CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-665/S-016
NDA 21-283/S-001

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-665 /SE1-016**	**SUBMISSION DATES**	4/27/01
			5/29/01
	21-283 /SE1- 001		7/23/01
CATEGORY:	4P		
TYPE:	Efficacy supplement for heart failure		
BRAND NAME:	Diovan®		
GENERIC NAME:	valsartan		
ALTERNATE NAMES:	GCP 48933		
DOSAGE STRENGTH:	40, 80, 160, 320 mg capsules and 40 mg tablet		
SPONSOR:	Novartis		
DPE:	I		
PRIMARY REVIEWERS:	B. Nhi Nguyen, Pharm.D.		
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DPE TEAM LEADER:	Patrick Marroum, Ph.D.		

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	• History of any other severe life-threatening disease. • Drug/alcohol use within past 2 years. • Investigational drug use within 1 month prior to Visit 1. • Participation in previous valsartan trial • History of noncompliance • Directly involved in execution of this protocol. • Any condition/lab abnormality which would interfere with evaluation of efficacy/safety.

The following medications were not allowed in this trial: antihypertensive agents except diuretics and specific ACE inhibitors (enalapril, lisinopril, captopril, quinapril); vasodilators (including hydralazine and long-acting nitrates. Sublingual nitroglycerin was allowed except 6 hours prior to hemodynamic measurements); antidepressants; antiarrhythmics (except amiodarone); psychotropic drugs (except for hypnotics and mild anxiolytics); anti-inflammatory drugs (except topical steroids and aspirin up to a maximum daily dose of 325 mg daily for cardioprotection); sympathomimetic drugs (such as pseudoepedrine, phenylpropanolamine) and bronchodilators; ergot preparations, antacids in amounts greater than package labeling, and thyroid medication (unless stable maintenance replacement dose for preceding 6 months).

Table 104.2. Schedule of procedures (104)

	Single-blind placebo run-in		Double-blind treatment ⇓ Randomization					
Visit	1	2	3.0	3.1	4	5	6.0	6.1
Day	-14	-1	0	1	14	27	28	29
Complete history/physical exam	X							
Signs/symptoms CHF	X	X		X	X	X		X
Interim/Final physical exam		X		X	X	X		X
ECG	X							
Chest X-Ray	X							
Safety laboratory tests (fasting)	X		X				X	
Serum potassium		X				X		
Serum pregnancy test	X		X				X	
Neurohormone measurements			X				X	
Administer lisinopril dose			X				X	
Right heart catheterization		X				X		
12 hour hemodynamics			X				X	
Adverse experiences		X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Dispense trial medication	X			X	X			

Primary Efficacy Variable: Change from baseline in pulmonary capillary wedge pressure (PCWP).

Secondary Efficacy Variables:
Change from baseline in:
1. Cardiac output (CO);

2. Right atrial pressure;
3. Cardiac index (CI);
4. Systemic vascular resistance (SVR);
5. Pulmonary vascular resistance (PVR);
6. Stroke volume index;
7. Mean pulmonary artery pressure;
8. Pulmonary artery diastolic pressure;
9. Pulmonary artery systolic pressure;
10. Heart rate;
11. Systemic diastolic blood pressure;
12. Systemic systolic blood pressure;
13. Mean systemic blood pressure (MAP);
14. Plasma renin activity (PRA);
15. Plasma aldosterone;
16. Plasma angiotensin II;
17. Plasma norepinephrine;
18. Atrial peptide.

PCWP at each time point was determined as the average of two measurements.
CO was measured by thermodilution at each time point. CO was determined as the average of three measurements after excluding the highest and lowest of five measurements.
Formulas for CI, MAP, SVR, SVI and PVR were prespecified in the protocol.

Statistical analyses:
The primary analysis was the mean change from baseline (Day 0 Hour 0) in PCWP over 4-8 hours on Day 28 and at 12 hours on Day 28.
Baseline value was defined as the last available pre-dose measurement prior to randomization for that variable (ie, the Day 0 hour 0 measurement).

For the primary variable and secondary variables 1-7 as well as 14-18, between-treatment analyses of change from baseline were to be performed at each individual time point at which data were collected (for hemodynamic variables: 0.5, 1, 2, 3, 4, 6, 8, and 12 hours for Visits 3 and 6, plus 0 hours for Visit 6).. For the primary variable and secondary variables 1-7, between-treatment analyses of mean change from baseline over 4, 6 and 8 hours and mean change from baseline over 0 to 12 hours were to be performed. Mean change from baseline over 0-12 hours was to be calculated from weights based on the trapezoidal-rule principle and the unequal time intervals between measurements (as prespecified in the protocol). Within-treatment analyses were to be performed for mean change from baseline in PCWP and CO over 4 to 8 hours and at 12 hours at Visits 3 and 6.
Between-treatments analysis:
A two-way analysis of covariance was to be performed on change from baseline for each variable analysis. The model will include all two-way interactions with treatment.
For each pair-wise comparison, 97.5% confidence intervals for the corresponding between-treatment difference was to be calculated, based on results from the analysis of covariance.

Within-treatment analysis: Within-treatment analyses of change from baseline will be performed using Student's t-test.

Safety analysis:
Monitoring of adverse experiences, laboratory evaluations, vital signs and body weight.

Amendments to the Protocol:

1. Amendment #1 (signed 3/2/95): changed the following exclusion criteria: MI, unstable angina, pulmonary edema, hospitalization for decompensated CHF changed to within one month preceding Visit 1; history of malignancy (except basal cell skin cancer changed to within past two years: antiarrhythmic exclusion changed to "Antiarrhythmic drugs with a substantial effect on myocardial performance at usual doses such as calcium antagonists, beta-blockers, flecainide, and disopyramide." Concomitant antiarrhythmics such as procainamide, quinidine, amiodarone, mexilitene or tocainide were to be allowed at recommended therapeutic doses if stablilized at least one week before randomization.
2. Amendment #2 (signed 6/15/95): allowed patients to have the Swan-Ganz catheter inserted the morning of Visits 3 and 5, with PCWP measurements taken one hour after catheter insertion; directed the patient's evening dose of diuretic (if given in divided doses) be held for the evening prior to to 12-hour hemodynamic measurements unless it is not medically acceptable to do so.
3. Amendment #3 (signed 6/23/95): allowed well-controlled type I diabetics into the trial.
4. Amendment #4 (signed 2/16/96): changed antidepressant exclusion: Excluded antidepressant drugs with significant cardiovascular effects, such as MAO inhibitors and tricyclics. Selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine, and sertraline) with the exception of venlafaxine, are allowed if the patient has been on a stable dose two months prior to Visit 1.

Other Administrative Issues:

According to the Study Report, an unplanned interim analysis for PCWP, DPAP, and systemic diastolic and systolic blood pressure provided data for 40 randomized patients, including 36 patients with Visit 3 and 6 measurements. These interim analysis results were presented, using masked treatment codes, to internal personnel at Ciba (the Sponsor) for decision-making puposes; it was noted that "results were not analyzed by or revealed to those directly involved in the conduct or final analysis of the trial prior to final data lock."

Results:

Patient Disposition:

Table 104.3 lists patient disposition. Sixty patients were not randomized due to adverse experience (7 patients), not meeting protocol criteria (38 patients), noncompliance (1 patient), withdrew consent (12 patients) and administrative problems (2 patients).

Table 104.3. Patient Disposition

	Placebo	Valsartan 80 BID	Valsartan 160 BID	Total
Enrolled	--	--	--	143
Discontinued during placebo run-in				60
Randomized	28	28	27	83
Completed double-blind	27	24	23	74
Discontinued prematurely in double-blind	1	4	4	9
For adverse experience	0	2	2	4
For death	0	1	1	2
Administrative	1	0	1	2
Lost to follow-up	0	1	0	1

Source: Volume 14: Exhibit 6.1-1; Table 6.1:1

Table 104.4. Drug Exposure (all randomized patients)

	Placebo	Valsartan 80 mg BID	Valsartan 160 mg BID
N	28	28	27
Mean (± SD) days on trial drug	31 (5)	27 (9)	27 (8)
Range (days)	28-53	1-37	2-42

Source: Volume 14: Table 6.4:1

Baseline characteristics are shown in Table 104.5. The study population was 100% male and a majority were Caucasian; the percent of Black patients was lower in the placebo group compared to valsartan groups.

Mean age was 62-65 years with a majority of elderly in the valsartan treatment groups. Mean height was 69-70 inches and mean weight was 194-201 lbs. All randomized patients were treated with an ACE inhibitor during the trial.

Table 104.5. Baseline characteristics (all randomized patients)

	Placebo (N=28) n (%)	Val 80 BID (N=28) n (%)	Val 160 BID (N=27) n (%)
Race			
Caucasian	22 (79)	17 (61)	15 (56)
Black	3 (11)	10 (36)	9 (33)
Other	3 (11)	1 (4)	3 (11)
Mean age (± SD)	62 (9)	65 (10)	65 (10)
Age range	45-80	36-81	48-82
Age ≥ 65	11 (39)	17 (61)	15 (56)
Mean CHF duration (yrs)	6 (7)	4 (3)	6 (6)
Visit 2 NYHA Class II	16 (57)	19 (68)	17 (63)
Class III	12 (43)	9 (32)	10 (37)
CHF etiology: Idiopathic	4	6	6
Ischemic	17	15	14
Hypertensive	4	6	5
Other	3	1	2
Visit 2 Previous ACEI: high	20	20	22
Low dose	8	8	5
Visit 1 Normal ECG	0/28	1/28	1/27
Visit 1 Normal CXR	2/28	0/28	2/27

Source: Volume 14: Table 7.1:1. Electronic database.

A review of Visit 1 background medications for randomized patients showed that over 75% used digoxin and furosemide. No beta blocker use was noted.

Baseline hemodynamic measurements:
Three patients in placebo, and two patients in each valsartan group had PAD, but not hour 4-8 PCWP measurements on Day 0. Three patients in placebo, 7 patients in valsartan 80 BID, and 5 patients in valsartan 160 BID were missing peak (4-8 hour) PCWP measurements on Day 28.
Baseline hemodynamic measurements are shown below (see Table).

Baseline imbalances exist between treatment groups. It appears that mean heart rates, pulmonary artery pressures (PAS and PAD), PCWP and PCWP are higher in the Valsartan 160 mg BID group compared to

the other treatment groups. In addition, baseline mean plasma norepinephrine levels and PRA are increased in the Valsartan 160 mg BID group compared to the other two treatment arms. SVR appears to be increased in the valsartan 80 BID group.
According to the sponsor, testing for treatment group baseline comparability showed a significant difference for the placebo vs. valsartan 160 mg BID group norepinephrine level ($p< 0.05$). Analysis of baseline differences in PCWP, PAD, and MPAP for valsartan 80 mg BID vs. 160 mg BID showed a trend toward significance at the $p=0.07$ level.

Table 104.6. Mean (± SD) Baseline Hemodynamic Measurements at Day 0, Hour 0 (All Randomized Patients) (104)

	Placebo (N=28) n (%)	Val 80 BID (N=28) n (%)	Val 160 BID (N=27) n (%)
Systemic SBP (mm Hg)	126 (21)	125 (20)	127 (22)
Systemic DBP (mm Hg)	73 (13)	75 (12)	75 (13)
MABP (mm Hg)	91 (14)	92 (13)	92 (15)
HR (bpm)	72(10)	74 (14)	77 (14)
PAS	49 (17)	47 (15)	55 (19)
PAD	22 (7)	21 (7)	25 (9)
MPAP	31 (10)	30 (10)	35 (12)
N	27	28	27
RAP	8.9 (5)	8.0 (3)	8.6 (5)
N	27	26	25
PCWP	21 (7)	20 (7)	24 (8)
N	26	27	26
CO	4.6 (1.1)	4.3 (1.1)	4.6 (1.5)
CI	2.2 (0.4)	2.1 (0.5)	2.2 (0.6)
SVI	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
N	26	27	26
PVR	593 (316)	608 (321)	682 (370)
N	25	27	26
SVR	1504 (475)	1633 (428)	1565 (489)

Source: Table 8.1:15a, 8.1.16a, electronic database

Table 104.7. Mean (± SD) Baseline plasma neurohormones (Day 0 Hour 0)

	Placebo (N=28)	Val 80 BID (N=27)	Val 160 BID (N=27)
N	28	27	27
Plasma norepinephrine	274 (184)	321 (148)	411 (303)
ANP	330 (339)	402 (324)	406 (262)
PRA	5.3 (9.0)	5.0 (8.2)	7.2 (11.5)
N	26	26	25
Angio II by HPLC	6.8 (17.9)	5.1 (5.8)	4.5 (5.4)
N	25	22	21
Aldosterone	94 (92)	104 (125)	97 (72)

Source: Volume 15: Table 11.1:6a

Pooling of Centers: Centers with less than 3 randomized patients per treatment group were pooled; first, these centers were sorted by total number of patients per center available for

analysis; and then by center numbers previously assigned at trial initiation. Pooling was to begin with the larger centers to be pooled and progress to smaller centers.
According to the sponsor, pooling criteria and pooling algorithm were "decided prior to unblinding double-blind treatment codes." No such information on pooling can be found in Protocol or Amendments.

Primary Efficacy Variable:
All groups, including placebo, showed a statistically significant mean decrease from baseline in mean PCWP at 4-6 hours post-dosing (seen on Day 0 and 28). All groups except Valsartan 80 mg BID, Day 28, showed a statistically significant decrease from baseline at 12 hours. Valsartan 160 mg BID, Day 28, with a higher baseline mean than the other groups, showed larger, statistically significant decreases from baseline at all measured time points.
Results of the prespecified primary analysis are shown in Table 104.8. The baseline mean is higher in the valsartan 160 mg BID group with larger decreases seen. No significant decreases compared to placebo are seen. Results for LS mean change (0-12 hours) for the valsartan groups (not shown) also did not show statistically significant results compared to placebo.

Table 104.8. Primary Efficacy Variable (all randomized patients): PCWP (mm Hg) Day 28

	Placebo	Valsartan 80 mg BID	Valsartan 160 mg BID
N	25	21	22
Baseline mean	20.26	20.36	24.86
Peak (4-8 hours) LS Mean Change from baseline	-4.39	-4.34	-6.22
97.5% Confidence Interval vs. placebo	--	(-3.96, 3.86)	(-2.05, 5.71)
p-value (vs. placebo)	--	0.98	0.28
12 hours post-dose LS Mean Change from baseline	-4.14	-3.14	-5.61
97.5% Confidence Interval vs. placebo	--	(-4.85, 2.85)	(-2.36, 5.29)
p-value (vs. placebo)	--	0.55	0.38

Source: Sponsor: Volume 14, Exhibit 8.1:1a. According to the sponsor, there were no statistically significant treatment-by-baseline or treatment-by-center interactions.

Day 0 results for PCWP at similar time points are shown in Table 104.9. There is a statistically significant decrease in PCWP for valsartan 160 mg compared to placebo at 4-8 hours post-dosing as well as the mean over 12 hours post-dose. Baseline PCWP appears higher in the valsartan 160 mg BID group; according to the sponsor, there was no statistically significant treatment-by-baseline interaction.

Table 104.9. Primary Efficacy variable (all randomized patients): PCWP (mm Hg) Day 0

PCWP, Day 0	Peak (4-8 hours)			12 hours post-dose			0-12 hours		
Treatment group	N	Baseline mean	LS Mean change	N	Baseline mean	LS Mean change	N	Baseline mean	LS Mean change
Placebo	25	21	-2.77	24	21	-2.16	25	21	-2.34
Val 80 BID	25	20	-3.72	26	20	-2.96	26	20	-3.02
Val 160 BID	25	24	-5.62	24	24	-5.15	25	24	-4.73

Treatment comparison	Difference (97% CI)	P value	Difference (97% CI)	P value	Difference (97% CI)	P value
Val 80 BID vs. Placebo	0.95 (-1.7, 3.6)	0.41	0.8 (-2.4, 4.0)	0.56	0.7 (-1.6, 3.0)	0.49
Val 160 BID vs. Placebo	2.9 (0.2, 5.5)	0.015*	3.0 (-0.2, 6.2)	0.038	2.4 (0.1, 4.7)*	0.02

Source: Sponsor: Volume 14, Exhibit 8.1-1b. LS Mean= Least square mean change from baseline. According to the sponsor, there were no statistically significant treatment-by-baseline or treatment-by-center interactions.
*=statistically significant

Figure104-2. Placebo-subtracted change from baseline in PCWP by hour and treatment group (all randomized patients) (Day 28).

