CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-818

MEDICAL REVIEW(S)

DIOVAN HCT

NOV 5 1997

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

NDA 20-818
Name of Drug : DIOVAN HCT (valsartan and hydrochlorothiazide, UPS)
Sponsor : Novartis Pharmaceuticals
Type of Submission : Original Package Insert
Date of Submission: 3/28/97
Date of Review : 11/05/97
Reviewer : Sughok K. Chun, MD 11/05/97

Medical Comments for the **package Insert** :

* Page 010, Line 209 -211
"...the effect of valsartan appeared to be maintained for up to two years"
changed to
"...the effect of valsartan appeared to be maintained for up to two years studied."

* Page 011, Line 267-269
"...the effect of the combination of valsartan and hydrochlorothiazide appeared to be maintained for up to two years"
changed to
"...the effect of the combination of valsartan and hydrochlorothiazide appeared to be maintained for up to two years studied."

* Page 012, Line 314-316
"when patients become pregnant, physician should advise the patient to discontinue the use of Diovan HCT as soon as possible."
changed to
"when patients become pregnant, physician should advise the patient to discontinue the use of Diovan HCT as soon as possible."

* Page 013, Line 336-337
"... or dialysis may be required as means of reversing hypotension ...."
delete
" dialysis".
Versartan is not removed from the plasma by dialysis (page 024, line 838) and the degree to which HCTZ is removed by hemodialysis has not been established (page 025, line 859-860).

* Page 026, Line 912-913
" ...blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased."
change
3 weeks to 4 weeks.
Page 026, line 918-919 and page 011, line 263 stated the maximal antihypertensive effect is attained about 4 weeks after initiation of therapy.

cc: Original
cc: HFD-110
cc: HFD-110 Project Manager
cc: HFD-110 GanleyC
cc: HFD-110 ChunS

MAY 23 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)
MEDICAL OFFICER'S REVIEW (2)

NDA # 20-818
Name of Drug: **Diovan HCT**

Sponsor: Novartis Pharmaceuticals
Type of Submission: Original
Date of Submission: March 28, 1997
Date Received: April 01, 1997
Date of Review : May 05, 1997 - May 23, 1997
Reviewer : Sughok K. Chun, M.D.

5/23/97

ADDENDUM TO MEDICAL REVIEW OF EFFICACY

Protocol 28: Randomized, double-blind, parallel group trial comparing the tolerability of titrated doses of VALSARTAN to titrated doses of LISINOPRIL both given once daily in elderly patients with essential HTN treated for 52 week (UK). vol 1.74.

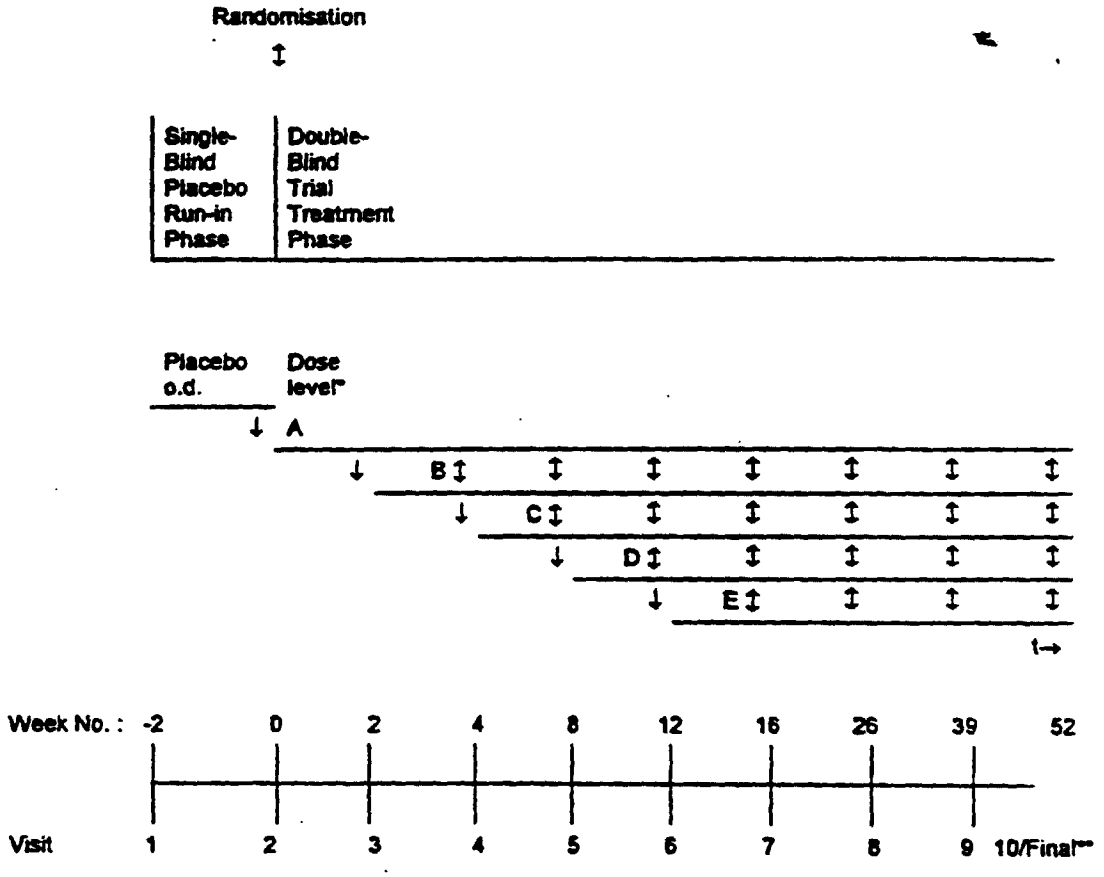
Objectives:

Primary aim : to compare the systemic tolerability of valsartan to lisinopril both given once a daily in elderly pts with essential HTN.
Secondary aim: to compare the efficacy profiles.

Design: Protocol 28 was a double-blind, active controlled trial of 52 wks duration comparing valsartan to lisinopril in elderly pts (≥65 yrs old). Pts with a mean siDBP between 96 and 110 mmHg were randomized in a 2:1 ratio to receive a starting dose of valsartan 40 mg or lisinopril 2.5 mg once daily. Medication could be titrated upwards, depending on siDBP. At Wks 2 or 4, the valsartan dose could be increased to valsartan 80 mg. At Week 2, the lisinopril dose could be increased to lisinopril 10 mg and at Week 4, to lisinopril 20 mg. At Weeks 8 and 12, open-label HCTZ 12.5 mg and 25 mg, respectively, could be added. Pts could remain on the same dose level or be back titrated to the next lower level if there were any concerns regarding safety. Efficacy and safety data from an interim report of Protocol 28 were included in the valsartan monotherapy **NDA 20-665** submission (vol. 1.200; Dr.Ganley's. review pages 102 -105).

The trial design is shown Figure 28-1.

Figure 28-1 : The trial design



* Dose level A: valsartan 40 mg or lisinopril 2.5 mg

Dose level B: valsartan 80 mg or lisinopril 10 mg

Dose level C: valsartan 80 mg or lisinopril 20 mg

Dose level D: valsartan 80 mg + hydrochlorothiazide 12.5 mg

or

lisinopril 20 mg + hydrochlorothiazide 12.5 mg

Dose level E: valsartan 80 mg + hydrochlorothiazide 25 mg

or

lisinopril 20 mg + hydrochlorothiazide 25 mg.

** Week 52 or in the event of premature discontinuation

To gather additional long-term data on valsartan/HCTZ, Protocol 28 was amended to include and additional 1 yr treatment period. Pts receiving either valsartan or lisinopril in combination with HCTZ in the core trial were eligible to enter the extension trial. Valsartan and lisinopril were administered in d/b fashion while the HCTZ was administered open-label. The efficacy analysis is shown in the study **Protocol 28E.**

Protocol 20: Multi-center, randomized, double-blind, between pts trial comparing the efficacy of VALSARTRAN 80 mg once daily to ENALPRIL 20 mg once daily in pts with uncomplicated essential HPT treated for 8 weeks and to assess and compare the tolerability of both drugs as monotherapy and in combination with HCTZ 12.5 mg once daily (France).

This study was submitted in NDA 20-665 and reviewed by DR. Charles Ganley (pages 93 - 96).

This trial was an active control study in d/b fashion and HCTZ could be added in open fashion for additional BP control. In the analysis of this study the pts receiving valsartan / HCTZ were not analyzed separately from the monotherapy group; therefore efficacy cannot be assessed for combination of valsartan/HCTZ vs. monotherapy.

INTEGRATED SUMMARY OF EFFICACY (ISE) vol. 1.88

This submission for valsartan in combination with HCTZ is comprised of 8 clinical trials conducted in pts with essential HTN; 2 controlled trials and 6 uncontrolled trials. The efficacy was evaluated in 5 of these trials. There was one placebo-controlled trial, **Protocol 301**, and one trial performed with an active control, **Protocol 19**.

Two trials were performed in which valsartan monotherapy was compared to an active control in d/b fashion and HCTZ could be added in open fashion for additional BP control, **Protocols 20 and 28.** In the analysis of these trials the pts receiving valsartan in combination with HCTZ were not analyzed separately from the monotherapy group; therefore efficacy cannot be assessed for the combination of valsartan/HCTZ.

Three trials were performed as **open-label extensions** of controlled valsartan monotherapy trials in which HCTZ could be added in open fashion for additional BP control, **Protocols 11E, 28E, and 31E**; the primary objective in these trials was safety and tolerability. These trials also contribute supportive evidence of long-term efficacy.

One trial was performed to assess the safety and tolerability of valsartan in hypertensive pts with volume depletion **(Protocol 24)**; a fixed combination of HCTZ and triamterene was

administered as background therapy to induce volume depletion. In this trial valsartan was administered as a single dose and efficacy of the combination cannot be assessed.

The primary measure of efficacy used in this clinical program was the change from baseline sitting DBP. BP was measured at trough 23-26 hrs post-dose. The results of the sit systolic BP generally paralleled the results observed with the primary measures of siDBP efficacy. Responder rates were also calculated for both controlled trials. For these trials, a successful responder was defined as a pt whose mean siDBP was < 90 mmHg or whose decrease in mean siDBP from baseline was ≥ 10 mmHg. The analyses were performed at endpoint (last available post-baseline BP carried forward).

Protocol 301, a double-blind, placebo controlled, multifactorial trial. After withdrawal of previous antihypertensive medication for at least 2 wks, pts entered a single-blind placebo run-in period for 2-4 wks. Pts were then randomized to receive 1 of 9 treatments (placebo, valsartan 80mg, valsartan 160mg, HCTZ 12.5mg, HCTZ 25mg, valsartan 80mg/HCTZ 12.5mg, valsartan 80mg/HCTZ 25mg, valsartan 160mg/HCTZ 12.5mg, or valsartan 160mg/HCTZ 25mg) once daily, irrespective of meals for 8 weeks. BP was measured in the clinic at baseline and treatment Weeks 2, 4 and 8.

871 pts randomized and 792 pts completed the trial. There were 865 pts included in the primary efficacy analysis at endpoint (6 randomized pts had no post-baseline BP measurements). There were no statistically significant differences in demographic or baseline characteristics between the treatment groups.

The least squares means of the changes from baseline in mean siDBP at endpoint are presented **Table 301-7**; the results of between-treatment comparisons for change from baseline in mean siDBP at endpoiint **Table 301-8**; the least squares mean change from baseline in mean at endpoint **Table 301-13**; the results of the between-treatment comparisons for change from baseline in mean siSBP **Table 301-14.** The percentage of pts with a successful response at trial endpoint and the results of the treatment comparisons are displayed **Tables 301-11 and -12.**

The study showed that all the combination treatments were more effective in comparison with the monotherapies in reducing mean siDBP at any point. The fitted response surface predics the reduction of mean sitDBP increases as the dose of the monotherapies increases while the other being fixed, indicating that both monotherapies contribute to the efficacy of the combination therapies, and there is a positive dose response for both monotherapies.

It was concluded that valsartan 80 mg and valsartan 160 mg in combination with HCTZ 12.5 mg or 25 mg has an added effect over component in lowering BP in pts with essential HTS.

administered as background therapy to induce volume depletion. In this trial valsartan was administered as a single dose and efficacy of the combination cannot be assessed.

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It was concluded that valsartan 80 mg and valsartan 160 mg in combination with HCTZ 12.5 mg or 25 mg has an added effect over component in lowering BP in pts with essential HTS.

Protocol 19 (nonresponders to valsartan) is a randomized, d/b, active-controlled, parallel design trial. After withdrawal of previous antihypertensive medication for at least 2 wks, pts entered a 2 wk single-blind placebo run-in period, followed by a 4 wk single-blind valsartan (80 mg once daily) run-in period. After 4 wks of treatment with valsartan 80 mg, pts whose mean siDBP was not adequately controlled (i.e. mean siDBP ≥ 95 mmHg) were randomized to one of four d/b treatment groups for a period of 8 wks : valsartan 80 mg, valsartan 160 mg, valsartan 80 mg / HCTZ 12.5 mg and valsartan 80 mg / HCTZ 25 mg once daily. .Trial medication was administered irrespective of meals.

781 pts were randomized, 631 pts completed the trial, and 702 pts were included in the primary efficacy analysis at endpoint. Six pts had no post-baseline BP measurements and were excluded from the primary efficacy endpoint analysis.

The least squares means of the changes from baseline in mean siDBP and siSBP at endpoint and pairwise comparisons are presented table ISE-1 and ISE-2 respectively.

Table ISE-1 (protocol 19)

Least Squares Mean Change from Baseline in Sitting BP (mmHg) at Endpoint			
Treatment Group	N	Diastolic	Systolic
Valsartan 80 mg	179	-5.1	-3.9
Valsartan 160 mg	171	-6.2	-6.5
Valsartan 80 mg/HCTZ 12.5 mg	176	-8.2	-9.8
Valsartan 80 mg/HCTZ 25 mg	176	-10.8	-16.0

Table ISE-2 (protocol 19)

Results of the Between Treatment Comparisons for Mean Change from Baseline in Sitting BP (mmHg) at Endpoint				
	Diastolic		Systolic	
Treatment comparison	Difference (mmHg)	p-value	Difference (mmHg)	p-value
Valsartan 160 mg vs Valsartan 80 mg	-1.1	0.2207	-2.7	0.0610
Valsartan 80 mg/HCTZ 12.5 mg vs Valsartan 80 mg	-3.2	0.0002*	-5.9	< 0.0001*
Valsartan 80 mg/HCTZ 25 mg vs Valsartan 80 mg	-5.8	<0.0001*	-12.1	< 0.0001*
Valsartan 80 mg/HCTZ 12.5 mg vs Valsartan 160 mg	-2.1	0.0173*	-3.2	0.0234*
Valsartan 80 mg/HCTZ 25 mg vs Valsartan 160 mg	-4.7	<0.0001*	-9.5	< 0.0001*
*Statistically significant ($p < 0.025$)				

The percentage of pts with a successful response at the trial endpoint is displayed tables ISE-3 and ISE-4.

