum	81	80	-20	87	73	-36	
Maximum	115	115	11	114	109	7	
Systolic BP (mmHg)							
Mean (S.D.)	154.2 (17.43)	149.9 (16.27)	-4.8 (14.33)	152.0 (14.60)	143.7 (12.48)	-8.3 (13.00)	0.027
Minimum	127	119	-54	124	120	-41	
Maximum	189	181	29	185	179	20	
Heart Rate (beats/min)							
Mean (S.D.)	76.1 (10.15)	74.8 (9.12)	-1.5 (10.98)	75.0 (9.19)	74.9 (8.47)	-0.1 (8.46)	0.661
Minimum	55	55	-25	53	57	-19	
Maximum	99	95	30	95	99	19	

Abstracted from Statistical Table 21

* p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

A highly significant difference was found between BL and Final Visit at peak in reduction in mean S / D BP (DBP p=0.001; SBP p=0.027); VerPM -8.3 / -8.4 vs. placb -4.8 / -4.1 mmHg (net-effect : S / D BP = -3.5 / -4.3 mmHg).

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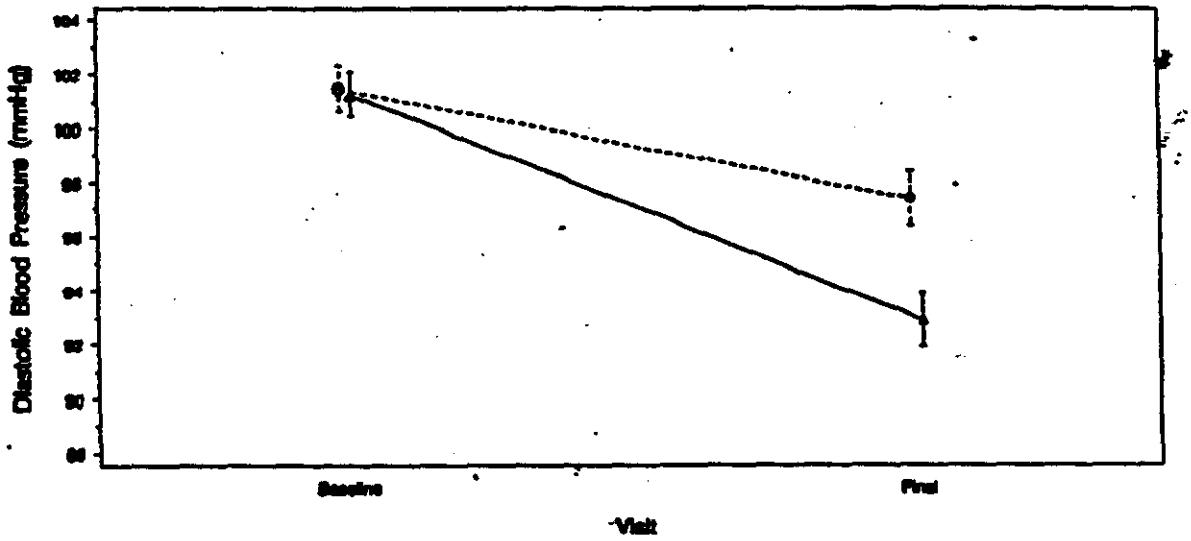
The difference in mean HR at peak (+1.4 bpm) with VerPM treatment was not stat. significant (p=0.661).

Figure 01-5

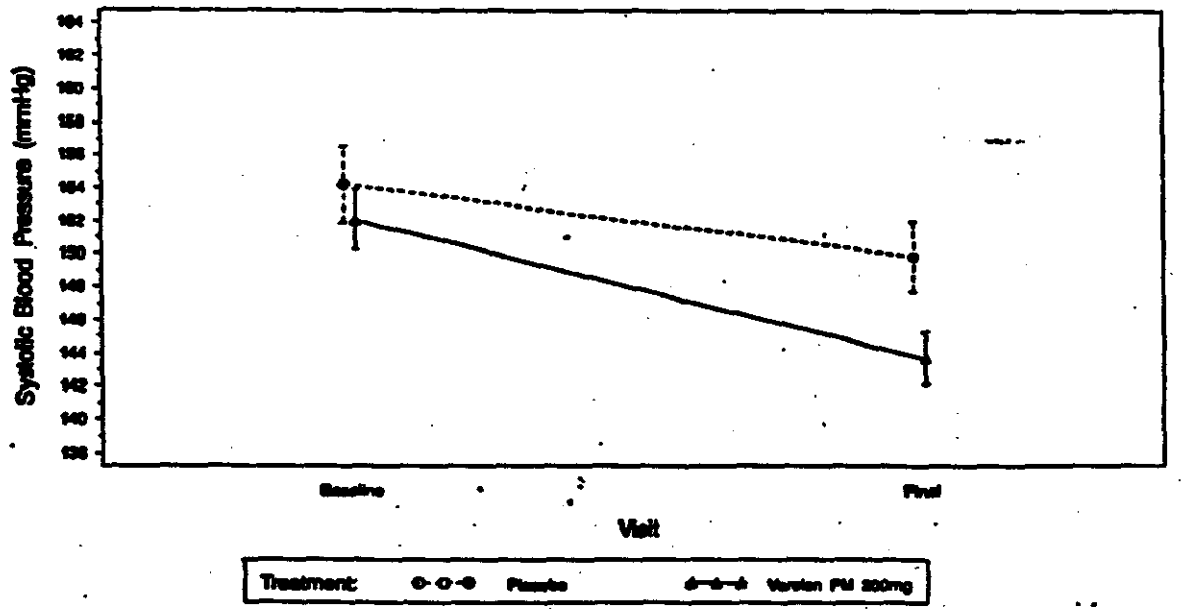
Mean (± 1 SE) Seated Manual Diastolic Blood Pressure at Peak (6 am ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP–Intent–to–Treat Patients



Mean (± 1 SE) Seated Manual Systolic Blood Pressure at Peak (6 am ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP–Intent–to–Treat Patients



Additional Analyses

- **Daytime (8am to 8pm) BP by ABPM and HR : Table 01-7**

There were significant reduction of mean values and changes from BL in the VerPM treated group (DBP p=0.0008; SBP p=0.0003); VerPM -5.9 / -4.5 vs. placb +0.9 / -0.4 mmHg (net- effect : S / D BP = -6.8 / -4.1 mmHg).

The mean change in HR in the VerPM group -4.6 bpm was stat. significant with +0.1 bpm in placb group (p=0.0008).

Table 01-7 Daytime Blood Pressure Recorded by ABPM and Heart Rate; Mean Values and Change From Baseline

	Placebo (N = 55)			Verelan PM (N = 61)			
Measurement	Baseline	Final	Change	Baseline	Final	Change	p - value*
Diastolic BP (mmHg) Mean (SD)	99.6 (6.1)	99.2 (7.7)	-0.4 (6.2)	100.3 (6.4)	95.7 (7.0)	-4.5 (6.6)	0.0008
Systolic BP (mmHg) Mean (SD)	156.8 (13.7)	157.6 (15.0)	+0.9 (9.0)	156.6 (12.9)	150.7 (12.6)	-5.9 (11.6)	0.0003
Heart Rate (beats/min) Mean	84.4 (10.8)	84.5 (11.7)	+0.1 (8.1)	84.3 (11.6)	79.7 (10.9)	-4.6 (7.6)	0.0008

Abstracted from Appendix 11, Tables 2A and B
* p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

- **Nighttime (10pm to 8am next day) BP by ABPM and HR : Table 01-8**

Mean changes in S / D BP at the Final Visit were stat. significant (DBP p=0.033; SBP p=0.033) : VerPM -2.0 / -1.4 vs. placb +1.7 / +1.7 mmHg (net-effect : S / D BP = -3.7 / -3.0 mmHg).

The mean change in HR (-1.5 bpm) with VerPM was not stat. significant (p=0.135).

Table 01-8 Nighttime Blood Pressure Recorded by ABPM and Heart Rate; Mean Values and Changes From Baseline

	Placebo (N = 55)			Verelan PM (N = 61)			
Measurement	Baseline	Final	Change	Baseline	Final	Change	p - value*
Diastolic BP (mmHg) Mean (SD)	86.3 (8.2)	87.9 (8.7)	+1.6 (6.7)	88.1 (6.2)	86.6 (8.1)	-1.4 (6.6)	0.033
Systolic BP (mmHg) Mean (SD)	142.8 (15.3)	144.5 (16.3)	+1.7 (10.8)	141.8 (11.4)	139.8 (12.4)	-2.0 (9.2)	0.033
Heart Rate (beats/min) Mean (SD)	75.3 (10.2)	75.0 (11.2)	-0.3 (6.6)	74.5 (10.8)	72.7 (8.9)	-1.8 (6.3)	0.135

Abstracted from Appendix 11, Tables 3A and B
* p-values for treatment effect from analysis of covariance F-test with effects for baseline value and treatment

- **Diastolic and Systolic Load recorded by ABPM : Table 01-9**

Diastolic and systolic loads were calculated by deriving the percentage of reading within a 24 hr period (10pm, Day 1 to 10pm, Day 2) above 90 or 140 mmHg respectively. The denominator was the number of analyzable BP readings during this period. The BP at the end of treatment was then compared to the BL load across treatment groups.

Table 01-9 Diastolic and Systolic Load

	Placebo (N = 55)		Verelan PM (N = 61)		
Measurement	Baseline	Final	Baseline	Final	p - value*
Diastolic Load (%) Mean (SD)	62.5 (18.3)	61.3 (20.4)	65.2 (14.2)	57.3 (21.7)	0.099
Systolic Load (%) Mean (SD)	69.6 (23.4)	70.7 (24.8)	68.3 (19.0)	61.1 (22.4)	0.011

Abstracted from Appendix 11, Tables 6A and B
* p-values for treatment effect from analysis of covariance F-test with effects for baseline and treatment

There was a stat. significant reduction in SBP load (p=0.011) but not in DBP load (p=0.099) at Final Visit in VerPM group compared with placb group.

- **Incidence of Positive Response : Table 01-10**

The incidence of positive response to treatment based on MBPM at trough was analyzed by the number of pts who had a $\geq$ 10 % reduction of DBP, or DBP $\leq$ 90 mmHg. 50% of pts in the VerPM group had a positive response compared with 26% of placb group (p=0.008).

Table 01-10 Number of Patients Who Responded to Treatment Based on Manual Diastolic Blood Pressure at Trough

Measurement	Placebo N = 58 (%)	Verelan PM N = 63 (%)	p-value*
Manual diastolic BP: decrease ≥10% or ≤90 mmHg	15 (26.3)	30 (50.0)	0.008
Manual diastolic BP: decrease ≥10%	10 (17.5)	22 (36.7)	0.020
Manual diastolic BP: ≤90 mmHg	12 (21.1)	22 (36.7)	0.063

Abstracted from Statistical Table 22A
* p-values from chi-square test

- **Trough-to-Peak Ratio**

Peak BP was defined as the largest hourly mean difference in BP at Final Visit compared with BL on ABPM recording. Trough BP was defined as the mean BP reduction during the 1 hr prior to the next dose.

$$\text{Trough to Peak Ratio} = \frac{\text{VeraPM(trough)} - \text{Placebo(trough)}}{\text{VeraPM (peak)} - \text{Placebo (peak)}}$$

ABPM Diastolic (mmHg)	VeraPM	placebo	
peak at hr 15	-6.8	-0.4	
trough at hr 24	-1.7		+1.7

Trough to Peak Ratio = 53.1%

ABPM Systolic (mmHg)	VeraPM	placebo
peak at hr 14	-7.8	+1.9
trough at hr 24	-1.6	+1.5

Trough to Peak Ratio = 31.9%

For a drug dosed once daily to be regarded as effective, it should retain at least 50% of its maximal (peak) BP lowering capabilities at the end of the dosing interval. In this study VerPM 200mg change of DBP Trough-to-Peak Ratio is 53.1% and it can be considered an effective antihypertensive used once daily for reducing DBP.

Efficacy Conclusions (Study 001)

The primary efficacy data demonstrated that VerPM 200mg is a significantly effective antihypertensive agent compared to placb. After 8 wks of treatment with VerPM 200mg, the decrease in DBP measured by ABPM was -3.1 mmHg for VerPM 200 mg as compared with +1.0 mmHg for placb group (p=0.047). Table 01-11 summarized the efficacy data.

Table 0-11 : Efficacy Summary Data VeraPM 200mg over Placebo (Study-001)
(change from Baseline to Final Visit values)

ABPM		Placebo	VeraPM	p-Value*
Primary	S/D BP at trough (S.D.)	+2.0 / +1.0 (12.86/9.19)	-3.9 / -3.1 (13.64/9.26)	0.007/0.047
Secondary	24 hr mean S/D BP (S.D.)	+1.3 / +0.6 (8.99/5.99)	-3.9 / -3.0 (8.92/5.42)	0.001/0.002
	Accelerated phase S/DBP (S.D.)	0 / -1.0 (11.85/7.40)	-7.2 / -5.4 (10.40/6.95)	0.001/0.004
	Nighttime S/D BP (S.D.)	+17 / +1.6 (10.8/6.7)	-2.0 / -1.4 (9.2/6.6)	0.033/0.033
	S/D Load (%)	+1.1 / -1.2	-7.2 / -7.9	0.011/0.099
Manual (seated BP)	S/D BP at trough (S.D.)	-2.1 / -3.0 (14.36/8.43)	-6.7 / -7.3 (14.28/9.59)	0.020/0.012
	S/DBP at peak (S.D.)	-4.8 / -4.1 (14.33/6.46)	-8.3 / -8.4 (13.00/8.50)	0.027/0.001

*p-value for treatment effect from analysis of covariance F-test with effects for baseline value and treatment.

There is a significant positive response (DBP $\leq$90 mmHg or $\geq$10% decrease) in seDBP at trough (p=0.008) with VerPM treatment compared with placb treatment.

VerPM 200mg showed DBP and SBP reduction over a 24-hr period with the greatest reduction occurring in the early morning hours when BP and HR are known to increase.

There was a slight reduction in HR in most of periods with VerPM, and stat. significant reduction was seen in the mean 24- hr HR (p=0.005) and daytime HR (p=0.0008).

SAFETY EVALUATION

Adverse Events (AEs)

AEs reported during the placb run-in **Phase A** were mild headache, upper respiratory symptoms, and dizziness. Five pts were d/ced from the study due to AEs : #1072 - ovarian cyst. #1151 - nausea & vomiting, #1153 - jaw pain & HTN, #1178 - dizziness, #1501 - peripheral edema.

During **Phase B** a total of 69 pts reported at lease one AE : placb 26 / 66 (39%) ~~vs.~~ VerPM

42 / 70 (60%). The most frequently reported AEs from the VerPM arm were infection, mostly upper respiratory (VerPM 11.4% vs. placb 4.5%), headache (VerPM 10.0% vs. placb 4.5%) and constipation (VerPM 4.3% vs. placb 0 %). The body system with ≥2% frequencies of AE are presented in Table 01-12.