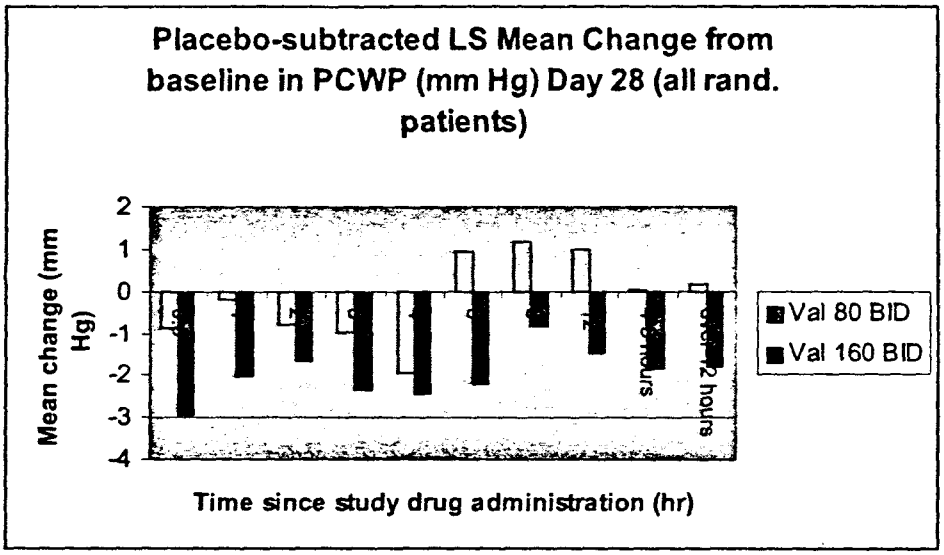
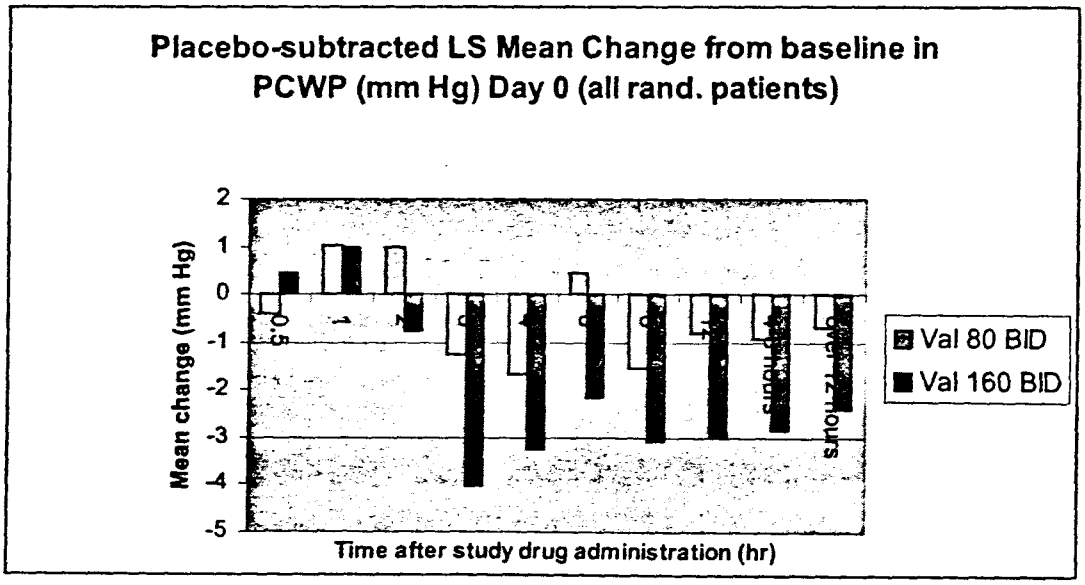


Figure 104-3. Placebo-subtracted change from baseline in PCWP by hour and treatment group (all randomized patients) (Day 0).



Source for Figures 2 and 3: Volume 14: Table 8.1:1a

Figures 104.2 and 3 show placebo-subtracted LS mean change from baseline in PCWP on Days 0 and 28. Statistically significant differences ($p < 0.025$ based on Bonferroni adjustment for 2 comparisons) were seen for valsartan 160 mg BID at 3, 4, and 8 hours, at 4-8 hours, and over 12 hours. Analysis of LS mean (placebo vs. valsartan) comparisons of changes from baseline PCWP on day 28 did not show statistically significant differences for either dose at any time point.

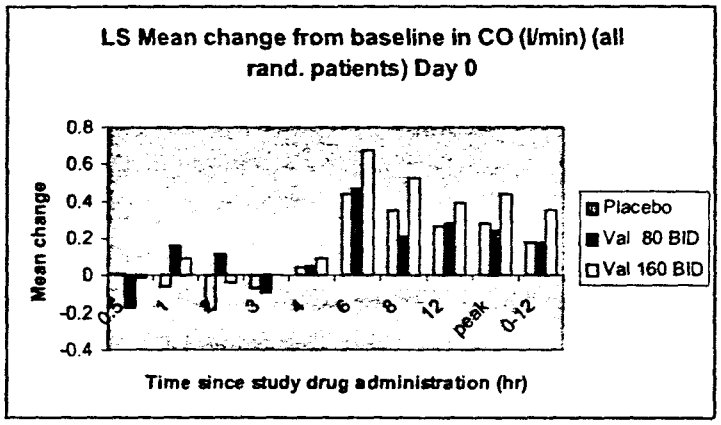
Seconday efficacy variables:

Hemodynamic measurements:

No statistically significant differences compared to placebo were noted in the analyses of CO, CI, and PVR. Significant changes from baseline were noted at 6 hours for placebo, valsartan 80 mg BID (both acute and chronic), and for valsartan 160 mg BID (Day 0 only).

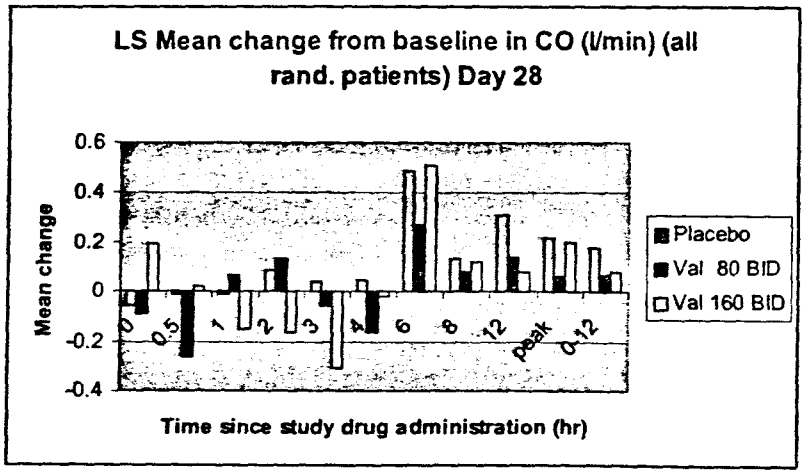
Cardiac Output:

Figure 104-4. LS Mean Change in CO (all rand. Patients) Day 0



Source for Figures 4 and 5: Volume 14: Table 8.1:2a

Figure 104-5. LS Mean change in CO (all rand. patients) Day 28



Changes from baseline in several secondary hemodynamic variable are difficult to interpret given the baseline differences between treatment groups. Therefore, they will not be presented here.

There were slight increases in heart rate in the placebo group (days 0 and 28) and slight decreases or no change in heart rate in the valsartan 160 BID group.

Neurohormone results:

Angiotensin II:: No significant differences were seen in the valsartan groups vs. placebo in the change from baseline (Visit 3, Day 0, hour 0) to selected time points on Day 0 or 28 for plasma renin activity (excluding degraded samples), angiotensin II (HPLC) (excluding degraded samples and outliers), atrial peptide, and serum norepinephrine (excluding degraded samples).

Analysis of plasma aldosterone showed significant decreases in both valsartan treatment groups compared to placebo at Day 28 (at 0, 6 and 0-12 hours). For valsartan 160 BID, significant decreases from baseline compared to placebo occurred on Day 0, 6 hours and Day 28, 12 hours as well. Given the effect of the drug, this would be an expected outcome.

Safety:

Deaths:

Patient ID	Site	Treatment	Study Day	Cause of Death
115	M0014T	Val 80 BID	Visit 4 (9/17/95)	Sudden Death at Home
158	M0019M	Val 160 BID	Visit 4 (12/5/95)	Cardiac Arrest

For further safety discussion please see the Integrated Summary of Safety.

For treatment-emergent adverse experiences please see the Integrated Summary of Safety.

Conclusions:

1. Significant decreases in PCWP were seen acutely for valsartan, compared to placebo, but not at Day 28.
2. Baseline differences between treatment groups made interpretation of results difficult.

Study 106: Multicenter, randomized, double-blind, placebo-controlled, parallel trial to assess the effect of valsartan on exercise capacity, quality of life, and signs and symptoms, in patients with stable, chronic, congestive heart failure (NYHA Class II-IV) (Phase III) (Protocol date: 12-16-96)

Source: Volumes 22 (Protocol); Volume 20 (study report); electronic datasets;

Sites: 120 centers (100 in US, 7 in South America, 13 in Canada)
Study Duration: August 18, 1997 (first patient enrolled) to May 23, 2000 (last patient completed).

Objectives:

- Compare effects of valsartan 40 mg bid, 80 mg bid, 160 mg bid and placebo, on the primary efficacy variables of exercise capacity and quality of life as well as on secondary variables including signs and symptoms of CHF, ejection fraction and NYHA class in patients with stable, chronic congestive heart failure (NYHA Class II-IV).
- Evaluate overall tolerability of each valsartan dose regimen in this patient population.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, parallel trial in patients with stable, chronic congestive heart failure (NYHA class II-IV), as shown in Figure xx. Patients were randomized to one of 4 treatment groups; during the first week postrandomization, the valsartan 160 mg bid group received valsartan 80 mg bid, and then, if standing SBP $\geq$ 80 mm Hg, underwent a forced titration to the 160 mg bid dose. The other treatment groups remained on their randomized dose of medication.
Patients received standard CHF background therapy and were stratified, at randomization, according to their use of ACE inhibitors as regular medications.

Figure 106-1. Study Design (106)

Screening/ washout	Single-blind placebo run-in	Double-blind treatment

⇓ Randomization

	Placebo	Valsartan 80 mg bid / Valsartan 80 mg bid / Valsartan 40 mg bid / Placebo
2 weeks	1-2 weeks	Valsartan 160 mg bid / Valsartan 80 mg bid / Valsartan 40 mg bid / placebo

Visit	1	(2)	3	4	5	6	7	8
Week	-2 to –1	-1 to 0	0	1	4	8	12	16

Inclusion Criteria:[6]	Exclusion Criteria:
• Males and females; ≥ 18 years of age, NYHA Class II-IV CHF diagnosed at least 3 months prior to Visit 1. Females must be postmenopausal for one year, surgically sterilized or using effective forms of contraception with negative pregnancy tests throughout the trial. • Resting ejection fraction < 35% on multiple gated acquisition radionuclide angiography (MUGA) obtained at/within one week prior to Visit 1. • Stable doses of heart failure medications for two weeks prior to Visit 1 and during placebo run-in period. • Ability to exercise between three and 14 minutes of a maximal exercise protocol (Modified Naughten Protocol) on each required exercise test (2-3 tests) during placebo run-in with an endpoint of fatigue or shortness of breath on each test. Two consecutive tests with a duration of exercise within 25% of each other are required for randomization. • Provide written informed consent.	• Pregnancy, nursing, or women of childbearing potential not practicing effective contraception. • Patients with: • Right heart failure due to pulmonary disease; • Postpartum cardiomyopathy; • Hemodynamically significant mitral stenosis or regurgitation (MR) except MR secondary to LV dilatation; • Hemodynamically significant obstructive lesions of LV outflow tract, including aortic stenosis and obstructive hypertrophic cardiomyopathy; • Infective cardiomyopathy (Chagas' disease); • Rapidly deteriorating or uncompensated heart failure; • Stroke, MI or cardiac surgery including percutaneous transluminal coronary angioplasty within past 3 months; • CAD likely to require CABG or PTCA; • unstable angina or angina precipitated by exercise within 3 months prior to Visit 1; • Hemodynamically significant or life-threatening VT occurring within 3 months prior to Visit 1 without current antiarrhythmic drug therapy; • Presence or history of any additional disturbance in cardiac rhythm, rate, or conduction which would contraindicate exercise testing or would likely result in premature discontinuation of exercise for arrhythmia; • Patients with pacemakers or automatic implantable cardioverter defribrillator (AICD); • Peristent standing systolic BP < 100 mm Hg; • Uncontrolled hypertension (BP persistently above 160/100 mm Hg); • Poorly controlled diabetes mellitus; • Serum creatinine > 2.5 mg/dl or SGOT > 3 times normal or other laboratory abnormalities indicative of serious disease other than CHF; • Limited ability to exercise for any reason other than CHF;

[6] Inclusion and Exclusion criteria were taken from the Protocol. Please see Protocol Amendments for changes to these criteria during the trial.

	• Serious lung disease likely to impact exercise capacity (patients with significant chronic obstructive lung disease may not be enrolled unless the FEV1/FVC > 0.60); • History of significant psychological symptoms or illness that would impact on exercise effort, compliance or self-assessment of well-being; • Any condition that would jeopardize evaluation of efficacy or safety; • Any condition that would be a contraindication to treadmill exercise; • Contraindication to use of angiotensin II antagonists; • Prior or current participation in valsartan CHF trials; • Other investigational drugs within 30 days prior to Visit 1; • The following medications within 3 months prior to Visit 1: angiotensin II receptor antagonists, chronic intermittent intravenous inotrope or vasodilator therapy; • The following medications within 2 weeks prior to Visit 1: beta-blockers except ophthalmic preparations in stable dosage, calcium channel blockers, drugs with potent vasodilatory effects (e.g. hydralazine, prazosin, and long acting nitrates);

Exercise Testing Criteria:

In order to be eligible for randomization, patients must have had two consecutive maximal exercise tests during the run-in period, both of which were terminated for dyspnea or fatigue, with exercise times between 3 and 14 minutes and with total exercise times that did not differ by more than 25% between the two tests. These criteria may be satisfied at Visits 1 and 2 or at Visits 2 and 3. If patients fail to meet stabilization criteria at Visit 2, a subsequent Visit 3 will be scheduled. If the criteria were met at Visit 3, then double-blind Visit 3 medication were to be dispensed after exercise testing and Visit 4 was to be scheduled. If the criteria were not met at Visit 3, then the patient was to be discontinued from the study.

Titration Criteria: All patients were to be evaluated at Visit 4 to determine eligibility to continue in the trial. If the average of three standing SBP readings, obtained two minutes apart, was not $\geq$ 80 mm Hg, then the patient was to be discontinued from the study (irrespective of treatment group).

Concomitant Medication: Patients should be on a stable pharmacologic CHF regimen for at least two weeks prior to Visit 1 and during the placebo run-in period. Permitted medications included diuretics, ACE inhibitors and digoxin. Excluded concomitant medications were: 1. Angiotensin II antagonists and chronic intermittent intravenous inotrope or vasodilator therapy within 3

months prior to Visit 1 and during the trial; 2. Beta blockers, calcium channel blockers and vasodilators (such as hydralazine and long-acting nitrates) during the two weeks prior to Visit 1 and during the trial. Patients requiring these drugs after enrollment were to be discontinued from the study prior to beginning treatment with the excluded medication.
Intermittent therapy with short acting drugs with acute hemodynamic effects (e.g., sublingual nitroglycerin, parenteral or aerosolized bronchodilators, oral or nasal decongestants) was permitted but these drugs were not to be administered within 6 hours prior to any visit.

