Neurohormones were measured in Studies 102, 103, 104 and 107.
No conclusions can be drawn from the neurohormone results in study 102.

Study 103 only showed significant differences for angiotensin II, measured at 12 hours (trough) in the valsartan 80 mg BID group.

In study 104, baseline differences could be seen for plasma norepinephrine and atrial peptide activity. Significant decreases were seen for plasma aldosterone, compared to placebo, in valsartan treatment groups at peak, and in the valsartan 160 mg BID group at trough.

Significant decreases, compared to placebo, are seen in 107 for plasma norepinephrine and BNP.

Summary:
The major positive results can be found in Study 107. In that trial, the time to morbid event was significantly prolonged in the valsartan treatment group; this primary endpoint appears to be driven by CHF hospitalizations. A detailed discussion can be found in the Study 107 review. Findings consistent with a treatment effect include: increase in EF (Study 106 and 107), improvement in signs/symptoms of CHF (107 only), decrease in plasma norepinephrine and BNP (Study 107), decrease in LVIDD (107), and improvement in LHFQ (107). One would have hoped for more robust findings in the other studies; it may be that the studies other than 107 were "underpowered" to detect these significant differences.
Interestingly, as seen in 107, the increase in ejection fraction does not seem to accompany survival benefit in this study population.

The subgroup results for morbidity and mortality are consistent with the theory that valsartan has a more favorable effect in the absence of ACE/beta blockers. Valsartan has less of a favorable effect (morbidity) in the US compared to nonUS; the exact reason for this is unclear (the use of ACE and beta blockers in the US and nonUS populations were not analyzed).

Figure 1. Chemical structure of valsartan

Integrated Summary of Safety:
NDA: 20-665
S-016

Sponsor: Novartis

1.0 Materials Utilized in Review:

In evaluating the safety of valsartan, the Medical Reviewer used the electronic archive, including the SAS database, supplied by the Sponsor with the submission of NDA 20-665, S-016. The safety database analyzed in this review represented data from all completed studies up until October 1st, 2000; information from the Safety Update will not be presented in this report, but will be filed, if needed, as an addendum.

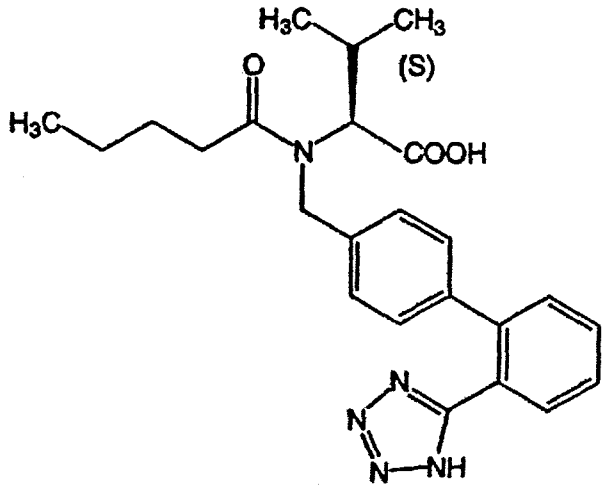
The approach used to characterize the safety profile of valsartan consisted of examination of the entire database for deaths, discontinuations, serious adverse events, as well as routine safety data (treatment emergent adverse events, laboratory tests, vital signs and ECG data).

2.0 Background-Pharmacologic Class

Valsartan is a orally active specific competitive angiotensin (Ang) II antagonist of the AT_1 subtype. Valsartan is currently approved for the treatment of hypertension in daily doses up to 320 mg.

3.0 Chemistry

Valsartan is described chemically as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is :



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water. The reader is referred to the Chemistry review for further detailed discussion.

4.0 Indication

In this NDA submission, the Sponsor is seeking an indication for valsartan for the treatment of congestive heart failure.

5.0 Post-Marketing Experience

Valsartan is approved for the treatment of hypertension in the US and is currently marketed in about 60 countries. To the best of this reviewer's knowledge, valsartan has not been withdrawn from any market.

6.0 Use in Pediatric Population

Valsartan has not been studied in population less than 18 years of age.

7.0 Animal Pharmacology/Toxicology

There is no new relevant animal safety/ toxicology data for review.