Table 01-12 : Incidence of Adverse Events occurring in ≥ 2% of patients by Body System and Severity During Phase B

	Placebo N = 66 (%)			Verelan PM N = 70 (%)		
Body System Adverse Event	Mild	Moderate	Severe	Mild	Moderate	Severe
Body as a Whole						
Generalized edema	0	0	0	2 (2.9)	0	1 (1.4)
Headache	1 (1.5)	2 (3.0)	0	4 (5.7)	2 (2.9)	1 (1.4)
Infection	2 (3.0)	1 (1.5)	0	7 (10.0)	1 (1.4)	0
Respiratory System						
Asthma	1 (1.5)	0	1 (1.5)	1 (1.4)	0	0
Bronchitis	1 (1.5)	0	0	2 (2.9)	1 (1.4)	1 (1.4)
Cough increased	0	0	0	3 (4.3)	0	0
Pharyngitis	1 (1.5)	0	0	1 (1.4)	2 (2.9)	0
Rhinitis	1 (1.5)	0	0	1 (1.4)	1 (1.4)	0
Sinusitis	0	0	0	2 (2.9)	1 (1.4)	0
Digestive System						
Constipation	0	0	0	1 (1.4)	2 (2.9)	0
Diarrhea	0	0	0	0	2 (2.9)	0
Dyspepsia	1 (1.5)	0	0	2 (2.9)	0	1 (1.4)
Tooth disorder	0	1 (1.5)	0	0	1 (1.4)	1 (1.4)
Nervous System						
Dizziness	0	1 (1.5)	0	2 (2.9)	1 (1.4)	0
Hypesthesia	0	0	0	1 (1.4)	1 (1.4)	0
Skin and Appendages						
Rash	1 (1.5)	2 (3.0)	0	0	1 (1.4)	1 (1.4)

Six AEs were considered by the investigators to be probably related to study drug; 1 AE with placb (abnormal ECG) and 5 events in the VerPM group (headache, dizziness and angina;, upper respiratory symptoms; rash, and constipation). Most AE reports were mild or moderate intensity across treatment groups except 8 pts in VerPM (total 10 events) and 4 pts in placb group (total 5 events) considered severe.

Four pts (#1256 at 8 wks VerPM, #1356 at 2wks VerPM, #1294 at 3wks VerPM, #1255 at 18 days VerPM) complained "dizziness" with no changes in BP around the episodes. One pt (#1054) complained "postural hypotension" with VerPM 200mg for 8 wks, however, there was no postural changes in BP same day at the visit B8.
The severe AEs in the VerPM group included prostate carcinoma, bronchitis, acute psychosis, edema, anxiety, rash, dyspepsia, and tooth disorder. Only edema, rash and dyspepsia are considered probably VerPM treatment related.

AEs leading to Withdrawal during Phase B : Table 01-13

Eight pts total of 14 AEs (placb 3 pts, VerPM 5 pts) withdrew from the study during Phase B were considered by the investigators to be at least possibly related to study drug as shown in Table 01-13. No deaths occurred during this study period.

Table 01-13: Adverse Events Resulting in Discontinuation during Phase B

Patient Number	Adverse Event	Status	Severity	Treatment Group	Relationship to Study Drug
10006B (1026)	Water retention	Ongoing	Mild	Verelan PM	Definitely not
10196B (1294)	Dizziness, headache, angina pectoris, falling down	Resolved Resolved Resolved Resolved	Moderate Moderate Moderate Moderate	Verelan PM	Probable Probable Probable Probable
10010B (1027)	Asthma	Ongoing	Severe	Placebo	Definitely not
10050B (1076)	Rash, facial edema, dyspepsia	Resolved Resolved Resolved	Moderate Mild Mild	Placebo	Possible Possible Possible
10049B (1071)	Rash	Resolved	Moderate	Verelan PM	Probable
10028B (1047)	Pruritic rash, dyspnea	Resolved Resolved	Severe Moderate	Verelan PM	Remote Remote
10025B (1338)	Acute psychosis, manic reaction*	Resolved	Severe	Verelan PM	Remote
10096B (1112)	Dissecting thoracic aortic aneurysm	Resolved	Moderate	Placebo	Definitely not

Vital Signs / Physical Examination (PE) / ECG

There were no apparent differences at BL and at Final Visit between treatment in vital signs or PE except an expected reduction of BP and HR in the Final Visit of VerPM treated group. At BL 14% of placb and 13% pts VerPM group had clinically significant abnormal ECG findings. During the course of the study 1st degree AV block was seen in 2 pts with VerPM group (PR interval changes : Pt#109, from 284 to 268 ms; pt#114, from 211 to 225 ms) and none in the placb group.

Laboratory Results

- Hematology parameters were generally WNL at BL and Final Visit. Minor clinically insignificant fluctuations of values were observed.

- Changes in serum chemistry during the study were slight elevation of cholesterol and abnormal liver function test (LFT) : placb 3 pts, VerPM 11 pts. However, the incidence of abnormal values were not significantly different across treatment groups and they were asymptomatic. Table 01-14 displays the abnormal chemistry values at BL and Final Visit.

Table 01-14 : Patients with Abnormal Chemistry Values

Placebo	Patient	Analyte	A-0 Value	B-8 Value	Normal Range
	102-1046	AST	28	51	0 - 55
		ALT	47	59	0 - 48
	113-1266	Cholesterol	182	213	<200
	114-1030	Cholesterol	184	212	<200
Verelan PM					
	101-1352	Cholesterol	188	249	<200
	102-1050	Cholesterol	198	217	<200
		T. bilirubin	1.1	1.4	0 - 1.3
	102-1054	ALT	21	56	0 - 48
	104-1110	ALT	30	62	0 - 48
	104-1138	Cholesterol	195	208	<200
	106-1176	Cholesterol	196	230	<200
	106-1193	AST	24	60	0 - 55
		ALT	40	105	0 - 48
	106-1426	Cholesterol	177	235	<200
	108-1249	Cholesterol	183	211	<200
	108-1247	T. bilirubin	1.2	1.8	0 - 1.3
	108-1257	Cholesterol	180	201	<200
		ALT	32	85	0 - 48

Minor clinically insignificant changes in urinary results were seen during the study.

Safety Conclusions (Study 001)

VerPM 200mg was generally well tolerated in this 8 wk study. AE was reported in placb 39% vs. VerPM 60%. Overall, the safety profile for VerPM is similar to that of verapamil HCl ; headache, dizziness, constipation, and abnormal LFT. No postural hypotension or bradycardia <50 bpm on the Final visit ECG were noted . Three serious AEs occurred; 2 in the VerPM group (prostate carcinoma and acute psychosis) and 1 in the placb group (dissecting thoracic aortic aneurysm) and they are not related to the test drug.

PROTOCOL VER-0596-002-US: Double-blind, randomized, multicenter trial evaluating the magnitude of blood pressure reduction with Verelan®PM 100mg, 200mg, 300mg, and 400mg when compared to placebo in patients with mild to moderate essential hypertension. Volume 1.38

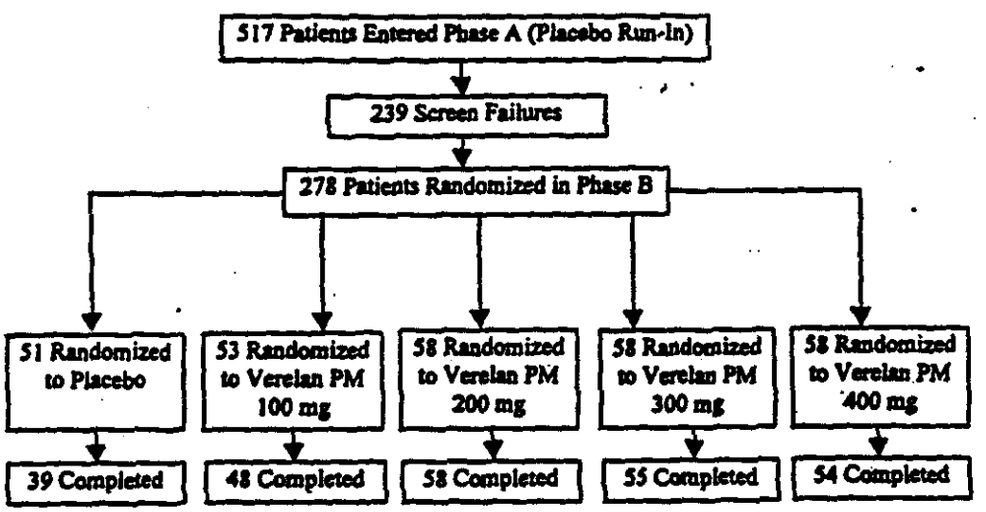
Objectives and Study Design are same as Protocol VER-0596-001-US except test products and dosing. VerPM 100mg and VerPM 200mg capsules are used and eligible pts at the end of Phase A are randomized to placb, VerPM 100mg, VerPM 200mg, VerPM 300mg, and VerPM 400mg.

Patient Population / Disposition

517 pts from 20 study sites entered the placb run-in Phase A segment. Of these, 278 pts met eligibility criteria and entered the randomized Phase B segment : placb (n=51), VerPM 100mg (n=53), VerPM 200mg (n=58), VerPM 300mg (n=53), VerPM 400 mg (n=55).

The disposition of pts is shown Table below. Discontinuation of study occurring in Phase A were predominantly (81%) due to failure to meet study entry criteria mostly BP requirements.

PATIENT DISPOSITION (Study VER-0596-002)



The reasons for premature D/C during Phase B is presented in Table 02-1.

Table 02-1: Reasons for Premature Discontinuation in Phase B

Reasons for Discontinuation	Placebo N=12 (51)	Verelan PM 100 mg N=5 (53)	Verelan PM 200 mg N=0 (58)	Verelan PM 300mg N=3 (58)	Verelan PM 400mg N=4 (58)
Adverse event	3	1	0	1	2
Investigator/ Sponsor decision	5*	1	0	0	0
Withdrew consent	2	0	0	1	2
Protocol violation/ Failure to meet study criteria	0	3	0	0	0
Death	0	0	0	1	0
Relapse	1	0	0	0	0
Other	1**	0	0	0	0

Abstracted from Statistical Table 5A

* Four (80%) of these reasons for discontinuation were listed as "lack of effect"; the remaining reason was "for patient's safety."

** Lack of efficacy, SBP >200 mmHg.

Of the 278 pts enrolled in Phase B, 257 (92.4%) were included in the ABPM intent-to-treat population. The MBPM intent-to treat population included all pts in the ABPM intent-to-treat population plus 2 pts treated with VerPM 300mg.

With the exception of 1 placb-treated pt, the ABPM efficacy-evaluable population includes all pts in the ABPM intent-to-treat population, and the MBPM efficacy-evaluable population includes all pts in the MBPM intent-to-treat population.

The demographic and BL characteristics were similar among treatment groups; there were no stat. significant differences among groups. Most of the pts were white (~84%), ~2/3 were male, and mean age 52.1 to 54.9 yrs.

EFFICACY RESULTS

Primary Efficacy

BP and HR by ABPM at trough (6pm to 10pm) : Table 02-2 and Figure 02-1.

At BL, mean S / D BP, and HR were comparable among treatment groups, 152.1 to 154.2 / 94.6 to 95.7 mmHg, 80.2 to 83.3 bpm.

Table 02-2 : Blood Pressure Recorded by ABPM and Heart Rate at Trough; Mean Change from Baseline -- ABPM Intent-to-Treat

Measurement	Placebo (N= 42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p – value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	1.3 (6.76)	1.2 (9.83)	-2.6 (9.52)	-5.2 (11.30)	-8.8 (8.77)	<0.001
Minimum Δ	-11	-20	-24	-37	-29	
Maximum Δ	15	33	20	33	16	
95% C.I.**	N/A	-3.7, 3.5	-7.2, -0.4	-10.4, -2.6	-13.3, -6.8	
Systolic BP (mmHg)						
Mean Δ (S.D.)	0.5 (10.16)	-0.5 (12.53)	-3.6 (12.13)	-6.1 (14.14)	-10.9 (13.66)	<0.001
Minimum Δ	-19	-32	-34	-38	-35	
Maximum Δ	25	26	25	41	32	
95% C.I.**	N/A	-5.7, 3.9	-8.6, 0.5	-11.7, -1.4	-16.3, -6.4	
Heart Rate (beats/min)						
Mean Δ (S.D.)	3.2 (8.68)	0.9 (9.18)	-0.7 (7.68)	-4.5 (9.70)	-7.4 (11.53)	<0.001
Minimum Δ	-19	-26	-28	-27	-38	
Maximum Δ	23	17	18	27	12	

* P-value is for treatment effect from analysis of variance F-test with effects for baseline value and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in ABPM trough blood pressure. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

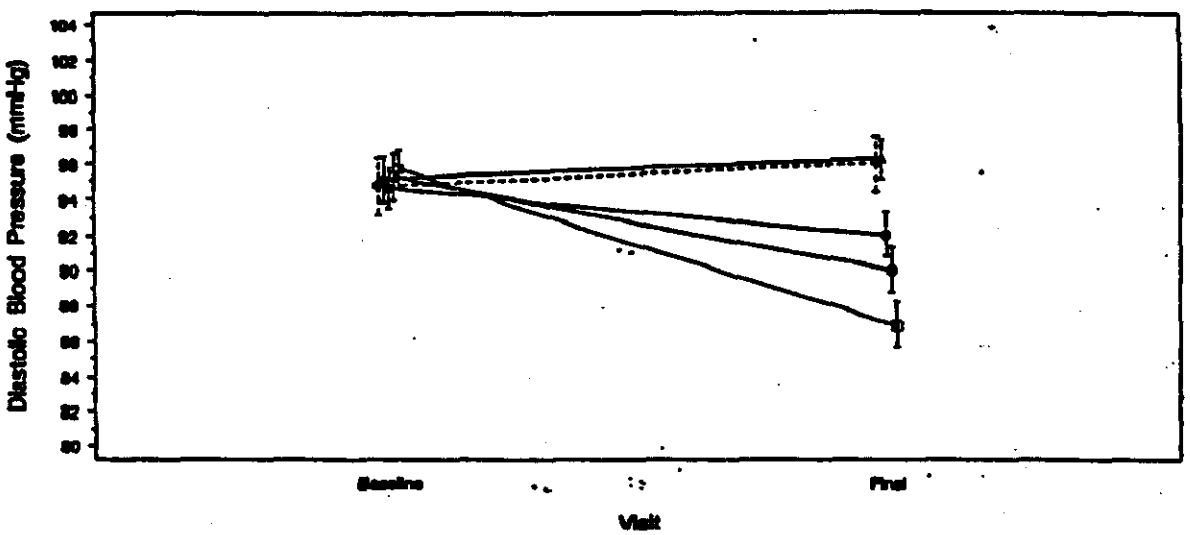
At Final Visit, VerPM at doses of 200, 300, and 400mg were stat. significantly more effective than placb in reducing DBP by ABPM at trough. A dose-response relationship was observed among VerPM treatment groups. The placb-subtracted mean changes in DBP were -0.1, -3.8, -6.5, and -10.0 mmHg in the VerPM 100, 200, 300, and 400mg groups, respectively.

Similar results were observed for the mean changes in SBP and HR at trough. The placb-subtracted mean change in SBP in the VerPM 100mg group was not stat. significant compared to placb, although the level of reduction in SBP was clinically significant in the context of the decrease in DBP.