Table 106.1. Schedule of Trial Procedures (106)

Period	Screen	Single-blind placebo			Double-blind treatment				
Visit		1	(2)	3 ⇓	4	5	6	7	8
Week		-2 to -1	-1 to 0	0	1	4	8	12	16
Informed consent	X								
History/Physical examination		X							
Adverse Experiences			X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X
Quality of Life Questionnaires		X	X	X	X	X	X	X	X
Interim/Final physical examination			X	X	X	X	X	X	X
NYHA Class		X	X	X	X	X	X	X	X
LV Ejection fraction (MUGA)		X							X
Signs/symptoms		X	X	X	X	X	X	X	X
12-lead ECG		X[1]							
CXR		X[2]							
Safety laboratory tests*		X				X	X	X	X
Chemistry only					X				
Serum pregnancy test (women of childbearing potential only)		X	X	X	X[3]	X[3]	X	X	X
Exercise tolerance test (ETT)**		X	X	X	X	X	X	X	X
Dispense trial medication		X	X	X	X	X	X	X	X
Termination sheet									X[4]

⇓ = Randomization *hematology, chemistry, urinalysis
**ETT was performed at approximately 12 hours after the patient's previous evening dose.
[1]Baseline ECG with interpretation. Additional ECGs will be done prior to each exercise test without a formal interpretation entered into the CRF.
[2]unless obtained within past 6 months.
[3]only for patients who discontinue prematurely from the study. [4]or earlier if premature discontinuation.

Signs and symptoms review: Signs and symptoms of CHF were to be reviewed by the physician at each visit with scores (absent/present) for paroxysmal nocturnal dyspnea, dyspnea at rest, dyspnea on effort, jugular venous pressure > 10 cm above right atrium, and third heart sound; edema, fatigue, rales and orthpnea were to be scored as prespecified in the protocol.

Safety monitoring: adverse experiences, routine laboratory evaluations, vital signs and body weight.

Criteria for removal of patients from trial:
1. Patient request;
2. When investigator considers it in the patient's best interest;
3. Intolerable adverse experiences;
4. Major protocol violation;
5. Noncompliance;

6. Development of hyperkalemia (> 5 mmol/L) or hypokalemia (< 3 mmol/L) refractory to treatment;
7. Deterioration of renal function with variation of serum creatinine of 50% as compared to baseline (Visit 1);
8. Development of any of the Exclusion criteria as above;
9. Development of any contraindication to exercise testing;
10. Persistent standing SBP < 80 mm Hg;
11. Symptoms due to hypotension (syncope, faintness, orthostatic dizziness).

Primary Efficacy Variables:

1. Change from baseline in mean exercise tolerance time (ETT), using a symptom-limited exercise tolerance test; baseline ETT was that obtained at the last visit of the placebo run-in period (Visit 2 or 3);
2. Change from baseline in overall score for the Minnesota Living with Heart Failure quality-of-life questionnaire (LHFQ).

Patients were to exercise on a calibrated treadmill according to a set schedule (prespecified in the protocol) and stopped exercising when they developed fatigue and/or dyspnea compatible with exhaustion and equal to a Borg scale of perceived exertion of 17-20. Within-patient variation was to be minimized by using the same operator for all ETT, maintaining a constant level of temperature/humidity, instructing the patient to use support rails for balance only, and using maximal testing unless safety reasons mandated termination.

Secondary Variables: 1. Signs/symptoms of CHF (PND, dyspnea at rest, dyspnea on effort, fatigue, orthpnea, JVP > 10 cm above right atriaum, edema, rales, or third heart sound); 2. Change from baseline in ejection fraction; 3. NYHA Classification; 4. Change from baseline in physical scores for the LHFQ; 5. Change from baseline in emotional scores for the LHFQ;

The LHFQ was to be self-administered under a specific procedure (as prespecified in the protocol). Patients unable to comprehend the questionnaire were to be excluded from this evaluation.

Statistical Plan:

Adjustment for multiple primary endpoints:
To achieve an overall significance level ≤ 0.05, an adjustment for two primary endpoints was to be made, with each primary endpoint tested at a 2-sided significance level of 0.02532, based on the Dunn-Sidak inequality ($\alpha' = 1 - (1-\alpha)^{1/2}$, where $\alpha' = 0.02532$ when $\alpha = 0.05$).

The null hypothesis tested is that there is no treatment difference among all valsartan doses and placebo versus the alternative hypothesis that at least one of the valsartan doses has a treatment effect different from placebo.

Sample Size Calculation: The sample size was determined to detect the following treatment difference for each primary endpoint with a power of > 80% at the two-sided significance level of 0.02532 (using the Dunnett's multiple-comparisons procedure adjustment for 3 treatments versus a control): 1. For ETT, a treatment difference of 55 seconds, assuming a standard deviation of 130 seconds; 2. For overall score of the Minnesota LHFQ, a treatment difference of 10 assuming a standard deviation of 24. These standard deviations, according to the sponsor, are estimated based on available clinical trial results. The sponsor has calculated a total of 540 completed patients (135 per treatment group); to allow for a 20% premature discontinuation rate, a total of

700 patients would need to be randomized in order to reach the targeted number of 540 patients completing the study.

Data Sets Analyzed:

1. ITT (all randomized patients who had baseline and post-baseline measurements for a given efficacy variable): The primary dataset for all variables was prespecified to include all randomized patients. For the primary efficacy variable of ETT, four analysis time points will be included: Week 8, Week 12, Week 16, and terminal visit (endpoint). Imputation for missing ETT measurements was to be made because of inability to walk due to severity of CHF or because of death; a value of zero was to be used for the missing ETT measurement. Otherwise, no value substitution will be made for the missing ETT measurement. The endpoint measurement consisted of the last value carried forward after imputation for missing ETT measurements. LHFQ scores (overall, physical, and emotional) will be analyzed at each visit as well as at endpoint. Signs/symptoms of CHF and NYHA classification will be analyzed at each visit as well as endpoint. Change from baseline in ejection fraction will be analyzed at the last visit only. No imputation for missing values is planned for these secondary variables. The endpoint (terminal visit) analysis is considered primary.

2. Clinically assessable patients (CAP) (all randomized patients who took double-blind study medication,did not violate specified protocol criteria, and had baseline and post-baseline measurements for a given efficacy variable): Results from clinically assessable patients will be analyzed at the endpoint (terminal visit) for the primary efficacy variables, ETT and overall LHFQ score. These analyses will be compared with the analysis of all randomized patients; the criteria for designating patients to be "clinically assessable" was to be determined prior to database lock for analysis.

Comparisons of valsartan versus placebo were based on a null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. ETT and overall LHFQ were the two primary efficacy endpoints to be analyzed for this trial. To adjust for multiplicity of two primary endpoints and to achieve an overall significance level of ≤ 0.05, each primary endpoint was analyzed at a 2-sided significance level of 0.02532 based on the Dunn-Sidak inequality: $\alpha' = 1 - (1-\alpha)^{1/2}$ (where $\alpha' = 0.02532$ when $\alpha = 0.05$).

Treatment group comparability:
Treatment group comparability was to be examined for the following variables using the Cochran-Mantel-Haenszel (CMH) chi-square test:

- Sex, race (White, Black, Other), significant medical history/other concomitant diagnosis (yes/no), CHF etiology (ischemic/nonischemic), background ACE inhibitor therapy (yes/no), background diuretic use at baseline (yes/no), background use of digoxin at baseline (yes/no), previous hospitalization for CHF (yes/no)

Treatment group comparability for all randomized patients was to be examined using the F-test for the baseline values of the following variables:

- Age, height, weight at Visit 1, duration of CHF.

Treatment group comparability for ETT, ejection fraction, and LHFQ scores at baseline will be examined using the F-test; treatment group comparability for baseline NYHA classification and signs and symptoms of CHF will be examined using the CMH chi-square test.

Primary Analysis, primary efficacy variable (ETT):
A two-factor ANCOVA was to be performed for change from baseline in ETT, with center and treatment group as factors and baseline mean ETT value and baseline ACE category (yes/no) as covariates. It was planned that treatment-by-center, treatment-by-baseline ETT, and treatment-by-baseline ACE category interaction terms will be included in this model. Missing ETT measurements during the double-blind period, because of inability to walk due to CHF or because of death, were given a value of zero. Otherwise, no value substitution was to be made for missing ETT measurements. After substitution for missing values, the last value will be carried forward for the endpoint (terminal visit) analysis.

Supplementary Analysis, primary efficacy variable (ETT):
A nonparametric analysis of ETT ranks was to be performed for robustness purposes (RANCOVA).

Analysis of primary efficacy variable (overall score LHFQ):
A two-factor ANCOVA was to be performed, with center and treatment group as factors and baseline overall LHFQ score and baseline ACE category (yes/no) as covariates. It is planned that treatment-by-center, treatment-by-baseline LHFQ, and treatment-by-baseline ACE category interactions terms will be included in the model. If a patient is missing 25% or less of the individual component scores for overall LHFQ at a visit, then the average of the available LHFQ component scores for the patient at that visit will be used in place of the missing component scores at that visit. If more than 25% of a patient's overall LHFQ component scores are missing at a visit, then the overall LHFQ value for the patient will be considered missing at that visit. After substitution for missing values, the last value will be carried forward for the endpoint (terminal visit) analysis.

Pooling of centers: Some centers may be pooled as necessary in order to achieve an examination of treatment-by-center interaction. Pooling was to be performed so that, for analysis of ETT change from baseline, all time points will have at least 3 randomized patients per treatment group in all pooled centers. A pooling algorithm was prespecified in the protocol.

Analyses of secondary efficacy variables: ANCOVA was to be used for analysis of change from baseline in ejection fraction as well as physical and emotional LHFQ scores. No imputation for missing values was planned for ejection fraction; the imputation for LHFQ scores was to be the same as described for overall LHFQ score.
A CMH chi-square test for different treatment means, adjusted for ACE category and baseline value, was to be used for analysis of NYHA class and signs/symptoms of CHF.

Amendments to the Protocol:

1. Amendment #1 (May 15, 1997 not signed): A) Changed sample size to approx. 700 patients randomized in order to obtain the 540 required patients who meet all randomization criteria, have baseline/post-baseline data for both primary efficacy variables, and completed all visits per protocol. B) Modified ETT inclusion criteria of exercise duration based on age (18-29 years, exercise duration of 3-14 mins; 30-50 years, duration of 3-12 mins; over 50 years, duration of 3-10 mins). C) Amended exclusion criterion for chronic obstructive lung disease (ratio of FEV1/FVC > 0.60 and FVC is > 60% of predicted). D) Amended randomization assignment numbers to country-specific sequences and included stratification. E) Amended recording of concomitant therapy to include all medications, including non-drug and non-prescription therapies. F) Added recording of exercise-related AE on the CRF.

2. Amendment #2 (May 8, 1998 not signed): A) Revised enrollment and randomization numbers for centers in the US and South America. B) Changed washout period (from 2 weeks) to 1-3 weeks. C) Amended inclusion MUGA result (from < 35% within 1 week prior to Visit 1) to ≤ 40% within 2 weeks of Visit 1. D) Included as background medications vasodilators (hydralazine and long-acting nitrates), alpha-adrenergic blockers and calcium channel blockers at a stable dose beginning at least 1 week prior to the MUGA scan. E) Eliminated exclusion of pacemaker or AICD.
3. Amendment #3 (signed, November 19, 1998): A) Added "that patients should be on a stable beta-blocker dose beginning at least one week prior to the baseline qualifying MUGA through the randomization visit. " B) Removed beta-blockers from excluded medications.
4. Amendment #4 (January 24, 2000, not signed): A) Added enrollment and randomization numbers for USA; B) Changed sample size calculation to include statistical adjustment for two primary endpoints, based on the Dunn-Sidak inequality, using a 2-sided significance level of 0.02532 for each primary endpoint. For each primary endpoint, a further sample-size adjustment was made for comparing 3 valsartan doses versus placebo based on Dunnett's procedure. C) Revised methods of adjustment for multiple endpoints and multiple comparisons. Stated a joint null hypothesis consisting of the two individual null hypotheses (for each primary endpoint, respectively) with testing based on Hochberg's multiple-testing step-up procedure to ensure an overall α-level at 0.05. Planned imputation for post-baseline ETT separately for each ACE category (assigning the lowest rank to death, next lowest rank to patients unable to walk possibly due to CHF, next rank to patients unable to walk due to reasons other than possibly due to CHF, and the next rank to patients who can walk). D) Analysis of LHFQ and imputation of missing values: For patients completing all 21 individual scores, the overall score will be the sum of the corresponding 21 individual scores. A patient missing more than 25% of individual scores will have a missing overall LHFQ for that visit. If a patient is missing 25% or less of individual scores at a visit, then the average of the non-missing individual scores for the patient at that visit will be used in place of the missing individual scores at that visit. E) Analysis of the two secondary LHFQ scores will be analogous to analysis of the overall LHFQ score. F) Pooling was to be performed so that, for the change from baseline for ETT and LHFQ, all common analysis time points will have at least 3 randomized patients available per treatment group in all pooled centers.

Results:

Patient Disposition:

Nine hundred five patients were enrolled. One hundred thirty-five were discontinued during the placebo run-in period (23 for an adverse experience, 6 for an abnormal laboratory value, 2 for abnormal test procedure results, 88 because they did not meet protocol criteria, 2 for noncompliance, 10 for withdrawal of consent; 3 were lost to follow-up and 1 patient died). Of those randomized, 83-85% of patients were from the US, 8-10% from Canada, and 7-8% from Argentina. There were no meaningful differences between treatment groups.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-665, and NDA 21-283 and finds the clinical pharmacology and biopharmaceutics section acceptable.

We recommend a bioequivalence waiver be granted for the 40 mg tablet. The 40 mg tablet should have similar dissolution specifications as the other strengths:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q = [ ] in 30 minutes

OCPB briefing held on August 28, 2001.
(Mehul Mehta, Patrick Marroum, and Nhi Nguyen were present.)

/S/

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I

/S/

Shari Targum, M.D.
Division of Cardio-Renal Drug Products

FT Initialed by Patrick Marroum, Ph.D._____
CC list: HFD-110: NDA 20-665 (SE1-016) and NDA 21-283 (SE1-001); HFD-860: (Mehta);
CDER Central Document Room

SUMMARY

Novartis submitted a heart failure efficacy supplement (SE1-016) to NDA 20-665, valsartan capsules (Diovan®), an angiotensin II receptor antagonist of the AT_1 receptor subtype. The efficacy supplement for NDA 20-665 contains five controlled studies (protocol 104, 106, 107, 107a, 103 and 110) and two descriptive pharmacokinetic studies, a single dose (protocol 102) and a multiple dose (protocol 105) study in heart failure patients.

Valsartan is approved for the treatment of hypertension and is currently available in 80 and 160 mg hard gelatin capsules. After approval of the CHF efficacy supplement, the sponsor intends to remove the capsules, and market film-coated tablets. The sponsor recently received approval for the 80, 160 and 320 mg tablets for the treatment of hypertension under NDA 21-283. The sponsor demonstrated bioequivalence of 2x 160 mg capsules with the 320 mg tablets and received biowaivers for the 80 and 160 mg tablets. Since the proposed starting dose for CHF is 40 mg q 12 hours, the sponsor is seeking a BE waiver for the 40 mg tablet (NDA 21-283 /SE1-001).

The pharmacokinetics are similar between patients with CHF and healthy volunteers with respect to linearity, Tmax (~3 hours), T ½ (~6.5 hours) and age effects. Linearity is evident with twice daily doses and single doses of 40 – 160 mg. Valsartan clearance was ~ 10-20% lower in elderly patients with CHF compared to young patients with CHF.

There are several differences in valsartan pharmacokinetics between healthy volunteers and patients with CHF. Clearance of valsartan appears to be reduced ~50% in patients with CHF compared to healthy subjects (~4.5 L/hr vs. 2.2 L/hr, respectively). Cmax and AUC are ~1.3 – 2 x higher in patients with CHF compared to healthy volunteers. Accumulation of valsartan is slightly greater (1.7 vs. 1.3) in patients with CHF when dosed at 40 to 160 mg twice daily compared to once daily in hypertensives.

A biowaiver for the 40 mg tablet is granted since the tablets are compositionally proportional, valsartan exhibits linear pharmacokinetic characteristics, and the in vitro dissolution profiles are similar across the different strengths. The approved specifications for all dosage strengths are:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q = [ ] in 30 minutes

Valsartan concentrations were determined by a validated HPLC method. The assay used was precise, accurate, sensitive and linear over the concentration range of 5.0 – 5,000 ng/mL.

APPENDIX I: Review of individual studies

Study 102. An Open-Label, Placebo-Controlled, Dose Ranging Trial to Determine the Acute Central Hemodynamic Effects of CGP 48933 in Patients with Stable, Chronic, Congestive Heart Failure (Phase II) (Protocol date: September 30, 1992)

This study was jointly reviewed with the medical officer, Dr. Shari Targum.