8.0 Description of Clinical Data Sources

8.1 Primary Source Data

Four safety datasets were submitted by the sponsor: A. Pooled data from 103, 104, 106, 107 (first 7 Visits) and active-controlled study 110 (primary dataset); B. Pooled data as in #1 without 110; C. Study 107 (long-term, double-blind, placebo –controlled); D. Open-label trials: 102, 105 and ANG 102.

- **Clinical Pharmacology**: This submission contained 2 small open-label clinical pharmacology studies (102, N=25, 105, N=18). Study 102 was jointly reviewed by the medical and clinical pharmacology and biopharmaceutics reviewer. Study 105 was reviewed by the clinical pharmacogy and biopharmaceutics reviewer.
- **Phase 2/3 Clinical Efficacy/Safety Studies** consisted of 5 randomized double-blind trials. This program included one large study with morbid/mortal outcomes (107), one 770 patient short-term trial (106) and three smaller short-term studies (103, 104, and 110).
- **8.1.1.Exclusions from Database**:

This database does not contain information from the 4-month Safety Update. Pertinent information will be filed, as needed, as an addendum to this review.

This safety review will focus mainly on the primary database (A, above) and Study 107 (C, above).

8.2 Safety Populations studied and their characteristics

8.2.1 Demographics

Demographic data for the Phase 2/3 trials are presented below. The primary safety dataset was a mostly male, mostly Caucasian population. Almost half were over 65, with a higher percentage of elderly and > 75 in the ACE comparator group. The active control group (ACE comparator) was 100% Caucasian. Most patients were classified as NYHA Class II and III.

Table 3. Baseline characteristics

	Valsartan					ACEI comparator	Placebo
	0 mg N=473 n (%)	80 mg N=2787 n (%)	160 mg N=2843 n (%)	320 mg N=2304 n (%)	Total N=3289 n (%)	N=86 n (%)	N=2745 n %)
Male	366 (77)	2217 (80)	2269 (80)	1840 (80)	2639 (80)	66 (77)	2205 (80)
Female	107 (21)	570 (21)	574 (20)	464 (20)	650 (20)	20 (23)	540 (20)
Mean age (yrs)	64	63	63	63	63	66	63
Age < 65 yrs	234 (49.5)	1506 (54)	1523 (54)	1245 (54)	1773 (54)	35 (41)	1431 (52)
Age ≥ 65 yrs	239 (50.5)	1281 (46)	1320 (46)	1059 (46)	1516 (46)	51 (59)	1314 (48)
Age ≥ 75 yrs	79 (17)	366 (13)	386 (14)	294 (13)	451 (14)	19 (22)	416 (15)
Race: Caucasian	416 (88)	2502 (90)	2522 (89)	2028 (88)	2918 (89)	86 (100)	2475 (90)
Black	38 (8)	204 (7)	234 (8)	199 (9)	271 (8)	0	190 (7)
Oriental/other	19 (4)	81 (3)	87 (3)	77 (3)	100 (3)	0	80 (3)
NYHA : Class I	1 (0.2)	2 (0.1)	4 (0.1)	3 (0.1)	4 (0.1)	0	5 (0.2)
II	252 (53)	1724 (62)	1761 (62)	1466 (64)	2006 (61)	56 (65)	1660 (61)
III	206 (44)	1015 (36)	1037 (37)	804 (35)	1221 (37)	27 (31)	1021 (37)
IV	14 (3)	46 (2)	41 (1)	31 (1)	58 (2)	3 (4)	59 (2)
Mean Sitting DBP (mm Hg)	73	75	75	76	75	77	76
Mean Sitting SBP (mm Hg)	120	124	124	125	123	126	124

Source: Volume 77: Table 2.2-1, 2.2-4, 2.2-7, 3.1-1, 3.1-4: Studies 103, 104, 106, 107 (first 4 months) and 110. ACEI comparator group combines lisinopril and enalapril from the active controls. Valsartan 0 mg group contains treatment interruptions from Study 107. Because of dose titrations, patients may be counted in more than one valsartan dose group, but only once in the Total column.

In terms of the primary safety database (103, 104, 106, 107 through Visit 7, and 110), mean weights were about 79-82 (±16) kg, Mean LVEF was 26-27% and mean duration of CHF was about 50-52 months. CHF etiology was about 55-57% ischemic heart disease, about 28-37% idiopathic cardiomyopathy (37% in the active control group, and about 28-31% in valsartan and

placebo), 4-8% hypertension, and 5-7% other. Results for standing diastolic and systolic blood pressures were similar to sitting BP values.