Figure 02-1

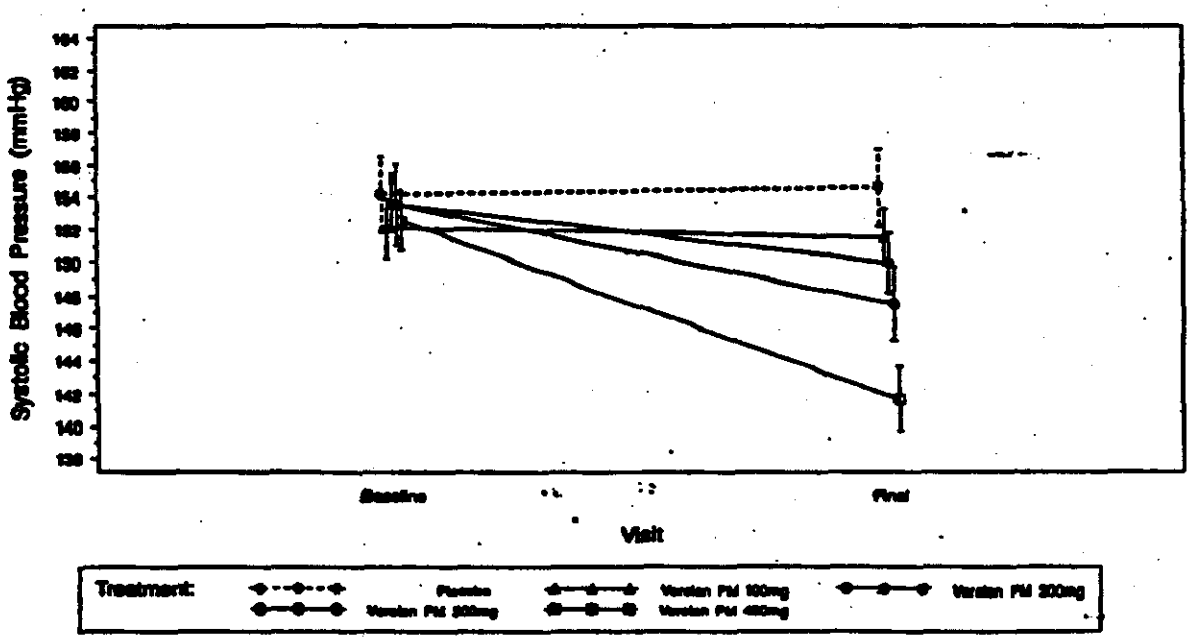
Mean (± 1 SE) ABPM Diastolic Blood Pressure at Trough (6 – 10 pm) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



Mean (± 1 SE) ABPM Systolic Blood Pressure at Trough (6 – 10 pm) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



Secondary Efficacy Variables

- **Seated MBPM at trough (7pm ± 1 hr)** : Table 02-3 and Figure 02-2

At BL there were no differences in mean values of seDBP, seSBP or HR at trough among the groups.

There were stat. significant differences among treatment groups in seDBP, seSBP or HR at trough at the Final Visit . The reduction of seDBP with VerPM at doses of 100, 200, 300, and 400mg were stat. significant compared with placb. A Dose-response relationship was demonstrated. The placb-subtracted mean changes in seDBP were -3.4, -6.1, -9.4, and -8.7 mmHg in the VerPM 100 , 200, 300, and 400mg treated groups, respectively.

Similar results were observed for the mean changes in seSBP and HR at trough, although the placb-subtracted mean change in seSBP in VerPM 100mg group was not stat. significant compared to placb.

Table 02-3 : Seated Blood Pressure, Measured Manually at Trough;
Mean Change from Baseline : Intent-to-Treat

Measurement	Placebo (N= 42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=55)	Verelan PM 400 mg (N=55)	p-value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	-0.6 (7.22)	-4.0 (7.54)	-6.8 (7.81)	-10.0 (6.96)	-9.3 (7.97)	<0.001
Minimum Δ	-16	-17	-24	-31	-32	
Maximum Δ	11	14	10	5	6	
95% C.I.**	N/A	-6.6, -0.1	-9.3, -2.9	-12.4, -6.4	-11.9, -5.4	
Systolic BP (mmHg)						
Mean Δ (S.D.)	-2.4 (14.50)	-3.6 (11.77)	-8.4 (13.73)	-11.1 (11.29)	-11.2 (14.75)	0.001
Minimum Δ	-34	-24	-38	-32	-46	
Maximum Δ	26	29	18	11	14	
95% C.I.**	N/A	-6.9, 4.5	-11.8, -0.9	-14.1, -3.3	-15.0, -2.5	
Heart Rate (beats/min)						
Mean Δ (S.D.)	2.7 (10.77)	-0.9 (9.70)	-2.5 (6.80)	-5.6 (7.82)	-6.7 (7.84)	<0.001
Minimum Δ	-30	-36	-17	-22	-30	
Maximum Δ	28	24	16	19	11	

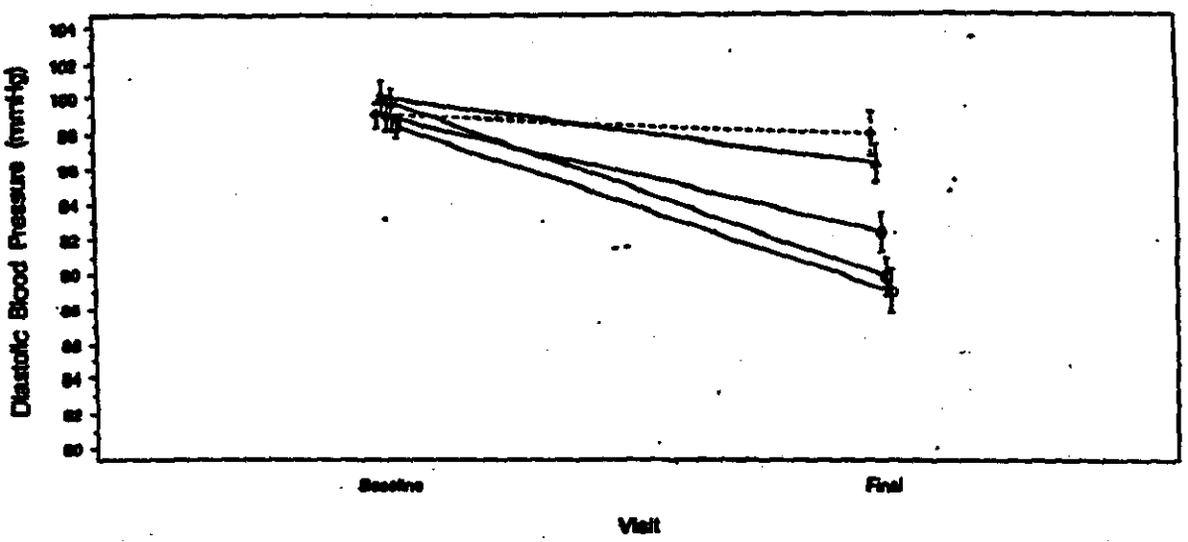
* P-value is for treatment effect from analysis of variance F-test with effects for baseline value and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in manual trough blood pressure. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

Figure 02-2 :

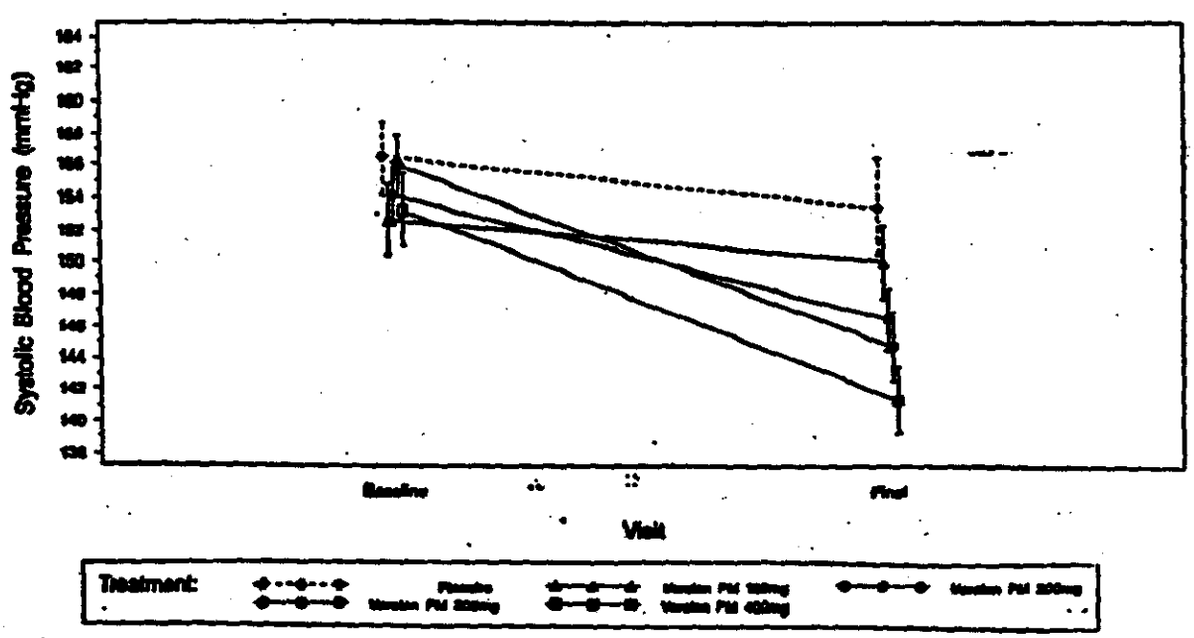
Mean (± 1 SE) Seated Manual Diastolic Blood Pressure at Trough (7 pm ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP–Intent–to–Treat Patients



Mean (± 1 SE) Seated Manual Systolic Blood Pressure at Trough (7 pm ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP–Intent–to–Treat Patients



- **24-hour BP by ABPM and HR :** Table 02-4 and Figure 02-3

Mean BL values for 24-hr ABPM BP and HR were similar among treatment groups. At Final Visit, VerPM at doses of 100, 200, 300, and 400mg groups were stat. significantly effective than placb in reducing 24-hr DBP and a dose response relationship was observed.

The placb-subtracted mean changes in DBP were -2.2, -5.5, -8.4, and -11.1 mmHg in the VerPM 100, 200, 300, and 400mg groups, respectively.

Similar results were observed for the mean change in SBP and HR over a 24-hr period, although mean changes in SBP in the VerPM 100mg group was not stat. significant compared to placb.

Table 02-4 : 24-Hour Blood Pressure Recorded by ABPM and Heart Rate; Mean Change from Baseline

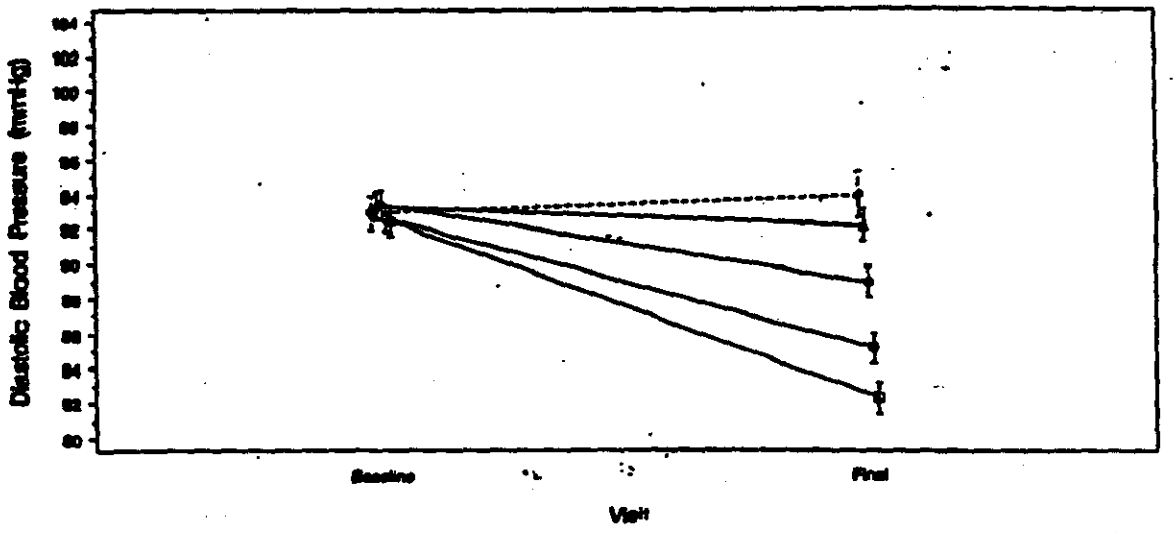
Measurement	Placebo (N= 42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p-value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	1.0 (4.53)	-1.2 (4.72)	-4.5 (6.07)	-7.5 (5.57)	-10.2 (6.36)	<0.001
Minimum Δ	-7	-11	-18	-21	-25	
Maximum Δ	11	7	11	5	7	
95% C.I.**	N/A	-4.1, -0.2	-7.7, -3.3	-10.6, -6.3	-13.4, -8.8	
Systolic BP (mmHg)						
Mean Δ (S.D.)	0.6 (7.61)	-2.1 (6.95)	-6.1 (9.81)	-9.4 (7.82)	-13.5 (9.90)	<0.001
Minimum Δ	-14	-19	-28	-27	-42	
Maximum Δ	23	13	15	5	6	
95% C.I.**	N/A	-5.7, 0.3	-10.3, -3.1	-13.2, -6.8	-17.8, -10.4	
Heart Rate (beats/min)						
Mean Δ (S.D.)	0.9 (6.44)	-1.3 (6.30)	-2.7 (6.54)	-4.6 (6.81)	-6.4 (6.03)	<0.001
Minimum Δ	-19	-22	-18	-28	-25	
Maximum Δ	16	14	12	12	4	

* P-value is for treatment effect from analysis of variance F-test with effects for baseline value and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in 24-hour blood pressure and heart rate recorded by ABPM. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

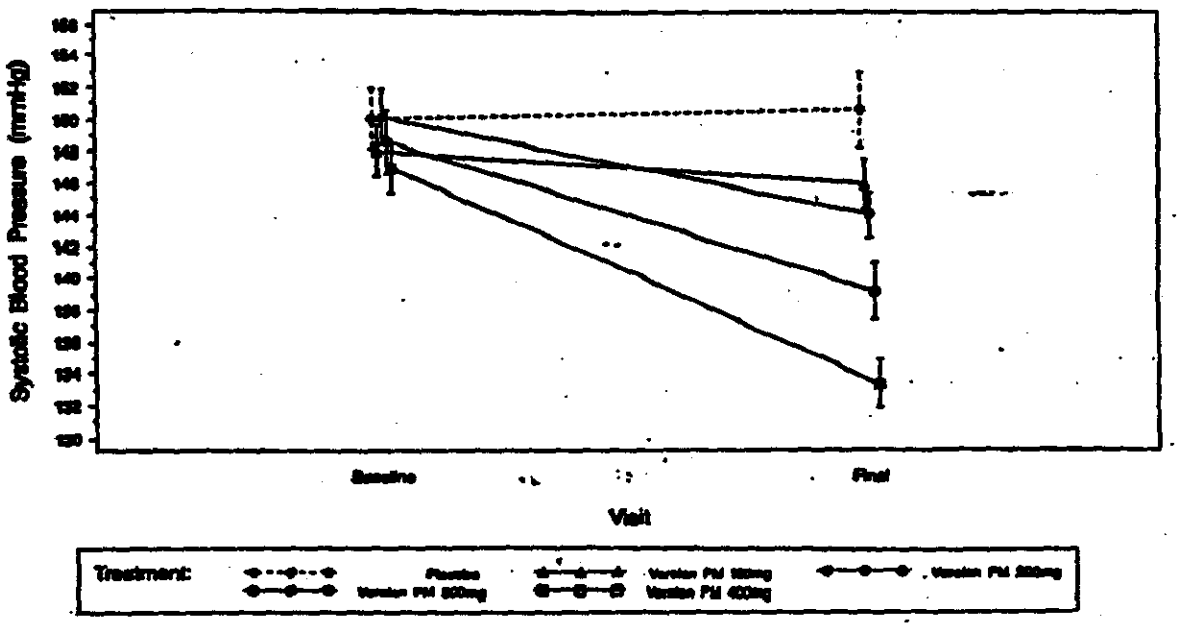
Figure 02-3 :
Mean (± 1 SE) 24 Hour (10 pm – 10 pm) ABPM Diastolic Blood Pressure at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



Mean (± 1 SE) 24 Hour (10 pm – 10 pm) ABPM Systolic Blood Pressure at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



- **BP by ABPM and HR during the accelerated phase (6am to 12noon) :** Table 02-5 and Figure 02-4

At BL mean BP and HR by ABPM during the accelerated phase were similar among groups. At the Final Visit, VerPM at doses of 100, 200, 300 and 400mg were stat. significantly effective than placb in reduction of DBP during the accelerated phase. A dose-response relationship was observed among the VerPM treatment groups.

The placb-subtracted mean changes in DBP were -3.6, -7.6, -11.5, and -14.3 mmHg in the VerPM 100, 200, 300, and 400mg groups, respectively.