Source: NDA Volume 12 (Study Report and Tables), 13 (Protocol); no .xpt datasets were submitted.
Valsartan and CGP48933 will be used interchangeably in this review.

Primary Objectives:
1. Evaluate, by right heart catheterization, central hemodynamic effects of single, open-label doses of CGP 48933 (valsartan) 10, 20, 40, 80 and 160 mg compared to placebo up to 24 hours after dosing, in patients with stable chronic congestive heart failure with a NYHA classification of III or IV.
2. Evaluate safety and tolerability of single open-label doses of CGP 48933 10, 20, 40, 80, and 160 mg in patients with stable chronic congestive heart failure.

Secondary Objectives:
1. Obtain preliminary information on correlation between plasma levels of CGP 48933 and its acute central hemodynamic effects compared to placebo.
2. Obtain preliminary information on effects of CGP 48933 on plasma renin activity, plasma aldosterone, and plasma angiotensin II concentration up to 24 hours after dosing, compared to placebo, and correlate these effects with its acute hemodynamic actions.

Sites: 3 centers in the US.

Duration: March 12, 1993 (first patient, first visit) to April 4, 1994 (last patient, last visit)

Study Design:
This was a single-dose, open-label, randomized parallel-group study in patients with Class III or IV CHF. Chronic CHF medications were allowed until 2 days prior to dosing; at that time, ACE inhibitors, vasodilators and inotropic agents (except digoxin) were discontinued. On the day of dosing, diuretics were held and digoxin was allowed; antiarrhythmics were allowed throughout the study. Patients were to fast 9 hours prior to dosing. Randomized patients underwent right heart catheterization, via Swan-Ganz catheter, as well as arterial cannulation. After stable baseline hemodynamic measurements, patients were given a single dose of drug or placebo, and central hemodynamic and neurohormonal measurements were taken at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. After all measurements were taken, the lines were removed, patients resumed their prior medications, and were discharged to follow-up one week after dosing.

Figure 1. Treatment algorithm

	CGP 48933 10 mg (N=5) CGP 48933 20 mg (N=4) CGP 48933 40 mg (N=3) CGP 48933 80 mg (N=4) CGP 48933 160 mg (N=5) Placebo (N=4) ⇓			
Visit	1	2	3	4
Day	-14 to -3	-1	0	7
Hour			0	

N=number randomized

Inclusion Criteria[1]	Exclusion Criteria
• Male or female patients 18 to 80 years. • Chronic stable CHF, present for at least 4 weeks, NYHA Class III or IV, and ejection fraction $\leq$ 35%, determined by MUGA (determined up to 6 weeks prior to enrollment if interval-free of intercurrent events). Patients on background therapy should be on stable doses for at least 2 weeks prior to entry into the trial. • Must be able to tolerate discontinuation of ACE inhibitors, vasodilators, and positive inotropes (except digoxin) for 3 days and diuretics for 24 hours.	• Female patients of childbearing potential. • History of acute MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 4 weeks prior to entry into study. • Angina pectoris requiring more than 5 tablets/week of prn sublingual nitroglycerin. • Clinically significant primary valvular dysfunction. • Presence or history of restrictive cardiomyopathy, constrictive pericarditis, dyspnea of non-cardiac origin, gastrointestinal disease or surgery which would impair drug absorption, any condition/lab abnormality which would interfere with this study. • Complex or life-threatening ventricular arrhythmias. • Clinically signficant renal, hepatic, or hematologic disorders, unless consistent with CHF. • Uncontrolled hypertension (BP $\geq$ 160/100). • Unstable insulin-dependent diabetes mellitus. • Presence/recent serious psychiatric disorder, personality problem or living condition suggesting that the patient would be unable to participate fully in this trial. • Inability to discontinue long-acting nitrates, positive inotropes, vasodilators, beta blockers, calcium channel blockers, ACE inhibitors and diuretics.

Randomization criteria (patients must meet all criteria in order to be randomized):

1. All baseline hemodynamic measurements were to be repeated at 20 minute intervals until 2 consecutive sets of heart rate (HR), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) measurements were within 10%, respectively. A maximum of 5 sets of measurements were to be done. If the fifth set of measurements was not within 10% of the fourth set, then the patient was to be discontinued from the trial.
2. The patient was to be clinically stable (i.e., no complications from Swan-Ganz or arterial cannula insertion, or change in any concomitant condition).
3. PCWP on the second set of measurements had to be $\geq$ 15 mm Hg.

[1] Taken from Protocol. Please see Amendments to the Protocol for changes in Inclusion/Exclusion criteria.

Sample Size: This study was to have a total of 36 evaluable patients, defined as those who satisfied entry criteria and completed all visits. There was no sample size calculation.

Primary Efficacy Variable:
Change from baseline in PCWP and CO measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

CO was determined by taking 5 measurements, excluding highest and lowest values, and averaging the remaining 3 values.

Secondary Efficacy Variables:
1. Change from baseline in right atrial pressure (RAP), diastolic, systolic and mean pulmonary artery pressure (PAP),CI, SVR, PVR, SVI, heart rate, and systolic, diastolic and mean systemic blood pressure (MAP) measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
2. Change from baseline, compared to placebo, in plasma renin activity, plasma aldosterone and plasma angiotensin II activity measured at 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.
3. CGP 48933 blood levels at 1, 2, 3, 4, 6, 8, and 12 hours after dosing.

CI, SVR, SVI, and PVR were calculated from formulas that were prespecified in the protocol.

Statistical Plan: There were no prespecified statistical analyses or interim analysis.

Safety Variables:
Physical examination (all visits), body weight (all visits), adverse experiences, laboratory testing (CBC, chemistry, urinalysis at Visits 1, 2, 3, 4), 12-lead ECGs (Visits 1 and 3), CXR(Visit 1), MUGA scan (within 6 weeks of Visit 1 or before Visit 2).

Laboratory: Central laboratory (National Health Laboratory).

Amendments to the Protocol (not signed):
1. (not dated) Under "presence of clinically significant renal, hepatic, or hematologic disorders" Specified exclusion criteria of hemoglobin < 10 g/dl.
2. (not dated). Changed entry criteria to "patients who are clinically stable for one week prior to entry into the trial" with stable background medications for 1 week prior to discontinuation of ACE inhibitors and diuretics.

Drug Supply: Drug Supply was provided by Ciba-Geigy. Batch and formulation numbers are as follows:

Table 1. Supply batch and formulation numbers

Treatment group	Batch Number	Formulation Number
Valsartan 10 mg	E-14937	H-3573
Valsartan 20 mg	E-14938	H-3574
Valsartan 40 mg	E-14939	H-3575
Valsartan 80 mg	E-14940	H-3576
Valsartan 160 mg	E-14941	H-3577
Placebo	E-14942	H-3577

Source: Sponsor: Volume 12 (Study report)

Medication was started on Visit 3 (Day 0) after all baseline measurements. All doses were administered in the fasting state with direct supervision.

Assay:
The assay used was precise, accurate, sensitive and linear over the concentrations of 5 – 3000 ng/mL (see table below). Plasma valsartan concentrations were determined by a validated HPLC method. The analysis was done at the laboratories of Bioanalytics and Pharmacokinetics, Rueil-Malmaison, France from January 24, 1994 to March 18, 1994.

Table 2. Quality of assay

	Precision (%)	Accuracy (%)	Sensitivity (ng/mL)	Linearity (ng/mL)
Valsartan	CV < 18%	Within 5%	5.00 – 3000	0.9987

Results:

Patient Disposition:
Thirty two patients were enrolled at Visit 1; seven patients were discontinued prior to randomization (6 did not meet protocol criteria and 1 withdrew consent). Twenty-five patients were randomized at Visit 2 and all completed the study; all were included in efficacy and safety analyses.
Of the baseline characteristics, all were NYHA Class III.

Protocol violations:
A total of 6 randomized patients were noted to have protocol violations related to entry criteria. These included: consecutive PCWP not within 10% (Valsartan 40:1 patient); HR measurements not within 10% (Valsartan 80: 1 patient; Valsartan 160: 1 patient); inducible VT (Valsartan 10: 1 patient); screening visit ejection fraction of 36% (Valsartan 160 mg: 1 patient); woman of childbearing potential (valsartan 40: 1 patient).

Baseline characteristics:
As seen in the table below, this was a mostly male population with a small sample size per treatment arm. Of note, mean baseline PCWP were not uniform, with a higher baseline in the placebo group; hence, interpretations of changes from baseline will be confounded by these baseline differences in the treatment groups.

There are also baseline differences between treatment groups in mean weight, duration of CHF, plasma renin activity as well as plasma aldosterone.

Table 3 . Baseline characteristics

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Male (%)	4 (100)	3 (60)	4 (100)	2 (67)	4 (100)	5 (100)
Race:						
Caucasian	2(50)	2 (40)	1 (25)	0	0	1 (20)
Black	2 (50)	3 (60)	3 (75)	3 (100)	4 (100)	4(80)
Mean age (+SD)	48 (10)	44 (12)	54 (9)	50 (10)	55 (15)	54 (13)
Mean weight (lbs)	202 (32)	170 (26)	200 (53)	167 (51)	216 (53)	152 (17)
Mean duration CHF (yrs)	4 (3)	5 (4)	7 (2)	4 (2)	3 (2)	4 (4)
Etiology: Ischemic	1 (25)	1 (20)	1 (25)	0	2 (50)	2 (40)
Idiopathic	1 (25)	2 (40)	1 (25)	2 (67)	2 (50)	1 (20)
Hypertensive	1 (25)	0	2 (50)	0	0	2 (40)
Other	1 (25)	2 (40)	0	1 (33)	0	0

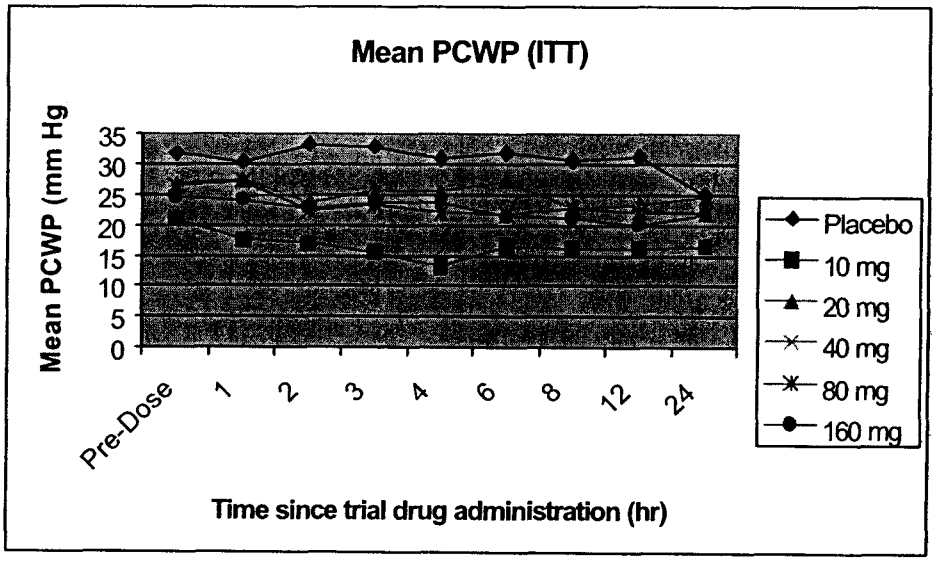
Table 3. Baseline characteristics (cont.)

	Placebo N=4	10 mg N=5	20 mg N= 4	40 mg N=3	80 mg N=4	160 mg N=5
Mean Baseline* PCWP (mm Hg) (+ SD)	31.8 (5)	21.0 (8)	26.8 (7)	25 .0(7)	26.5 (6)	24.6 (8)
Mean Baseline* CO (l/min) (+ SD)	3.9(1)	4.2 (1)	3.6(0.6)	4.1 (0.5)	4.0 (1)	4 (0.9)
Mean Baseline* plasma renin activity	6.1(6)	3.1 (4)	2.6 (3)	0.2 (0.2)	3.8 (3)	3 (6)
Mean baseline* plasma Aldosterone	12 (12)	6 (7)	13 (5)	8 (4)	6.8 (4)	17.2 (29)
Mean baseline* plasma Angiotensin II	34.3 (12)	30.6 (20)	31 (22)	27 (8)	48 (31)	34.4 (18)

Source: Volume 12: Tables 7.1:1, 7.1:2, , 8.1:1A, 11.1:2A *Baseline =Pre-Dose value

Primary efficacy variable:
Figures 2-5 show the primary efficacy variables, including change from baseline, over time.
The placebo group, with the highest mean value at baseline, also shows the largest decrease at 24 hours.
A dose-response relationship was not seen.

Figure 2. PCWP over time (ITT)



Source for Figures 2 and 3: Volume 12: Tables 8.1:1A, 8.1:1B

Figure 3. Change from baseline in PCWP

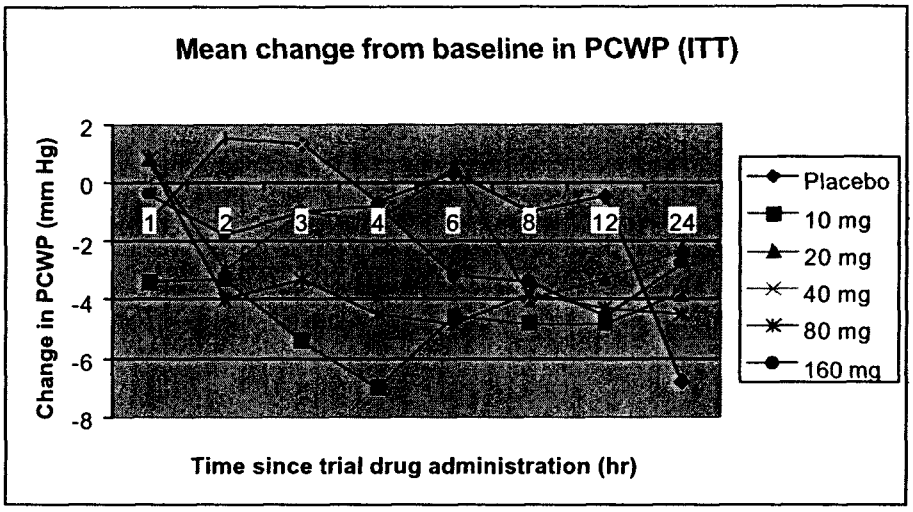
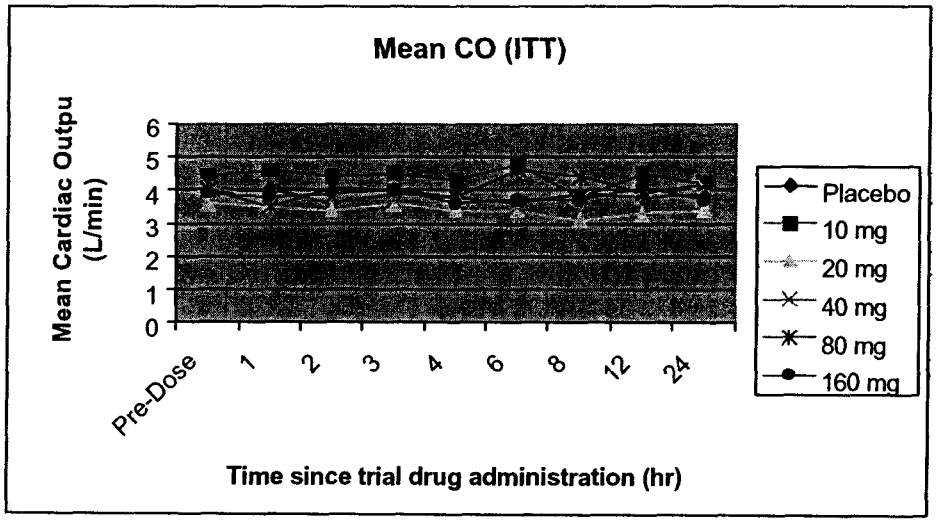


Figure 4. Cardiac Output (CO) over Time (ITT)



Source for Figures 4 and 5: Volume 12: Tables 8.1:1Aand 8.1:1B

Figure 5. Change from baseline in Cardiac Output (ITT)

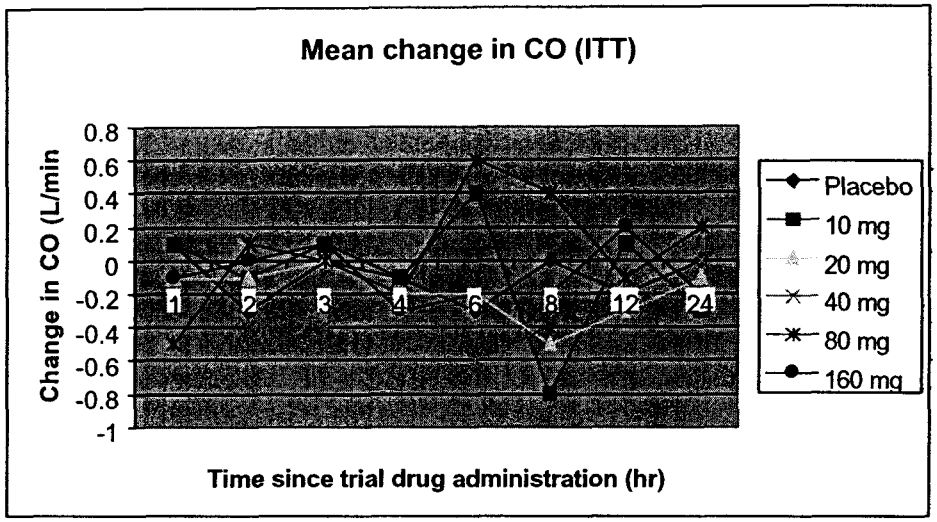


Table 4. Primary Efficacy Variables: Change from Baseline at 24 hours (ITT)

	PCWP	CO
	Change from baseline at 24 hours	Change from baseline at 24 hours
Placebo	-6.8 (2.4)	-0.04 (1.4)
Valsartan 10 mg*	-3.8 (3.3)	-0.3 (0.8)
Valsartan 20 mg	-2.3 (7.4)	-0.1 (0.8)
Valsartan 40 mg	-3.7 (2.1)	-0.03 (0.6)
Valsartan 80 mg	-4.5 (6.9)	0.2 (0.9)
Valsartan 160 mg	-2.8 (7.0)	-0.2 (1.5)

Source: Volume 12: Study Report and Table 8.1:1B * patient 11/507 did not have 24 hour efficacy measurements and was not included in this table.