Table 4. Summary of baseline background cardiovascular therapy (primary dataset)

	Valsartan					ACEI comparator	Placebo
	0 mg N=473 n (%)	80 mg N=2787 n (%)	160 mg N=2843 n (%)	320 mg N=2304 n (%)	Total N=3289 n (%)	N=86 n (%)	N=2745 n (%)
ACE inhibitors	433 (92)	2493 (90)	2524 (89)	2097 (91)	2887 (88)	2 (2)	2511 (92)
Diuretics	426 (90)	2385 (86)	2422 (86)	1957 (85)	2807 (85)	69 (80)	2326 (85)
Digoxin	349 (74)	1846 (66)	1887 (66)	1543 (67)	2195 (67)	38 (44)	1853 (68)
Nitrates (short and long-acting)	209 (44)	1046 (38)	1048 (37)	847 (37)	1174 (36)	25 (29)	1015 (37)
Beta blockers	151 (32)	975 (35)	959 (34)	760 (33)	1074 (33)	55 (64)	930 (34)
Amiodarone	62 (13)	341 (12)	360 (13)	294 (13)	401 (12)	5 (6)	359 (13)
Calcium channel blockers	59 (13)	305 (11)	313 (11)	259 (11)	347 (11)	1 (1)	337 (12)

Source: Volume 77: Table 3-3. Includes 103, 104, 106, 107 (first 4 months) and 110. Valsartan patients are counted only once in the total column. In study 107, valsartan treatment interruptions were captured in the 0 mg column and included in the total column.

8.2.2. Extent of Exposure to valsartan

The two tables to follow list duration of exposure by dose in the Phase 2/3 Clinical Trials. Most of the exposure to valsartan appears to be in total daily doses up to 320 mg.

Table 5. Minimum exposure (days) by total daily dose—short-term

	Valsartan (total daily dose)					Active control*	Placebo
	0 mg	80 mg	160 mg	320 mg	Total		
# Days							
≥1	473	2787	2840	2302	3285	86	2743
≥30	121	534	614	2047	3041	83	2649
≥60	60	355	477	1953	2886	63	2536
≥90	18	288	296	1346	2727	6	2478

Source: Sponsor: Volume 77: Table 2.1-1: Data from 103, 104, 106, 107 (through Visit 7), 110. Patients may be counted in more than one valsartan dose group, but only once in the total column. In 107, patients with valsartan treatment interruptions during double-blind are counted in the '0 mg' column but excluded from the Total Valsartan column.

*Combines enalapril and lisinopril treatment groups.

Table 6. Minimum exposure (days) by total daily dose— (107)

	Valsartan (total daily dose)					Placebo
	0 mg	80 mg	160 mg	320 mg	Total	
# Days						
≥1	1191	2508	2342	2118	2508	2497
≥30	540	461	525	1944	2409	2428
≥60	361	310	396	1900	2323	2371
≥90	228	276	344	1848	2268	2330
≥ 180	67	224	268	1693	2155	2235
≥ 360	9	162	199	1543	1968	2063
≥ 720	0	69	77	722	1061	1108

Source: Volume 77: Table 2.1-3. . Patients may be counted in more than one valsartan dose group, but only once in the total column. Patients with valsartan treatment interruptions during double-blind are counted in the '0 mg' column but excluded from the Total Valsartan column.

Table 7. Summary of exposure (days) by total daily dose (short-term)

	Valsartan (total daily dose)					Active control	Placebo
	0 mg	80 mg	160 mg	320 mg	Total		
N	473	2787	2843	2304	3285	86	2743
Mean (SD)	24 (30)	29 (31)	30 (32)	81 (27)	107 (32)	74 (20)	114 (26)
Range	1-188	1-188	0-154	0-203	1-232	6-92	1-253

Source: Volume 77: Table 2.1-4. Includes 103, 104, 106, 107 (first 4 months) and 110. Active control combines lisinopril and enalapril. Patients may be counted in more than one dose group, but only once in the total. In 107, treatment interruptions were captured in the 0 mg group and excluded from the total column.