Similar results were observed for the mean changes in SBP and HR during the accelerated phase, although the mean change in SBP with VerPM 100mg treatment was not stat. significant compared to placebo.

Table 02-5 : Blood Pressure Recorded by ABPM and Heart Rate During the Accelerated Phase; Mean Change from Baseline

Measurement	Placebo (N= 42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p – value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	0.5 (7.32)	-3.1 (6.01)	-7.1 (8.34)	-11.0 (7.20)	-13.8 (8.12)	<0.001
Minimum Δ	-16	-20	-26	-34	-34	
Maximum Δ	17	8	13	2	6	
95% C.I.**	N/A	-6.4, -0.8	-10.8, -4.4	-14.5, -8.5	-17.5, -11.1	
Systolic BP (mmHg)						
Mean Δ (S.D.)	-1.0 (9.71)	-4.5 (9.09)	-9.5 (12.45)	-14.5 (10.89)	-19.2 (12.39)	<0.001
Minimum Δ	-22	-27	-44	-41	-50	
Maximum Δ	21	15	11	5	2	
95% C.I.**	N/A	-7.4, 0.4	-13.1, -3.9	-17.7, -9.2	-22.8, -13.6	
Heart Rate (beats/min)						
Mean Δ (S.D.)	0.0 (8.08)	-2.5 (7.59)	-3.5 (8.43)	-6.5 (8.31)	-7.2 (7.52)	<0.001
Minimum Δ	-21	-20	-35	-30	-27	
Maximum Δ	17	18	13	13	7	

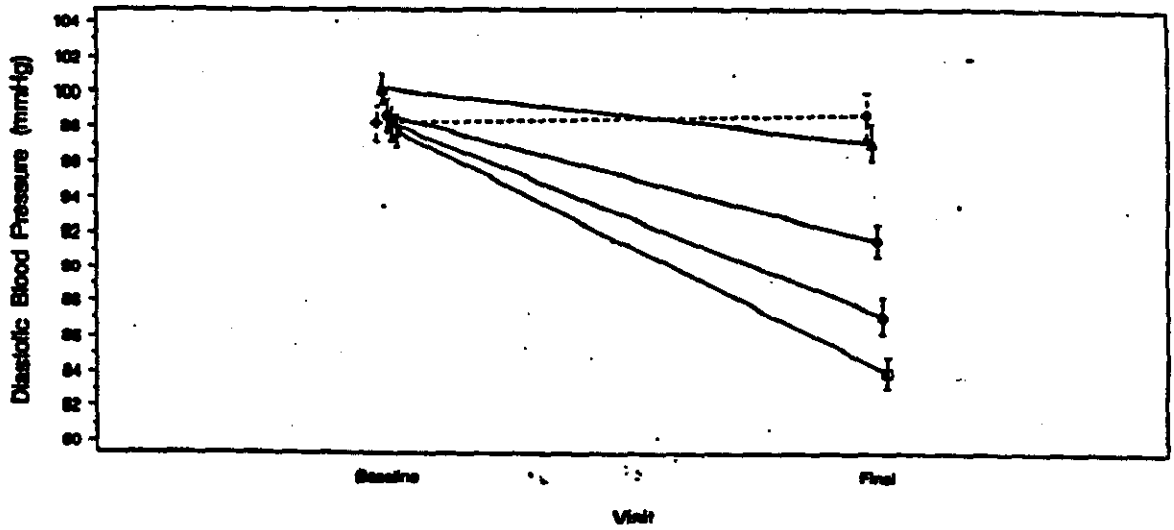
* P-value is for treatment effect from analysis of variance F-test with effects for baseline value and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in blood pressure and heart rate recorded by ABPM during the accelerated phase. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

Figure 02-4 :

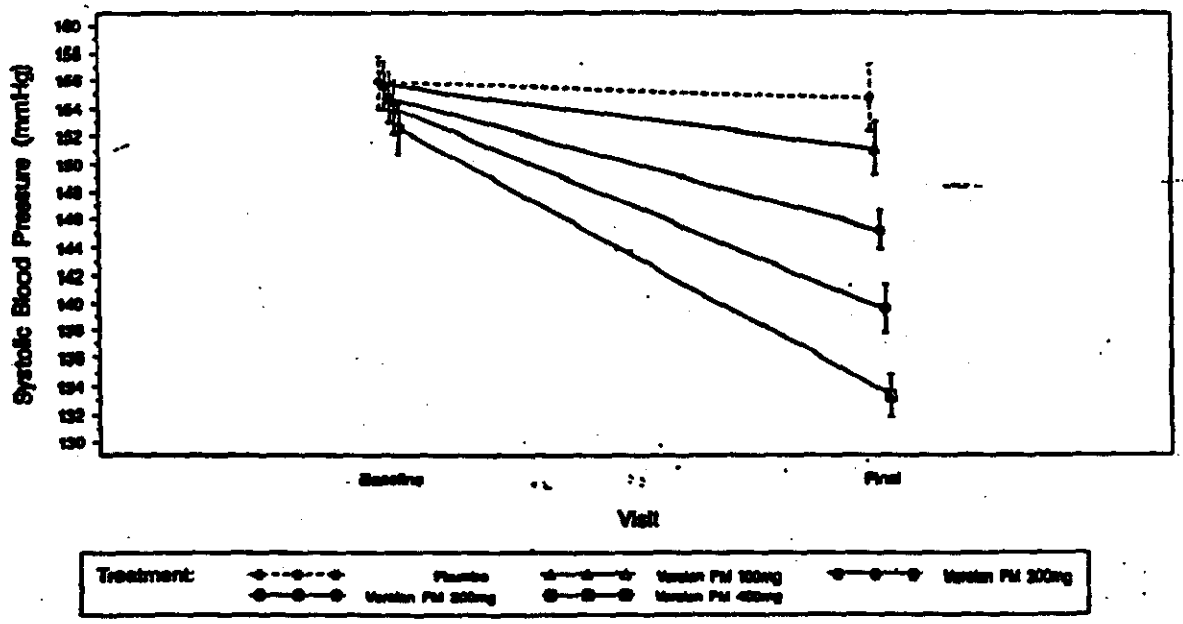
Mean (± 1 SE) ABPM Diastolic Blood Pressure During Accelerated Phase (6 am – 12 noon) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



Mean (± 1 SE) ABPM Systolic Blood Pressure During Accelerated Phase (6 am – 12 noon) at Baseline and Final Visit by Treatment Group

ABPM – Intent – to – Treat Patients



- **Seated BP by MBPM and HR at peak (8am ± 1 hr):** Table 02-6 and Figure 02-5

At BL mean values at peak hour BP and HR were similar among the groups. At Final Visit, VerPM at doses of 100, 200, 300, and 400mg were stat. significant in reducing DBP at peak. A dose response relationship was observed among the VerPM treated groups.

The placb-subtracted mean changes in DBP were -3.5, -7.2, -10.0, and -13.2 mmHg in VerPM 100, 200, 300, and 400mg groups, respectively.

Similar results were observed for the mean changes in SBP at peak except with VerPM 100mg group compared to placebo.

Table 02-6 : Seated Blood Pressure, Measure Manually and Heart Rate at Peak ; Mean Change from Baseline

Measurement	Placebo (N= 42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=55)	Verelan PM 400 mg (N=55)	p – value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	-1.0 (7.26)	-4.6 (6.11)	-8.2 (7.08)	-11.0 (7.73)	-14.2 (8.79)	<0.001
Minimum Δ	-14	-20	-25	-34	-31	
Maximum Δ	13	8	8	3	14	
95% C.I.**	N/A	-6.3, -0.7	-10.1, -4.3	-13.1, -6.9	-16.5, -9.8	
Systolic BP (mmHg)						
Mean Δ (S.D.)	-3.2 (15.23)	-3.9 (10.80)	-9.3 (14.07)	-14.3 (13.13)	-19.1 (15.93)	<0.001
Minimum Δ	-36	-28	-42	-54	-48	
Maximum Δ	32	24	22	13	14	
95% C.I.**	N/A	-6.1, 4.8	-12.0, -0.2	-16.8, -5.3	-22.3, -9.4	
Heart Rate (beats/min)						
Mean Δ (S.D.)	0.9 (10.66)	0.1 (10.73)	-0.2 (9.29)	-4.8 (8.40)	-6.1 (9.12)	0.002
Minimum Δ	-29	-25	-21	-32	-34	
Maximum Δ	20	33	26	13	12	

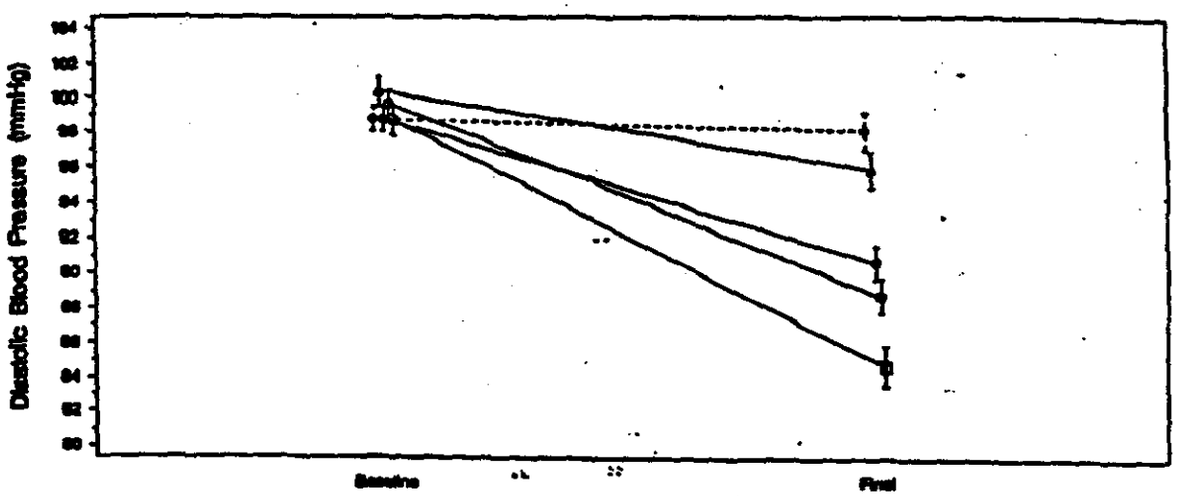
* *P*-value is for treatment effect from analysis of variance *F*-test with effects for baseline value and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in blood pressure and heart rate measured manually at peak. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

Figure 02-5 :

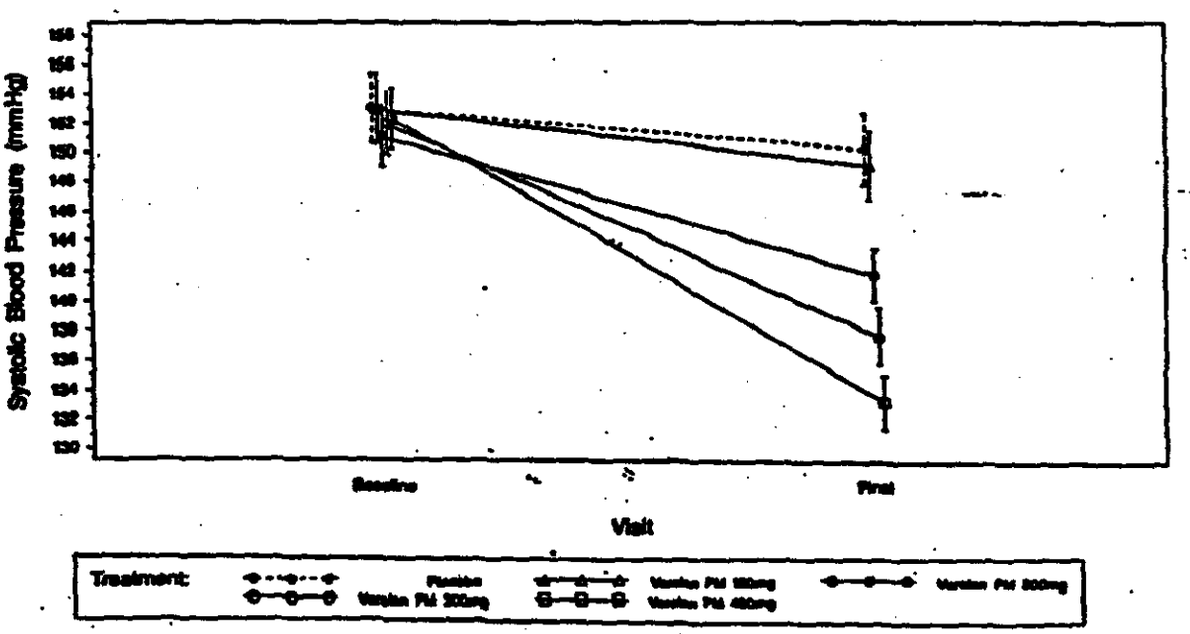
Mean (± 1 SE) Seated Manual Diastolic Blood Pressure at Peak (8 am ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP – Intent – to – Treat Patients



Mean (± 1 SE) Seated Manual Systolic Blood Pressure at Peak (8 am ± 1 hour) at Baseline and Final Visit by Treatment Group

MBP – Intent – to – Treat Patients



Additional Analysis

- **Daytime and Night time BP by ABPM and HR : Table 02-7 and Table 02-8**

There were no apparent differences between treatment groups in daytime and nighttime BP or HR at BL. At the Final Visit placb-subtracted mean changes in DBP and SBP in both periods were stat. significant in the VerPM 200, 300, and 400mg groups compared to placb.

Table 02-7 : Daytime Blood Pressure Recorded by ABPM and Heart Rate; Mean Values and Changes from Baseline

Measurement	Placebo (N=42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p- value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	0.6 (5.84)	-1.4 (5.50)	-5.3 (7.38)	-8.9 (7.13)	-12.4 (7.17)	<0.001
Minimum Δ	-7.6	-18.8	-20.7	-25.3	-30.3	
Maximum Δ	13.1	8.6	15.7	7.3	5.5	
95% C.I.**	N/A	-4.4, 0.3	-8.7, -3.2	-12.2, -6.8	-15.7, -10.3	
Systolic BP (mmHg)						
Mean Δ (S.D.)	0.1 (9.65)	-2.4 (8.65)	-6.9 (11.18)	-10.9(10.25)	-16.4 (11.12)	<0.001
Minimum Δ	-17.6	-29.1	-32.9	-33.7	-43.0	
Maximum Δ	26.6	11.9	20.0	10.8	4.2	
95% C.I.**	N/A	-6.4, 1.3	-11.2, -2.7	-15.1, -6.9	-20.7, -12.2	
Heart Rate (beats/min)						
Mean Change (S.D.)	1.5 (8.57)	-2.4 (7.49)	-3.4 (8.42)	-6.3 (8.51)	-9.2 (8.06)	<0.001
Minimum Δ	-20.2	-22.7	-27.4	-29.4	-32.9	
Maximum Δ	21.1	15.4	13.2	-15.0	3.4	

Table 02-8 : Nighttime Blood Pressure Recorded by ABPM and Heart Rate; Mean Values and Changes from Baseline

Measurement	Placebo (N=42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p- value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	1.3 (4.42)	-1.0 (5.30)	-3.8 (6.14)	-6.1 (5.31)	-8.0 (6.73)	<0.001
Minimum Δ	-7.1	-12.6	-16.24	-20.9	-24.8	
Maximum Δ	11.7	9.8	7.84	10.5	8.4	
95% C.I.**	N/A	-4.4, -0.3	-7.2, -2.8	-9.4, -5.4	-11.7, -6.9	
Systolic BP (mmHg)						
Mean Δ (S.D.)	1.0 (7.61)	-1.9 (7.17)	-5.4 (10.02)	-7.9 (6.90)	-10.8 (10.35)	<0.001
Minimum Δ	-18.5	-18.8	-28.9	-23.1	-41.8	
Maximum Δ	19.2	13.4	12.2	10.4	9.5	
95% C.I.**	N/A	-6.0, 0.1	-10.1, -2.8	-11.9, -6.0	-15.6, -8.0	
Heart Rate (beats/min)						
Mean Δ (S.D.)	0.31 (7.20)	-0.16 (6.44)	-2.0 (6.45)	-3.0 (6.87)	-3.5 (5.34)	<0.01
Minimum Δ	-20.3	-20.9	-23.5	-28.5	-18.1	
Maximum Δ	14.7	12.0	10.1	10.7	6.5	

* P-value is for treatment effect from analysis of variance F-test with effects for baseline values and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in nighttime blood pressure and heart rate recorded by ABPM. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

- **Diastolic and Systolic Load by ABPM :** Table 02-9

At the Final Visit VerPM 100, 200, 300, and 400mg were stat. significantly more effective than placb in reducing DBP load. Similar results were observed in SBP load except for VerPM 100mg treatment group.