The above table shows change from baseline at 24 hours for both primary efficacy variables. For PCWP, the placebo group had the highest pre-dose values and showed the largest change from baseline at 24 hours.

Secondary efficacy variables:
The secondary efficacy variables were reviewed. No dose-response relationship or significant changes from baseline compared to placebo could be ascertained; this result may be due in part to the small sample size as well as baseline differences. Therefore, these data will not be presented.

Neurohormone results:
Neurohormone results over time are represented in the next figures. It should be noted that the valsartan 40 mg group, unlike the other groups, shows unusually flat neurohormonal responses.
There appear to be elevations in plasma renin activity and angiotensin II at the higher doses, although a clear dose-relationship is not seen.

Figure 6. Plasma Renin Activity (PRA)
Source: Volume 12: Table 11.1:2A

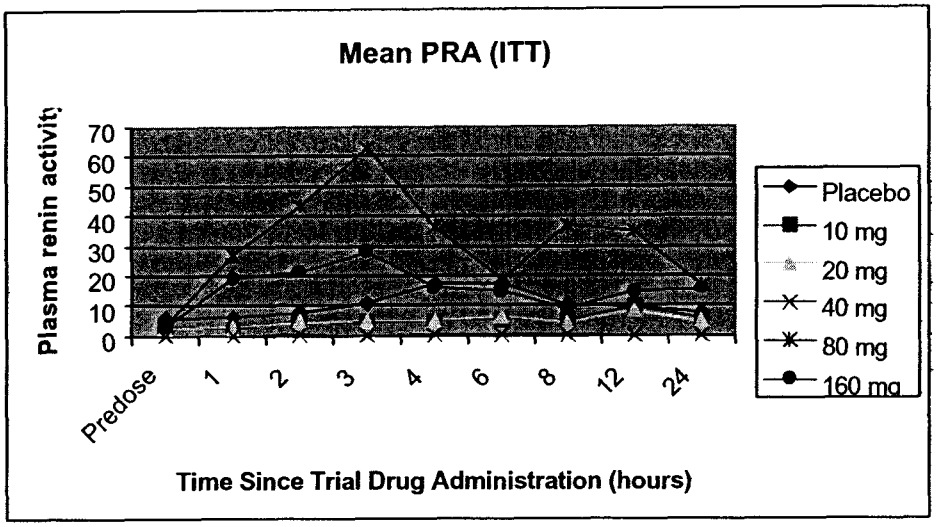
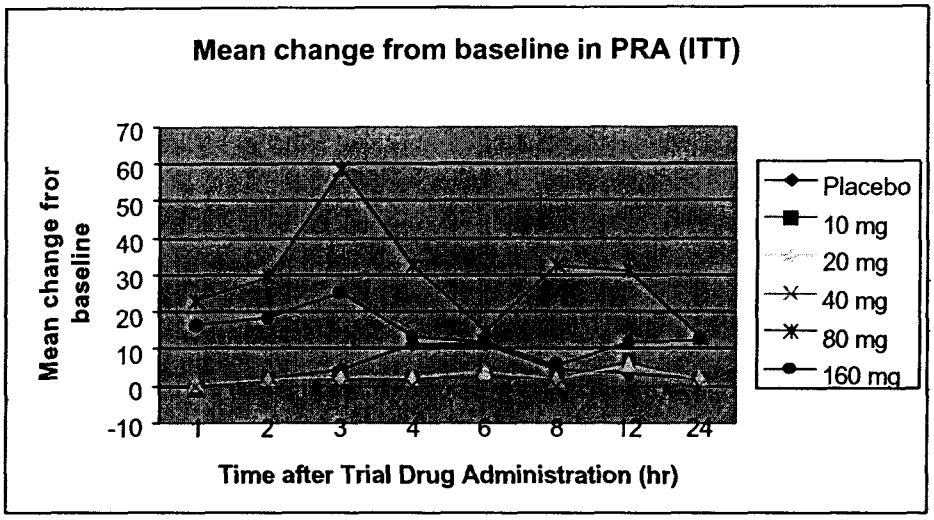


Figure 7. Change from baseline in Plasma Renin Activity (PRA)



Source: Volume 12: Table 11.1:2B

Figure 8. Plasma Angiotensin II

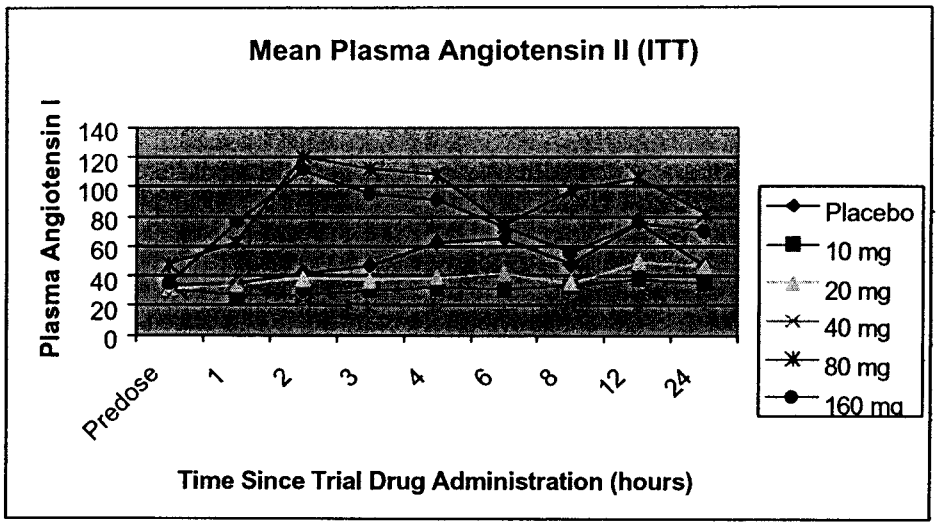
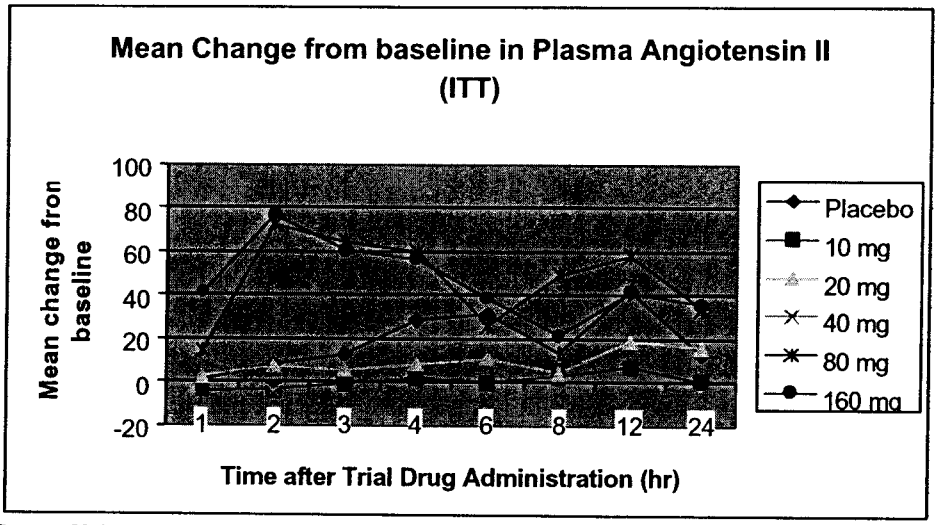


Figure 9. Change from baseline in Angiotensin II



Source: Volume 12: Tables 11.1:2A and B

Figure 10. Plasma Aldosterone

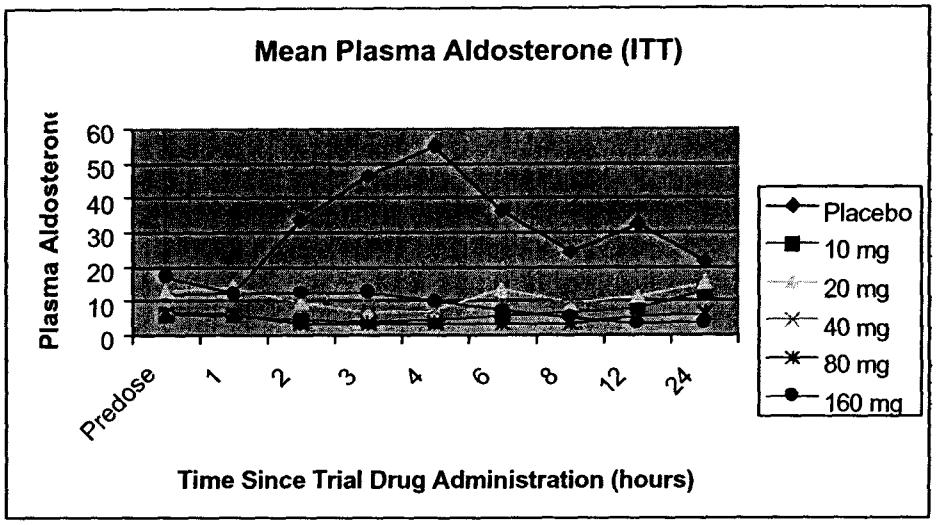
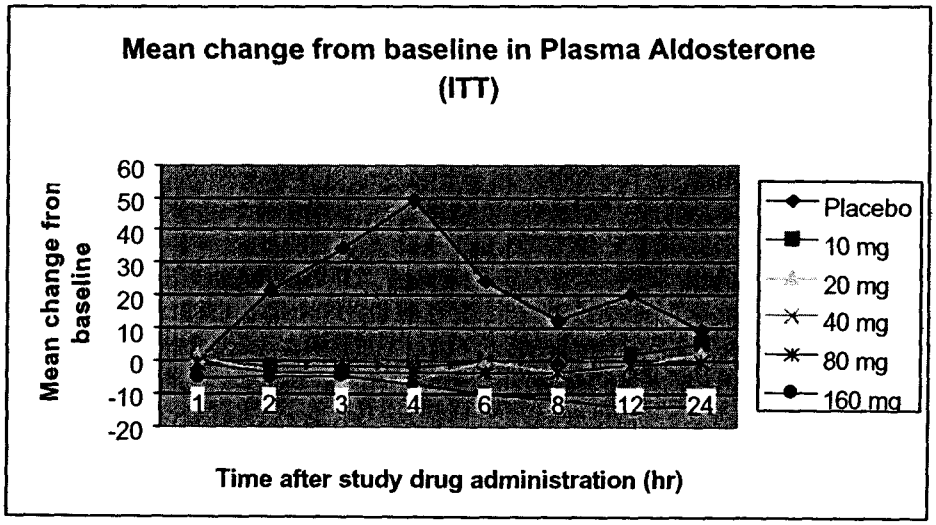


Figure 11. Change from Baseline in Plasma Aldosterone



Pharmacokinetic/pharmacodynamic results

The pharmacokinetic data are highly variable (see table 5). Cmax was reached ~ 3 hours after dosing.

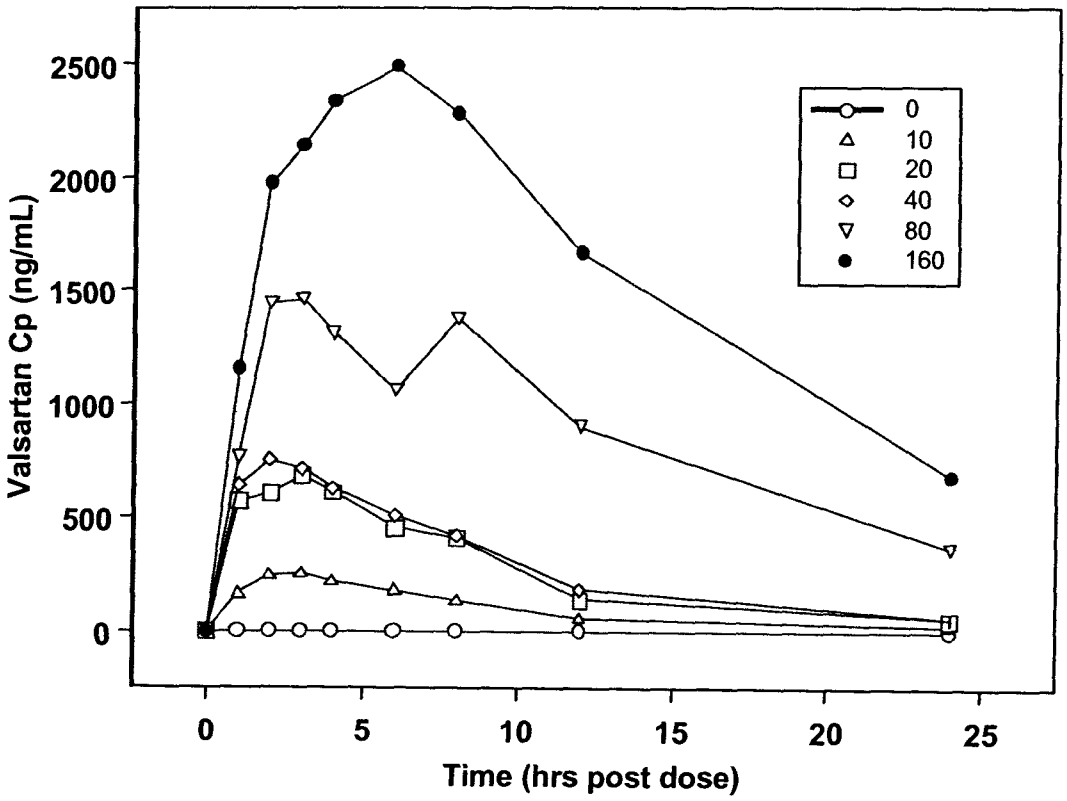
Table 5. Mean pharmacokinetic parameters

Dose (mg)	N	Cmax (ng/ml)			Tmax	(hr)	AUC (0-24 hr) ng x hr/ml		
		Mean	SD	CV (%)	Median	Range	Mean	SD	CV (%)
10	5	280	68	24	3	2-6	2380	370	16
20	2	684	149	22	2.5	2-3	6380	2750	43
40	3	843	308	36	2	1-8	7150	1430	20
80	4	2150	1490	69	3	2-8	21200	18900	89
160	4	2770	1130	41	6	1-6	38000	25000	66

Source: Sponsor: Volume 12: Study Report

Valsartan exhibits a 2-compartment pharmacokinetic model as shown by the shape of the plasma concentrations time curves in Figure 12.