Table ISE-3 (protocol 19)

Percentage of Patients with a Successful Response	
Treatment group	Endpoint
Valsartan 80 mg	35.8%
Valsartan 160 mg	36.8%
Valsartan 80 mg/HCTZ 12.5 mg	50.6%
Valsartan 80 mg/HCTZ 25 mg	59.1%

Table ISE-4 (protocol 19)

Results of the Between Treatment Comparisons for the Proportion of Patients Achieving a Successful Response at Endpoint	
Treatment group	Endpoint
Valsartan 160 mg vs Valsartan 80 mg	0.8324
Valsartan 80 mg/HCTZ 12.5 mg vs Valsartan 80 mg	0.0050*
Valsartan 80 mg/HCTZ 25 mg vs Valsartan 80 mg	<0.0001*
Valsartan 80 mg/HCTZ 12.5 mg vs Valsartan 160 mg	0.0102*
Valsartan 80 mg/HCTZ 25 mg vs Valsartan 160 mg	<0.0001*
*Statistically significant (p<0.025)	

The study showed valsartan 80 mg in combination with HCTZ 12.5 mg or 25 mg was effective in lowering mean siDBP in pts who did not adequately respond to valsartan 80 mg once daily. No additional clinically significant efficacy was achieved in this same population treated with 160 mg once daily.

Onset of Antihypertensive Effect

The raw mean reductions in DBP by week in two trials **(protocols 301 and 19)** are summarized table ISE-5.

Table ISE-5 (protocols 301 & 19)

Raw Mean Change in mean siDBP (mmHg) from Baseline at Selected Times (Protocol 301)				
	Week of Active Treatment			
Treatment Group	2	4	8	Endpoint*
Placebo	-3.3	-5.4	-4.7	-4.0
Valsartan 80 mg	-6.7	-9.3	-9.2	-8.3
Valsartan 160 mg	-8.7	-11.0	-10.7	-10.4
HCTZ 12.5 mg	-6.6	-7.8	-7.4	-7.6
HCTZ 25 mg	-7.9	-8.9	-9.7	-9.1
Valsartan 80 mg/ HCTZ 12.5 mg	-9.9	-11.3	-12.1	-12.1
Valsartan 80 mg/ HCTZ 25 mg	-12.1	-14.5	-15.1	-14.8
Valsartan 160 mg/ HCTZ 12.5 mg	-11.5	-15.0	-13.6	-13.5
Valsartan 160 mg/ HCTZ 25 mg	-13.3	-16.2	-16.3	-16.1
*Last available post-baseline blood pressure carried forward				
Raw Mean Change in siDBP (mmHg) from Baseline at Selected Times (Protocol 19)				
	Week of Active Treatment			
Treatment Group	2	4	8	Endpoint*
Valsartan 80 mg	-5.2	-5.8	-5.4	-5.3
Valsartan 160 mg	-5.4	-6.6	-5.9	-5.7
Valsartan 80 mg/ HCTZ 12.5 mg	-6.8	-8.4	-8.8	-7.9
Valsartan 80 mg/ HCTZ 25 mg	-8.1	-9.9	-10.8	-10.4

These data demonstrate that during repeated dose-therapy with valsartan/HCTZ, maximal reductions in siDBP were generally achieved within 4 wks of the initiation of therapy.

Efficacy and Dose Response

Two d/b, controlled trials have demonstrated the efficacy of valsartan/HCTZ administered once daily in the treatment of essential HTS; Protocol 301 (placebo controlled) and Protocol 19 (active controlled).

Protocol 19 was a trial conducted in a selected population, i.e. pts with an inadequate response to valsartan 80 mg during a 4-wk, single-blind, dosing period; and Protocol 301 was the definitive dose-response, multifactorial trial (pivotal study). Combinations of valsartan 80 mg with HCTZ were studied in both trials. Protocol 301 also studied combinations of valsartan 160 mg with HCTZ.

Table ISE-6 summarizes the least squares means of the changes from baseline in trough siDBP at endpoint. The data presented from Protocol 301 has the placebo effect subtracted.

Table ISE-6 (protocols 301 & 19)

Least Squares Mean Change from Baseline in mean siDBP (mmHg) at Endpoint		
Protocol Double-Blind Treatment Duration	301* 8 weeks	19 8 weeks
Valsartan 80 mg	-4.5 (n=99)[1]	-5.1 (n=183)
Valsartan 160 mg	-5.3 (n=97)[1]	-6.2 (n=172)
HCTZ 12.5 mg	-3.0 (n=99)[1]	-
HCTZ 25 mg	-5.2 (n=100)[1]	-
Valsartan 80 mg/HCTZ 12.5 mg	-7.7 (n=96)[1,2,4]	-8.2 (n=176)[2,3]
Valsartan 80 mg/HCTZ 25 mg	-11.2 (n=91)[1,2,5]	-10.8 (n=177)[2,3]
Valsartan 160 mg/HCTZ 12.5 mg	-9.4 (n=96)[1,3,4]	-
Valsartan 160 mg/HCTZ 25 mg	-11.2 (n=94)[1,3,5]	-

*Placebo response in Protocol 301 = -4.1 mmHg (n=93);

the least squares means from Protocol 301 have the placebo effect subtracted.

[1] statistically significant compared to placebo, $p<0.025$
[2] statistically significant compared to valsartan 80 mg, $p<0.025$
[3] statistically significant compared to valsartan 160 mg, $p<0.025$
[4] statistically significant compared to HCTZ 12.5 mg, $p<0.025$
[5] statistically significant compared to HCTZ 25 mg, $p<0.025$

Table ISE-7 summarizes the least squares means of the changes from baseline in trough systolic BP at endpoint. The data presented from Protocol 301 has the placebo effect subtracted.

Table ISE-7 (protocols 301 & 19)

Least Squares Mean Change from Baseline in mean siSBP (mmHg) at Endpoint		
Protocol Double-Blind Treatment Duration	301* 8 weeks	19 8 weeks
Valsartan 80 mg	-6.9 (n=99)[1]	-3.9 (n=179)
Valsartan 160 mg	-10.2 (n=97[1])	-6.5 (n=171)
HCTZ 12.5 mg	-5.4(n=99)[1]	-
HCTZ 25 mg	-10.8 (n=100)[1]	-
Valsartan 80 mg/HCTZ 12.5 mg	-14.6 (n=96)[1,2,4]	-9.8 (n=176)[2,3]
Valsartan 80 mg/HCTZ 25 mg	-19.2 (n=91)[1,2,5]	-16.0 (n=176)[2,3]
Valsartan 160 mg/HCTZ 12.5 mg	-15.8 (n=96)[1,3,4]	-
Valsartan 160 mg/HCTZ 25 mg	-20.5 (n=94)[1,3,5]	-

*Placebo response in Protocol 301 = -1.9 mmHg (n=93);

the least squares means from protocol 301 have the placebo effect subtracted.

[1] statistically significant compared to placebo, $p<0.025$
[2] statistically significant compared to valsartan 80 mg, $p<0.025$
[3] statistically significant compared to valsartan 160 mg, $p<0.025$
[4] statistically significant compared to HCTZ 12.5 mg, $p<0.025$
[5] statistically significant compared to HCTZ 25 mg, $p<0.025$

The pattern of response observed in the reduction of DBP was also seen with SBP.

The proportion of pts with a successful response (mean siDBP < 90 mmHg or a reduction of $\geq$ 10 mmHg from baseline) at trial endpoint is summarized table ISE-8.

Table ISE-8 (protocols 301 & 19)

Proportion of Patients with a Successful Response at Endpoint		
Protocol Double-Blind Treatment Duration	301 8 weeks	19 8 weeks
Placebo Response	29% (n=93)	-
Valsartan 80 mg	54% (n=99)[1]	35.8% (n=179)
Valsartan 160 mg	59% (n=97)[1]	36.8% (n=171)
HCTZ 12.5 mg	41% (n=99)[1]	-
HCTZ 25 mg	54% (n=100)[1]	-
Valsartan 80 mg/HCTZ 12.5 mg	64% (n=96)[1,4]	50.6% (n=176)[2,3]
Valsartan 80 mg/HCTZ 25 mg	81% (n=91)[1,2,5]	59.1% (n=176)[2,3]
Valsartan 160 mg/HCTZ 12.5 mg	76% (n=96)[1,3,4]	-
Valsartan 160 mg/HCTZ 25 mg	81% (n=94)[1,3,5]	-

[1] statistically significant compared to placebo, $p<0.025$
[2] statistically significant compared to valsartan 80 mg, $p<0.025$
[3] statistically significant compared to valsartan 160 mg, $p<0.025$
[4] statistically significant compared to HCTZ 12.5 mg, $p<0.025$
[5] statistically significant compared to HCTZ 25 mg, $p<0.025$

Four doses of valsartan/HCTZ were evaluated in Protocol 301, a placebo controlled trial in an unselected population; two doses were evaluated in Protocol 19, an active controlled trial in a selected population of pts with an inadequate response to valsartan 80 mg monotherapy.

In Protocol 301 all doses of valsartan/HCTZ showed statistically significant reductions in diastolic and systolic BP in comparison to placebo. Additionally, all doses of the combination showed statistically significantly greater reductions in BP at endpoint, compared to the respective components. This confirms the contribution of both components to the efficacy of the combination.

In Protocol 19, the doses of valsartan 80 mg/HCTZ showed statistically significantly greater reductions in BP compared to valsartan 80 mg monotherapy; thus confirming that the addition of HCTZ 12.5 mg or 25 mg in pts with an inadequate response to valsartan 80 mg provides additional efficacy.

Subgroups/Special patient population analysis

In the two controlled trials (protocols 301 & 19) assessing the efficacy of valsartan/HCTZ, subgroup analyses of the primary efficacy variable by age, race, and sex were performed. While no rigorous statistical analysis was done, summary statistics were performed.

Sex :

Table ISE-9 displays the raw mean change from baseline in mean siDBP by sex in Protocols 301 and 19 at endpoint.

Table ISE-9 (protocols 301 & 19)

Raw Mean Change from Baseline in mean siDBP (mmHg) by Sex at Endpoint				
	Protocol 301		Protocol 19	
Treatment Group	Female	Male	Female	Male
Placebo	-2.5 (n=35)	-4.9 (n=58)	-	-
Valsartan 80 mg	-9.3 (n=36)	-7.7 (n=63)	-5.4 (n=66)	-5.2 (n=113)
Valsartan 160 mg	-12.1 (n=37)	-9.3 (n=60)	-7.3 (n=62)	-4.8 (n=109)
HCTZ 12.5 mg	-10.2 (n=42)	-5.6 (n=57)	-	-
HCTZ 25 mg	-10.4 (n=45)	-8.0 (n=55)	-	-
Valsartan 80 mg/HCTZ 12.5 mg	-11.4 (n=38)	-12.5 (n=58)	-8.0 (n=59)	-7.8 (n=117)
Valsartan 80 mg/HCTZ 25 mg	-16.0 (n=44)	-13.7 (n=47)	-12.6 (n=53)	-9.4 (n=123)
Valsartan 160 mg/HCTZ 12.5 mg	-14.7 (n=38)	-12.6 (n=58)	-	-
Valsartan 160 mg/HCTZ 25 mg	-18.2 (n=43)	-14.1 (n=51)	-	-

These data demonstrate that valsartan/HCTZ is effective in both males and females.

Age :

Table ISE-10 displays the raw mean change from baseline in mean siDBP by age in Protocols 301 and 19 at endpoint.

Table ISE-10 (protocols 301 & 19)

Raw Mean Change from Baseline in mean siDBP (mmHg) by Age at Endpoint				
	Protocol 301		Protocol 19	
Treatment Group	< 65	≥ 65	< 65	≥ 65
Placebo	-4.0 (n=85)	-3.8 (n=8)	-	-
Valsartan 80 mg	-7.8 (n=86)	-11.3 (n=13)	-5.2 (n=152)	-5.5 (n=27)
Valsartan 160 mg	-10.2 (n=82)	-11.6 (n=15)	-5.5 (n=145)	-6.9 (n=26)
HCTZ 12.5 mg	-7.0 (n=82)	-10.1 (n=17)	-	-
HCTZ 25 mg	-8.7 (n=87)	-11.8 (n=13)	-	-
Valsartan 80 mg/HCTZ 12.5 mg	-12.2 (n=82)	-11.4 (n=14)	-7.6 (n=151)	-9.6 (n=25)
Valsartan 80 mg/HCTZ 25 mg	-14.5 (n=80)	-16.9 (n=11)	-9.7 (n=141)	-13.2 (n=35)
Valsartan 160 mg/HCTZ 12.5 mg	-13.1 (n=81)	-15.2 (n=15)	-	-
Valsartan 160 mg/HCTZ 25 mg	-17.2 (n=77)	-11.1 (n=17)	-	-

Race :

Table ISE-11 displays the raw mean change from baseline in mean siDBP by race in Protocols 301 and 19 at endpoint. The subgroup "other" is comprised of pts of Hispanic, Asian or other origin.