Table 02-9 : Diastolic and Systolic Load Recorded by ABPM

Measurement	Placebo (N=42)	Verelan PM 100 mg (N=49)	Verelan PM 200 mg (N=58)	Verelan PM 300 mg (N=53)	Verelan PM 400 mg (N=55)	p- value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	2.7 (13.49)	-5.4 (16.6)	-13.1 (23.50)	-24.9 (21.29)	-33.5 (21.13)	<0.001
Minimum Δ	-19.5	-58.0	-56.1	-72.9	-85.2	
Maximum Δ	30.8	19.2	36.0	25.5	21.1	
95% C.I.**	N/A	-14.5, -1.7	-23.8, -7.8	-35.1, -20.1	-43.6, -28.8	
Systolic BP (mmHg)						
Mean Δ (S.D.)	0.8 (16.41)	-4.4 (19.21)	-9.7 (21.1)	-17.8 (21.2)	-31.2 (23.82)	<0.01
Minimum Δ	-32.1	-60.6	-52.9	-68.5	-95.1	
Maximum Δ	53.8	33.4	56.8	18.5	7.1	
95% C.I.**	N/A	-12.7, 2.3	-18.3, -2.8	-26.5, -10.7	-40.6, -23.6	

* P-value is for treatment effect from analysis of variance F-test with effects for baseline values and treatment.

** Confidence interval for the difference between placebo and Verelan PM treatment groups in mean change from baseline to final visit in diastolic and systolic load recorded by ABPM. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

- **Incidence of Positive Response :** Table 02-10

At the Final visit, the percentages of responders in each of VerPM 200, 300, and 400mg groups were stat. significantly higher than the placebo group.

Table 02-10 : Number of Responders on Manual DBP at trough

Measurement	Placebo N = 42 (%)	Verelan PM 100 mg N = 49 (%)	Verelan PM 200 mg N = 58 (%)	Verelan PM 300 mg N = 55 (%)	Verelan PM 400 mg N = 55 (%)	p-value*
Manual DBP: decrease ≥10% or ≤90 mmHg	9 (23.1)	17 (34.7)	28 (49.1)	37 (68.5)	32 (59.3)	<0.001
95% C.I.**	NA	-7.2, 30.4	7.5, 44.6	27.3, 63.6	17.6, 54.8	
Manual DBP: decrease ≥10%	6 (15.4)	12 (24.5)	19 (33.3)	26 (48.1)	25 (46.3)	0.003
95% C.I.**	NA	-7.4, 25.6	1.3, 34.6	15.3, 50.3	13.4, 48.4	
Manual DBP: ≤90 mmHg	8 (20.5)	13 (26.5)	24 (42.1)	29 (53.7)	29 (53.7)	0.001
95% C.I.**	NA	-11.7, 23.7	3.6, 39.6	14.8, 51.6	14.8, 51.6	

* P-value is from chi-square test unadjusted for multiple comparisons.
** Confidence interval for the difference between placebo and Verelan PM treatment groups in percentage of responders based on manual trough blood pressure. Verelan PM statistically significantly superior to placebo when 95% confidence interval does not include zero.

Trough-to-Peak Ratio

	Diastole	Systole
VerPM 100mg	81.3%	61.2%
VerPM 200mg	51.9%	59.3%
VerPM 300mg	79.1%	71.1%
VerPM 400mg	69.7%	63.7%

The VerPM 200, 300, and 400mg dose levels showed acceptable trough-to-peak ratio and maintained clinically significant reduction in BP during the last 4-hrs of dosing interval. Despite good trough-to-peak ratios for the VerPM 100mg dose, trough BP reductions were not considered to be clinically meaningful.

- **Center-by-Treatment Interactions**

No stat. significant interactions were found between treatment group and pooled center for any of efficacy endpoints.

Efficacy Conclusions (Study 002)

The results of this study demonstrate that VerPM at doses of 200mg, 300mg, and 400mg are significantly more effective than placb on reducing S / D BP at trough, over a 24-hr period with the greatest reduction of BP occurring in early morning hours. The antihypertensive effect of VerPM increased with dose in this study. These results are summarized in Table 02-11.

Table 02-11 : Efficacy Summary (Study -002)

Primary Efficacy :BP mean change by ABPM from baseline at Trough
(6pm to 10pm)

Measurement	Placebo (N= 42)	Verapamil PM 100 mg (N=49)	Verapamil PM 200 mg (N=58)	Verapamil PM 300 mg (N=53)	Verapamil PM 400 mg (N=55)	p – value*
Diastolic BP (mmHg)						
Mean Δ (S.D.)	1.3 (6.76)	1.2 (9.83)	-2.6 (9.52)	-5.2 (11.30)	-8.8 (8.77)	<0.001
95% C.I.**	N/A	-3.7, 3.5	-7.2, -0.4	-10.4, -2.6	-13.3, -6.8	
Systolic BP (mmHg)						
Mean Δ (S.D.)	0.5 (10.16)	-0.5 (12.53)	-3.6 (12.13)	-6.1 (14.14)	-10.9 (13.66)	<0.001
95% C.I.**	N/A	-5.7, 3.9	-8.6, 0.5	-11.7, -1.4	-16.3, -6.4	

Mean Changes in Secondary Efficacy Parameters

Measurement	Placebo	Verapamil PM 100 mg	Verapamil PM 200 mg	Verapamil PM 300 mg	Verapamil PM 400 mg	p – value*
Seated Blood Pressure at Trough, Measured Manually, MBP Intent-to-Treat						
Diastolic BP (mmHg) Mean Δ (S.D.)	-0.6 (7.22)	-4.0 (7.54)**	-6.8 (7.81)**	-10.0 (6.96)**	-9.3 (7.97)**	<0.001
Systolic BP (mmHg) Mean Δ (S.D.)	-2.4 (14.50)	-3.6 (11.77)	-8.4 (13.73)**	-11.1 (11.29)**	-11.2 (14.75)**	0.001
24-Hour Blood Pressure Recorded by ABPM, ABPM Intent-to-Treat						
Diastolic BP (mmHg) Mean Δ (S.D.)	1.0 (4.53)	-1.2 (4.72)**	-4.5 (6.07)**	-7.5 (5.57)**	-10.2 (6.36)**	<0.001
Systolic BP (mmHg) Mean Δ (S.D.)	0.6 (7.61)	-2.1 (6.95)	-6.1 (9.81)**	-9.4 (7.82)**	-13.5 (9.90)**	<0.001
Blood Pressure Recorded by ABPM During the Accelerated Phase, ABPM Intent-to-Treat						
Diastolic BP (mmHg) Mean Δ (S.D.)	0.5 (7.32)	-3.1 (6.01)**	-7.1 (8.34)**	-11.0 (7.20)**	-13.8 (8.12)**	<0.001
Systolic BP (mmHg) Mean Δ (S.D.)	-1.0 (9.71)	-4.5 (9.09)	-9.5 (12.45)**	-14.5 (10.89)**	-19.2 (12.39)**	<0.001
Seated Blood Pressure at Peak, Measured Manually, MBP Intent-to-Treat						
Diastolic BP (mmHg) Mean Δ (S.D.)	-1.0 (7.26)	-4.6 (6.11)**	-8.2 (7.08)**	-11.0 (7.73)**	-14.2 (8.79)**	<0.001
Systolic BP (mmHg) Mean Δ (S.D.)	-3.2 (15.23)	-3.9 (10.80)	-9.3 (14.07)**	-14.3 (13.13)**	-19.1 (15.93)**	<0.001

* P-value is for treatment effect from analysis of variance F-test with effects for baseline value and treatment.

**Confidence interval for the difference between placebo and Verapamil PM treatment groups in pairwise comparisons are statistically significant ($p<0.05$).

SAFETY RESULTS

All pts who entered the Phase B, except 1 pt who was randomized to placb and never returned, are included for the safety evaluation. The mean duration of exposure were similar among treatment groups and shown in Table 02-12.

Table 02-12 : Extent of Exposure

Days of Study Medication	Placebo N = 50	Verelan PM 100 mg N = 53	Verelan PM 200 mg N = 58	Verelan PM 300 mg N = 58	Verelan PM 400 mg N = 58
1 to < 8	50	53	58	58	58
8 to < 15	49	53	58	57	58
15 to < 29	46	52	58	57	56
29 to < 43	42	49	58	56	55
43 to 56	40	48	58	55	55
>56	21	23	33	26	26
Mean (SD)	49.60 (16.30)	55.51 (12.02)	58.53 (4.11)	56.40 (10.38)	55.90 (9.88)
Median	56	56	57	56	56
Minimum	7	8	50	2	12
Maximum	63	77	72	79	66

Adverse Events

- **Phase A Adverse Events**

Mild to moderate AEs, headache, dizziness, upper respiratory infection, asthma etc. were reported during this placb lead-in period. Eight pts were d/ced from the study due to AE during Phase A were : edema, HTN, menorrhagia, headache, abnormal ECG & CHF, anxiety & headache, generalized edema, headache & leg craps.

- **Phase B Adverse Events**

A total of 165 (60%) pts; placb 30 (60%) , VerPM 100mg 34 (53%), 200mg 30 (52%), 300 mg 31 (53%), and 400mg 40 (69%) pts reported ≥1 AE during the Phase B.
The most frequent reported AE in the VerPM groups were headache, upper respiratory infection, and constipation. Few AE s were considered by the investigators to be probably or definitely related to the study drug. The only dose-related AE due to VerPM was constipation.
The most frequent AE (≥ 5% in VerPM group) are summarized in Table 02-13.

Table 02-13 : Incidence of Adverse Events Occurring in ≥ 5% of Patients in Any Verapamil PM Treatment Group During Phase B

Body System Adverse event	Placebo N = 50		Verelan PM 100 mg N=53		Verelan PM 200 mg N=58		Verelan PM 300 mg N=58		Verelan PM 400 mg N=58	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Body as a Whole										
Asthenia	3	(6.0)	3	(5.7)	3	(5.2)	0		0	
Back pain	2	(4.0)	3	(5.7)	1	(1.7)	1	(1.7)	0	
Flu syndrome	3	(6.0)	1	(1.9)	2	(3.4)	6	(10.3)	1	(1.7)
Headache	10	(20.0)	5	(9.4)	7	(12.1)	8	(13.8)	9	(15.5)
Infection	5	(10.0)	10	(18.9)	4	(6.9)	4	(6.9)	10	(17.2)
Pain	1	(2.0)	0		2	(3.4)	3	(5.2)	1	(1.7)
Cardiovascular System										
Abnormal ECG	3	(6.0)	1	(1.9)	1	(1.7)	0		4	(6.9)
Digestive System										
Constipation	1	(2.0)	2	(3.8)	2	(3.4)	6	(10.3)	13	(22.4)
Diarrhea	2	(4.0)	0		0		2	(3.4)	3	(5.2)
Nausea	0		0		0		0		5	(8.6)
Metabolic/Nutritional										
Peripheral edema	1	(2.0)	3	(5.7)	3	(5.2)	0		5	(8.6)
Respiratory System										
Pharyngitis	2	(4.0)	0		3	(5.2)	1	(1.7)	2	(3.4)
Rhinitis	2	(4.0)	1	(1.9)	0		3	(5.2)	2	(3.4)
Skin and Appendages										
Rash	0		1	(1.9)	1	(1.7)	0		3	(5.2)

Most of the AEs reported in this study were mild to moderate in intensity.

There were 7 reports of dizziness (2 of these 6 also reported postural hypotension, and 1 reported syncope. Two additional postural hypotension were reported. None of them appeared to be related decrease of BP or HR. All of them completed the study.

#2488 : dizziness, VerPM 100mg 8 wks, no postural BP change 3 days post episode.
#2132 : dizziness, syncope, postural hypotension at bathroom in the middle of night, lost consciousness and hit his forehead after VerPM 100mg 9 days. The pt admitted to have been drinking heavily that night. No postural changes in BP 4 days pre- and 3 days post-episode.
#2026 : dizziness, VerPM 200mg 4 wks, no BP postural change 1 wk after the episode.
#2336 : dizziness, VerPM 200mg 2 wks, no BP change 1 wk after the episode.
#2093 : dizziness, postural hypotension, VerPM 300mg 3 wks, no BP postural change 2 days post-episode.
#2112 : postural hypotension, VerPM 400mg 3 wks, seBP 150/100 to stBP 138/100 3 days post-episode.
#2152 : postural hypotension, VerPM 400mg 4 days, seBP 136/88 to stBP 120/70 mmHg 3 days post-episode.
#2023 : dizziness, VerPM 400mg 1 day, seBP 140/98 to stBP 130/98 6 days post-episode.
#2309 : dizziness, VerPM 400mg 6 wks, no BP postural changes 1 day pre- and 2 wks post-episode.

Severe AEs were severe headache one each placb and VerPM 200mg; and severe back pain reported in 2 placb pts; severe AE 1 pt each, accidental injury, headache, and impotence in the placb group; flu syndrome and myocardial infarction, dizziness/postural hypotension/syncope (#2132) in the VerPM 100mg group; headache and dyspepsia in VerPM 200mg group; death and constipation in VerPM 300mg group; and chest pain and insomnia in VerPM 400mg group.

Serious AEs reported in 4 cases during VerPM treatment were considered probably or remotely related to the test drug were:

#20263B : 58 y/w/m on VerPM 100mg for 56 days, **visual disturbance** (?TIA). Condition resolved and pt remained study and completed the study.

#20098B : 63 y/w/m on VerPM 400mg for 62 days. He experienced **arm and chest discomfort** 2x and underwent to triple CABG.

#20150B : 78 y/w/m on VerPM 100mg for 38 days. **Acute myocardial infarction**, hospitalized.

#20149B : 68y/w/m on VerPM 300mg for 2 days. Pt complained of **left arm pain and he became restless**. Pt refused to go hospital . Later in the evening his wife found him death.(cardiac arrest, probably due to acute coronary event).

Adverse Events leading to Withdrawal during Phase B (Table 02-14) were 7 pts, a total of 11 AEs : placb 3 (6.0%) , VerPM 100mg 1 (1.9%), VerPM 300mg 1 (1.7%), VerPM 400mg 2 (3.4%) pts. Eight of the 11 events were considered by the investigators to be possibly / probably related to study drug. Two of these events were serious AE (#20150B acute myocardial infarction and #20149B death) and remainder were non-serious. Six pts d/ced the study during the Phase B due to non-serious events were:

#20131B : 67 y/His/f on placb for 22 days, d/ced due to mod HTN.

#20136B : 57 y/w/f on placb for 17 days, d/ced due to mod. HTN.

#20231B : 54 y/w/m on placb for 11 days, d/ced due to mod. constipation and abdominal pain.

#20109B : 54 y/w/m on VerPM 300mg for 21 days, d/ced due to mod. gout. Hx. of ongoing gout. Not Rx related.

#20138B : 51 y/b/f on VerPM 400mg for 20 days, d/ced due to mild abnormal ECG and mod. HTN. Repeat ECG normal. Remotely Rx related.