Figure 12. Valsartan plasma concentration vs. time after single dose



Individual Cmax and AUC were fitted using NONMEM (ver 5.0, level 1.1) to the following equation:

$$Y = \alpha * Dose^{\beta}$$

where Y is the predicted Cmax or AUC, α is the slope of the fit and β determines the linearity of the fit. The parameter estimates are shown in Table 9.

Single doses of valsartan are dose proportional over the range of 10 mg to 160 mg. βeta for both Cmax and AUC are close to one, suggesting that valsartan exhibits linear pharmacokinetics over the concentration range of 0-2500 ng/mL. The 95% confidence interval for Cmax is (0.732, 1.128) and for AUC is (0.962, 1.258). The residual error estimation is ~43% and ~50% for Cmax and AUC, respectively, implying that a considerable portion of the variability is unexplained by the model. Although valsartan exhibits linear pharmacokinetics, it should be noted that the pharmacokinetics are quite variable.

Table 6. Summary of model parameter estimates

	Cmax (ng/mL)		AUC (ng*hr/mL)	
	α	**β**	**α**	**β**
Mean	31.9	0.93	165	1.11
SE (%)	26.3 %	9.4	27.6 %	8.4 %
Residual error (CV%)	42.5 %		50.5 %	
SE (%)	28.2 %		30.0 %	

Figure 13. Observed and predicted AUC at five different doses

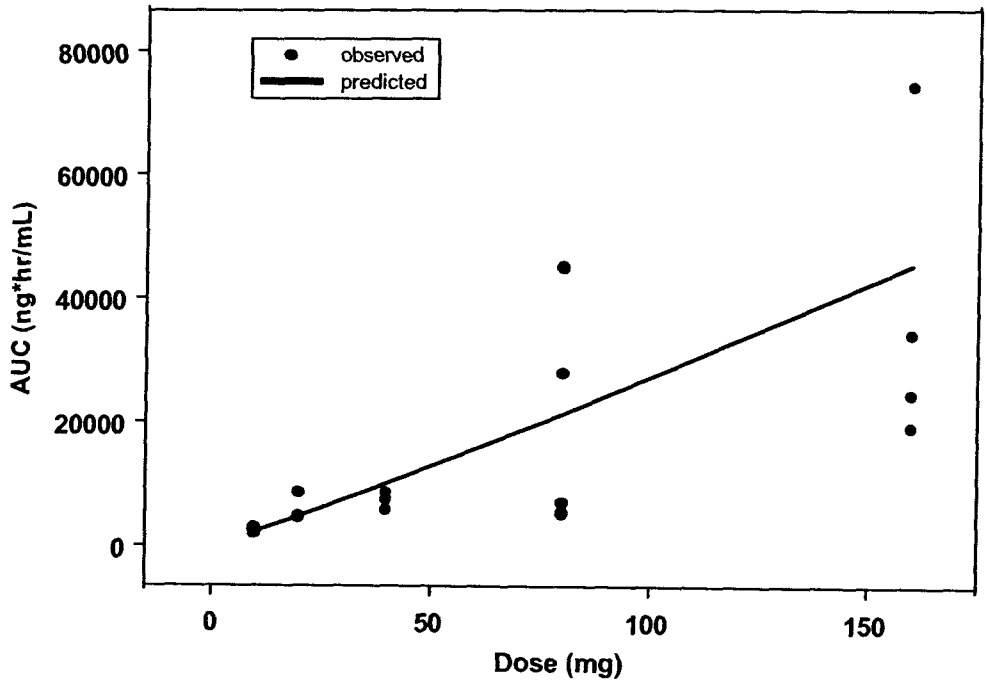
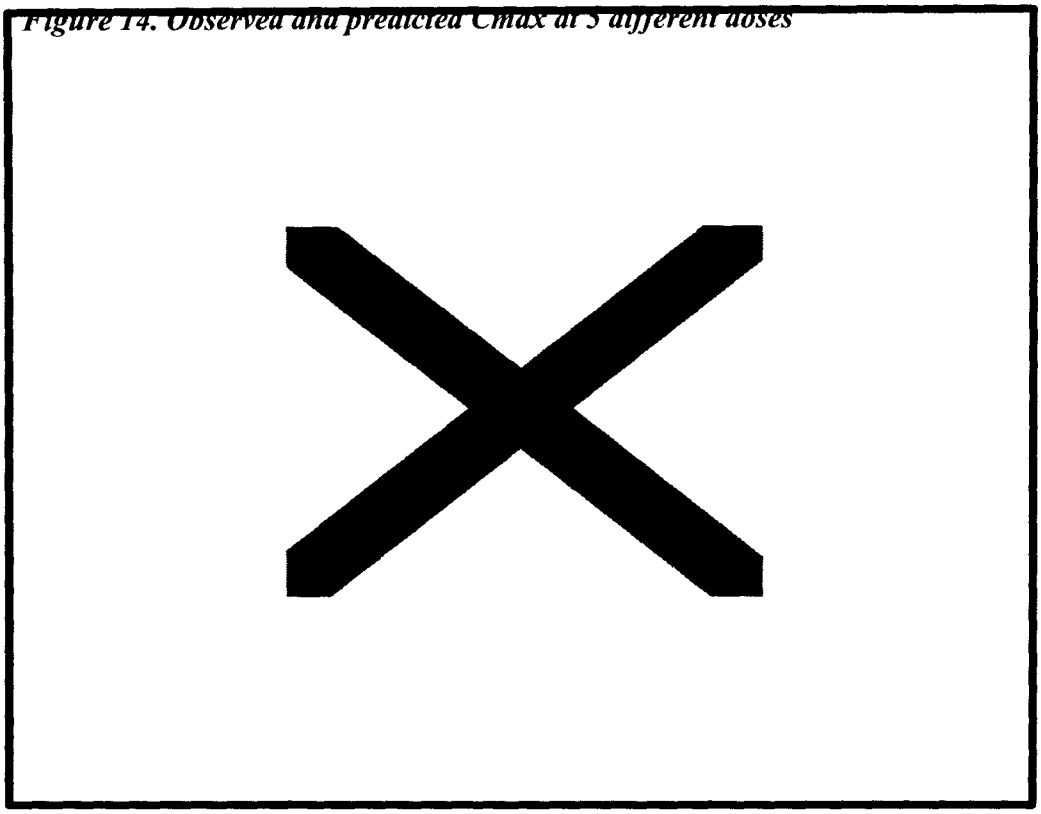


Figure 14. Observed and predicted Cmax at 5 different doses



There was not an evident PK/PD relationship with PCWP or CO.

Figure 15. Mean PCWP and valsartan concentration relationship

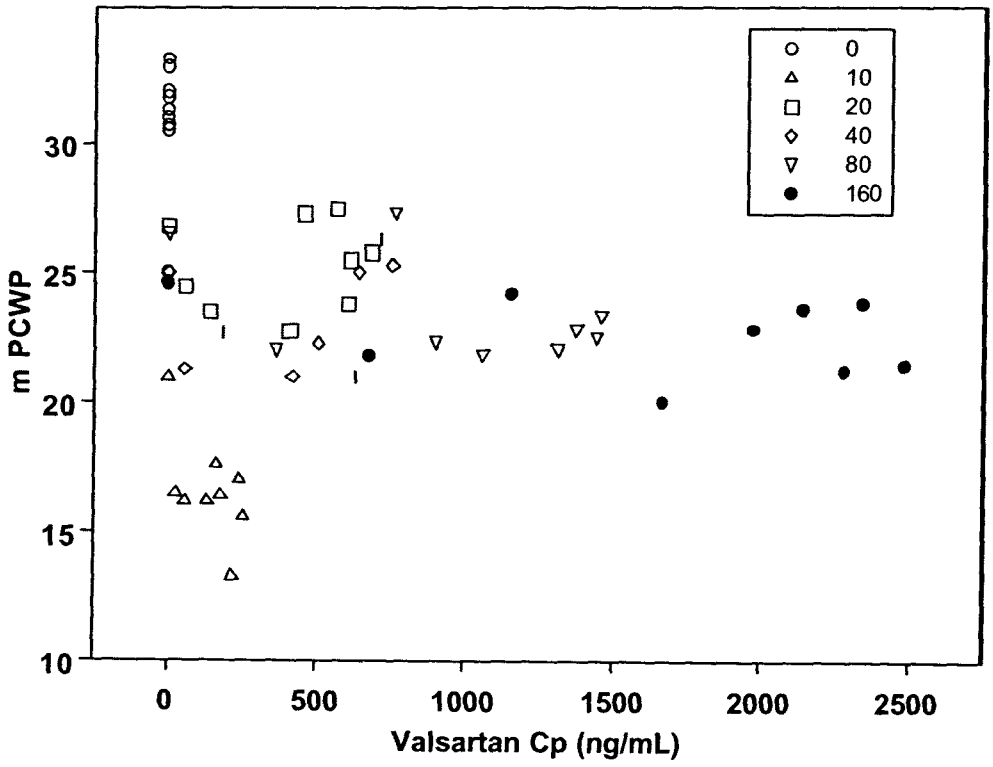
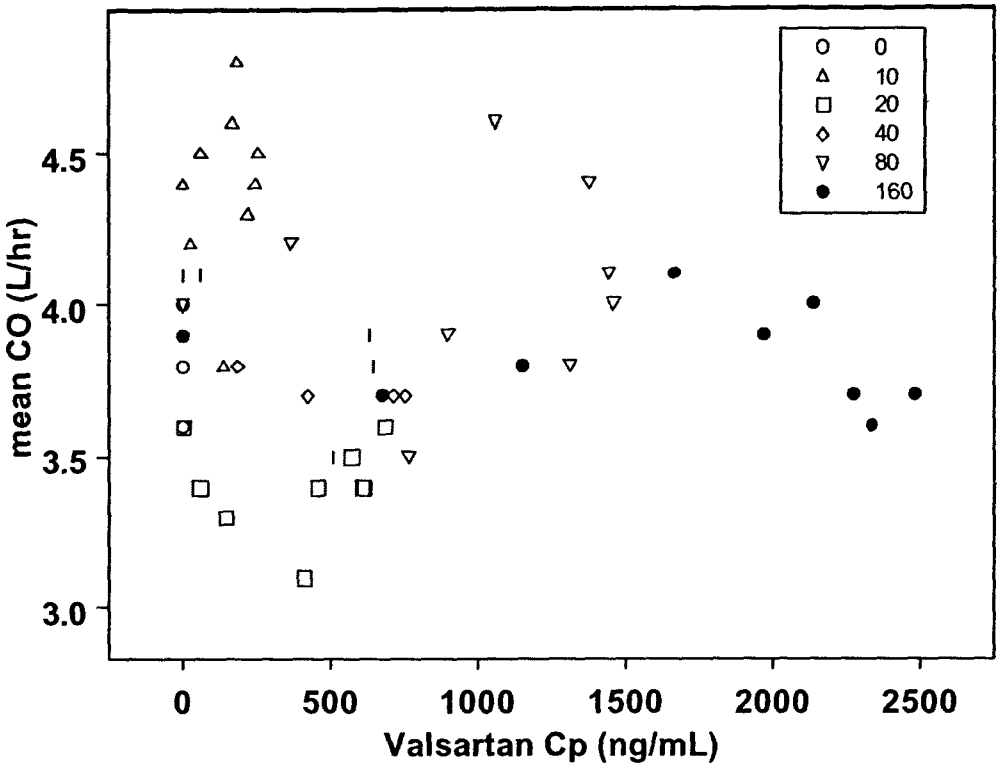


Figure 16. Mean CO and valsartan concentration relationship



There was a slight trend in the placebo-adjusted change from baseline PRA, aldosterone and angiotensin II (see figures 17, 18, and 19).

Figure 17

PK/PD relationship for plasma renin activity

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma renin activity (ng/mL/hr) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

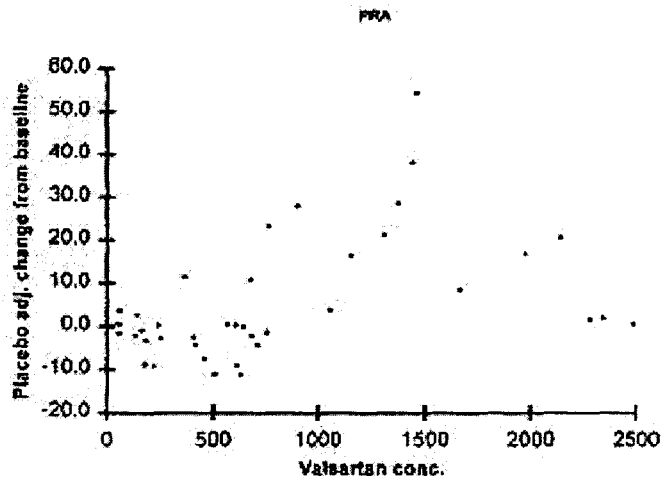


Figure 18

PK/PD relationship for plasma aldosterone concentration

Plot of plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.

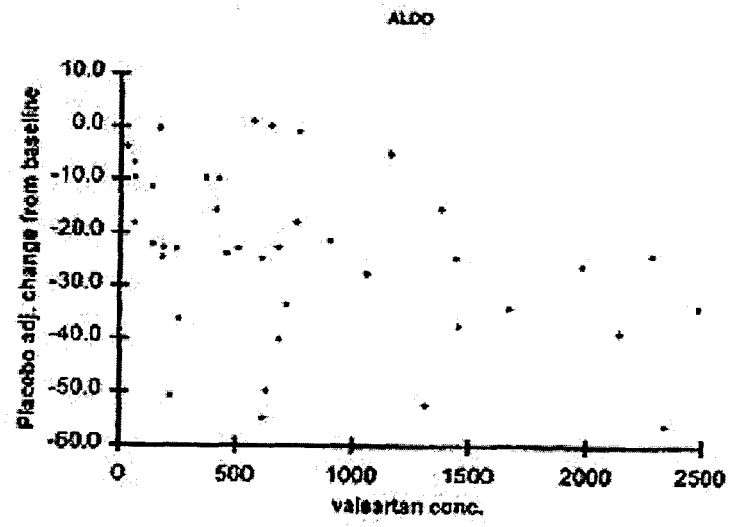
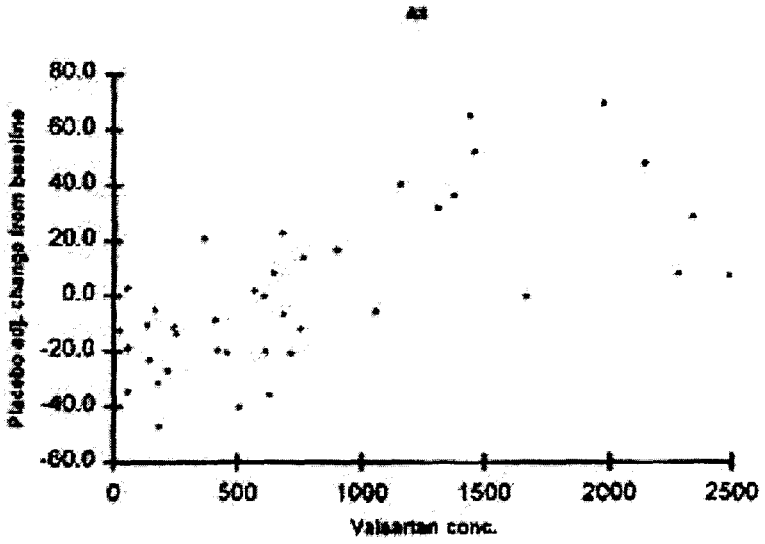


Figure 19

PK/PD relationship for plasma angiotensin II concentration

Plasma valsartan concentration (ng/mL) vs. placebo adjusted change from baseline for plasma angiotensin II (Ang II) concentration (ng/L) following a single 10 mg to 160 mg doses of valsartan in CHF patients.



Safety

There were no premature discontinuations after randomization. There were no deaths during this trial. Out of 25 randomized patients, 10 (8 on valsartan, 2 on placebo) reported adverse experiences.

There was one serious adverse experience (deterioration in CHF). A 65 year old 81 kg male with Class III CHF, randomized to valsartan 160 mg, was admitted to the CCU, 24 hours after dosing with trial medication, for IV infusions of dopamine (2mcg/kg/min) and dobutamine (10 mcg/kg/min). After 27 days, the patient was discharged with adjusted medications.