Table ISE-11 (protocols 301 & 19)

	Raw Mean Change from Baseline in mean siDBP (mmHg) by Race at Endpoint		
Treatment Group	Protocol 301		
	White	Black	Other
Placebo	-4.5 (n=70)	-0.2 (n=13)	-5.2 (n=10)
Valsartan 80 mg	-9.0 (n=75)	-6.3 (n=15)	-6.2 (n=9)
Valsartan 160 mg	-10.5 (n=75)	-8.6 (n=12)	-11.5 (n=10)
HCTZ 12.5 mg	-7.5 (n=65)	-8.3 (n=22)	-6.7 (n=12)
HCTZ 25 mg	-9.1 (n=77)	-10.6 (n=11)	-7.6 (n=12)
Valsartan/HCTZ 80/12.5	-12.1(n=69)	-11.2 (n=12)	-12.4 (n=15)
Valsartan/HCTZ 80/25	-15.1 (n=71)	-12.9 (n=9)	-14.2 (n=11)

Valsartan/HCTZ 160/12.5	-14.3 (n=78)	-10.3 (n=10)	-9.0 (n=8)
Valsartan/HCTZ 160/25	-16.5 (n=68)	-18.4 (n=15)	-10.7 (n=11)
	Protocol 19		
Valsartan 80 mg	-5.6 (n=127)	-4.5 (n=28)	-4.5 (n=24)
Valsartan 160 mg	-6.3 (n=123)	-2.2 (n=23)	-6.0 (n=25)
Valsartan/HCTZ 80/12.5	-8.1 (n=121)	-8.6 (n=29)	-5.7 (n=26)
Valsartan/HCTZ 80/25	-11.1 (n=125)	-9.1 (n=25)	-8.1 (n=26)

These data demonstrate that valsartan/HCTZ is an effective antihypertensive agent in all races studied

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Three trials were performed as open-label extensions of controlled valsartan monotherapy trials in which HCTZ could be added in open fashion for additional BP control, Protocols 11E, 28E, and 31E; the primary objective in these trials was safety and tolerability.

Protocol 11E

Protocol 11E was the open label extension to Protocol 11. Protocol 11 was a randomized, d/b, placebo-controlled, fixed-dose, parallel design trial that assessed the efficacy and safety of once-daily valsartan (20, 40, and 80 mg) for 6 wks in white pts with essential HTS (mean siDBP 95-115 mmHg, inclusive). White pts were selected for this trial for European registration purposes. This trial was conducted in the United States; the data from this core trial was included in the valsartan monotherapy NDA #20-665 (see Dr. Ganley's review pages 39 - 44).

After 6 wks of d/b therapy in the core trial, pts entered an open-label extension phase with all pts receiving valsartan 20 mg once daily. Pts were titrated at 2 wk intervals to valsartan 40 mg and then valsartan 80 mg if BP was not controlled (mean siDBP $\geq$ 90 mmHg). Pts whose BP was still not controlled had HCTZ 12.5 mg and 25 mg once daily added to their regimen at the extension wk 6 visit. The duration of the entire open-label period, including dose-titration, was to be 98 wks.

Protocol 11E-first year:

A total of 399 pts were enrolled into the first yr open-label extension. Of those enrolled, 253 completed the 1st yr extension. During the extension phase, 214 (53.6%) pts were treated

with valsartan monotherapy alone. A total of 253 (63.4%) pts required titration to at least valsartan 80 mg at some point during the trial in order to maintain BP control. A total of 185 (46.4%) pts required the addition of HCTZ.

The mean changes from baseline in trough mean sitting DBP are summarized table ISE-12.

Table ISE-12 (protocol 11E, first year)

	Mean Change From Baseline In Trough Sitting DBP (mmHg)			
Extension Week	All extension patients treated with valsartan monotherapy alone		All extension patients ever treated with valsartan/ HCTZ combination	
	N	Mean	N	Mean
2	209	-10.2	185	-4.5
4	204	-12.5	185	-6.5
6	194	-13.0	185	-8.0
10	180	-14.5	184	-9.5
14	176	-13.6	179	-10.2
22	170	-12.9	173	-10.5
30	159	-13.0	162	-10.6
38	149	-13.5	148	-11.1
46	138	-14.3	140	-12.7
58	131	-13.4	133	-11.9

Protocol 11E-second year:

A total of 253 pts were enrolled in the 2nd-yr open-label extension; 123 pts (48.6%) were treated with valsartan monotherapy alone and 130 (51.4%) were treated with valsartan/HCTZ at some point during this extension trial.

The mean changes from baseline in trough siDBP by week are presented table ISE-13.

Table ISE-13 (protocol 11E, second year)

	Mean Change From Baseline In Trough siDBP (mmHg)			
Extension Week	All extension patients treated with valsartan monotherapy alone		All extension patients ever treated with valsartan/ HCTZ combination	
	N	Mean	N	Mean
58	123	-14.1	130	-11.9
70	123	-13.2	127	-12.5
82	120	-13.2	121	-12.3
98	110	-12.4	114	-11.8

11E-third year:

A total of 73 pts were enrolled in the 3rd yr extension trial. All of these pts (100%) were receiving valsartan 80 mg in combination with HCTZ.

The mean changes from baseline in trough siDBP by week are presented in table ISE-14.

Table ISE-14 (protocol 11E, third year)

Mean Change from Baseline in Trough Sitting Diastolic BP		
Extension Week	N	
98	73	-12.2
114	73	-12.5
130	72	-12.1
146	68	-12.6

For the three year duration of this open-label extension trial, pts treated with valsartan/HCTZ had reductions in mean siDBP > 10 mmHg at all timepoints, with no evidence of tolerance.

Protocol 28E:

Protocol 28E was an extension trial to Protocol 28. Protocol 28 was a d/b, active controlled trial of 52 wks duration comparing valsartan to lisinopril in elderly pts (≥65 years old).

To gather additional long-term data on valsartan/HCTZ, Protocol 28 was amended to include additional 1 yr treatment period. Pts receiving either valsartan or lisinopril in combination with HCTZ in the core trial were eligible to enter the extension trial. Valsartan and lisinopril were administered in d/b fashion while the HCTZ was administered open-label.

A total of 69 pts entered this extension trial, 48 receiving valsartan/HCTZ and 21 receiving lisinopril /HCTZ. The mean changes from baseline in sitDBP are summarized table ISE-15.

Table ISE-15 (protocol 28E)

Mean Change from Baseline in mean siDBP (mmHg)				
	Valsartan/HCTZ		Lisinopril/HCTZ	
Treatment Week	N	Mean change	N	Mean change
12[1]	48	-13.4	21	-12.1
52	48	-16.6	21	-17.1
72	43	-17.1	19	-19.1
96 endpoint[2]	48	-15.3	21	-17.1

[1] 19 (39.6%) of valsartan pts and 8 (38.1%) of lisinopril pts were not receiving HCTZ prior to this visit.

[2] Last available blood pressure measurement carried forward

The proportion of pts considered responders are displayed in the table ISE-16.

Table ISE-16 (protocol 28E)

Proportion of Patients with a Successful Response		
Treatment Week	Valsartan/HCTZ N (%)	Lisinopril/HCTZ N (%)
12[1]	37 (77%)	14 (67%)
52	45 (94%)	21 (100%)
72	45 (98%)	19 (100%)
96 endpoint[2]	41 (85%)	20 (95%)

[1] 19 of valsartan pts and 8of lisinopril pts were not receiving HCTZ prior to this visit.

[2] Last available blood pressure measurement carried forward

Protocol 31E:

Protocol 31E was the open-label extension to Protocol 31. Protocol 31 was a randomized, d/b, placebo-controlled, fixed-dose, parallel design trial that assessed efficacy and safety of once-daily valsartan (20, 80, 160, and 320 mg) for 8 wks pts with essential HTN (mean siDBP 95-115 mmHg). The data from this core trial was included in NDA #20-665 (Dr. Ganley's review pages 57 - 70).

After 8 wks of d/b therapy in Protocol 31, pts at selected centers entered an open-label extension phase with all pts receiving valsartan 160 mg once daily. In pts whose BP control was inadequate at any time after 4 wks of valsartan 160 mg, HCTZ 12.5 mg or 25 mg once daily could be added. The total duration of this extension trial was 52 wks.

A total of 376 pts enrolled in this open-label extension trial. Of those enrolled, 291 completed the extension trial. During the extension phase, 179 (47.6%) pts were treated with valsartan monotherapy alone and 197 (52.4%) required the addition of HCTZ.

The mean changes from baseline in trough mean siDBP are summarized ISE-17.

Table ISE-17 (protocol 31E)

Mean Changes from Baseline in Trough mean siDBP (mmHg) by Visit				
Extension Week	Valsartan Monotherapy		Valsartan/HCTZ	
	N	Mean	N	Mean
4[1]	177	-13.1	197	-6.4
8	159	-15.0	197	-10.7
16	150	-13.7	183	-11.4
28	145	-14.4	171	-12.7
40	143	-14.3	162	-14.5
52	138	-14.1	156	-14.2

[1] First visit at which HCTZ could be dispensed.

Conclusions

Based on the 2 controlled (Protocols 301 and 19) and 3 uncontrolled trials (Protocols 11E, 28E, and 31E) in which the efficacy of the combination of valsartan/HCTZ was evaluated, the following conclusions can be drawn regarding the efficacy of valsartan/HCTZ in the treatment of essential hypertension:

- The maximum effect of valsartan/HCTZ occurs within 4 wks of the onset of therapy. (Protocols 19 and 301)

- The antihypertensive effect of valsartan/HCTZ persists over 24 hrs. (Protocols 19 and 301)
- Valsartan/HCTZ is effective in doses of 80/12.5 mg to 160/25 mg. (Protocols 19 and 301)
- Both components contribute to the antihypertensive efficacy of the combination. (Protocol 301)
- There is a positive dose-response when the dose of one or both components is increased. (Protocol 301)
- Valsartan/ HCTZ is effective in pts with an inadequate response to valsartan monotherapy. (Protocols 19, 11E, 28E, and 31E)
- Valsartan/HCTZ is effective in both male and female patients, younger and older patients, and in all racial subgroups. (Protocols 19 and 301)

Valsartan/HCTZ is effective in the long-term treatment of hypertension without evidence of tolerance. (Protocols 11E, 28E, 31E)

cc: original
cc: HFD-110
cc: HFD-110 project manager
cc: HFD-110 GanleyC
cc: HFD-110 WilliamsA
cc: HFD-110 Chuns
cc: HFD-710 NuriW

MAY 5 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD110)
MEDICAL OFFICER'S REVIEW

NDA # 20-818
Name of Drug: **DIOVAN HCT** Tablets (valsartan hydrochlothiazide)

Sponsor: Novartis Pharmaceuticals Corporation, East Hanover, New Jersy
Type of Submission: Original
Date of Submission: March 28, 1997
Date Received: April 01, 1997
Date of Review : 4/15/97 - 4/30/97
Reviewer : Sughok K. Chun, M.D. 5/5/97

This is a medical review of efficacy data. The safety review shall be done by Akinwole Williams, M.D., HFD-110. This NDA is accompanied by a CANDA (one CD-ROM).

General Information
Name of Drug
Generic : valsartan and hydrochlorothiazide (HCTZ)
Trade : Diovan HCT
Pharmacologic Catagory: Angiotensin II Receptor Antagonist (AT1 subtype) and diuretic.
Dosage Form: 80 mg/ 12.5 mg
160 mg/ 12.5 mg
Route of Administration: Oral
Related Drugs: valsartan, losartan, hydrochlorothiazide (HCT)

Table 1 listed controlled trials and Table 2 for uncontrolled trials. There are only 2 controlled clinical studies. The study **protocol 19** was reviewed by Charles Ganley, M.D. 10/4/96 (Medical Review of NDA 20-665, pages 88 - 93). This efficacy review is for only the study protocol 301 and abbreviate review of the protocol 19. The protocols **11E** and **31E** are extention studies of Protocols 11 and 31 in the NDA 20-665 for valsartan respectively and they are not considered as the controlled studies.

Table 1 Summary of Controlled Trials

Location CTR Data Listing CRF	Protocol no.	Study design. Diagnosis / criteria for inclusion	Drug dose (mg) Regimen	Duration (weeks)	No. of patients (m/f)	No. W/B/O	Age (mean per group)	Results	Number of patients in ISS and % with adverse events
NDA 20-665 1.159/1 1.165/2 1.278/1	19 USA Start:13Apr94 End:25Jan95	Double-blind Multi-center Parallel SDBP: ≥95-≤120 mmHg	placebo run-in	2	1038			Least sq mean change in MSDBP (endpoint)	N %
			valsartan 80 OD	4(run-in)	914				
			valsartan 80 OD	8	183(116/67)	131/28/24	52.9	-5.1	179 50%
			valsartan 160 OD	8	172(109/63)	124/23/25	52.5	-6.2	172 50%
			valsartan80OD+ HCTZ 12.5 OD	8	176(117/59)	121/29/26	53.0	-8.2*	176 51%
			valsartan80 OD+ HCTZ 25 OD	8	177(124/53)	125/26/26	54.3	-10.8* *p<0.025 compared to both valsartan 80 OD and 160 OD	176 51%
			Total	14	708 (466/242)	501/106/ 101	53.2		
1.29/1 1.35/2 1.121/1	301 USA Start: 14Mar95 End: 29Nov95	Double-blind Multi-center Placebo-control Multifactorial Parallel SDBP: ≥95-≤115 mmHg	placebo run-in	2-4	997			Least sq.mean chng in MSDBP(endpoint)	
			placebo	8	94 (58/36)	70/14/10	51.6	-4.12	93 52%
			valsartan 80 OD	8	99 (63/36)	75/15/9	52.3	-8.63*	99 57%
			valsartan160 OD	8	99 (61/38)	75/13/11	52.1	-9.42*	97 43%
			HCTZ 12.5 OD	8	100 (58/42)	66/22/12	52.2	-7.16*	100 55%
			HCTZ 25 OD	8	100 (55/45)	77/11/12	52.0	-9.28*	100 54%
			valsartan 80 OD + HCTZ 12.5 OD	8	96 (58/38)	69/12/15	51.7	-11.83*#	
			valsartan 80 OD + HCTZ 25 OD	8	92 (47/45)	72/9/11	51.6	-15.28*#	
			valsartan160 OD + HCTZ 12.5 OD	8	97 (58/39)	78/11/8	52.9	-13.51*#	
	301 cpnt'd		valsartan160 OD + HCTZ 25 OD	8	94 (51/43)	68/15/11	52.6	-15.31*# *p<0.05compared	

			Total	10-12	871 (509/362)	650/122/99	52.1	to placebo *p<0.05 compared to corresponding valsartan monotherapy *p<0.05 compared to corresponding HCTZ monotherapy