Table 8. Summary of exposure (days) by total daily dose (107)

	Valsartan (total daily dose)					Placebo
	0 mg	80 mg	160 mg	320 mg	Total	
N	1191	2508	2345	2120	2508	2497
Mean (SD)	52 (72)	69 (171)	84 (190)	540 (306)	604 (300)	629 (281)
Range	1-629	1-1105	0-1074	0-1113	1-1203	1-1138

Source: Volume 77: Table 2.1-6

Patients may be counted in more than one dose group, but only once in the total. Treatment interruptions were captured in the 0 mg group and excluded from the total column.

In analyzing mean duration of exposure by subgroup (age, gender, race) no meaningful differences were seen in the short-term studies (primary database). In Study 107, there appeared to be less mean days of exposure for the elderly (< 65 years, n=1367, mean days of exposure for valsartan=625.6; ≥ 65 years, n=1141, mean days of exposure= 577.9, ≥ 75 years, n=318, mean days of exposure =540.6).

Table 9. Numbers randomized and in safety analyzable database: all pooled trials combined, including 103, 104, 106, 107, 110

	Valsartan (total daily dose)					Lisinopril	Enalapril	Placebo	Total
N	0 mg	80 mg	160 mg	320 mg	Total				
randomized	1191	2787	2856	2368	3289	15	71	2745	6120
Safety analyzable	1190	2785	2855	2368	3282	15	71	2740	6108

Source: Volume 77: Table 4-2

Table 10. Patient Disposition (double-blind short-term)

	Valsartan N (%)	Active control		Placebo N (%)
		Lisinopril N (%)	Enalapril (n (%)	
Randomized	778 (100)	15 (100)	71 (100)	246 (100)
Completed	658 (85)	14 (93)	62 (87)	220 (89)
Premature discontinuation during double-blind	120 (15)	1 (7)	9 (13)	26 (11)
Adverse Event	67 (9)	0	3 (4)	9 (4)
Abnormal lab	2 (0.3)	0	0	0
Unsatisfactory therapeutic effect	1 (0.1)	0	0	1 (0.4)
Did not meet protocol criteria or noncompliant	24 (3)	0	0	5 (2)
Withdrew consent	7 (0.9)	1 (7)	1 (1)	4 (2)
Lost to follow-up	5 (0.6)	0	0	1 (0.4)
Administrative problems	4 (0.5)	0	0	2 (0.8)
Death	10 (1)	0	5 (7)	4 (2)

Source: Volume 77: Table 4-1. Includes 103, 104, 106, 110

Patient disposition for Study 107 can be found in that study review.

8.3 Adequacy of Safety Database

The Safety Database appears to be adequate for the Demographic population as noted above.

9.0. Human Pharmacokinetic Considerations

The Medical Reviewer failed to identify pharmacokinetic findings useful in explaining the occurrence of adverse events observed during clinical trials of valsartan. The reader is referred to the Clinical Pharmacology and Biopharmaceutics review for the human pharmacokinetics of valsartan and detailed information on the subject.

10.0. Integrated Review of Safety

10.1. Deaths:

The following table provides a summary of deaths by treatment and study.

Table 11. Number of deaths by principal cause (double-blind short-term trials)

	Valsartan N=778 n (%)	Active control N=86 n (%)	Placebo N=246 n (%)
Total deaths	10 (1.3)	5 (5.8)	4 (1.5)
CHF	4 (0.5)	0	0
Cardiac arrest	2 (0.3)	0	0
Sudden death unexplained	2 (0.3)	2 (2.3)	2 (0.8)
CVA NOS	1 (0.1)	0	0
Intestinal infarction	1 (0.1)	0	0
Cardiac failure NOS	0	1 (1.2)	0
Myocardial infarction	0	1 (1.2)	1 (0.4)
Pneumonia NOS	0	1 (1.2)	0
Ventricular fibrillation	0	0	1 (0.4)

Source: Volume 87: Table 5.2-1. Includes: 103, 104, 106, 110

Table 12. Number of deaths by principal cause assessed by investigator (107)