Table 7. Treatment-emergent adverse experiences (occurring in at least 2 patients on valsartan)

(all randomized patients)

Adverse event by primary term	Placebo (n=4) n (%)	Total valsartan (n=21) n (%)
Deterioration of basic disease	0	2 (9.5)
Dizziness	0	3 (14.5)

Source: Volume 12, Table 9.1:5

For further discussion, including evaluation of laboratory results, please see the Integrated Summary of Safety.

Medical Reviewer's Comments:
This was a small, single-dose open-label study investigating hemodynamic and pharmacokinetic effects with valsartan compared to placebo. The small sample size, as well as baseline differences between the treatment groups, limit interpretation of the data. No dose-response pattern could be seen in reviewing the hemodynamic data.

PK Reviewer's Comments:
Valsartan exhibits linear pharmacokinetics over the concentration range of 5-2,500 ng/mL. However, the data are highly variable. The linearity is consistent with previous reports in healthy volunteers. Tmax, ~3 hours, is also similar to previous reports. T ½ seems to be longer in patients with CHF than in healthy volunteers (median of ~9 hours compared to ~6 hours, respectively.) However, only two plasma samples were taken after 10 hours in this single dose study, so the T ½ may be inaccurate.

There was a weak trend towards an increase in placebo adjusted mean change from baseline for PRA and Ang II, and a decrease in aldosterone concentrations with increasing valsartan concentrations. However, no definitive conclusions regarding these trends can be made from this study.

Medical Reviewer's Conclusions:
No efficacy conclusions will be drawn given the limited data. Valsartan appeared to be well tolerated in this study.

PK Reviewer's Conclusions:
Valsartan exhibits 2-compartment linear pharmacokinetics over the concentration range of 5 to 2,500 ng/mL (doses of 10 mg to 160 mg).

Single doses of valsartan in this small patient study do not show an apparent concentration response relationship with respect to PCWP and CO.

An open-label, two phase, four period, multiple dose study to assess the pharmacokinetics of valsartan in patients with congestive heart failure

PROTOCOL: 105
VOLUME: 9 and 10
PAGES: 6-1 to 6-258

PRINCIPAL INVESTIGATOR: Jon Ruckel, MD
CLINICAL LABORATORY: Northwest Kinetics, Tacoma WA
CITATION: not applicable
TRIAL PERIOD: August 2, 1997 to November 6, 1997

OBJECTIVES:
- Primary: Determine the steady state pharmacokinetics of twice daily valsartan in patients with CHF (NYHA class II or III).
- Secondary: Determine single dose pharmacokinetics of valsartan in patients with CHF (NYHA class II or III).
- Secondary: Assess the tolerability of twice daily valsartan in patients with CHF.

STUDY DESIGN: open label, two-phase, four period single and multiple dose study
DURATION: Approximately 25 days.
POPULATION: Eighteen out of 20 enrolled chronic stable (1 month) CHF patients with NYHA Class II or III completed the study. Patients had to have an EF $\leq$ 40% as determined by a MUGA or ECHO. All patients were between the ages of 18 – 75 years.

PROCEDURE: The procedures are as outlined in Table 1.

Table 1. Procedures

Period	Day*	Visit	Treatment**	Valsartan Cp
Screening	-21 to –2	1	-	
Baseline	-1	2	-	
Phase I	1	3	40, 80 or 160 mg	Day 1: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hr post dose
Phase II, Period 1	2-8	4-5	40 q 12h x 7 d	Day 7: trough Day 8: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose
Phase II, Period 2	9-15	6	80 q 12h x 7 d	Day 14: trough Day 15: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose
Phase II, Period 3	16-22	7	160 mg q 12h x 7 d	Day 21: trough Day 22: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hrs post dose

* relative to dose 1 given on Day 1
** Subjects fasted for 10 hours prior to dosing on Day 1, the nights of Day 7, 14, and 21, and for 4 hours after dosing on Day 1, 8, 15, and 22.

Safety evaluations occurred as specified times during each treatment period and included physical exams, vital signs and adverse event monitoring.

Other medications
Patients on standard therapy for CHF were required to be on stable doses for at least 4 weeks prior to the baseline period.

Drug supply
The study drug was provided by Novartis, Suffern, NY. All patients were instructed to swallow the medication whole at 8 am and 8 pm with 200 mL of water.

Table 2. Batch and formulation for valsartan

Treatment	Dose	Batch No.	Formulation No.
Valsartan	40 mg capsule	E-15918R1	H-4030
	80 mg capsule	E-15866	H-4031
	160 mg capsule	E-15920	H-4032

ASSAY: Plasma valsartan concentrations were determined by a validated HPLC method. The assay was suitable for analyzing valsartan (See Table 3).

Table 3. Assay Quality

	Precision (CV %)	Accuracy (%)	Sensitivity (ng/mL)	Linearity (ng/mL)
Valsartan	< 11%	Within 2.5	5.0 – 5,000	≥ 0.9307

ANALYSIS:
Pharmacokinetics
Single dose - Tmax, T ½, Cmax, AUC_{0-24}, and $AUC_{0-\infty}$ were determined for each dose.
Multiple dose - τ, Tmax, Cmin, AUC_{τ}, apparent CL/wt, accumulation factor (Cmax of multiple dose/Cmax of single dose), and fluctuation index (Cmax-Cmin/Caverage, where Caverage is $AUC_{\tau}/12$) were determined for each dose.
Clearance was evaluated between two age groups (< 65 years and > 65 years).

The sponsor assessed dose proportionality based on β determined from fitting Cmax and AUC parameters vs. dose to a power model ($P=\alpha*dose^{\beta}$). Dose proportionality was evaluated for AUC_{0-24}, $AUC_{0-\infty}$ and Cmax for the single dose and AUC_{τ} and Cmax for multiple dose.

Statistics
Two sample t-tests were performed to compare age groups (≤ 65 years old and > 65 years old) for AUC and clearance (adjusted to body weight), and to examine if there was an age dependent effect on the AUC and clearance of valsartan in the patients studied.

RESULTS: Eighteen of twenty patients completed the trial. One discontinued because she developed renal insufficiency and the other discontinued because he developed PSVT.

Table 4. Demographics

	Mean (SD)	Range
Race (W/B)	15/3	
Males/Females	14/4	
Age (yr)	63.1 (10.1)	43-79
Ejection fraction (%)	27.9 (6.8)	18-39
Weight (kg)	90.7 (20.5)	71-140
Height (cm)	172.2 (10.7)	150-187

PHARMACOKINETIC RESULTS: Valsartan exhibits a 2-compartment body model as can be seen from the plasma concentration time curves for single and multiple dose in Figures 1 and 2, respectively.

Figure 1. Valsartan concentrations after single dose for three doses

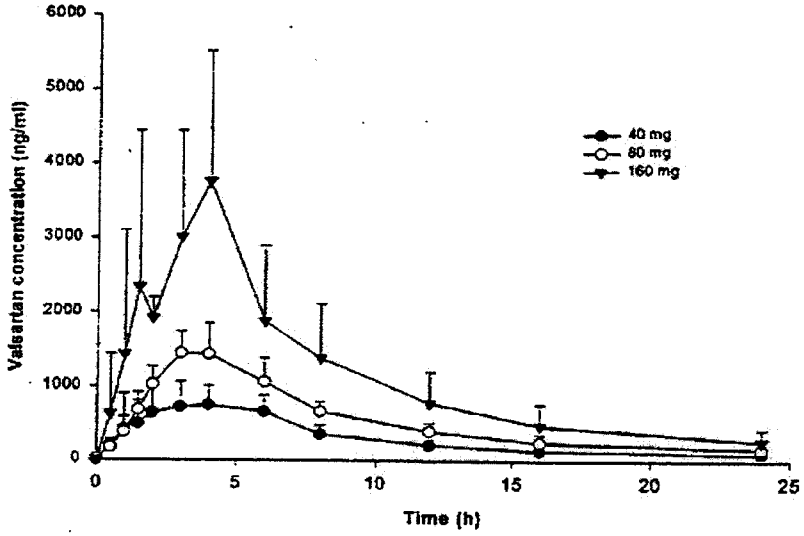
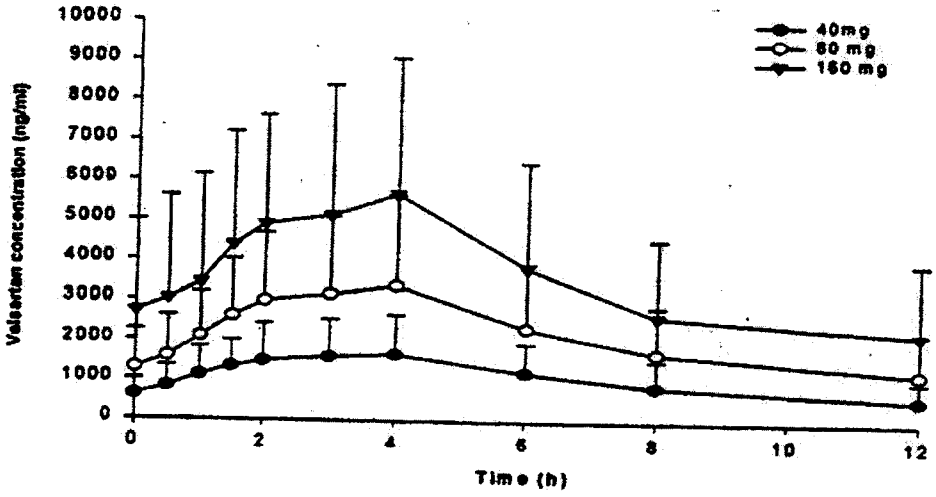


Figure 2. Valsartan concentrations at steady state for three doses



Pharmacokinetic parameters from single and multiple dose are shown in Table 5 and 6, respectively. Tmax is attained in ~3 hours. T ½ is ~ 6.5 hours. There is high variability in Cmax and AUC after both single and multiple doses. The mean AUC after multiple dose was more than 50% higher than after single dose, although there was some overlap in AUCs.

Table 5. Mean (SD) PK parameters after single dose valsartan in CHF patients

n	Dose (mg)	Cmax (ng/mL)	Tmax (hr)*	AUC $_{(0\text{-}24)}$ (ng*hr/mL)	AUC$_{0-\infty}$ (ng*hr/mL)	T ½ (hr)
4	40	870 (304)	4	7296 (2497)	8363 (2969)	6.8 (0.9)
5	80	1560 (336)	4	12811 (1903)	13449 (2089)	5.7 (0.2)
6	160	4209 (2045)	3.5	27832 (12264)	30099 (13539)	6.5 (2.0)

* median

The fluctuation index was ~1.4 across all doses. Cmax after multiple dose is higher than after single dose, suggesting accumulation. The accumulation factor was similar except for the 80 mg dose. The higher value observed for the 80 mg dose could be due to one patient who had an accumulation factor of 6.9. This subject had the lowest Cmax after the first 80 mg dose.

Table 6. Mean (SD) steady state valsartan pharmacokinetics in 18 CHF patients

Dose (mg)	Cmax (ng/mL)	Tmax (hr)*	AUC $_{(0\text{-}12)}$ (ng*hr/mL)	T ½ (hr)	Accumulation factor
40	1940 (971)	3	13119 (7220)	5.2 (1.9)	1.6 (0.5)
80	3951 (2290)	2.5	25936 (15670)	6.5 (2.4)	2.7 (2.1)
160	6403 (3190)	2.0	43540 (25897)	6.6 (3.9)	1.7 (0.4)

* median

The sponsor's fit of the steady state AUC and Cmax data estimated a β of 0.85 and 0.86, respectively, suggesting that valsartan exhibits linear pharmacokinetics with multiple dose (see Table 7). The fit for single dose also suggest dose proportionality.

Table 7. Summary of model parameter estimates

	Single dose				Multiple dose			
	Cmax (ng/mL)		AUC$_{0-24}$ (ng*hr/mL)		Cmax (ng/mL)		AUC$_{0-12}$ (ng*hr/mL)	
	ln α	β	ln α	β	ln α	β	ln α	β
Mean	2.64	1.09	5.43	0.92	4.3	0.86	6.24	0.85
SE (%)	68	15	62	14	33	7	28	6
90% CI		0.83, 1.36		0.67,1.17		0.74, 0.98		0.75, 0.95

CI = confidence interval

Figures 3 to 6 show the mean (SD) data that also supports the linearity with single and multiple doses.

Figure 3. Mean (SD) valsartan AUCs following single doses of 40, 80 and 160 mg in CHF patients

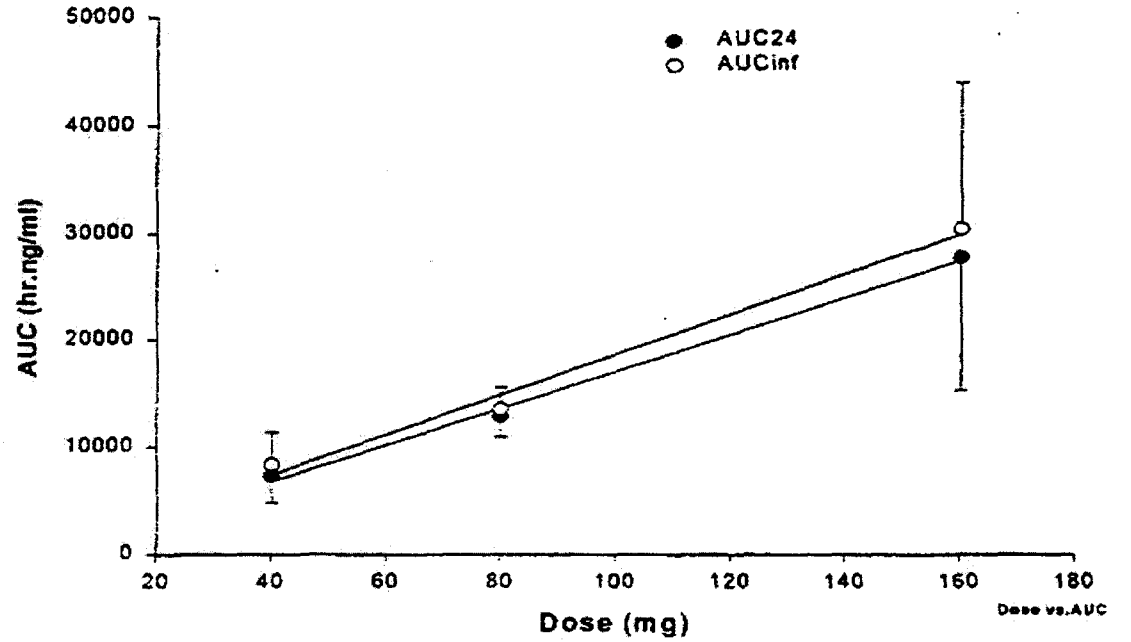


Figure 4. Mean (SD) Cmax following single doses of 40, 80 and 160 mg in CHF patients

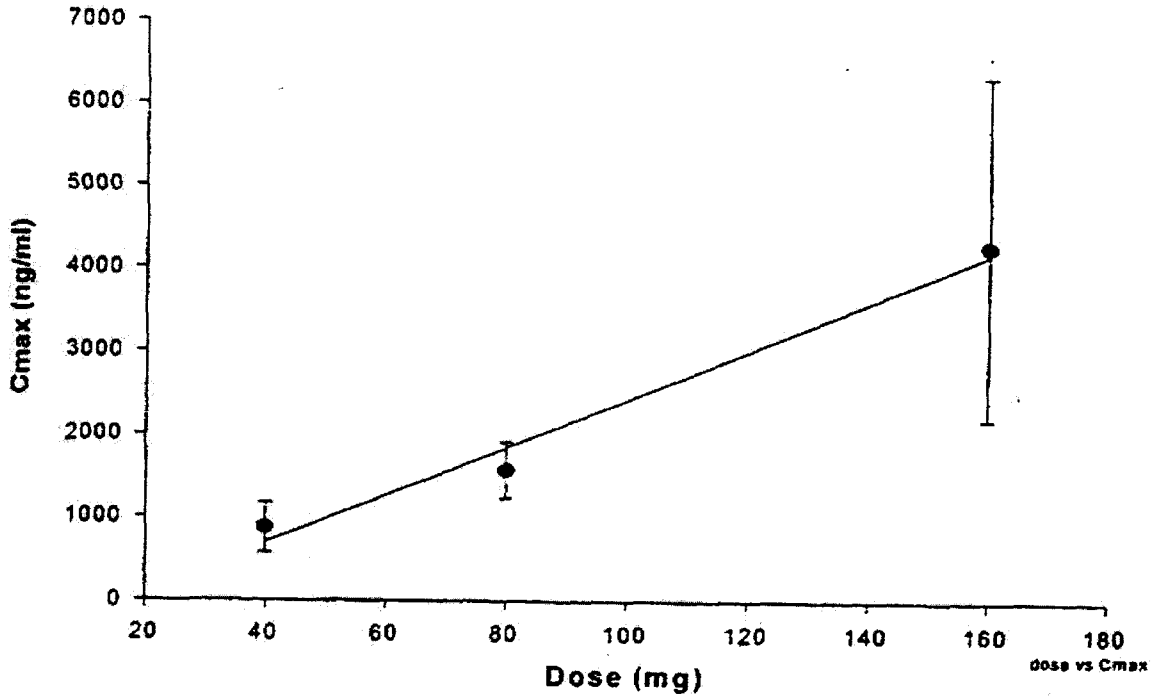


Figure 5. Mean (SD) valsartan AUC_{0-12} following multiple doses of 40, 80 and 160 mg in CHF patients