Table 2 Uncontrolled Trials

Location CTR Data Listing CRF	Protocol no.	Study design. Diagnosis / criteria for inclusion	Drug dose (mg) Regimen	Duration (weeks)	No. of patients (m/f)	No. W/B/O	Age (mean per group)	Results	Number of patients in ISS and % with adverse events
								Week 58 chng from	N %
NDA 20-665 1.212/1 1.227/177 1.269/1	11Ext 1st year USA Start: 12Apr93 End: 18Jul95	Open-label Multi-center Tolerability Successful completion of core trial	valsartan 20 OD valsartan 40 OD valsartan 80 OD valsartan OD + HCTZ 12.5 OD valsartan OD + HCTZ 25 OD valsartan OD + HCTZ 50 OD	98 96 94 92 92 92	399 319 253 157 118 2			baseline MSDBP summary statistics -13.4 (valsartan combined) -11.9 (valsartan/ HCTZ combined)	395 81% 185 88%
			Total	98	399 (281/118)	399/0/0	55.0		

	Location CTR Data Listing CRF	Protocol no.	Study design. Diagnosis / criteria for inclusion	Drug dose (mg) Regimen	Duration (weeks)	No. of patients (m/f)	No. W/B/O	Age (mean per group)	Results	
NDA 20-665	11 Ext/2nd year	Open-label	valsartan 20 OD	98	41			Week 98 chng from		
2.5/1	USA	Multi-center	valsartan 40 OD	96	45			baseline MSDBP		
2.14/2	Start:16May94	Tolerability	valsartan 80 OD	94	48			-12.4 (valsartan	123	70%
2.19/2	End: 03Aug95	Successful	valsartan 20	92				combined)		
		completion of	+ HCTZ 25 OD		1					
		core trial	valsartan 80 OD	92						
		required	+ HCTZ 12.5 OD		51					
			valsartan 80 OD							
			+ HCTZ 25 OD	98	89			-11.8 (valsartan/	130	76%
								HCTZ combined)		
			Total		253(174/79)	253/0/0	54.6			
								Week 146 chng from baseline MSDBP summary statistics		
1.56/1	11 Ext 3rd year	Open-label	valsartan 80 OD	52	18(14/4)	18/0/0	52.9	-12.5	11	52.4%
1.58/1	USA	Multi-center	+ HCTZ 12.5 OD							
1.102/1	Start:19Apr95	Tolerability	valsartan 80 OD	52	55(40/15)	55/0/0	55.3	-12.6	39	70.9%
	End: 19Aug96	Successful	+ HCTZ 25 OD							
		completion of core trial required + one year on combo	Total	52	73(54/19)	73/0/0	54.7			
NDA 20-665	20	Double-blind	placebo run-in	2				Least sq. mean change in MSDBP (endpoint)	N	%
1.185/1	Prof. J.Mallion	Multi-center								
1.187/53	France	Parallel	valsartan 80 OD	8-12	94 (47/47)		56.3	-13.3	94	26%
1.282/1	Start:22Feb94	HCTZ add-on	valsartan80 OD+	4				-16.1		5%
	End: 06Sep94	SDBP:	HCTZ 12.5 OD							
		>95-<120	enalapril 20 OD	8-12	95(47/48)		59.4	-12.4	95	28%
		mmHg	enalapril20 OD+	4				-14.5		5%
	20 cont'd		HCTZ 12.5 OD							
			Total	14	189(94/95)	182/3/4	57.9			

NDA 20-665	24	Double-blind	HCTZ 50 OD/	8	60			Least sq mean max change in MSDBP	
2.2/1	Dr. Anderton	Multi-center	amiloride 5mg						
2.4/50	United Kingdom	3-way crossover							
2.4/294	Start:07Feb94	2 week washout	valsartan 80 OD	1 day	35 (10/25)	33/1/1			
	End: 06Jun95	between doses	atenolol 50 OD	1 day	35 (10/25)	33/1/1	65.2	-21.2	
		Vol. depleted	lisinopril 10 OD	1 day	35 (10/25)	33/1/1	65.2	-21.5	
		patients			35 (10/25)		65.2	-20.5	
		First dose effect SDBP: ≥96-≤119 mmHg	Total	8		33/1/1	65.2		35 51%

Protocol 301: A multipe Dose, Randomized, Double-Blind, Placebo Controlled, Multifactorial, Parallel Trial Comparing the Combination Therapy of Valsartan (80 or 160 mg) and HCTZ (12.5 or 25 mg) to Valsartan Monothreapy (80 or 160 mg), HCTZ (12.5 or 25 mg) and Placebo in Hypertensive Patients Age 18-80 Years.
vol. 1.29 & 1.30

Objectives:

The primary objective was to determine the safety and efficacy of the combination therapy valsartan/HCTZ compared to the component monotherapies and compared to placebo.

Design

This was a multiple dose, multi-center, randomized, double-blind (d/b), placebo controlled, multifactorial, parallel group comparing the combination therapy of valsartan/HCTZ, to its component monotherapies, valsartan and HCTZ, and to placebo in patients age 18-80 years with essential hypertension. Randomization into one of the nine treatment arms occurred following a two to four week placebo run-in period.

Randomization into one of the nine treatment arms occurred following a two to four week placebo run-in period [mean sitting diastolic blood pressure (siDBP) $\geq$ 95 mmHg and $\leq$ 115 mmHg].

At Visit 2, all eligible pts were randomized to one of nine treatment groups. D/B treatment medication was allocated in blocks of nine. Study design is shown table 301-1.

Table 301-1 : Trial configuration:

Period	Washout	Placebo Run-in/ Washout	Double-blind treatment Randomization ↓
	0	1	2 3 4 5
Visit Week Duration	0 -6	1 -4 2-4 weeks	2 3 4 5 0 2 4 8 8 weeks
Treatment		placebo	valsartan 80 mg valsartan 160 mg HCTZ 12.5 mg HCTZ 25 mg valsartan 80 mg/HCTZ 12.5 mg valsartan 160 mg/HCTZ 12.5 mg valsartan 80 mg/HCTZ 25 mg valsartan 160 mg/HCTZ 25 mg Placebo

Dosage / Administration

Valsartan was supplied as 80 mg and 160 mg identically appearing capsules. HCTZ 12.5 mg and 25 mg were also supplied as identically appearing capsules and were different in appearance from the valsartan capsules. Placebo capsules matching the valsartan and HCTZ capsules were also supplied.

Throughout the placebo run-in and d/b treatment period, pts took 2 capsules of trial medication orally, once-a-day at approximately 8:00 a.m., irrespective of meals, except on the morning of scheduled visits.

On scheduled visit days, pts reported to the investigator's office in a fast state between 7:00 a.m. and 10:00 a.m.; thereby, visit procedures would take place 23 to 26 hrs after the last dose of trial medication. After all visit procedures were performed, trial medication was administered.

Concomitant treatments

The use of medications that might interfere with the evaluation of efficacy, safety, and tolerability were not allowed throughout the trial. Pts were informed that they were not permitted to take any other drug, including over the counter preparations, during the trial with the exception of cardiac aspirin and any medication specifically permitted by the investigator.

Trial Procedures

The flow chart is shown table 301-2.

Table 301-2 : Flow Chart

Period	Washout	Single-Blind Placebo Run-in/ Washout	Double-Blind Treatment Randomization ↓			
Visit	0	1	2	3	4	5
Week	-6	-4	0	2	4	8
Informed Consent	X					
Discontinue Anti-hypertensive Medications	X					
Complete History		X				
Complete Physical Exam		X				
Interim/Final Physical Exam			X	X	X	X
12-Lead ECG		X				
Chest X-ray		X				
CBC, Chemistry, Urinalysis		X	X			X
Serum Electrolytes only				X	X	
Serum Pregnancy Tests		X	X		X	X
Adverse Experience			X	X	X	X

Concomitant Medications		X	X	X	X	X
Collect Unused Medications			X	X	X	X
Dispense Single-Blind Placebo		X				
Dispense Double-Blind Trial Medications			X	X	X	
Termination Sheet						X

Blood Pressure (BP) and Pulse Measurements:

BP and pulse measurements were to be performed at each visit between 7:00 a.m. and 10:00 a.m. BP were to be measured by the same clinician, in the same arm, using the same sphygmomanometer, prior to administering that day's dose. At all visits, all BP measurements were to be taken three times in the sitting position, and once standing.

Sample size determination

A total of 765 pts (85 per treatment group) who met all admission criteria and completed all visits of the trial were to be enrolled.

The sample size was calculated to detect a treatment difference of 4 mmHg in mean sitDBP with a statistical power of 90%, assuming a standard deviation of 8 mmHg. The two-sided significance level of 0.05 was used.

Efficacy

Primary variables

Change from baseline (pre-dose measurement at the randomization visit 2) in mean sitDBP. As planned in the protocol, three measurements were to be taken at each visit, and the mean sitDBP was the average of the measurements available.

Secondary variables

Change from baseline in mean sitting systolic BP (sitSBP). Three measurements were to be taken at each visit, and the mean sitSBP was the average of the measurements available.

Other variables

Variable 1: Change from baseline in standing diastolic blood pressure (stDBP),

Variable 2: Change from baseline in standing systolic blood pressure (st SBP),

Variable 3: Change from baseline in sitting pulse,

Variable 4: Change standing pulse,

Variable 5: Change from baseline in body weight.

Criteria for efficacy

The combination group vs. each of the monotherapies in reduction from baseline mean sitDBP. A combination therapy was considered effective if there was a statistically ($p < 0.05$)

significant treatment difference in favor of the combination group vs. the placebo group in reduction from baseline in mean sitDBP.

It was considered that both the monotherapies contributed to the efficacy of the combination if there was a statistically significant treatment difference in favor of the combination group vs. each of the monotherapies in reduction from baseline in mean siDBP.

Data sets analyzed

Three different sets of pts defined below were analyzed,

1) **All randomized pts at endpoint (intent-to-treat)**: All randomized pts who had a baseline (at Visit 2) and at least one post-baseline measurement. The endpoint was defined as the pt's last post-baseline measurement of the corresponding variable carried forward;

2) **All randomized pts at Visit 5**: All randomized pts who had both baseline and Visit 5 measurements.

3) **All clinically assessable pts at endpoint**: All randomized pts who met the following criteria:

   a) At Visit 2, the mean sitDBP$\geq$ 95 mmHg;

   b) Did not take any antihypertensive drug other than trial drug at any time during the trial;

   c) At the visit with the last sitDBP measurement, time from previous intake of study medication to BP measured was between 12 to 30 hours (inclusive);

   d) Total duration on trial drug during d/b period was at least 25 days. The endpoint was again defined as the pt's last post-baseline measurement of the corresponding variable carried forward.

The above criteria was determined prior to unblinding the treatment codes.

The results from the analysis based on all randomized pts at endpoint were compared with those based on all randomized pts at Visit 5 and all clinically assessable pts, respectively, to examine the effect of exclusions and drop-outs. The analysis performed for all randomized pts at endpoint was considered as the primary analysis.

As planned in the protocol, all statistical tests were two-sided, and no interim analysis was performed.

Statistical methodology :Refer to the stastic reviw.

Between-treatment analysis

The primary and secondary efficacy variables were analyzed for each of the three data sets :standing BP, pulses, and body weight were analyzed at endpoint and Visit 5 only.

A two-way analysis of covariance with treatment group and trial center as factors and baseline as a covariate was performed. Both treatment-by-center and treatment-by-baseline interactions were included in the model.

For a given combination, the primary hypotheses were that the combination therapy was equal to each of the component monotherapies vs. that they were not equal. The following pair-wise comparisons were performed:

1) Valsartan 160 mg/HCTZ 25 mg vs. valsartan 160 mg;
2) Valsartan 160 mg/HCTZ 25 mg vs. HCTZ 25 mg.
3) Valsartan 160 mg/HCTZ 12.5 mg vs. valsartan 160 mg;
4) Valsartan 160 mg/HCTZ 12.5 mg vs. HCTZ 12.5 mg;
5) Valsartan 80 mg/HCTZ 25 mg vs. valsartan 80 mg;
6) Valsartan 80 mg/HCTZ 25 mg vs. HCTZ 25 mg;
7) Valsartan 80 mg/HCTZ 12.5 mg vs. valsartan 80 mg;
8) Valsartan 80 mg/HCTZ 12.5 mg vs. HCTZ 12.5 mg;

The statistical test for each of the above pair-wise comparisons was performed at the two-sided significance level of 0.05. The statistical significance levels were not adjusted since, for a given combination, both null hypotheses had to be rejected in favor of the combination in order to conclude that each component of the combination contributed to the efficacy of the combination.

In addition, the following pair-wise comparisons between each of the active treatment groups and the placebo group were also performed. The hypotheses for each of the comparisons were that the two treatments were equal vs. that they were not equal.

9) Valsartan 80 mg vs. placebo;
10) Valsartan 160 mg vs. placebo;
11) HCTZ 12.5 mg vs. placebo;
12) HCTZ 25 mg vs. placebo;
13) Valsartan 80 mg/HCTZ 12.5 mg vs. placebo;

The statistical test for each of the above pair-wise comparisons was performed at the two-sided significance level of 0.05.

Confidence interval (95 %) was computed for each of the above 16 pair-wise comparisons.

The proportion of pts achieving a successful reduction in mean sitDBP during the d/b period was compared by means of a one-way logistic model with treatment as the factor for all randomized pts at endpoint and Visit 5, respectively. A success was defined as a mean sitDBP< 90 mmHg or a $\geq$ 10 mmHg decrease compared to baseline. All sixteen between-treatment comparisons mentioned previously were performed for the proportion of successful response.

A second-order response surface analysis with the dose as the predictor variable was also performed for change from baseline in mean sitDBP at endpoint and Visit 5, respectively, to examine the relationship between the efficacy response and the dose. A test for lack- of-fit was performed at significance level of 0.1.

Within-treatment analysis

With respect to each of the seven efficacy variables, within-treatment analysis was performed by a paired t-test at endpoint and Visit 5. In addition, for primary and secondary variabl , within-treatment analysis was also performed for all clinically assessable pts at endpoint.

Summary statistics

Summary statistics were provided by treatment group and visit for the seven variables. Changes from baseline in each of the seven variables were also summarized by treatment group and visit.

Summary statistics for mean sitDBP and mean sitSBP by age group (<65 and $\geq$ 65), treatment group, and visit; by sex, treatment group, and visit; by race (white, black, and other), treatment group, and visit were provided as well.

In addition, for each of the variables, both mean and mean change from baseline were plotted against visit by treatment group. Bar charts for the proportions of pts achieving a successful response in the control of mean sitDBP were provided.

Bar charts for raw mean and the predicted mean from the fitted response surface model were also provided.