Principal cause of death	Valsartan n (%)	Placebo n (%)
Total number of randomized patients	2511 (100)	2499 (100)
Total deaths	505 (20.1)	499 (20.0)
Sudden death—unespected, instantaneous or during sleep (observed or presumed)	194 (7.7)	177 (7.1)
Pump failure, progressive CHF even if terminal event was arrhythmia or vascular event	143 (5.7)	130 (5.2)
Other non-cardiovascular event	43 (1.7)	130 (5.2)
Sudden death-premonitory worsening, CHF	22 (0.9)	34 (1.4)
Non-cardiovascular event—cancer	20 (0.8)	24 (1.0)
Unknown	15 (0.6)	22 (0.9)
Other vascular event	15 (0.6)	24 (1.0)
Acute myocardial infarction – documented	14 (0.6)	11 (0.4)
Vascular event—stroke	13 (0.5)	6 (0.2)
Acute myocardial infarction—presumed	12 (0.5)	18 (0.7)
Sudden death—premonitory worsening, arrhythmia	6 (0.2)	13 (0.5)
Sudden death—premonitory	6 (0.2)	3 (0.1)

worsening, ischemia		
Vascular event—cardiac procedure	2 (0.1)	3 (0.1)

Source: Volume 77: Table 5-32

10.2. Serious Adverse Events

Table 13. Clinical Serious Adverse Events (Incidence ≥1.0 % for Valsartan Treatment Group and greater than placebo) in Double-blind controlled Studies, by Primary Term: Short-term*

Serious AE: Primary Term	Valsartan N=3282 n (%)	Active control N=86 n (%)	Placebo N=2740 n (%)
Total—any body system	548 (17)	11 (13)	490 (18)
Hypotension NOS	32 (1)	0	15 (0.5)

*Data from Studies 103, 104, 106, 107, 110 through visit 7.
Source: Volume 87: Table 5.2-4

Table 13a. Clinical Serious Adverse Events (Incidence ≥ 1.0 % for Valsartan Treatment Group and greater than placebo) in Long-term Placebo-Controlled (107) by Primary Term:

Serious AE: Primary Term	Valsartan N=2506 n (%)	Placebo N=2494 n (%)
Total: any body system	1282 (51)	1342 (54)
Angina pectoris	63 (3)	49 (2)
Dehydration	49 (2)	33 (1)
Hyperkalemia	40 (2)	23 (0.9)
Dizziness (exc vertigo)	39 (2)	36 (1)
Syncope	62 (3)	60 (2)
Renal failure NOS	25 (1)	15 (0.6)
Renal impairment	44 (2)	20 (0.8)

Source: Volume 87: Table 5.2-6.

The table below lists adverse experiences in the short-term controlled clinical trials. Only dizziness (exc. Vertigo) appeared to increase in frequency with increasing dose (2.3% in 0 mg, 7.7% in 80 mg BID, 7.4% in 160 mg BID, and 9.0% in 320 mg BID groups). The incidence of dizziness and hypotension NOS were statistically significant for valsartan compared to placebo. The incidence of cough was 4.9% in placebo and 4.8% in valsartan.

Table 14. Treatment Emergent Adverse experiences: double-blind short-term trials (Incidence ≥ 1.0 % in the valsartan group and greater than placebo)

Preferred term	Valsartan (N=3282) n (%)	Active control (N=86) n (%)	Placebo (N=2740) n(%)
Any—Total	2380 (73)	53 (62)	1876 (69)
Anemia NOS	43 (1)	0	23 (0.8)

Angina pectoris	76 (2)	1 (1)	58 (2)
Angina (combined)*	109 (3)	1 (1)	98 (4)
Cardiac failure congestive	34 (1.0)	0	20 (0.7)
Congestive heart failure (combined)**	153 (5)	1 (1)	165(6)
Vertigo NEC	60 (2)	2 (2)	26 (0.9)
Vision blurred	47 (1)	0	8 (0.3)
Diarrhea NOS	148 (5)	2 (2)	100 (4)
Fatigue	89 (3)	2 (2)	52 (2)
Weight increased	35 (1)	0	16 (0.6)
Hyperkalemia	79 (3)	0	29 (1)
Arthralgia	90 (3)	1 (1)	58 (2)
Epistaxis	32 (1.0)	0	18 (0.7)
Back pain	86 (3)	4 (5)	51 (2)
Dizziness (exc. Vertigo)	568 (17)	7 (8)	255 (9)
Dizziness postural	81 (3)	0	32 (1)
Syncope	60 (2)	0	34 (1)
Renal impairment NOS	58 (2)	1 (1)	19 (0.7)
Renal impairment and failure (combined)***	96 (3)	1 (1)	38 (1)
Hypotension NOS	218 (7)	0	65 (2)
Postural hypotension	68 (2)	0	20 (0.7)