#20265B : 67 y/w/f on VerPM 400mg for 14 days, d/ced due to mod. edema, mild constipation, and mild skin rash. Probably Rx related.

Vital Signs / PE / ECGs

There were no clinically relevant differences in vital signs, PE or ECGs at BL and end of treatment except lower BP and HR in the VerPM groups. No hypotension or HR <50 bpm on the final ECG were reported.

At BL 29 pts had abnormal ECGs. Significant **abnormal ECG changes** were seen 22 pts at the Final visit ; placb 5 (12%), VerPM 100mg 6 (12%), VerPM 200mg 2 (3%), VerPM 300mg 3 (5%), VerPM 400mg 6 (10%) pts. There was no significant difference in shifting of ECG from normal at BL to abnormal at Final visit. The incidence of **1st degree AV block** in each groups were placb 0/50, VerPM 100mg 1/53, 200mg 2/58, 300mg 1/58, and 400mg 4/58 pts. Three of 7 pts had 1st degree AV block at both BL and end of study (#2485 VerPM 200mg, BL 205 to 221 ms; #2499 VerPM 300mg, BL 240 to 226 ms; #2008 VerPM 400mg, BL 240 to 260 ms).

Laboratory Results

In general **hematology** and **chemistry** parameters were WNL at BL and Final Visit. The percentages of pts with shifts from normal to abnormal were comparable among treatment groups except **abnormal liver function tests (LFT).**

Pts who had shifts from normal at BL to abnormal at Final Visit in LFT are summarized in Table 02-14. The majority of pts (11/16. 69%) with changes in LFT had mild increases (< 2x the upper limit of normal), and possible dose-related effects were observed in the VerPM treated groups : placb 1/51 (1.9%), VerPM 100mg 1/53 (1.9%), VerPM 200mg 5/58 (8.6%), VerPM 300mg 3/58 (5.2%), and VerPM 400mg 6/58 (10.3%).

Two pts (#20255B VerPM 200mg & #20353B VerPM 400mg) had LFT values >3x of BL (both asymptomatic), probably related to VerPM. Pt #20255, repeated LFT 12 days later returned to normal.

Minor clinically insignificant changes in urinalysis were seen over the course of the study.

Table 02-14 : Patients with Abnormal Chemistry Values

Patient Identification	Demographics (Age, Gender, Race)	Analyte	A-0 Value	B-8 Value	Normal Range
Placebo Group					
20182B (2267)	25 M W	Total Bilirubin	1.2 mg/dL	1.4 mg/dL	0.0-1.3 mg/dL
Verelan PM 100 mg					
20130B (2183)	70 M B	SGPT/ALT	44 U/L	56 U/L	0-48 U/L
Verelan PM 200 mg					
20023B (2011)	52 M A	SGPT/ALT	26 U/L	74 U/L	0-48 U/L
20047B (2041)	59 M W	SGPT/ALT	41 U/L	61 U/L	0-48 U/L
20066B (2101)	47 M W	SGPT/ALT	33 U/L	59 U/L	0-48 U/L
20255B (2362)	*68 M W*	*SGPT/ALT* *Alk. Phos.*	*23 U/L* *87 U/L*	*113 U/L* *263 U/L*	*0-48 U/L* *20-125 U/L*
20329B (2462)	35 M W	SGPT/ALT	45 U/L	81 U/L	0-48 U/L
Verelan PM 300 mg					
20260B (2375)	46 M W	SGPT/ALT SGOT/AST	47 U/L 30 U/L	67 U/L 49 U/L	0-48 U/L 0-42 U/L
20279B (2393)	33 M W	SGOT/AST	37 U/L	44 U/L	0-42 U/L
20331B (2464)	29 B M	SGPT/ALT	15 U/L	54 U/L	0-48 U/L
Verelan PM 400 mg					
20060B (2090)	*53 M W*	*SGPT/ALT* *SGOT/AST*	*16 U/L* *23 U/L*	*88 U/L* *47 U/L*	*0-48 U/L* 0-42 U/L
20353B (2294)	48 M W	SPGT/ALT	38 U/L	55 U/L	0-48 U/L
20188B (2023)	41 M W	SPGT/ALT	47 U/L	55 U/L	0-48 U/L
20200B (2249)	64 M W	SGPT/ALT	37 U/L	52 U/L	0-48 U/L
20284B (2397)	56 M W	SGPT/ALT	39 U/L	58 U/L	0-48 U/L
20087B (2122)	36 M W	SGOT/AST	18 U/L	48 U/L	0-42 U/L

Note: M = male, F = female, W = white, B = black, A = Asian, Alk. Phos. = alkaline phosphatase.
Abnormalities for two patients in italics were reported as adverse events.

Safety Conclusions (Study 002)

VerPM doses 100, 200, 300, and 400mg and placb were well tolerated in this 8-wk study. The overall incidence of discontinuation due to AE was low (2.5%). The percentage of pts with AEs were comparable among treatment groups, except digestive system in the VerPM 400mg group (constipation 22% vs. 2% - 10%; nausea 9% vs. 0% of other groups). Seven pts complained dizziness with/without hypotension and 2 additional pts reported postural hypotension, 1 pt with dizziness/syncope during VerPM treatment, however, none of them showed significant postural changes in BP or HR pre- or post-episode measurements. Higher incidence of abnormal LFT was observed with VerPM treated groups (placb 1.9% vs. VerPM 400mg 10.3%). Constipation and abnormal LFT are known AEs of verapamil.

Four serious AEs were reported during the study, 1 death (cardiac arrest, probably due to acute coronary event), 1 acute myocardial infarction, 1 severe angina leading to CABG, 1 with visual disturbance/ ?TIA. These events are remotely related with VerPM treatment.

INTEGRATED SUMMARY OF EFFICACY (ISE) : (Volume 1.41)

Efficacy analysis of primary and secondary efficacy variables were conducted on the individual Study 001, VerPM 200mg vs. placb; and Study 002, VerPM 100, 200, 300, and 400mg vs. placb. Efficacy data from the placb and VerPM 200mg treatment groups for the studies 001 and 002 have been pooled. Placb subtracted values and associated 95% confidence intervals were provided for the VerPM 100, 200, 300, and 400mg treatment groups as well as the pooled placb and VerPM 200mg arm from the 001 and 002 studies.

Additionally, efficacy variables were analyzed by treatment group by gender, age, race, and severity of HTN as measured by mean daytime DBP by ABPM.

Patient Disposition

A total of 803 pts with mild to moderate HTN were enrolled to Phase A; 415 pts who met inclusion criteria were randomized to Phase B. Two pts who were dispensed study drug but never returned for treatment were dropped from the analysis.

The demographic and characteristics at BL were similar across treatment groups. Approx 2/3 of the pts were male, with mean age of 53 yrs (range 25 to 84 yrs). There was a stat. significant difference in the race of pts ($p=0.02$ in the ABPM and $p=0.016$ in the MBPM intent-to-treat population) with a higher proportion of black pts in the placb group compared with the VerPM treatment groups.

EFFICACY SUMMARY : Tables ISE-1A and -1B

The results of studies showed stat. significant superiority of once daily, nighttime dosing (10pm $\pm$ 1 hr) of VerPM 200mg, 300mg, and 400mg over placb in reduction of DBP and SBP over a 24-hr duration and in the critical morning hours when BP and HR are known to increase. Mean reductions in DBP and SBP for the primary and secondary variables are presented in Table ISE-1. All reductions in this table showed stat. significant differences from placb in favor of VerPM ($p<0.05$), with the exception of SBP ($p=0.052$) in study 002 for the 100mg group.

Primary Efficacy : BP at Trough (6pm to 10pm) by ABPM :

VerPM 200mg group showed stat. significant reduction in mean DBP in Study 001 ($p=0.047$), Study 002 ($p=0.017$), pooled VerPM 200mg group ($p=0.001$).

Table ISE-1A : Mean Change(mmHg) from Baseline in DBP and SBP for VerPM 200mg Treatment Arms of Study 001, Study 002 and pooled Data

	Study 001		Study 002		Study 001 and 002 Pooled	
	Verapamil PM 200 mg		Verapamil PM 200 mg		Verapamil PM 200 mg	
	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)
Primary Efficacy Variable:						
DBP and SBP recorded by ABPM at trough (7pm ± 1 hr, Day 1)	-3.1	-3.9	-2.6	-3.6	-2.9	-3.7
Secondary Efficacy Variables:						
DBP and SBP recorded by ABPM during the accelerated phase (6am to 12 noon, Day 2)	-5.4	-7.2	-7.1	-9.5	-6.2	-8.3
DBP and SBP recorded by ABPM over 24 hours (10 pm, Day 1 to 10 pm, Day 2)	-3.0	-3.9	-4.5	-6.1	-3.7	-5.0
DBP and SBP measured manually at trough (7 pm ± 1 hr, Day 1)	-7.3	-6.7	-6.8	-8.4	-7.0	-7.5
DBP and SBP measured manually at peak (8 am ± 1 hr)	-8.4	-8.3	8.2	-9.3	-8.3	-8.8

Statistical comparisons of Verapamil PM mg vs. PBO based upon analysis of covariance F-tests with effects for baseline value and treatment. All mean changes for Verapamil PM 200 mg significantly different from PBO ($p<0.05$) except SBP recorded by ABPM at trough for Verapamil PM 200 mg group in Study 002 ($p=0.052$).

Table ISE-1B : Placebo-Subtracted Mean Change (mmHg) from Baseline in DBP and SBP for VerPM 300 mg and 400 mg Treatment Arms for Study 002

	Verapamil PM 300 mg		Verapamil PM 400 mg	
	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)
Primary Efficacy Variable:				
DBP and SBP recorded by ABPM at trough (7pm ± 1 hr, Day 1)	-6.5	-6.5	-10.0	-11.4
Secondary Efficacy Variables:				
DBP and SBP recorded by ABPM during the accelerated phase (6am to 12 noon, Day 2)	-11.5	-13.4	-14.3	-18.2
DBP and SBP recorded by ABPM over 24 hours (10 pm, Day 1 to 10 pm, Day 2)	-8.4	-10.0	-11.1	-14.1
DBP and SBP measured manually at trough (7 pm ± 1 hr, Day 1)	-9.4	-8.7	-8.7	-8.8
DBP and SBP measured manually at peak (8 am ± 1 hr)	-10.0	-11.1	-13.2	-15.9

Statistical comparisons between Verapamil PM 300 mg and 400 mg versus PBO based upon 95% confidence intervals for placebo-subtracted means. All placebo-subtracted mean changes significantly different from PBO ($p<0.05$).

Placb-subtracted mean change in DBP at trough by ABPM in VerPM 200mg group in Study 001 was -4.2 mmHg (95% C.I. of -7.6 to -0.8); in Study 002, -3.8 mmHg (95% C.I. of -7.2 to -0.4); and as pooled data, -4.0 mm Hg (95% C.I. of -6.4 to -1.6).

Similar results were found in mean change in SBP in the VerPM 200mg group. Placb-subtracted mean change in SBP in trough by ABPM in Study 001 was -5.9 mmHg (95% C.I. of -10.8 to -1.0); in Study 002, -4.0 mmHg (95% C.I. of -8.6 to 0.5); and pooled data, -5.1 mmHg (95% C.I. of -8.4 to -1.7). The mean change of HR in pooled data was -3.7 bpm ($p<0.001$).

.A dose response in reduction of DBP and SBP by ABPM at trough was evident with increasing VerPM doses. Pts receiving VerPM 300mg had a placb-subtracted mean change in DBP of -6.5 mmHg (95% C.I. of -10.4 to -2.6); at VerPM 400mg, -10.0 mmHg (95% C.I. of -13.3 to -6.8).

Secondary Efficacy Variables

- **Accelerated phase (6am to 12 noon) by ABPM :**

The pooled VerPM 200 mg group showed stat. significant reduction in mean DBP ($p<0.001$), SBP ($p<0.001$), and HR ($p=0.002$) over placb.
The placb-subtracted mean change in DBP was -5.9 mmHg (95% C.I. of -7.9 to -3.8), SBP -7.9 mmHg (95% C.I. of -10.9 to 14.9), and HR -2.7 bpm.

A dose response in reduction of DBP during the accelerated phase was seen with increasing VerPM doses: VerPM 300 mg placb-subtracted net change in DBP of -11.5 mmHg (95%C.I. of -14..5 t o-8.5); VerPM 400mg -14.3 mmHg (95%C.I. of -17.5 to -11.1).

- **24-hr BP by ABPM :**

VerPM 200 mg treated group showed stat. significant reduction in the mean pooled DBP ($p<0.001$), SBP ($p<0.001$), and HR ($p<0.001$) over placb.
The placb-subtracted mean change in DBP was -4.5 mmHg (95% C.I. of -6.0 to -3.0), SBP -6.0 mmHg (95% C.I. of -8.4 to -3.6), and HR -3.2 bpm .

A dose response in reduction of DBP over 24 hrs was seen. The placb-subtracted mean change in VerPM 300mg was -8.4 mmHg (95%C.I. of -10.6 to -6.3); VerPM 400mg -11.1 mmHg (95%C.I. of -13.4 to -8.8).

- **BP at trough (7pm ± 1 hr) by MBPM :**

VerPM 200 mg group showed stat. significant reduction in mean DBP ($p<0.001$), SBP ($p=0.001$), HR ($p=0.006$) over placb. The placb-subtracted mean change in DBP was -4.9 mmHg (95% C.I. of -7.3 to -2.6), SBP -5.3 mmHg (95% C.I. of -9.1 to -1.4).
The placb-subtracted mean S/D BP change at trough with VerPM 300mg.treatmen was -8.7/-9.4 mmHg, with VerPM 400mg treatment was -8.7/-8.8 mmHg.

- **BP at peak (8am) by MBPM :**

VerPM 200 mg group showed stat. significant reduction in mean DBP ($p<0.001$), SBP ($p<0.001$), and HR($p=0.327$) over placb. The placb-subtracted mean changes in DBP was -5.5 mmHg (95% C.I. of -7.5 to -3.5) , SBP -4.7 mmHg (95% C.I. of -8.4 to -0.9).

A dose-response in DBP was seen in placb-subtracted mean change: VerPM 100mg -3.5 mmHg, 300mg -10.0 mmHg, 400mg -13.2 mmHg. A similar dose response was seen in reduction of SBP in Study 002.

- **Incidence (%) of positive responder by MBPM :**

Fifty percent of pts receiving VerPM 200 mg had $\geq$10% decrease in DBP or DBP $\leq$90 mmHg compared with 25% of pts receiving placb ($p=0.001$) at the Final Visit. Pts receiving VerPM 300mg 69%, 400mg 59%.

Efficacy Results in Subset Population

BP recorded by ABPM at trough by Gender : Table ISE-2.

At BL S/DBP mean values were similar : placb group, Male 155.9/97.1 mmHg, Female 153.8/93.1 mmHg; VerPM 200mg group, Males 154.3/97.4 mmHg , Females 154.2/94.3 mmHg. The reduction in DBP was stat. significant for VerPM 200 mg over placb in Males ($p=0.004$) but not in Females ($p=0.083$). The placb-subtracted mean change in DBP was -4.1 mmHg for Males and -3.7 mmHg for Females receiving VerPM 200 mg. Differences in significance levels for Males and Females can be attributed in part to difference in sample size.