Results

Accounting of patients

A total of 997 pts were enrolled in this trial. Of the enrolled pts, 871 pts were randomized at Visit 2 into the d/b treatment period and 792 pts completed the trial. One hundred and twenty six pts were discontinued prematurely during the single-blind period, and 79 pts were discontinued prematurely during the d/b period. There were 865 pts included in the primary efficacy analysis at endpoint, 867 pts in the adverse experience (AE) evaluation, and 854 pts in the safety laboratory evaluation (6 randomized pts had no post-baseline efficacy measurements, 4 pts had no post- baseline AE data as they were lost to follow-up, and 17 pts had no post-baseline laboratory data). table 301-3 displays the disposition of pts by treatment group.

Table301-3 : Distribution of patients by treatment (all pts)

Number of patients	P	V80	V160	H12.5	H25	V80/H12.5	V160/H12.5	V80/H25	V160/H25	Total
Enrolled	-	-	-	-	-	-	-	-	-	997
Randomized	94	99	99	100	100	96	97	92	94	871
Completed	83	90	89	81	90	95	91	86	87	792
Discontinued prematurely during double-blind period										
Total	11	9	10	19	10	1	6	6	7	79
For adverse experience	4	3	6	8	3	1	3	6	7	41
For abnormal laboratory value	0	0	0	0	0	0	0	0	0	0
For unsatisfactory therapeutic response	2	3	1	2	1	0	0	0	0	9
Other	5	3	3	9	6	0	3	0	0	29
In primary efficacy analyses										
Endpoint	93	99	97	99	100	96	96	91	94	865*
Visit 5	86	92	90	84	94	96	92	88	87	809**
Assessable patients	84	92	87	82	92	88	91	87	88	791
Safety analyses										
Adverse experiences	93	99	97	100	100	96	96	92	94	867***
Laboratory tests	91	98	96	98	99	96	94	90	92	854

Note: P=Placebo, V80=Valsartan 80, V160=Valsartan 160, H12.5=HCTZ 12.5, and H25=HCTZ 25.
Within-treatment analysis

* Six randomized, prematurely discontinued patients had no post-randomization measurements.

** Seventeen prematurely discontinued patients who stopped taking trial drug between Visit 4 and the scheduled Visit 5, per the protocol, had blood pressure measurements at Visit 5 and were therefore included in the Visit 5 analysis.

*** Four patients were lost to follow-up after the randomization visit and were excluded for adverse experience evaluation

Protocol violations and acceptability of patients

Eight pts had violations of the protocol which warranted discontinuation from the trial. Four pts had clinically significant lab abnormalities, one pt became pregnant during the course of the trial, one pt stopped taking trial medication and started taking an unacceptable medication, one pt was randomized in error having not met the randomization BP criteria, and one pt was noncompliant with trial medication. Eighteen additional pts took unacceptable medications related to an AE; however, these pts were discontinued from the trial due to the AE or for unsatisfactory therapeutic effect. The remaining protocol violations that occurred during this trial were not considered clinically significant nor were they felt to affect the outcome of the trial. The most common protocol violation was pts taking prohibited medications..

Clinically assessable patients analysis for the primary and secondary efficacy variables

Eighty pts (9.2%) were excluded from the assessable pts analysis. Tasble 301-4 summerized frequency distribution of reasons for exclusion. Of these, there were 74 pts with post-baseline efficacy measurements.

Table 301-4 : Frequency distribution of reasons for exclusion from the clinically assessable pts analysis

Treatment Group	Reasons				Number of Patients Excluded*
	(1)	(2)	(3)	(4)	
Placebo	0	4	2	7	10
Valsartan 80 mg	1	1	4	4	7
Valsartan 160 mg	0	1	9	7	12
HCTZ 12.5 mg	1	5	10	14	18
HCTZ 25 mg	1	3	4	3	8
Valsartan 80 mg/ HCTZ 12.5 mg	2	0	6	0	8
Valsartan 160 mg/ HCTZ 12.5 mg	1	1	4	4	6
Valsartan 80 mg/ HCTZ 25 mg	0	0	2	4	5
Valsartan 160 mg/ HCTZ 25 mg	0	0	4	5	6
Totals	6	15	45	48	80

Reasons for exclusion from the clinically assessable pts analysis were:

(1) mean sitDBP was less than 95 mmHg at randomization visit (Visit 2),

(2) took antihypertensive drug other than trial drug during the trial,

(3) at the visit with last BP measurements, the time from previous intake of morning dose to BP measured was not between 12 to 30 hours (inclusive), and

(4) total duration on trial medication duringd/b period was less than 25 days.

*In some cases patients were excluded for multiple reasons.

Extent of exposure / Analysis of doses administered

The mean total duration (days) on trial drug in the d/b treatment period are presented by treatment group below table 301-5.

Table 301-5: Mean total duration (days) on trial drug in double-blind period by treatment group

Treatment Group	Number of Patients	Mean Duration (Days)
Placebo	94	53
Valsartan 80 mg	99	54
Valsartan 160 mg	99	53
HCTZ 12.5 mg	100	50
HCTZ 25 mg	100	54
Valsartan 80 mg/HCTZ 12.5 mg	96	57
Valsartan 160 mg/HCTZ 12.5 mg	92	54
Valsartan 80 mg/HCTZ 25 mg	97	55
Valsartan 160 mg/HCTZ 25 mg	94	53

Results - Patient characteristics / Comparability of treatment groups

Demographic and baseline data

Overall, the nine treatment groups were comparable with respect to demographic and medical history characteristics, as well as baseline measurements for the seven efficacy variables.

Demographic and medical history characteristics

Variables sex, race, age, weight, and height were examined statistically for all randomized pts. No statistically significant treatment differences were found with respect to any of the demographic and medical history variables. Patients' age ranged from 22 to 86 (mean age = 52 years). Summary statistics for sex, race, age, weight, and height are presented by treatment group are shown Exhibit 7.1.-1 (vol 1.29, page 27) and Exhibit 7.1.-2 (vol 1.29, page 28).

Baseline measurements

Comparability at baseline with respect to mean sitDBP and mean sitSBP,stDBP and stSBP, sitting and standing pulses, and body weight were tested statistically. No statistically significant treatment differences at baseline were found. Table 301-6 provides summary statistics (mean $\pm$ standard deviation) for baseline mean siBP.

Table 301-6: Summary statistics for baseline mean sitting BP(mmHg) by treatment group (all randomized pts)

Treatment group		Mean (+ S.D.)	
	Number of patients	Mean sitting diastolic blood pressure	Mean sitting systolic blood pressure
Placebo	94	101.44 (+5.01)	152.71 (+17.08)
Valsartan 80 mg	99	101.48 (+4.89)	153.66 (+14.40)
Valsartan 160 mg	99	101.51 (+4.80)	153.32 (+15.13)

HCTZ 12.5 mg	100	101.17 (+4.50)	153.59 (+16.39)
HCTZ 25 mg	100	100.76 (+4.57)	151.95 (+15.45)
Valsartan 80mg/HCTZ 12.5mg	96	100.99 (+4.87)	153.00 (+14.41)
Valsartan 160mg/HCTZ 12.5mg	97	100.96 (+4.48)	154.53 (+15.38)
Valsartan 80mg/HCTZ 25mg	92	100.36 (+4.60)	152.01 (+14.19)
Valsartan 160mg/HCTZ 25mg	94	101.38 (+4.84)	155.86 (+14.78)

Results - Efficacy

The efficacy results are presented below in the order of primary variable, secondary variable, and other variables.

PRIMARY VARIABLE: CHANGE FROM BASELINE IN MEAN SITTING DBP

Between-treatment analysis results for all randomized pts at endpoint: The least square treatment means from the two-way analysis of covariance are tabulated in table 301-7.

Table 301-7: Least square treatment means for change from baseline in mean sitting DBP(mmHg) at endpoint (all randomized pts)

	Placebo	Valsartan 80 mg	Valsartan 160 mg
Placebo	-4.12 (n=93)	-8.63 (n=99)	-9.42 (n=97)
HCTZ 12.5 mg	-7.16 (n=99)	-11.83 (n=96)	-13.51 (n=96)
HCTZ 25 mg	-9.28 (n=100)	-15.28 (n=91)	-15.31 (n=94)

Note: n=number of randomized patients.

The differences between the least square treatment means and the results of the treatment comparisons are given table 301-8.

Table 301-8: Results of the between-treatment comparisons for change from baseline in mean sitting DBPat endpoint (all randomized pts)

Comparison		Difference (mmHg)	Confidence interval (95%)	p-value
Valsartan 160mg/HCTZ 25mg	vs. valsartan 160mg	-5.89	(-8.30, -3.47)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. HCTZ 25mg	-6.03	(-8.43, -3.62)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. placebo	-11.19	(-13.62, -8.76)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. valsartan 160mg	-4.09	(-6.49, -1.69)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-6.35	(-8.75, -3.96)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. placebo	-9.39	(-11.81, -6.97)	<0.001*
Valsartan 160mg	vs. placebo	-5.30	(-7.71, -2.89)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. valsartan 80mg	-6.65	(-9.11, -4.19)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. HCTZ 25mg	-6.00	(-8.44, -3.56)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. placebo	-11.16	(-13.63, -8.70)	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. valsartan 80mg	-3.19	(-5.62, -0.77)	0.0099*
Valsartan 80mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-4.67	(-7.08, -2.26)	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. placebo	-7.71	(-10.14, -5.27)	<0.001*
Valsartan 80mg	vs. placebo	-4.51	(-6.93, -2.09)	<0.001*
HCTZ 25mg	vs. placebo	-5.16	(-7.56, -2.76)	<0.001*
HCTZ 12.5mg	vs. placebo	-3.04	(-5.44, -0.63)	0.0133*

* indicates a statistical significance at the level of 0.05 (p <0.05)

Statistically significant treatment differences in change from baseline to endpoint in mean siDBP were observed in favor of all the combination treatments and all the active monotherapies versus placebo. Furthermore, all of the combination treatments produced a statistically significantly greater reduction in mean siDBP compared to each of the monotherapies, indicating both of the active monotherapies contributed to the efficacy of the combination therapies.

These results demonstrated that all of the combination treatments were more effective in comparison with the monotherapies in reducing mean siDBP..

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Between-treatment analysis results for all randomized patients at Visit 5: The least square treatment means from the two-way analysis of covariance are tabulated in table 301-9.

Table 301-9: Least square treatment means for change from baseline in mean sitting DBP(mmHg) at Visit 5 (all randomized pts)

	Placebo	Valsartan 80 mg	Valsartan 160 mg
Placebo	-4.76 (n=86)	-9.44 (n=92)	-9.74 (n=90)
HCTZ 12.5 mg	-7.13 (n=84)	-11.83 (n=94)	-13.63 (n=96)
HCTZ 25 mg	-9.74 (n=92)	-15.39 (n=88)	-15.62 (n=87)

Note: n=number of randomized patients.

Table 301-10: Results of the between-treatment comparisons for change from baseline in mean sitting DBPat Visit 5 (all randomized pts)

Comparison		Difference (mmHg)	Confidence interval (95%)	p-value
Valsartan 160mg/HCTZ 25mg 160mg	vs. valsartan	-5.88	(-8.33, -3.43)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. HCTZ 25mg	-5.88	(-8.32, -3.44)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. placebo	-10.86	(-13.32, -8.40)	<0.001*
Valsartan 160mg/HCTZ 12.5mg 160mg	vs. valsartan	-3.89	(-6.32, -1.47)	0.0017*
Valsartan 160mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-6.50	(-8.97, -4.03)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. placebo	-8.87	(-11.31, -6.44)	<0.001*
Valsartan 160mg	vs. placebo	-4.98	(-7.42, -2.54)	<0.001*
Valsartan 80mg/HCTZ 25mg 80mg	vs. valsartan	-5.95	(-8.39, -3.51)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. HCTZ 25mg	-5.66	(-8.09, -3.22)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. placebo	-10.64	(-13.09, -8.19)	<0.001*
Valsartan 80mg/HCTZ 12.5mg 80mg	vs. valsartan	-2.39	(-4.79, 0.02)	0.0519
Valsartan 80mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-4.70	(-7.16, -2.25)	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. placebo	-7.07	(-9.49, -4.66)	<0.001*
Valsartan 80mg	vs. placebo	-4.69	(-7.12, -2.25)	<0.001*
HCTZ 25mg	vs. placebo	-4.98	(-7.41, -2.55)	<0.001*
HCTZ 12.5mg	vs. placebo	-2.37	(-4.85, 0.11)	0.0612

* indicates a statistical significance at the level of 0.05 (p <0.05)

The results for change from baseline in mean siDBP at Visit 5 were consistent with the results at the endpoint except for the comparisons valsartan 80 mg/HCTZ 12.5 mg vs .valsartan 80 mg and HCTZ 12.5 mg vs. placebo, where the treatment differences in mean reduction were not statistically significant (p=0.0519 and 0.0612, respectively). Table 301-10.

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Between-treatment analysis results for all clinically assessable patients at endpoint: The results were consistent with the Visit 5 analysis results.

Analysis results for the proportion of successful response: The proportion of pts achieving a successful response is presented by treatment groups in table 301-11. A successful response was defined as a post-baseline mean siDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline (Visit 2).

Table 301-11: Proportion of pts achieving a successful response in the control of mean sitting DBP at endpoint and Visit 5 (all randomized pts)

Treatment group	Proportion of successful response	
	Endpoint	Visit 5
Placebo	29% (n=93)	31% (n=86)
Valsartan 80 mg	54% (n=99)	57% (n=92)
Valsartan 160 mg	59% (n=97)	61% (n=90)
HCTZ 12.5 mg	41% (n=99)	38% (n=84)
HCTZ 25 mg	54% (n=100)	57% (n=94)
Valsartan 80mg/HCTZ 12.5mg	64% (n=96)	64% (n=96)
Valsartan 160mg/HCTZ 12.5mg	76% (n=96)	77% (n=92)
Valsartan 80mg/HCTZ 25mg	81% (n=91)	83% (n=88)
Valsartan 160mg/HCTZ 25mg	81% (n=94)	80% (n=87)

Note: n=number of randomized patients.

The results of the treatment comparisons for the proportion are given table 301-12..