Source: Volume 77: Table 5.1-1. Includes: 103, 104, 106, 110 and 107 through Visit 7. Each patient is counted once per preferred term and per total daily dose within each body system. Active control=ACE inhibitors (lisinopril and enalapril). Incidence ≥ 1% is rounded off to the nearest integer.
*sum total: angina pectoris, angina pectoris aggravated and angina unstable.
**sum total: cardiac failure NOS, cardiac failure aggravated, cardiac failure chronic, cardiac failure congestive, congestive cardiac failure aggravated.
***sum total: renal failure NOS, renal failure acute, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal impairment NOS.

In 107, Dizziness and hypotension NOS are also seen in more frequently in the valsartan group. Congestive heart failure aggravated, reported in 11% of valsartan and 15.5% of placebo, was apparently a statistically significant difference.

Table 15. Treatment-emergent adverse experiences (107) long-term (incidence ≥ 1.0 % in valsartan and greater than placebo)

	Valsartan (N=2506) n (%)	Placebo (N=2494) n (%)
Anemia NOS	119 (5)	110 (4)
Arrhythmia NOS	39 (2)	31 (1)
Myocardial infarction*	89 (4)	78 (3)
Ventricular extrasystoles**	27 (1)	22 (0.9)
Vertigo NEC	78 (3)	51 (2)
Vision blurred	55 (2)	22 (0.9)
Diarrhea NOS	238 (10)	193 (8)
Fatigue	117 (5)	106 (4)
Malaise	24 (1)	21 (0.8)
Gastroenteritis NOS	43 (2)	25 (1)
Herpes zoster	27 (1)	22 (0.9)
Blood creatinine increased	54 (2)	27 (1)

Diabetes mellitus aggravated	29 (1)	18 (0.7)
Hyperglycemia NOS	62 (3)	55 (2)
Hyperkalemia	163 (7)	81 (3)
Hyperlipidemia NOS	42 (2)	29 (1)
Arthralgia	195 (8)	172 (7)
Back pain	145 (6)	122 (5)
Dizziness (exc vertigo)	627 (25)	451 (18)
Dizziness postural	92 (4)	54 (2)
Renal failure NOS	54 (2)	31 (1)
Renal impairment	135 (5)	76 (3)
Renal impairment or failure¶	256 (10)	166 (7)
Wheezing	26 (1)	13 (0.5)
Hypotension NOS	347 (14)	19 (0.8)
Intermittent claudication	35 (1)	19 (0.8)
Postural hypotension	95 (4)	48 (2)

Source: Volume 77: Table 5.1-3. Incidences ≥1 have been rounded off to the nearest integer.
*Note: in this population, the incidence of angina pectoris, angina pectoris aggravated and unstable angina were all respectively higher in the placebo groups.
**Note: in this population, the incidence of ventricular bigeminy, ventricular fibillation, and ventricular tachycardia were higher in the valsartan group by 0.1-0.2% .
¶ sum total: renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure aggravated, renal failure chronic, renal failure chronic aggravated, renal impairment NOS

Table 16. Number (and percent) of patients who prematurely discontinued from study treatment due to adverse experiences (short-term double-blind studies) (≥ 1% for valsartan)

Preferred term	Valsartan (n=776)	Active control (n=86)	Placebo (n=246)
Total (any body system)	67 (9)	4 (5)	9 (4)
Dizziness (exc vertigo)	17 (2)	0	0
Hypotension NOS	19 (2)	0	0

Source: Volume 87: Table 5.1-41. Includes: 103, 104, 106 and 110. Active control combines lisinopril and enalapril groups.

One patient was discontinued from valsartan (320 mg BID) and none from the other groups because of angioneurotic edema; 4 patients were discontinued from valsartan—none from the other groups—because of renal impairment or failure.