Table ISE-2 : Blood Pressure Recorded by ABPM and Heart Rate at Trough by Gender: Mean Change From Baseline: Pooled Data

	Males			Females		
Measurement	Placebo N=55	Verelan PM 200mg N=60	p-value*	Placebo N=42	Verelan PM 200mg N=39	p-value*
Diastolic BP (mmHg)						
Mean Δ (SD)	+1.0 (7.35)	-3.1 (9.57)	0.004	+1.3 (9.26)	-2.4 (8.99)	0.083
Minimum Δ	-11	-25		-25	-24	
Maximum Δ	+15	+20		+19	+22	
Systolic BP (mmHg)						
Mean Δ (SD)	+2.0 (8.94)	-3.5 (13.33)	0.002	+0.5 (14.70)	-4.1 (12.04)	0.100
Minimum Δ	-15	-40		-48	-29	
Maximum Δ	+19	+26		+27	+27	
Heart Rate (bpm)						
Mean Δ (SD)	+2.5 (8.05)	-3.6 (9.87)	<0.001	+2.1 (11.12)	+1.0 (8.68)	0.301
Minimum Δ	-14	-33		-32	-12	
Maximum Δ	+23	+26		+39	+30	

Abstracted from Statistical Tables 9.1B.1 and 9.1B.2

* p-values for treatment effect from analysis of covariance F-test with effects for Baseline value and treatment

- **BP by ABPM at trough by age group** (<50 yrs, ≥50 and <65 yrs, ≥65 yrs) : Table ISE-3.

Table ISE-3 : Blood Pressure as Recorded by ABPM and Heart Rate at Trough by Age Group: Mean Change from Baseline: Pooled Data

	< 50 Years of Age			≥ 50 and < 65 Years of Age			≥ 65 Years of Age		
Measurement	Placebo N=32	Verelan PM 200mg N=48	p-value*	Placebo N=55	Verelan PM 200mg N=57	p-value*	Placebo N=10	Verelan PM 200mg N=14	p-value*
Diastolic BP (mmHg)									
Mean Δ(SD)	+0.4 (7.16)	-1.3 (8.58)	0.346	+2.2 (9.02)	-3.4 (10.33)	0.006	-2.2 (5.57)	-5.9 (6.89)	0.139
Minimum Δ	-11	-25		-25	-24		-7	-19	
Maximum Δ	+16	+17		+19	+22		+8	+4	
Systolic BP (mmHg)									
Mean Δ (SD)	+2.0 (10.90)	-1.8 (10.26)	0.086	+1.3 (12.63)	-4.7 (14.62)	0.018	-0.7 (9.86)	-6.1 (13.41)	0.104
Minimum Δ	-26	-34		-48	-34		-19	-40	
Maximum Δ	+27	+19		+25	+27		+16	+11	
Heart Rate (bpm)									
Mean Δ (SD)	+2.8 (8.14)	-2.1 (9.47)	0.008	+1.3 (10.52)	-0.9 (9.57)	0.127	+6.2 (6.05)	-7.0 (10.18)	0.003
Minimum Δ	-12	-33		-32	-31		-2	-28	
Maximum Δ	+21	+18		+39	+30		+18	+4	

Abstracted from Statistical Tables 10.1B.1 through 10.1B.3

* p-values for treatment effect from analysis of covariance F-test with effects for Baseline value and treatment

VerPM 200mg was stat. significantly superior in the reduction of DBP (p=0.006) and SBP (p=0.018) only in the **50 to 64 yrs of age group**. Pts in this middle age group had a placb-subtracted mean change in DBP of -5.6 mmHg, compared with -3.7 mmHg in the ≥65 yrs, and -1.7 mmHg in the <50 yrs of group. The placb-subtracted mean change in SBP was -6.0 mmHg in the 50 to 64 yrs group, -5.4 mmHg in ≥65 yrs group, and -3.8 mmHg in <50 yrs group. The differences in significance levels can be attributed in part to difference in sample size among three age categories.

- **BP by ABPM at trough by race : Table ISE-4.**

At BL BP mean values were similar : placb group, Whites 154.3/94.6, Blacks 156.5/97.4 mmHg; VerPM 200 mg group, Whites 154.1/95.5 and Blacks 152.4/97.4 mmHg.
In the VerPM 200 mg group the reduction in mean DBP was stat. significant in **White** pts (p=0.006) and approaching significance in **Black** pts (p=0.066). Changes in mean DBP was not significant in "other" races, the sample size was too small to be meaningful. Sample size was also limited in the Blacks, however, this group showed a placb-subtracted mean change in DBP of -4.1 mmHg vs. Whites -3.9 mmHg. Placb-subtracted mean change in SBP was greatest in the Black population -8.9 mmHg compared with -4.0 mmHg in the White population.

Table ISE-4 : Blood Pressure Recorded by ABPM and Heart Rate at Trough by Race: Mean Change from Baseline: Pooled Data

	White Patients			Black Patients			Patients of Other Races		
Measurement	Placebo N=67	Verelan PM 200mg N=96	p-value*	Placebo N=21	Verelan PM 200mg N=13	p-value*	Placebo N=9	Verelan PM 200mg N=10	p-value*
Diastolic BP (mmHg)									
Mean Δ(SD)	+1.2 (8.40)	-2.7 (9.23)	0.006	+1.3 (7.41)	-2.3 (7.59)	0.066	-1.1 (8.85)	-5.0 (12.57)	0.309
Minimum Δ	-25	-34		-9	-14		-12	-25	
Maximum Δ	+19	+22		+17	+12		+15	+13	
Systolic BP (mmHg)									
Mean Δ (SD)	+0.5 (11.93)	-3.5 (12.43)	0.025	+5.6 (9.30)	-3.3 (8.41)	0.002	-2.5 (13.90)	-6.8 (20.90)	0.668
Minimum Δ	-48	-34		-8	-18		-19	-40	
Maximum Δ	+25	+27		+27	+10		+18	+26	
Heart Rate (bpm)									
Mean Δ (SD)	+1.9 (8.98)	-2.5 (9.07)	0.001	+3.4 (11.51)	+0.8 (11.53)	0.545	+2.7 (8.43)	-2.4 (13.21)	0.178
Minimum Δ	-32	-31		-14	-33		-12	-25	
Maximum Δ	+23	+30		+39	+14		+13	+26	

Abstracted from Statistical Tables 11.1B.1 through 11.1B.3

* p-values for treatment effect from analysis of covariance F-test with effects for Baseline value and treatment

- **BP by ABPM at trough by severity of hypertension** : Table ISE-5.

Seventy-four percent of the study population had mean daytime DBP by ABPM 90 to 104 mmHg, however, the 26% of pts in the **DBP 104 to 114 mmHg group** had greater reduction in both DBP and SBP. The placb-subtracted mean change in DBP in these moderate HTN group was -6.4 mmHg, compared with -3.0 mmHg in the mild HTN group. Placb-subtracted change in SBP in the moderate HTS group was -11.5 mmHg compared with -2.5 mmHg in the mild HTN group.

Table ISE-5 : Blood Pressure as Recorded by ABPM and Heart Rate at Trough by Severity of Hypertension: Mean Change from Baseline: Pooled Data

	DBP ≥ 90 and ≤ 104 mmHg			DBP ≥105 and ≤ 114 mmHg		
Measurement	Placebo N=75	Verelan PM 200mg N=84	p-value*	Placebo N=22	Verelan PM 200mg N=35	p-value*
Diastolic BP (mmHg)						
Mean Δ (SD)	+1.3 (8.20)	-1.7 (8.98)	0.019	+0.7 (8.35)	-5.7 (9.73)	0.015
Minimum Δ	-25	-24		-11	-25	
Maximum Δ	+19	+22		+14	+11	
Systolic BP (mmHg)						
Mean Δ (SD)	+1.1 (12.45)	-1.4 (12.34)	0.088	+2.2 (9.09)	-9.3 (12.60)	<0.001
Minimum Δ	-48	-40		-15	-34	
Maximum Δ	+27	+27		+19	+15	
Heart Rate (bpm)						
Mean Δ (SD)	+2.1 (9.61)	-1.4 (9.38)	0.007	+3.2 (9.04)	-3.9 (10.37)	0.012
Minimum Δ	-32	-33		-14	-31	
Maximum Δ	+39	+30		+21	+18	

Abstracted from Statistical Tables 12.1B.1 and 12.1B.2

* p-values for treatment effect from analysis of covariance F-test with effects for Baseline value and treatment

Discussions and Conclusions of Efficacy Data

Two pivotal clinical study, placebo-controlled, randomized, double-blind, parallel group studies comparing VerPM to placb at dose of 200 mg (Study 001) and 100, 200, 300, and 400 mg (Study 002) in adult pts with mild to moderate HTS were conducted in the US to demonstrate the efficacy of VerPM when taken at nighttime. The primary objective was to evaluate the magnitude of reduction in the mean DBP at trough (6pm to 10pm) from BL to the end of 8 wk treatment as recorded by ABPM. Secondary efficacy objectives included the magnitude of reduction during the morning "accelerating phase (6am to 12 noon)" by ABPM, 24 -hr mean DBP by ABPM, mean seDBP at peak by MBPM. Subset analysis evaluating the efficacy by gender, age, race, and severity of HTN were added to the ISE.

Individual study results were stat. significant at a level of $p \leq 0.05$, two-tailed, for all primary and secondary endpoints for the VerPM 200, 300, and 400mg treatment groups. For the VerPM 100mg group, significant differences from placb were seen in the following secondary efficacy variables: seDBP by MBPM at trough and peak; and over 24-hr and during accelerated phase DBP by ABPM. Stat. significance was not achieved for the primary efficacy endpoint at the 100mg dose in Study 002. Despite the lack of demonstrated primary efficacy, the 100mg dose is provided to allow for greater dosage titration flexibility, particularly in the renal and hepatic impaired, and in the elderly.

Subset analysis suggested a consistent pattern of response for gender, age, and race. For severity of HTN, it appeared that moderate HTN (mean daytime DBP 105 to 114 mmHg) responded better than mild HTN (mean daytime DBP 90 to 104 mmHg).

The results in this ISE support that VerPM at a dose of 200mg, 300mg or 400mg once daily at night (10pm $\pm$ 1 hr) has the ability to significant reduction of BP at all times of the day and night, and most importantly, during the early morning hours when BP and HR are known to increase.

INTEGRATED SUMMARY OF SAFETY (ISS) : (volume 1.42)

ISS focuses on safety data obtained from two pivotal, d/b Phase III studies (001 & 002) and five pharmaceutical studies as shown in Table ISS-1.

Pharmacokinetic studies : Approx. 40 to 70% of subjects reported treatment-emergent AEs during Phase II PK studies, a total of 116 subjects enrolled. The most frequent AEs were headache and constipation, less often nausea/vomiting, hypesthesia, dizziness and first degree AV block. Three of 27 subjects in study 0896002 (only study with multiple dose 5 days) were withdrew from the study due to AEs. All of these AEs occurred within 2 hours after Isoptin 80 mg dose (#17, hypotension & bradycardia; #21, chest pain (first degree AV block); #23, headache, chest pain (irregular ECG), slurred speech, blurred vision and numbness in both arms).

Table ISS-1 : Summary of Clinical Studies in the Verapamil PM Program

Protocol Number	Start/ Completion Dates	Country	Investigator	Study Design	Dose(s)	Number Completed	*Age Mean (Range)	*Sex (M/F) Race (%) (W/B/O)	Duration of Treatment/ Formulation	Location of CRFs Vol/ p	ICS Vol/p
Phase I Pharmacokinetic Studies											
0796006	January 14, 1997 February 7, 1997	Ireland	Dr. A. Fitzpatrick	Open-label, singledose, two-treatment, two-period, randomized, Crossover	Verelan PM 200 mg Isoptin 80 mg x 3	24	28.17 yr (19-39)	24/0 100/0/0	Single dose/ VER-capsule ISO-tablet	91/1	13/1
0896001	January 27, 1997 February 21, 1997	Ireland	Dr. A. Fitzpatrick	Open-label, singledose, three-treatment, three-period, randomized, crossover (Food effect)	Verelan PM 200 mg Isoptin 80 mg x 3	24	28.38 yr (18-38)	24/0 100/0/0	Single dose/ VER-capsule ISO-tablet	N/A	13/1
0896002	March 6, 1997 April 24, 1997	Ireland	Dr. A. Fitzpatrick	Open-label, multiple dose, two treatment, two period, randomized, crossover (Steady State)	Verelan PM 200 mg Isoptin 80 mg q 8 hrs	24	27.79 yr (20-39)	24/0 100/0/0	5 days/ VER-capsule ISO-tablet	91/65	20/1
0197005	May 29, 1997 July 5, 1997	Ireland	Dr. A. Fitzpatrick	Open, single dose., Four-treatment, four period, crossover, (Dose-Proportionality)	Verelan PM 100 mg, 200 mg, 300 mg, and 200 mg x 2	24	27.83 yr (18-38)	24/0 100/0/0	Single dose/ VER-capsule	91/398	26/1
1095006	September 12, 1996 October 15, 1996	Ireland	Dr. J. Stewart	Single-dose, five treatment, five period,crossover randomized	verapamil **(A)240 mg, **(B)240 mg **(C)240 mg, **(D)240 mg, and Isoptin 80 mg	10	29.8 yr (20-38)	10/0 100/0/0	Single dose/ VER-capsule ISO-tablet	N/A	33/1
Phase III Adequate and Well-Controlled Studies											
001	October 28, 1996 June 18, 1997	U.S.	Multicenter	Double-blind, multi-site, placebo-controlled, parallel group, randomized	Verelan PM 200 mg Placebo	137	52 (30 - 79)	89/48 70/20/10	8 weeks/ capsule	92/1	33/17
002	October 29, 1996 September 15, 1997	U.S.	Multicenter	Double-blind, multi-site, placebo-controlled, parallel group, randomized	Verelan PM 100, 200, 300, and 400 mg Placebo	278	53 (25 - 84)	175/103 84/12/8	8 weeks/ capsule	94/1	38/1

VER = Verelan PM; ISO = Isoptin; *Completed patients; N/A = not applicable; Vol p = Volume page
**A, B, C, D varied by in-vitro rates of dissolution

Clinical studies : All Phase A and B safety data are pooled from the data obtained in the studies 001 and 002.

A total of 803 pts were enrolled into Phase A; 415 of these pts met entrance criteria were randomized to Phase B. Two pts who were randomized but never returned subsequent visits were excluded in this analysis. A total of 388 pts d/ced the study during Phase A; 81% due to the failure to meet BP criteria. Among pts randomized to receive VerPM 93% and randomized to placb 80 % completed the studies. One of the most common reasons for D/C among placb-treated pts was "lack of efficacy". A summary of pts disposition and reasons for D/C are presented in Table ISS-2.

Table ISS-2 : Patient Disposition

	Treatment Groups											
	Placebo N=117*		Verelan PM 100mg N=53		Verelan PM 200mg N=129*		Verelan PM 300mg N=58		Verelan PM 400mg N=58		All Verelan PM patients N=298	
Completed Study N (%)	94	(80)	48	(91)	119	(92)	55	(95)	54	(93)	276	(93)
Discontinued prematurely												
Protocol violation	0		3	(6)	0		0		0		3	(1)
Relapse	2	(2)	0		1	(1)	0		0		1	(<1)
Withdrew consent	6	(5)	0		3	(2)	1	(2)	2	(3)	6	(2)
Lost to follow-up	1	(1)	0		1	(1)	0		0		1	(<1)
Death	0		0		0		1	(2)	0		1	(<1)
Investigator/Sponsor decision	6	(5)	1	(2)	0		0		0		1	(<1)
Adverse event	6	(5)	1	(2)	5	(4)	1	(2)	2	(3)	9	(3)
Other	2	(2)	0		0		0		0		0	
Total Discontinued	23	(20)	5	(9)	10	(8)	3	(5)	4	(7)	22	(7)

Abstracted from Statistical Table 1.2
* Pooled data from Studies 001 and 002

Fifteen pts (3.6%) prematurely d/ced the studies 001 & 002 due to AEs. The percentage of pts who D/C due to AE was highest overall in the placb group comparable among the VerPM groups : placb 6 (5.2%) ; VerPM 100 mg 1 (1.9%) ; VerPM 200 mg 5 (3.9%); VerPM 300 mg 1 (1.7%) ; VerPM 400 mg 2 (3.4%). The most common reasons for D/C were rash, edema, and constipation.

The duration of exposure across treatment groups was similar, mean of 56 days (2 to 79 days).