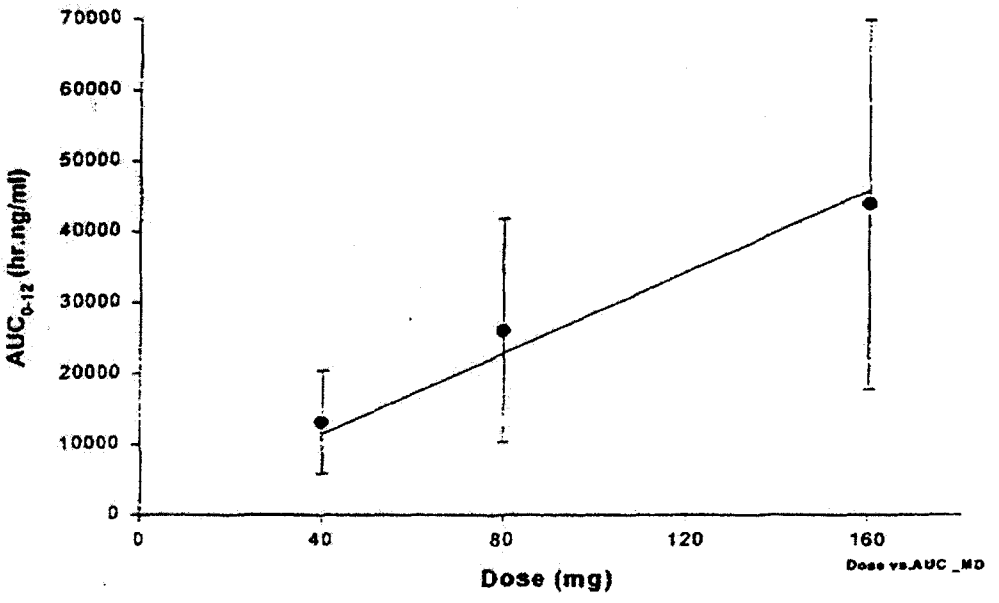
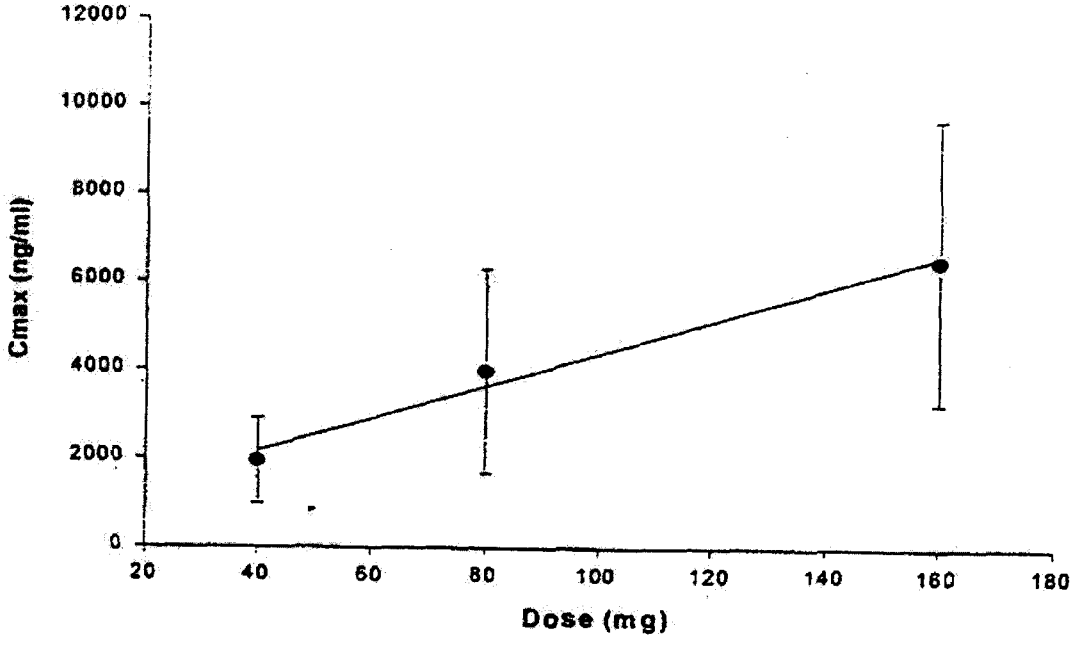


Figure 6. Mean (SD) valsartan Cmax following multiple doses of 40, 80 and 160 mg in CHF patients



Clearance of valsartan was ~ 10-20% lower in nine patients aged ≤ 65 years old compared to nine patients > 65 years old. There was no statistically significant difference between the two groups. Additionally, there was considerable variability (~50%) resulting in overlap in clearances (see Table 8 and Figure 7).

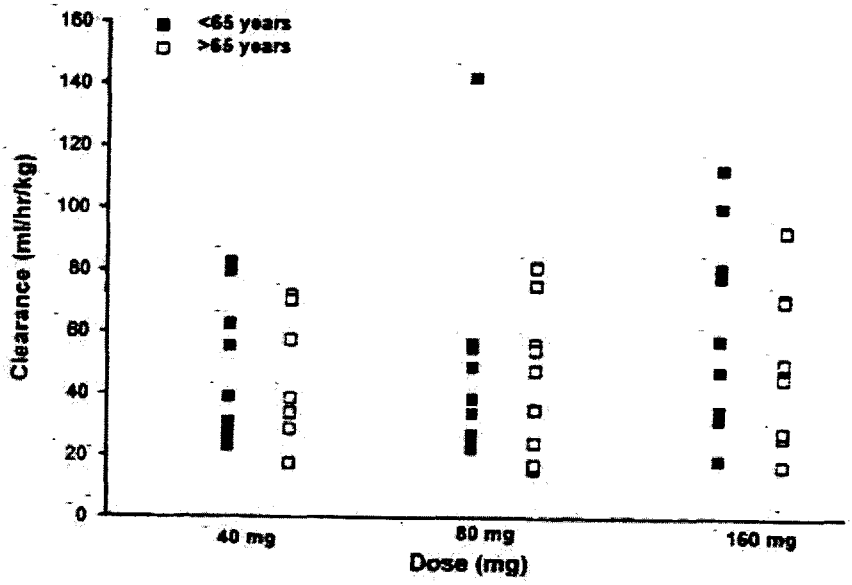
Table 8. Clearance (mL/hr/kg) of young and elderly patients with CHF*

Dose (mg)	≤ 65 years old	> 65 years old
40	47.4 (23.1)	41.0 (20.7)
80	49.7 (36.7)	45.1 (23.8)
160	62.1 (32.1)	49.4 (24.4)

* mean (SD)

Figure seven shows the large variability in clearance between patients ≤ 65 years old and patients > 65 years old.

Figure 7. Comparison of clearance by age in patients with CHF



SAFETY RESULTS: Eighteen of twenty patients reported adverse experiences in this study. Most A/Es were rated as mild to moderate by the investigator. The most common A/E were dizziness (n=11), hypotension (n=7), headache (n=5), dyspnea (n=5), fatigue (n=3), leg edema (n=3), viral infection (n=3) and coughing (n=3). The investigator did not deem these experiences to be dose related. There were no clinically significant adverse laboratory results or vital sign measurements.

REVIEWER'S COMMENTS:

Table 9. Pharmacokinetic comparison between healthy volunteers and patients with CHF

Similarities
Linear pharmacokinetics
Tmax in ~3 hours
T ½ is ~6.5 hours
Reduced clearance in elderly
Differences
Accumulation factor of ~1.7 in CHF (vs. 1.3)
CL ~ 4.5 L/h in CHF (vs. 2.2 L/h) [1]
Cmax and AUC ~ 1.3 – 2x higher in CHF

[1] After adjusting for systemic bioavailability of 23% for the capsule, clearance would be ~1.04 L/h, which is ~ 50% of that observed in healthy volunteers.

The apparent age effect is in agreement with results from previous studies.

CONCLUSIONS:
Valsartan exhibits linear pharmacokinetics with single and multiple doses in patients with CHF. Tmax is ~3 hours and T ½ is approximately 6.5 hours. Clearance is reduced by ~50% in patients with CHF compared to healthy volunteers. Valsartan clearance was ~ 10-20% lower in elderly patients with CHF compared to young patients with CHF. A twice daily dose accumulates by a factor of 1.7 compared to single dose.

Valsartan was well tolerated in this patient population.

Request for waiver for 40 mg tablet

Source: NDA 21-283 (SE1-001), submission date 7/23/01

SUMMARY:

Information to support a biowaiver for the 40 mg tablet:
- Compositionally proportional (see Table 1)
- Linear pharmacokinetics (study 102 and 105 included in this review)
- Similar in vitro dissolution profiles in three media

BACKGROUND:
In the clinical trials for CHF, hard gelatin capsules were used.

The sponsor has demonstrated bioequivalence between two 160 mg capsules and the 320 mg tablets. A BE waiver for the 80 mg and 160 mg tablets was recently granted. The approved dissolution method and specifications for the 80 mg, 160 mg and 320 mg tablets are:

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q = [ ] in 30 minutes

REVIEW:
- Compositionally proportional

Table 1. Composition of Diovan 40, 80, 160 and 320 mg film-coated tablets

Ingredient	Amount per tablet (mg)				Function	Reference to standard
	40	80	160	320		
Valsartan	40.00	80.0	160.0	320.0	Active ingredient	Novartis monograph
Microcrystalline cellulose	[				]	NF
Crospovidone	[				]	NF
Colloidal anhydrous silica/ colloidal silicon dioxide	[				]	NF
Magnesium stearate	[				]	NF
Core weight	[			]		
Coating						
Coating premix[1]	[				]	Novartis monograph
Purified water[2]	[				]	USP
Total tablet weight	80.30	161.0	319.0	636.0		

[1] The coating premixes are commercially available products composed as given in the table below.
[2] removed during processing

- Dissolution

The dissolution data for the 40 mg tablet was generated on Batch # x 226 0799 in 3 media using 1000 mL.

Table 2. Individual dissolution results using a paddle

Batch Dosage strength	Medium Speed	Time (min)
X226 0799 40 mg	pH 6.8 50 rpm	10 20 30 45
X226 0799 40 mg	pH 4.5 50 rpm	10 20 30 45 60 90 120
X226 0799 40 mg	pH 4.5 75 rpm	15 30 60 120
X226 0799 40 mg	pH 1.0 75 rpm	15 30 60 120

[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
		[illegible]	[illegible]
		[illegible]	[illegible]

Table 3. Individual dissolution data for the 320 mg tablet in three media

Batch Dosage strength	Medium Speed	Time (min)	% dissolved
X361 1199 320 mg	pH 6.8 75 rpm	15	98, 99, 100, 99, 98, 100, 100, 101, 101, 100, 101
		30	100, 99, 100, 100, 99, 100, 102, 102, 101, 101, 102, 100
		60	100, 99, 101, 99, 99, 100, 102, 101, 101, 102, 101
		120	102, 99, 101, 99, 99, 100, 102, 102, 101, 101, 102, 101
X361 1199 320 mg	pH 6.8 50 rpm	10	87, 84, 86, 85, 90, 84, 87, 90, 86, 86, 90, 87
		20	91, 92, 93, 89, 93, 94, 93, 92, 93, 91, 94, 94
		30	92, 94, 95, 90, 94, 95, 93, 93, 91, 92, 95, 91
		45	93, 95, 100, 91, 95, 95, 93, 94, 92, 92, 95, 92

	X361 1199 320 mg	pH 4.5 75 rpm	15
			30
			60
			120

Batch Dosage strength	Medium Speed	Time (min)	% dissolved
X361 1199 320 mg	pH 1.0 50 rpm	10	0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0
		20	11, 12, 11, 11, 11, 11, 13, 14, 12, 12, 14, 12, 10
		30	34, 33, 31, 34, 31, 33, 28, 33, 31, 34, 31, 29
		45	43, 42, 43, 42, 43, 45, 40, 43, 42, 43, 41, 41

X361 1199 320 mg		pH 1.0 75 rpm	15
			30
			60
			120

These data were compared with in vivo data for the 320 mg tablet (Batch # x 361 1199) The F2 values calculated by the sponsor are shown in Table 2. The F2 value for the 40 mg tablet using the pH 6.8 buffer medium at 50 RPM was between 50 and 100.

Table 3. Dissolution and F2 for the 40 mg tablet in different media

Medium	Speed	F2
0.1 N HCl	75	70
pH 6.8 buffer	50	52
pH 4.5 buffer	50	36
pH 4.5 buffer	75	54

REVIEWER'S COMMENTS:
The sponsor does not specify the type of media used in the dissolution testing of the 40 mg tablet. After discussion with Robert Clark, from Novartis, on August 25, 2001, it was determined that the medium used was the same as the approved medium.

The sponsor did not need to calculate F2 at 15 minutes for the dissolution in pH 6.8, 50 rpm since more than [ ] was dissolved by 15 minutes.

The comparison of the dissolution between the 40 mg and 320 mg tablet at pH 4.5, 50 rpm failed. This is most likely because at pH 4.5, valsartan is not very soluble. Thus, it will take longer for a larger amount to dissolve (320 mg) compared to a smaller amount (40 mg). This difference in dissolution is not expected to result in differences in bioavailability in vivo.

CONCLUSION:
A bioequivalence waiver is granted for the 40 mg tablet and the specifications should be the same as what was previously approved.

Medium: 1000 ml of 0.067 M phosphate buffer, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q = [ ] in 30 minutes

APPENDIX II: FORMULATION

The formulation was similar in all studies. For composition see page 27 of the review.

Table 1. Formulations and batch numbers of valsartan

Protocol No	Strength (mg)	Formulation No.	Batch No.
Pharmacokinetic studies			
102	10	H-3573	1053/1
	20	H-3574	1050/2
	40	H-3575	1051/3
	80	H-3576	1052/2
	160	H-3577	1059/3
105	40	H-4030	E-15918R1
	80	H-4031	E-15866
	160	H-4032	E-15920
Pivotal Clinical Study			
107	40	H-4030	B970038
			B970089[c]
			B980162[c]
			E-15865
			E-15918R1
			H-5040
			H-5064
	80	H-4031	B970046[c]
			B970086[c]
			B980013[c]
			B980014[c]
			B980034[c]
			E-15866[a]
			X066 0399[c]
	160	H-4032	B970043[c]
			B970044[c]
			B970088[c]
			B980002[c]
			B980035[c]
			B980068[c]
			B980069[c]
			B980075[c]
			B980166[c]
			B980172[c]
			E 39/98[c]
			E-15867[b]
			E-15920[b]
			H-5038[b]
			H-5066[b]

[a] compared to the final market image (capsule formulation currently marketed), capsule content is identical and capsule shell and size differ.

[b] compared to the final market image (capsule formulation currently marketed), capsule content is identical and capsule shell is slightly different.

[c] Site of clinical supply manufacture and packaging different than the rest because of the merger of Ciba Pharmaceuticals and Sandoz Pharmaceuticals Corporation.

APPENDIX III: Sponsor's proposed package insert

13 pages redacted from this section of the approval package consisted of draft labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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9/6/01 02:20:33 PM
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