Table 17. Number (and percent) of patients discontinued from trial treatment (incidence > 1% in valsartan) due to adverse experiences --Long-term trial (107)

	Valsartan N=2506 n (%)	Placebo N=2494 n (%)
Total—any body system	249 (10)	181 (7)
Dizziness (exc vertigo)	41 (2)	11 (0.4)
Renal impairment NOS	27 (1)	6 (0.2)
Renal failure or impairment*	45 (2)	14 (1)
Hypotension NOS	32 (1)	20 (0.8)

Source: Volume 87: Table 5.1-43. A patient is counted once per preferred term within each body system.
*sum total: renal failure NOS, renal failure acute, renal failure acute on chronic, renal failure aggravated, renal impairment NOS

Laboratory changes:

Table 18. Number (%) of patients with specified percent change from baseline to final visit for selected biochemistry variables (primary dataset)

	Valsartan n (%)	Active control n (%)	Placebo n (%)
Creatinine ≥ 50% increase	123 (4)	1 (1)	24 (0.9)
Uric Acid ≥ 50% increase	93 (3)	2 (3)	48 (2)
Potassium * ≥ 20% decrease ≥ 20% increase (to endpoint)	81 (3) 298 (10)	0 5 (6)	104 (4) 128 (5)
BUN ≥ 50% increase	506 (17)	4 (5)	169 (6)
SGPT ≥ 150% increase	33 (1)	2 (3)	26 (1)
SGOT ≥ 150% increase	11 (0.4)	0	10 (0.5)
Alkaline phosphatase ≥ 100% increase	17 (0.6)	1 (7)	14 (0.6)
Total bilirubin ≥ 100% increase	74 (3)	1 (7)	14 (0.6)
Glucose ≥ 50% decrease ≥ 50% increase	44 (2) 108 (5)	0 1 (7)	38 (2) 110 (5)
Sodium ≥ 5% decrease ≥ 7% increase	53 (2) 12 (0.4)	1 (1) 1 (1)	42 (2) 14 (0.5)
Calcium ≥ 10% decrease ≥ 10% increase	59 (2) 78 (3)	3 (20) 3 (20)	45 (2) 57 (2)

Source: Volume 77: Table 6-7. *excludes values ≥ 7.0 mEq/l.
Includes 103, 104, 106, 107 (first 4 months) and 110

Table 19. Number (%) of patients with specified change from baseline for selected biochemistry variables (107)

	Valsartan n (%)	Placebo n (%)
Creatinine ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N= 2480 163 (7) 362 (15)	N=2475 87 (4) 150 (6)
Uric Acid ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N=2318 112 (5) 235 (10)	N=2333 96 (4) 184 (8)
Potassium * ≥ 20% increase (to endpoint) ≥ 20% increase (any point)	N=2307 262 (11) 791 (34)	N=2295 160 (7) 479 (21)
BUN ≥ 50% increase (to endpoint) ≥ 50% increase (any point)	N=2480 609 (25) 1161 (47)	N=2475 389 (16) 661 (27)

Source: Volume 77: Table 6-8, 6-10. *excludes values ≥ 7.0 mEq/l.

Hematology: There were small mean decreases from baseline in hemoglobin and hematocrit levels for the valsartan groups.

Table 20. Number (%) of patients with hematology values exceeding specified % change from baseline limit to final test result (primary dataset)

	Valsartan n (%)	Active control n (%)	Placebo n (%)
Hemoglobin			
≥ 20% decrease	56 (2)	1 (1)	20 (0.8)
≥ 50% increase	3 (0.1)	0	2 (0.1)
Hematocrit			
≥ 20% decrease	67 (2)	0	5 (0.2)
≥ 50% increase	10 (0.4)	3 (4)	53 (2)
WBC			
≥ 50% decrease	12 (0.4)	0	30 (1)
≥ 50% increase	78 (3)	3 (4)	156 (6)
Absolute neutrophils			
≥ 50% decrease	49 (2)	0	30 (1)
≥ 50% increase	177 (6)	0	156 (6)

Source: Volume 77: Table 6-16. Includes: 103, 104, 106, 107 (first 4 months), 110. N= patients with baseline + at least one post-baseline value

Table 21. Number (%) of patients with hemoglobin/hematocrit values exceeding specified % change from baseline to final result (107)

≥ 20% decrease	Valsartan N=2313 n (%)	Placebo N=2328 n (%)
Hemoglobin	70 (3)	44 (2)
Hematocrit	85 (4)	57 (3)

Source: Volume 77: Table 6-17.