Table 301-12: Results of the between-treatment comparisons for the proportion of pts achieving a successful response in the control of mean sitting DBP at endpoint and Visit 5 (all randomized pts)

Comparison		p-value	
		Endpoint	Visit 5
Valsartan 160mg/HCTZ 25mg	vs. valsartan 160mg	0.0011*	0.0054*
Valsartan 160mg/HCTZ 25mg	vs. HCTZ 25mg	<0.001*	0.0011*
Valsartan 160mg/HCTZ 25mg	vs. placebo	<0.001*	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. valsartan 160mg	0.0112*	0.0200*
Valsartan 160mg/HCTZ 12.5 mg	vs. HCTZ 12.5mg	<0.001*	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. placebo	<0.001*	<0.001*
Valsartan 160mg	vs. placebo	<0.001*	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. valsartan 80mg	<0.001*	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. HCTZ 25mg	<0.001*	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. placebo	<0.001*	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. valsartan 80mg	0.1571	0.3263
Valsartan 80mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	0.0022*	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. placebo	<0.001*	<0.001*

Valsartan 80mg	vs. placebo	<0.001*	<0.001*
HCTZ 25mg	vs. placebo	<0.001*	<0.001*
HCTZ 12.5mg	vs. placebo	<0.001*	<0.001*

* indicates a statistical significance at the level of 0.05 (p <0.05)

The results at endpoint and Visit 5 were consistent. All the combination treatments and active monotherapies had a statistically significantly higher success rate compared to the placebo. All the combination treatments had a statistically significantly higher success rate compared to the corresponding monotherapies except for the valsartan 80 mg/HCTZ 12.5 mg group where the success rate (64% at endpoint) was not statistically significantly higher than the success rate in the valsartan 80 mg group (54% at endpoint).

The analysis results for all clinically assessable pts at endpoint were consistent with the endpoint analysis results.

Within-treatment analysis: The results of within-treatment analysis are summarized in Table 8.1:1 (vol 1.29, pages 187 - 191). In each of the treatment groups, statistically significant decreases from baseline were observed at endpoint and Visit 5. All the active treatment groups had a clinically meaningful decrease from baseline. The same results were observed for all clinically assessable pts at endpoint.

SECONDARY VARIABLE: CHANGE FROM BASELINE IN MEAN SITTING SYSTOLIC BP

Between-treatment analysis results for all randomized pts at endpoint: The least square treatment means from the two-way analysis of covariance are given table 301-13.

Table 301-13: Least square treatment means for change from baseline in mean sitting SBP(mmHg) at endpoint (all randomized pts)

	Placebo	Valsartan 80 mg	Valsartan 160 mg
Placebo	-1.93 (n=93)	-8.82 (n=99)	-12.13(n=97)
HCTZ 12.5 mg	-7.32 (n=99)	-16.53 (n=96)	-17.77 (n=96)
HCTZ 25 mg	-12.74 (n=100)	-21.16 (n=91)	-22.47 (n=94)

Note: n=number of randomized patients.

The differences between the least square treatment means and the results of the treatment comparisons are summarized in table 301-14.

Table 301-14: Results of the between-treatment comparisons for change from baseline in mean sitting SBP at endpoint (all randomized pts)

Comparison		Difference (mmHg)	Confidence interval (95%)	p-value
Valsartan 160mg/HCTZ 25mg	vs. valsartan 160mg	-10.34	(-14.41, -6.27)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. HCTZ 25mg	-9.73	(-13.81, -5.65)	<0.001*
Valsartan 160mg/HCTZ 25mg	vs. placebo	-20.53	(-24.63, -16.44)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. valsartan 160mg	-5.64	(-9.60, -1.69)	0.0053*
Valsartan 160mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-10.45	(-14.40, -6.49)	<0.001*
Valsartan 160mg/HCTZ 12.5mg	vs. placebo	-15.84	(-19.82, -11.86)	<0.001*

Valsartan 160mg	vs. placebo	-10.19	(-14.16, -6.23)	<0.001*
Valsartan 80mg/HCTZ 25mg 80mg	vs. valsartan	-12.34	(-16.37, -8.31)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. HCTZ 25mg	-8.42	(-12.45, -4.39)	<0.001*
Valsartan 80mg/HCTZ 25mg	vs. placebo	-19.23	(-23.27, -15.18)	<0.001*
Valsartan 80mg/HCTZ 12.5mg 80mg	vs. valsartan	-7.71	(-11.70, -3.71)	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. HCTZ 12.5mg	-9.20	(-13.19, -5.21)	<0.001*
Valsartan 80mg/HCTZ 12.5mg	vs. placebo	-14.59	(-18.61, -10.58)	<0.001*
Valsartan 80mg	vs. placebo	-6.89	(-10.86, -2.92)	<0.001*
HCTZ 25mg	vs. placebo	-10.81	(-14.78, -6.83)	<0.001*
HCTZ 12.5mg	vs. placebo	-5.39	(-9.36, -1.42)	0.0078*

* indicates a statistical significance at the level of 0.05 ($p < 0.05$)

The results for change from baseline in mean siSBPat endpoint were consistent with the results for mean siDBP at endpoint. All the combination treatments and active monotherapies had a statistically significantly greater mean reduction compared to the placebo. All the combination treatments had a statistically significantly greater mean reduction compared to each of the corresponding monotherapies.

These results demonstrated that all the combination treatments were more effective in comparison with the monotherapies in reducing mean siSBP.

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Between-treatment analysis results for all randomized pts at Visit 5: The results for change from baseline in mean siSBP at Visit 5 were consistent with the endpoint results.

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Between-treatment analysis results for all clinically assessable pts at endpoint: The results were consistent with the results of the endpoint analysis.

Within-treatment analysis: All the active treatment groups had a statistically significant and clinically meaningful decrease from baseline at endpoint and Visit 5. The same results were observed for all clinically assessable pts at endpoint.

Other variables

Variable 1: Change from baseline in standing DBP

Between-treatment analysis results:

The results for stDBP at endpoint and Visit 5 were consistent with the results for mean sitDBP at endpoint and Visit 5, respectively.

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Within-treatment analysis results:

In each of the treatment groups, statistically significant decreases from baseline were observed at endpoint and Visit 5. All active treatment groups had a clinically meaningful decrease from baseline.

Variable 2: Change from baseline in standing systolic BP

Between-treatment analysis results:

The results for stSBP at endpoint and Visit 5 were consistent with the results for mean siSBP at endpoint and Visit 5, respectively.

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

Within-treatment analysis results:

In each of the treatment groups, statistically significant decreases from baseline were observed at endpoint and Visit 5. All active treatment groups had a clinically meaningful decrease from baseline

Variable 3: Change from baseline in sitting pulse

Between-treatment analysis results:

No statistically or clinically significant differences between the treatment groups compared were observed at endpoint or Visit 5, indicating none of the treatments had any effect on sitting pulse.

Within-treatment analysis results:

No statistically or clinically significant changes from baseline were observed for any of the treatment groups at either endpoint or Visit 5.

Variable 4: Change from baseline in standing pulse

Between-treatment analysis results:

No statistically or clinically significant differences between the treatment groups compared were observed at endpoint or Visit 5, indicating none of the treatments had any effect on standing pulse.

Within-treatment analysis results:

Neither statistically nor clinically significant changes from baseline were observed for any of the treatment groups at either endpoint or Visit 5.

Variable 5: Change from baseline in body weight

Between-treatment analysis results:

No clinically significant differences between the treatment groups compared were observed at either endpoint or Visit 5, indicating none of the treatments had any effect on body weight. The only statistically significant finding was the difference (< 2 lbs.) between the valsartan 160 mg/HCTZ 12.5 mg group and the HCTZ 12.5 mg treatment group.

Within-treatment analysis results:

No clinically significant changes from baseline were observed for any of the treatment groups at either endpoint or Visit 5. The HCTZ 12.5 mg group was the only treatment group that had a statistically significant change (< 1.5 lbs.) from baseline.

Summary statistics:

All summary statistics were computed based on all randomized pts.

Primary and secondary variables by age

Summary statistics for mean sitting diastolic and systolic BP by age group (<65 or ≥ 65), treatment group are shown table 301-15.

Table 301-15: Summary statistics for age, weight, and height by treatment group (all randomized pts)

Treatment group	< 65 (years)		>= 65 (years)	
	N	Raw mean	N	Raw mean
Placebo	85	-3.98	8	-3.83
Valsartan 80 mg	86	-7.83	13	-11.33
Valsartan 160 mg	82	-10.16	15	-11.56
HCTZ 12.5 mg	82	-7.02	17	-10.08
HCTZ 25 mg	87	-8.65	13	-11.77
Valsartan 80 mg/HCTZ 12.5 mg	82	-12.16	14	-11.43
Valsartan 160 mg/HCTZ 12.5 mg	81	-13.14	15	-15.18
Valsartan 80 mg/HCTZ 25 mg	80	-14.52	11	-16.94
Valsartan 160 mg/HCTZ 25 mg	77	-17.23	17	-11.10

All active treatments were effective in reducing mean siDBP regardless of age group. Due to the small number of pts $\geq$ 65 years of age, it is difficult to draw any conclusions about the differences observed between the two age groups. Similar results were observed for mean siSBP.

Primary and secondary variables by sex

All active treatments were effective in reducing mean sitting diastolic and systolic BP regardless of sex.. Table 301-16.

Table 301-16: Mean change from baseline in mean sitting DBP (mmHg) at endpoint by sex (all randomized pts)

Treatment group	Female		Male	
	N	Raw mean	N	Raw mean
Placebo	35	-2.46	58	-4.87
Valsartan 80 mg	36	-9.29	63	-7.72
Valsartan 160 mg	37	-12.10	60	-9.31
HCTZ 12.5 mg	42	-10.21	57	-5.58
HCTZ 25 mg	45	-10.38	55	-7.98
Valsartan 80 mg/HCTZ 12.5 mg	38	-11.39	58	-12.49
Valsartan 160 mg/HCTZ 12.5 mg	38	-14.71	58	-12.63
Valsartan 80 mg/HCTZ 25 mg	44	-15.97	47	-13.73
Valsartan 160 mg/HCTZ 25 mg	43	-18.16	51	-14.41

Primary and secondary variables by race (table 301-17)

Table 301-17: Mean change from baseline in mean sitting DBP (mmHg) at endpoint by race (all randomized pts)

Treatment group	White		Black		Other	
	N	Raw mean	N	Raw mean	N	Raw mean
Placebo	70	-4.49	13	-0.21	10	-5.20
Valsartan 80 mg	75	-8.95	15	-6.31	9	-6.15
Valsartan 160 mg	75	-10.51	12	-8.56	10	-11.53
HCTZ 12.5 mg	65	-7.46	22	-8.27	12	-6.72
HCTZ 25 mg	77	-9.07	11	-10.61	12	-7.56
Valsartan 80 mg/HCTZ 12.5 mg	69	-12.12	12	-11.22	15	-12.44
Valsartan 160 mg/HCTZ 12.5 mg	78	-14.32	10	-10.27	8	-9.00
Valsartan 80 mg/HCTZ 25 mg	71	-15.14	9	-12.93	11	-14.24
Valsartan 160 mg/HCTZ 25 mg	68	-16.51	15	-18.36	11	-10.67

All active treatments were effective in reducing mean siDBP regardless of race. Due to the small number of black and other pts in each treatment group, it is difficult to draw any conclusions about the differences observed among the various races. Similar results were observed for mean siSBP.

Graphs for the efficacy variables (all randomized patients):

Plots for mean and mean change from baseline in mean siDBP vs. visit are presented by treatment group in Figures 301-1A; -1B, respectively. Plots for mean and mean change from baseline in mean siSBP are given by treatment group in Figures301-2A; -2B, respectively. Plots for standing diastolic and systolic BP, are given in Figures 301-3A; -3B respectively.

Charts for the proportion of pts achieving a successful response in the control of siDBPof all randomizedd pts and all clinically assessable pts are presented in Figure 301-4A; -4B respectively.

Charts for raw mean and predicted mean from the fitted response surface model for sitting diastolic BP are presented in Figures 301-5.

Figure 301-1A: Mean sitDBP vs. Visi by Treatment Group (all randomized pts)

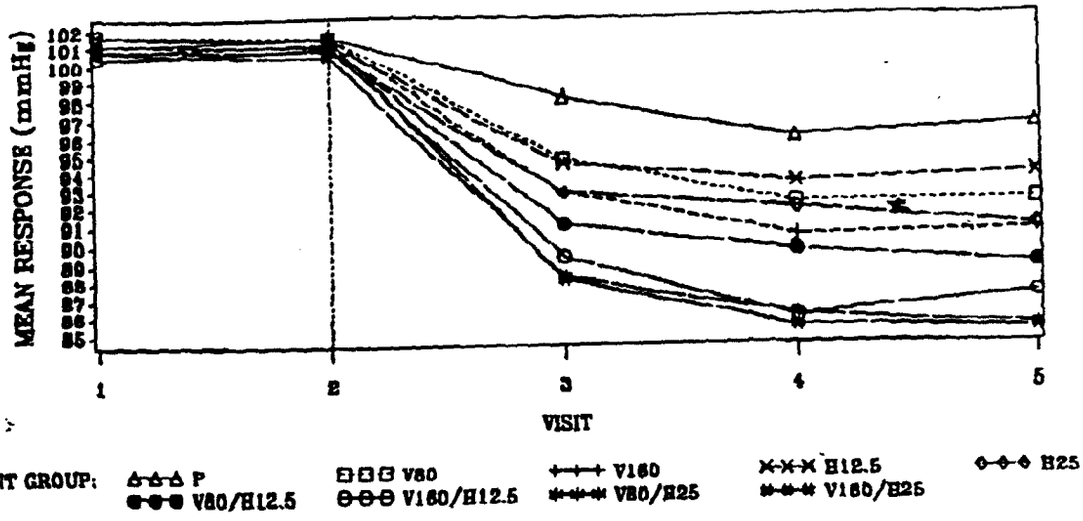
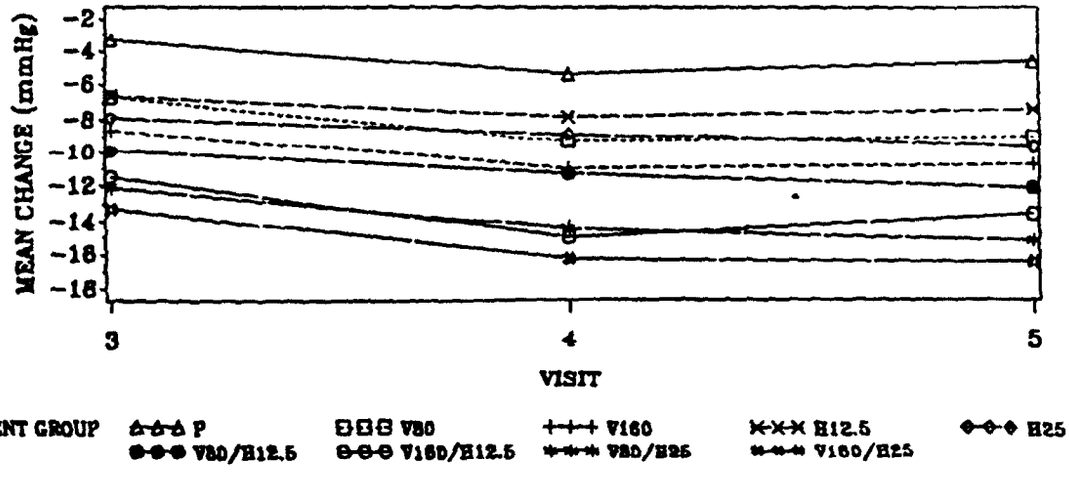


Figure 301-1B:Mean Change from Baseline in sitDBP vs. visit by Treatment Group (all randomized pts)



NOTE: P=PLACEBO, V80=VALSARTAN 80MG, V160=VALSARTAN 160MG, H12.5=HCTZ 12.5MG, H25=HCTZ 25MG
BASELINE IS THE RANDOMIZATION VISIT (VISIT 2).
POST-RANDOMIZATION VISITS OCCURRED AT THE FOLLOWING WEEKS: 2 (VISIT 3), 4 (VISIT 4), AND 8 (VISIT 5).
THE NUMBER OF PATIENTS MAY BE DIFFERENT FROM VISIT TO VISIT.