Of the 415 pts enrolled in studies 001 & 002, 413 (99.5%) were included in the safety population (received ≥1 dose). The **demographics and BL characteristics** were similar across treatment groups for age, sex, and height. Approx. 2/3 of pts were male, with a mean age of 53 yrs. There was a stat. significantly higher proportion of black pts in the placb group (p=0.019) compared with the active treatment groups. Table ISS-3.

Table ISS-3 : Demographics and Baseline Characteristics

Variable	Placebo N=116*	Verelan PM 100 mg N=53	Verelan PM 200 mg N=128*	Verelan PM 300 mg N=58	Verelan PM 400 mg N=58	p-value**
Age (yrs)						
Mean (SD)	54.0 (9.74)	52.8 (10.76)	52.9 (10.30)	53.9 (10.81)	52.4 (10.55)	0.814
Minimum	25	34	30	29	31	
Maximum	81	78	77	77	84	
Race N (%)						
White	81 (69.8)	45 (84.9)	104 (81.3)	50 (86.2)	53 (91.4)	0.019
Black	25 (21.6)	6 (11.3)	13 (10.2)	5 (8.6)	5 (8.6)	
Hispanic	8 (6.9)	2 (3.8)	7 (5.5)	3 (5.2)	0	
Other	2 (1.7)	0	4 (3.1)	0	0	
Sex N (%)						
Male	66 (56.9)	38 (71.7)	86 (67.2)	39 (67.2)	37 (63.8)	0.330
Female	50 (43.1)	15 (28.3)	42 (32.8)	19 (32.8)	21 (36.2)	
Weight (kg)						
Mean (SD)	83.7 (15.55)	90.3 (12.82)	85.3 (13.71)	83.9 (10.55)	85.7 (14.95)	0.067
Minimum	47.7	59.1	50.0	63.6	55.9	
Maximum	116.4	120.2	118.2	119.1	125.9	
Height (cms)						
Mean (SD)	171.1 (11.09)	174.0 (9.31)	172.7 (8.90)	173.9 (7.12)	172.4 (11.01)	0.291
Minimum	121.9	154.9	152.4	162.6	144.8	
Maximum	193.0	198.8	190.5	194.9	193.0	

Abstracted from Statistical Table 3

* Pooled data from Studies 001 and 002

** P-values are from analysis of variance F-tests for continuous variables and Fisher's exact test for categorical variables.

Pts were prohibited from using certain concomitant medications, including anti-hypertensive drugs other than study drug. Across treatment groups, the most commonly used concomitant medications were acetaminophen, aspirin, and ibuprofen.

ADVERSE EVENTS

Treatment-emergent AEs reported during Phase B were defined as new or worsened during d/b treatment. Pts with multiple events were counted only once, for the most intense severity and the AE with most definite relationship to study drug.

Incident of Adverse Events During Phase A Placb run-in period
286 / 803 (36.0%) pts reported ≥1 AE. The most frequently reported AEs were headache and upper resp. infection. One serious AE was #2186, 74 yr/w/m with moderate colitis.

388 /803 (48.3%) of pts were withdrawn prior to entering Phase B, mostly due to entrance criteria unmet. Thirteen(3.4%) pts withdraw due to AE: 3 cases each due to headache and HTN; 1 case each generalized edema, ovarian cyst, pain, abnormal ECG, diarrhea, nausea & vomiting, edema, peripheral edema, leg cramp, myalgia, dizziness, anxiety, CHF and menorrhagia.

Incidence of AEs by Drug relationship During Phase B
233 of 413 (56.4%) pts reported ≥1 AE during Phase B :placb 48.3% to VerPM 400mg 69.0%. The most frequently reported AEs were headache (range of 9.4% to 15.5%), infection (range of 6.9% to 18.9%), and constipation (range of 0.9% to 22.4%). A stat. significant difference ($p<0.001$) was observed in the digestive system : placb group, 6.9%; VerPM 100mg 13.2%; 200mg 10.2%; 300mg 15.5%; 400mg 36.2%. Few AEs were considered by

the investigators to be probably or definitely to the study drug. The only dose-related trend observed AE related to VerPM was constipation: placb 0.9%, VerPM 100mg 3.8%, 200mg 3.9%, 300mg 210.3%, and 400mg 22.4%.

Dizziness with/without symptom of orthostatic hypotention was noted in placb 1/117 (0.9%), VerPM 13/298 (4.4%) group with very minor postural changes of BP or HR. One pt (#2132 had an episode of dizziness/hypotension/syncope after 9 days of VerPM 100mg, however, a few days pre and post episode there was no significant postural changes in BP or HR. The pt had heavy alcohol intake prior to this episode.

AEs occurring in ≥2% of any treatment group are presented in Table ISS-4.

Table ISS-4 : Incidence of Treatment-Emergent Adverse Events in ≥2% of Any Treatment Group During Phase B

Body System Adverse Event	Placebo N=116*	Verelan PM 100mg N=53	Verelan PM 200mg N=128*	Verelan PM 300mg N=58	Verelan PM 400mg N=58	All Verelan PM N=297
Body as a Whole						
Headache	13 (11.2)	5 (9.4)	14 (10.9)	8 (13.8)	9 (15.5)	36 (12.1)
Infection	8 (6.9)	10 (18.9)	12 (9.4)	4 (6.9)	10 (17.2)	36 (12.1)
Flu syndrome	3 (2.6)	1 (1.9)	3 (2.3)	6 (10.3)	1 (1.7)	11 (3.7)
Back pain	2 (1.7)	3 (5.7)	1 (0.8)	1 (1.7)	0	5 (1.7)
Pain	2 (1.7)	0	3 (2.3)	3 (5.2)	1 (1.7)	7 (2.4)
Chest pain	1 (0.9)	0	0	2 (3.4)	1 (1.7)	3 (1.0)
Asthenia	4 (3.4)	3 (5.7)	3 (2.3)	0	0	6 (2.0)
Generalized edema	0	0	3 (2.3)	0	0	3 (1.0)
Digestive						
Constipation	1 (0.9)	2 (3.8)	5 (3.9)	6 (10.3)	13 (22.4)	26 (8.8)
Dyspepsia	2 (1.7)	0	4 (3.1)	2 (3.4)	2 (3.4)	8 (2.7)
Diarrhea	2 (1.7)	0	2 (1.6)	2 (3.4)	3 (5.2)	7 (2.4)
Nausea	1 (0.9)	0	0	0	5 (8.6)	5 (1.7)
Respiratory						
Pharyngitis	3 (2.6)	0	6 (4.7)	1 (1.7)	2 (3.4)	9 (3.0)
Sinusitis	3 (2.6)	2 (3.8)	5 (3.9)	1 (1.7)	1 (1.7)	9 (3.0)
Rhinitis	3 (2.6)	1 (1.9)	2 (1.6)	3 (5.2)	2 (3.4)	8 (2.7)
Cough increased	0	0	3 (2.3)	0	2 (3.4)	5 (1.7)
Bronchitis	1 (0.9)	0	4 (3.1)	0	0	4 (1.3)
Epistaxis	0	0	1 (0.8)	0	2 (3.4)	3 (1.0)
Nervous						
Dizziness	1 (0.9)	1 (1.9)	5 (3.9)	1 (1.7)	2 (3.4)	9 (3.0)
Cardiovascular						
ECG abnormal	4 (3.4)	1 (1.9)	1 (0.8)	0	4 (6.9)	6 (2.0)
Postural hypotension	0	1 (1.9)	1 (0.8)	1 (1.7)	2 (3.4)	5 (1.7)
Metabolic and Nutritional						
Peripheral edema	1 (0.9)	3 (5.7)	3 (2.3)	0	5 (8.6)	11 (3.7)
Edema	0	0	2 (1.6)	2 (3.4)	1 (1.7)	5 (1.7)
Skin and Appendages						
Rash	3 (2.6)	1 (1.9)	3 (2.3)	0	3 (5.2)	7 (2.4)

* Pooled data from Studies 001 and 002

Incidence of Serious AE during Phase B
A total of 7 pts (1.7%) reported serious AEs: placb 1, VerPM 6. Abnormal vision, AMI, severe angina necessitating PTCA and sudden death one each were considered to be possibly or remotely related to VerPM.

Incidence of AEs by Sex During Phase B
The incidence of AE in the male and female population was very similar overall and within each body system.

Incidence of AEs by Age During Phase B

Comparable percentages of pts in the age categories experiencing ≥1 AEs in the combined VerPM group were similar :< 50 yrs old, 56.5%; 50-64 yrs old, 61.9%; ≥65 yrs old 60.5%.

Incidence of AEs by Race During Phase B
Because most pts in studies 001 & 002 were white, no meaningful conclusion based on AEs by race could be made. Pts experienced ≥1 AE for whites 62.5%, blacks 48.3%.

Adverse Events leading to Withdrawal During Phase B
15 (3.6%) pts d/ced from studies 001 and 002 due to AEs. The percentage of pts who d/ced due to AEs was highest overall in the placb group: placb 6(5.2%), VerPM 100 mg 12(1.9%), 200mg 5(5.9%), 300mg 1(1.7%), and 400mg 2(3.4%). The most common reasons for D/C with VerPM treatment were rash, edema, and constipation .Adverse events causing premature D/C during Phase B are summarized in Table ISS-5.

Table ISS-5 : Adverse Events resulting in Withdrawal during Phase B

Patient Number	Adverse Event	Status	Severity	Treatment Group	Relationship to Study Drug
10050B (1076)	Dyspepsia Facial edema Rash	Resolved Resolved Resolved	Mild Mild Moderate	Placebo	Possible Possible Possible
10096B (1112)	Dissecting thoracic aortic aneurysm	Resolved	Moderate	Placebo	Definitely not
10010B (1027)	Asthma	Ongoing	Severe	Placebo	Definitely not
20131B (2184)	Hypertension	Ongoing	Moderate	Placebo	Probable
20136B (2194)	Hypertension	Resolved	Moderate	Placebo	Possible
20231B (2326)	Abdominal pain Constipation	Resolved Resolved	Moderate Moderate	Placebo	Possible Possible
20150B (2177)	Myocardial infarction	Resolved	Severe	Verelan PM 100 mg	Remote
10196B (1294)	Accidental injury Angina pectoris Dizziness Headache	Resolved Resolved Resolved Resolved	Moderate Moderate Moderate Moderate	Verelan PM 200 mg	Probable Probable Probable Probable
10006B (1026)	Generalized edema	Ongoing	Mild	Verelan PM 200 mg	Definitely not
10028B (1047)	Dyspnea Rash	Resolved Resolved	Moderate Severe	Verelan PM 200 mg	Remote Remote
10049B (1071)	Rash	Resolved	Moderate	Verelan PM 200 mg	Probable
10025B (1338)	Acute psychosis, manic reaction*	Resolved	Severe	Verelan PM 200 mg	Remote
20109B (2174)	Gout	Ongoing	Moderate	Verelan PM 300 mg	Definitely not
20138B (2195)	Hypertension Abnormal ECG	Resolved Resolved	Moderate Mild	Verelan PM 400 mg	Possible Remote
20265B (2381)	Constipation Edema Rash	Ongoing Ongoing Ongoing	Mild Moderate Mild	Verelan PM 400 mg	Probable Probable Probable

Patient Death
One pt (<1%) died during the VerPM clinical program. Pt#20149B (2185) was 68 y/m on VerPM 300 mg for 2 days suffered with chest discomfort and died that afternoon, probably cardiac arrest due to acute coronary event.

CLINICAL LABORATORY RESULTS

Hematology parameters were generally WNL at BL and Final Visit in Studies 001 & 002. No clinically relevant changes or trends were noted from BL to the end of treatment.

Blood chemistry parameters were generally WNL at the BL and end of treatment except elevation of LFT (SGOT and/or SGPT). Pts who shifted from normal at BL to abnormal at Final Visit are shown in Tables 01-14 and 02-14. No dose-related effect were observed in the VerPM treatment groups. Among them only 2 (1.6%) pts (#10127B & #20255B) in the VerPM 200 mg had clinically significant abnormalities (>3 times of the upper limit of the normal range).
They were asymptomatic. Elevation of LFT has been known to associated with verapamil treatment and it is labeled in the WARNINGS section of the package insert.

Urinalysis showed clinically non-significant changes over the course of the studies.

Electrocardiogram clinically significant changes from BL to Final Visit were:
placb 4 (3%); VerPM 100mg 3 (6%); 200mg 1 (1%); 400mg 3 (5%).6.

Table ISS-6 : Number (%) of patients AV Block at BL and Final visit

Direction of change	placebo n=116	VerPM 100mg n=53	VerPM 200mg n=128	VerPM 300mg n=58	VerPM 400mg n=58	VerPM treated n=297
no change: 1st AV block at BL & Final visit	0	0	3(2.3)	1(1.7)	1(1.7)	5(1.7)*
Normal at BL to 1st AV block at Final visit	0	1(1.9)	1(0.8)	0	3(5.2)	5(1.7)

* 2 pts decreased 3 pts increased (VerPM 200 mg, 211 to 225 ms; VerPM 200 mg, 205 to 221 ms; VerPM 400 mg, 240 to 260 ms from BL to Final visit).

Discussion and Conclusion of ISS

In the two Phase III, placebo-controlled, d/b studies, VerPM was safe and well tolerated at doses of 100mg, 200mg, 300mg, and 400mg.

The percentages of pts reporting at least one AE were slightly higher in the VerPM groups (64% [100mg], 56% [200mg], 53% [300mg], 69% [400mg]) than in the placb group (48%), mostly due to dose-related increase of constipation (<1% [placb], 4% [100 & 200 mg], 10% [300mg], 22% [400mg VerPM]). Constipation is known to occur with verapamil HCl use. The percentage of pts in the combined VerPM group who experienced constipation (8.8%) was comparable to the percentage cited in the Verelan®SR (Wyeth-Ayerst Laboratories) package insert (7.3%).

Two pts developed clinically significant LFT abnormalities (> 3x of BL) and 5 pts developed dose-related prolongation of P-R interval at the end of 8 weeks VerPM treatment. Elevation in LFT and 1st degree AV block are listed in the verapamil product labeling.

The results of this studies -001 & -002 confirm the safety and tolerability of once daily, nighttime (10pm ± 1 hour) administration of VerPM at doses of 100, 200, 300, and 400mg. The safety profile observed in this clinical program was similar and there were no differences in qualitative or quantitative to that seen with the well recognized safety profile of sustained release dosage forms of verapamil HCl including Verelan® SR.

CONCLUSIONS

The submitted clinical Studies -001 & -002 demonstrated the VerPM 200mg, 300mg and 400mg once a day at nighttime (10pm ± 1 hour) administration is superior over placebo in reducing DBP and SBP over a 24 hours duration and in the critical morning hours when BP and HR are known to increase. VerPM 100mg did not show the significant antihypertensive effect compared to placb. However, 100mg dosage form is needed for dosage titration flexibility, particularly in the renal or hepatic impaired, elderly and small size people. The safety profile observed in this clinical program was similar to that seen with the well recognized safety profile for sustained release dosage forms of verapamil HCl.

I recommend an approval of Verapamil PM, Extended Release Capsules 100mg, 200mg, and 300mg, once a day at nighttime for the treatment of essential hypertension.

Submitted Draft Labeling for Verapamil PM is acceptable.
The draft Labeling for Verapamil PM is identical to the Calan®SR capsules (Searle) / Verelan®SR (Elan) except the followings:

- Added a table of adverse reactions to orally administered Verapamil PM at rates of 2.0% or greater or occurred at lower rates but appeared to be drug-related in clinical trials in hypertension Studies -001 and -002

and

- DESCRIPTION, DOSAGE AND ADMINISTRATION and HOW SUPPLIED for the Verapamil PM.

cc: Original
cc: HFD-110
cc: HFD-110 Project Manager
cc: HFD-110 LipickyR
cc: HFD-110 GainleyC
cc: HFD-110 ChunS