Figure 301-2A: Mean sit systolic BP vs.Visit by Treatment Group (all randomized pts)

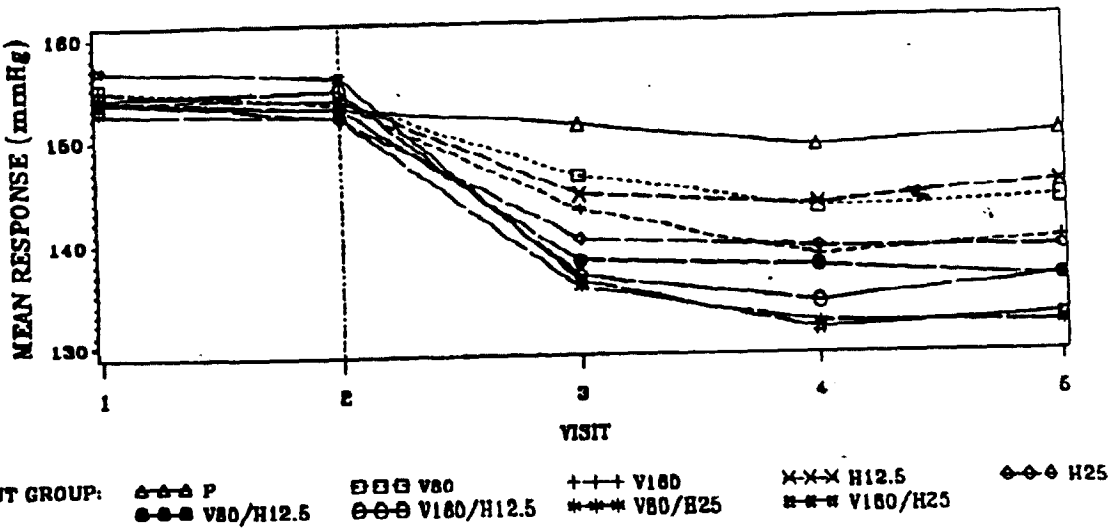
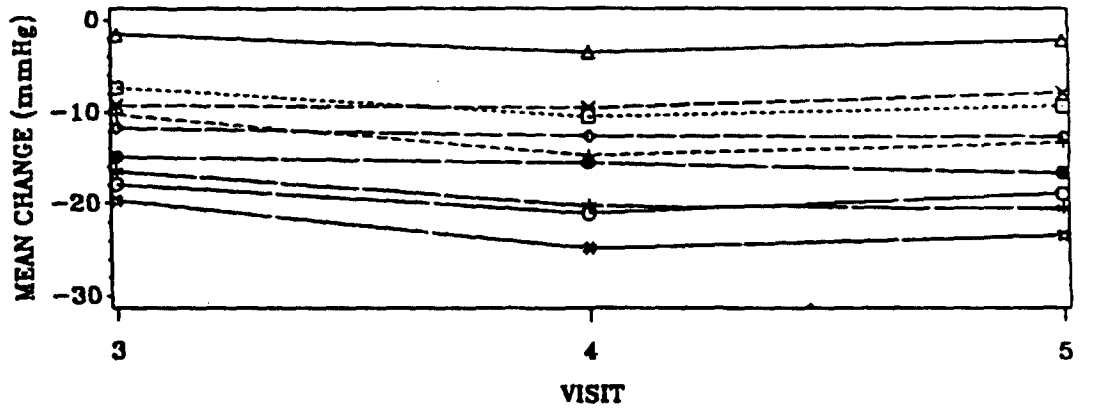


Figure 301-2B: Mean Change from Baseline in sitSBP vs. by Treatment Group (all rangomized pts)



NOTE: P=PLACEBO, V80=VALSARTAN 80MG, V160=VALSARTAN 160MG, H12.5=HCTZ 12.5MG, H25=HCTZ 25MG
BASELINE IS THE RANDOMIZATION VISIT (VISIT 2).
POST-RANDOMIZATION VISITS OCCURRED IN THE FOLLOWING WEEKS: 2 (VISIT 3), 4 (VISIT 4), AND 8 (VISIT 5).
THE NUMBER OF PATIENTS MAY BE DIFFERENT FROM VISIT TO VISIT.

Figure 301-3A: Mean Standing DBP vs. by Treatment Group (all randomized pts)

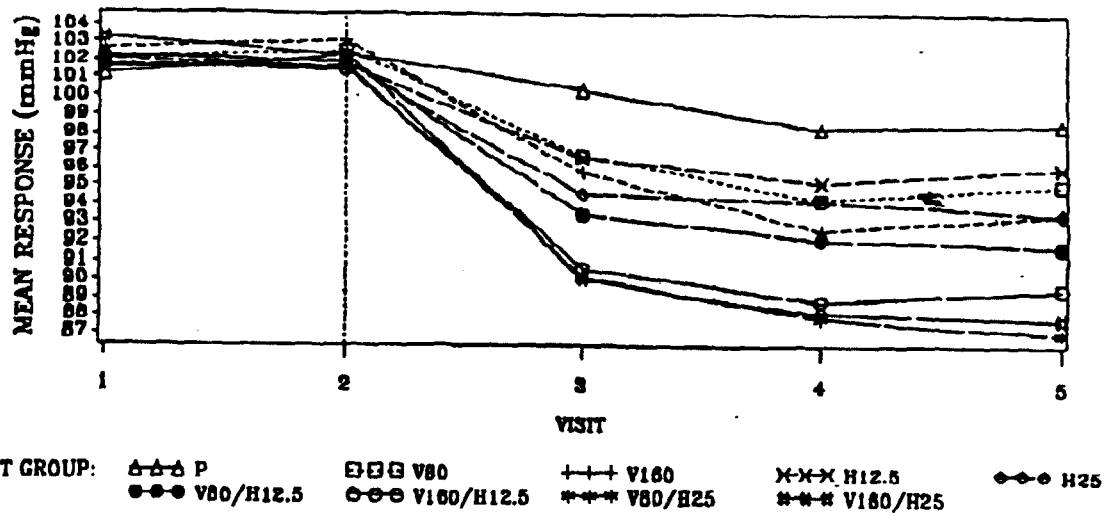
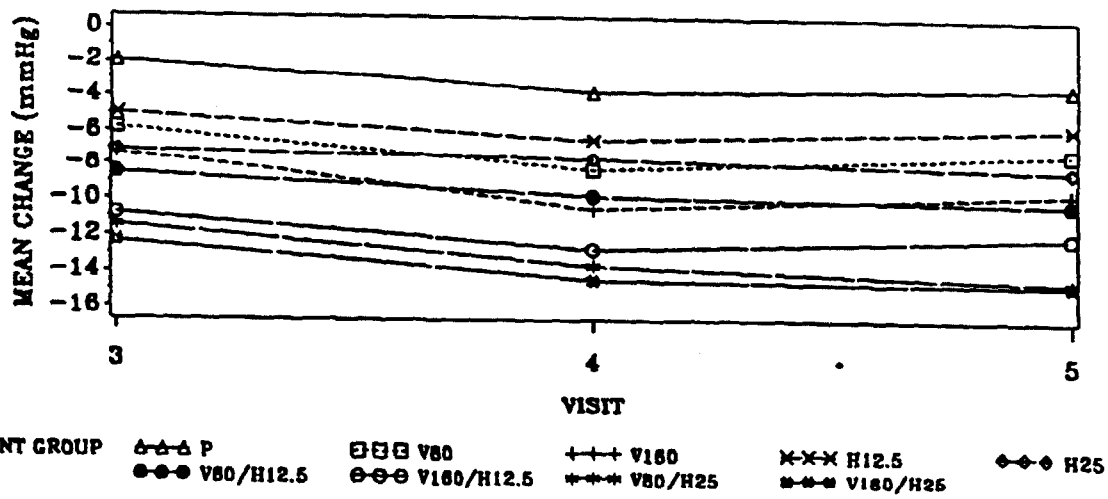


Figure 301-3B: Mean Change from Baseline in stDBP vs. by Treatment Group (all rendomized pts)



NOTE: P=PLACEBO, V80=VALSARTAN 80MG, V160=VALSARTAN 160MG, H12.5=HCTZ 12.5MG, H25=HCTZ 25MG
BASELINE IS THE RANDOMIZATION VISIT (VISIT 2).
POST-RANDOMIZATION VISITS OCCURRED IN THE FOLLOWING WEEKS: 2 (VISIT 3), 4 (VISIT 4), AND 8 (VISIT 5).
THE NUMBER OF PATIENTS MAY BE DIFFERENT FROM VISIT TO VISIT.

Figure 301-4A: Proportion of pts achieving a successful response in the contol of sitDBP at endpoint by treatment group (all randomized pts)

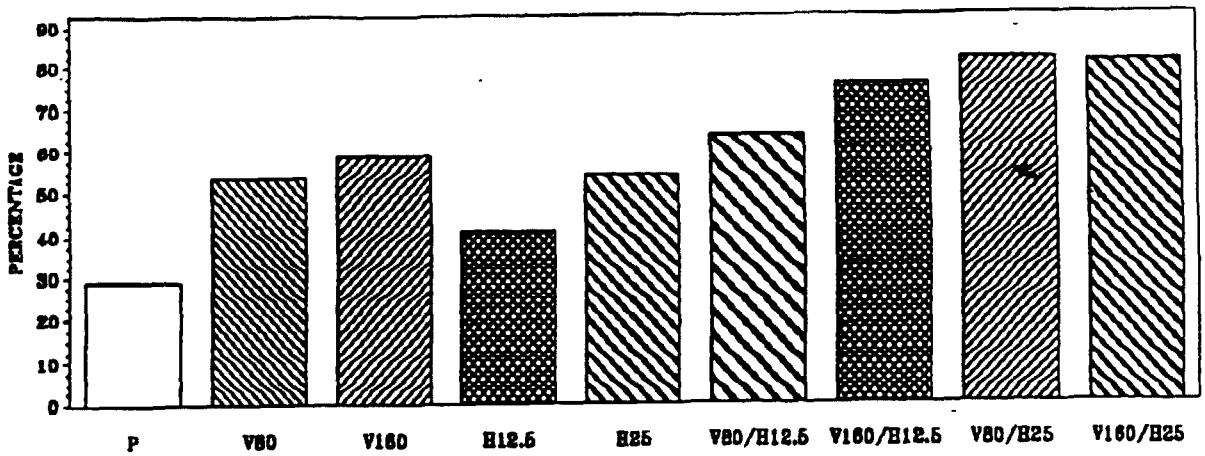
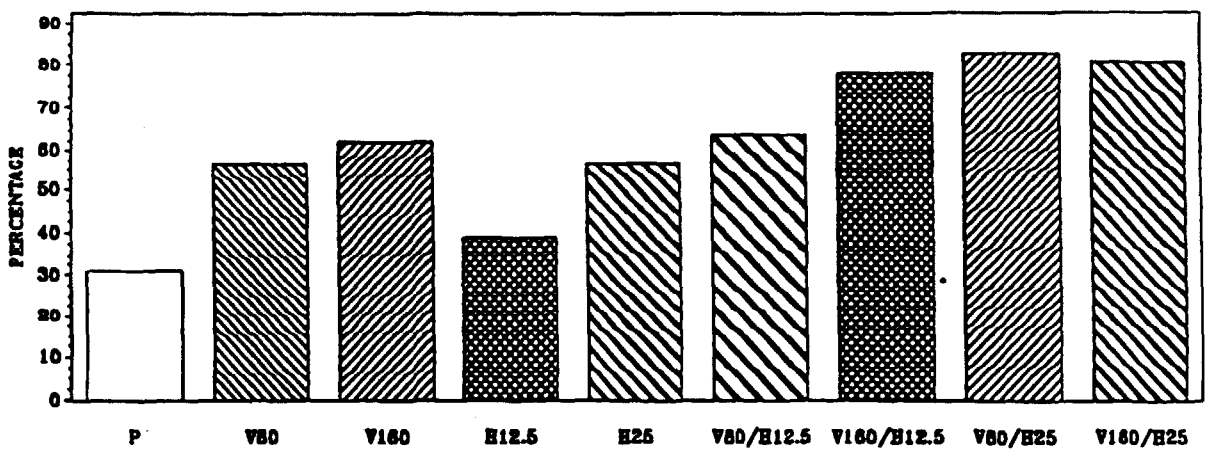
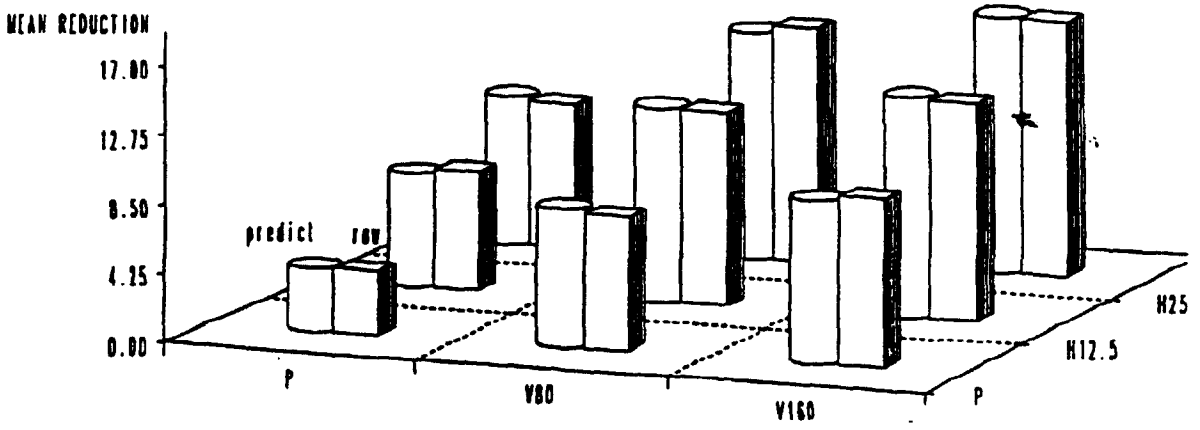


Figure 301-4B: Proportion of pts achievingg a successful response in the control of sitDBP at Visit 5 by treatment group (all clinically assessable pts))



NOTE: P=PLACEBO, V80=VALSARTAN 80MG, V160=VALSARTAN 160MG, H12.5=HCTZ 12.5MG, H25=HCTZ 25MG
A SUCCESSFUL RESPONSE IS DEFINED AS THE MEAN SITTING DIASTOLIC BLOOD PRESSURE IS LESS THAN 90 mmHg OR A GREATER THAN (OR EQUAL TO) 10 mmHg DECREASE COMPARED TO BASELINE.

Figure 301-5: Raw and predicted mean reductions from baseline in mean sitDBP (mmHg) at endpoint by treatment group (all randomized pts)



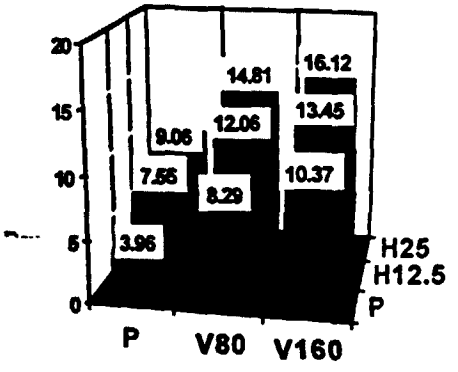
NOTE: THE PREDICTED MEAN REDUCTIONS WERE OBTAINED FROM THE RESPONSE SURFACE ANALYSIS.
CYLINDER = PREDICTED MEAN, CUBE = RAW MEAN.
P = PLACEBO. V80 = VALSARTAN 80 MG. V160 = VALSARTAN 160 MG. H12.5 = HCTZ 12.5 MG. and H25 = HCTZ 25 MG.

Dose-response analysis

Primary variable: Change from baseline in mean sitting DBP

Results of response surface analysis with dose as predictor for all randomized pts at endpoint: The raw treatment means for reduction from baseline to endpoint in mean siDBP are plotted Figure 301-6.

Figure 301-6: Raw mean for reduction from baseline in mean siDBP (mmHg) at endpoint (all randomized pts)



Note: P=Placebo, V80=Valsartan 80 mg, V160=Valsartan 160 mg, H12.5=HCTZ 12.5 mg, and H25=HCTZ 25 mg.

The predicted treatment means from the fitted response surface and the raw treatment means are presented in table 301-18.

Table 301-18 : Predicted and raw means for reduction from baseline in mean sitting DBP(mmHg) at endpoint (all randomized pts)

Treatment Group	Predicted Mean Change (mmHg)	Raw Mean Change (mmHg)
Placebo	-3.93	-3.96
Valsartan 80 mg	-8.62	-8.29
Valsartan 160 mg	-10.07	-10.37
HCTZ 12.5 mg	-7.25	-7.55
HCTZ 25 mg	-9.38	-9.06
Valsartan 80 mg/HCTZ 12.5 mg	-12.10	-12.06
Valsartan 160 mg/HCTZ 12.5 mg	-13.71	-13.45
Valsartan 80 mg/HCTZ 25 mg	-14.40	-14.81
Valsartan 160 mg/HCTZ 25 mg	-16.18	-16.12

The least square estimates for the coefficients of the regression equation are presente

Table 301-19 : Results of the response surface analysis for change from baseline in mean sitting DBP at endpoint (all randomized pts)

Regression Term	2nd order regression		
	Least Squares Estimate	Standard Error	P-Value
Intercept	-12.10	0.63	<0.001*
Coefficient			
Linear (VAL)	-3.23	0.34	<0.001*
Quadratic (VAL)	1.62	0.60	0.0068*
Linear (HCTZ)	-2.89	0.35	<0.001*
Quadratic (HCTZ)	0.59	0.60	0.3200
Cross product(VAL*HCTZ)	-0.17	0.42	0.6927
Lack of Fit	-	-	0.825

VAL = [Dose (Valsartan) - 80] / 80. HCTZ= [Dose (HCTZ) -12.5] / 12.5.

The second order regression equation for change from baseline in mean sitting diastolic blood pressure on dose was of the form, $y = \beta_0 + \beta_1 VAL + \beta_3 VAL^2 + \beta_3 HCTZ + \beta_4 HCTZ^2 + \beta_5 VAL*HCTZ$.

* Indicates statistical significance (P-value < 0.05)

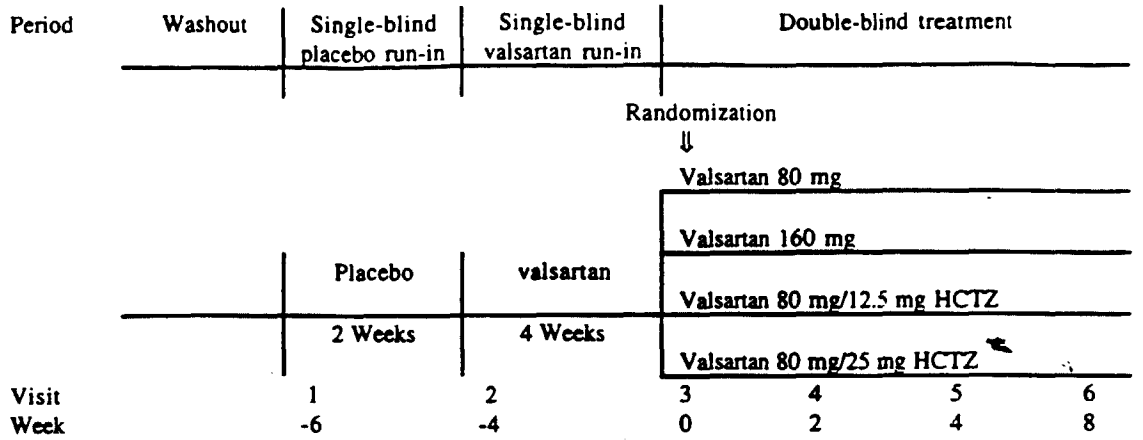
No statistically significant lack-of-fit (p=0.825) was noted for the second order response surface model. The fitted response surface predicts the reduction of mean sitDBP increases as the dose of the one of the monotherapies increases while the other being fixed, indicating that both of the monotherapies contribute to the efficacy of the combination therapies, and there is a positive dose response for both monotherapies.

The results of the response surface analysis demonstrated that all the combination treatments were more effective in comparison with the monotherapies in reducing mean siDBP at endpoint.

Results of response surface analysis with dose as predictor for all randomized pts at Visit 5: The model fitting results for change from baseline in mean siDBP at Visit 5 were consistent with those at endpoint and similar conclusions hold.

Protocol 19: A double-blind, randomized, active controlled, parallel design trial comparing the efficacy of the combination of HCTZ 12.5mg or 25 mg plus valsartan 80 mg once daily to valsartan 160 mg once daily in hypertensive pts inadequately controlled with valsartan 80 mg once daily (vol. 1.159, NDA 20-665).

The detail medical review referred to DR. Charles Ganley's review of NDA 20-665, pages 88 - 93.



This was a multicenter, double-blind, randomized, active-controlled, parallel group trial in which hypertensive pts [mean siDBP $\geq$ 95 and $\leq$ 120] who had been completely withdrawn from their previous antihypertensive medication for at least 2 weeks, received single-blind valsartan 80 mg once daily for 4 weeks following a 2 week single-blind placebo run-in period. After 4 weeks of treatment with valsartan 80 mg, those pts whose mean siDBP was not adequately controlled (MSDBP $\geq$ 95 and $\leq$ 115 mmHg) were randomized to one of 4 double-blind treatment groups:

908 pts entered into the valsartan 80 mg run-in phase at Visit 2. Among those entered into valsartan 80 mg run-in, 708 pts were randomized at Visit 3 into the double-blind treatment period, and 631 pts completed the trial.

Efficacy Results

Primary variable: Change from baseline in trough mean sitting diastolic blood pressure

Between-treatment analysis results for all randomized patients at endpoint:

The least square treatment means from the two-way analysis of covariance and the results of treatment comparisons are summarized table 19-1and the results of between treatment comparisons in the proportion of pts achieving a successful response in the control of mean siDBP at endpoint and Visit 6 is shown table 19-2.

Table 19-1: Results of between treatment comparisons at endpoint in mean sitting DBP (all randomized patients at endpoint)

Treatment group	Least squares mean change from baseline (mmHg)
Valsartan 80 mg	-5.09
Valsartan 160 mg	-6.16
Valsartan 80 mg/HCTZ 12.5 mg	-8.24
Valsartan 80 mg/HCTZ 25 mg	-10.83

Treatment comparison	Difference (mmHg)	Confidence interval (97.5%)	p-value
Valsartan 160 mg vs Valsartan 80 mg	-1.07	(-3.04, 0.89)	0.2207
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 80 mg	-3.15	(-5.06, -1.24)	0.0002*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 80 mg	-5.75	(-7.66, -3.83)	<0.0001*
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 160 mg	-2.08	(-4.03, -0.12)	0.0173*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 160 mg	-4.68	(-6.63, -2.72)	<0.0001*

*: indicate a statistical significance at 0.025 level (p<0.025).

Statistically significant treatment differences in mean siDBP were observed, which were greater in for the combination of valsartan and HCTZ than valsartan alone. No statistically significant difference was observed between valsartan 80 mg/HCTZ 12.5 mg vs. valsartan 160 mg.

Table 19-2: Results of between treatment comparisons in the proportion of pts achieving a successful response in the control of mean siDBP at endpoint and Visit 6 (all randomized pts at endpoint and Visit 6)

Treatment group	Proportion of patients achieving a successful response in the control of mean sitting diastolic blood pressure	
	Endpoint	Visit 6
Valsartan 80 mg	35.75%	36.42%
Valsartan 160 mg	36.84%	38.85%
Valsartan 80 mg/HCTZ 12.5 mg	50.57%	54.38%
Valsartan 80 mg/HCTZ 25 mg	59.09%	61.96%

Treatment group	p-value	
	Endpoint	Visit 6
Valsartan 160 mg vs Valsartan 80 mg	0.8324	0.6538
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 80 mg	0.0050*	0.0013*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 80 mg	<0.0001*	<0.0001*
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 160 mg	0.0102*	0.0058*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 160 mg	<0.0001*	<0.0001*

*: indicates a statistical significance at 0.025 level (p<0.025)

At endpoint, statistically significant treatment differences in the proportion of successful responses were observed, favoring the valsartan and HCTZ combination over valsartan alone. No statistically significant difference was observed between valsartan 80 mg and valsartan 160 mg, however.

Secondary variable: Change from baseline in trough mean sitting systolic BP

Between-treatment analysis results for all randomized patients at endpoint:

The least square treatment means from the two-way analysis of covariance and the results of treatment comparisons are summarized table 19-3 :

Table 19-3: Results of between treatment comparisons at endpoint in mean sitting systolic BP (all randomized pts at endpoint)

Treatment group	Least squares mean change from baseline (mmHg)
Valsartan 80 mg	-3.85
Valsartan 160 mg	-6.53
Valsartan 80 mg/HCTZ 12.5 mg	-9.77
Valsartan 80 mg/HCTZ 25 mg	-15.99

Treatment comparison	Difference (mm Hg)	Confidence interval (97.5%)	P-value
Valsartan 160 mg vs Valsartan 80 mg	-2.68	(-5.89, 0.53)	0.0610
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 80 mg	-5.92	(-9.04, -2.79)	<0.0001*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 80 mg	-12.1	(-15.3, -9.02)	<0.0001*
Valsartan 80 mg/HCTZ 12.5 mg vs. Valsartan 160 mg	-3.24	(-6.44, -0.04)	0.0234*
Valsartan 80 mg/HCTZ 25 mg vs. Valsartan 160 mg	-9.46	(-12.7, -6.26)	<0.0001*

*: indicate a statistical significance at 0.025 level ($p<0.025$).

The results were consistent with that obtained from the endpoint analysis of mean siDBP, favoring the valsartan and HCTZ combination over valsartan alone.

No statistically significant center-by-treatment interaction was observed. However, a statistically significant baseline-by-treatment interaction was detected at the 0.05 level. Statistically significant differences in the slopes from the analysis of covariance model were found between the valsartan 80 mg/HCTZ 25 mg and valsartan 80 mg treatment groups, and between the valsartan 80 mg/HCTZ 25 mg and valsartan 160 mg treatment groups, respectively. This result supported the conclusion that valsartan 80 mg/HCTZ 25 mg was favored over valsartan 80 mg alone, albeit the treatment difference may slightly depend upon the baseline value.

The results of between-treatment comparisons at endpoint in standing diastolic and systolic BP are similar to that of sitting diastoloc and systolic BP.

CONCLUSION OF EFFICACY DATA EVALUATION

The controlled clinical study protocol 301 indicate that valsartan 80 mg and 160 mg in combination with HCTZ 12.5 mg has an added effect over the component monotherpies in lowering BP in patiets with essential HTN. This efficacy data is also supported by the previously submitted NDA 20-665 the study protocol 19.

cc: original

cc: HFD-110

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cc: HFD-110 ChunS.