Table 22. Mean change from baseline in DBP and SBP at selected timepoints (107)

	Time	Valsartan N=2506			Placebo N=2494		
		n	Baseline mean	Mean (SD) change	n	Baseline mean	Mean (SD) change
Sitting SBP	6 months	2203	123.8	-5.8 (15.9)	2261	124.5	-1.9 (15.4)
	1 year	2018	123.9	-5.2 (16)	2093	124.9	-1.3 (15.9)
	2 years	1209	124	-5.6 (17.1)	1248	124.6	-2.4 (15.9)
	3 years	123	123.9	-3.4 (17.6)	130	124.1	-0.8 (18.5)
	Endpoint	2494	123.4	-7.1 (17.8)	2482	120.4	-3.7 (17.5)
Sitting DBP	6 months	2201	75.8	-4 (10)	2261	75.8	-1.4 (10)
	1 year	2017	75.8	-3.8 (10.1)	2093	76.1	-1.2 (10.1)
	2 years	1209	76.2	-4.5 (10.7)	1247	76.3	-2.5 (10.7)
	3 years	122	74.9	-5 (10.1)	130	75.1	-3.3 (10.1)
	Endpoint	2494	75.5	-4.7 (11)	2482	75.6	-3 (10.8)

Source: Volume 77: Table 7-1

Summary:

1. There was an increased discontinuation from valsartan treatment, compared to placebo, due to adverse events in clinical trials.
2. An increased incidence of dizziness, hypotension, renal impairment and hyperkalemia are seen with valsartan (compared to placebo). Increases in creatinine, potassium and BUN are also seen in the valsartan group compared to placebo. It is not known whether these increases translate into hospitalization (non-CHF) for valsartan.
3. Decreases in SBP and DBP are noted with valsartan compared to placebo.

Individual Study Reviews:

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)

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.
This study was jointly reviewed with B. Nhi Nguyen, Pharm.D.

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 102.1. 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) ⇓		N=number randomized
Visit	1	2	3	4
Day	-14 to -3	-1	0	1 7
Hour			0	24

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 ≤ 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 ≥ 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 ≥ 15 mm Hg.

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

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

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 102.1. 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 102.2. 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.

Table102. 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

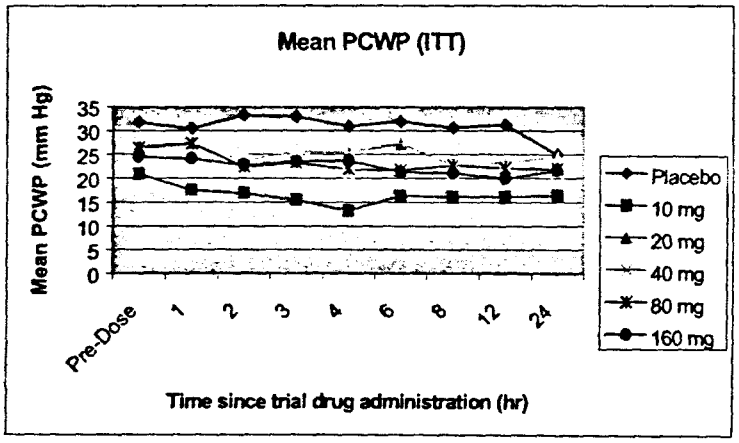
Table 102.3. Baseline characteristics (cont.)

	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 102.2-5 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 102.2. PCWP over time (ITT)



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

Figure 102.3. Change from baseline in PCWP

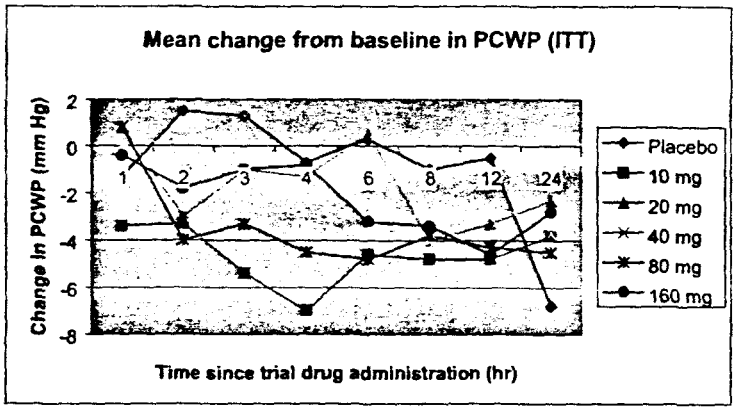
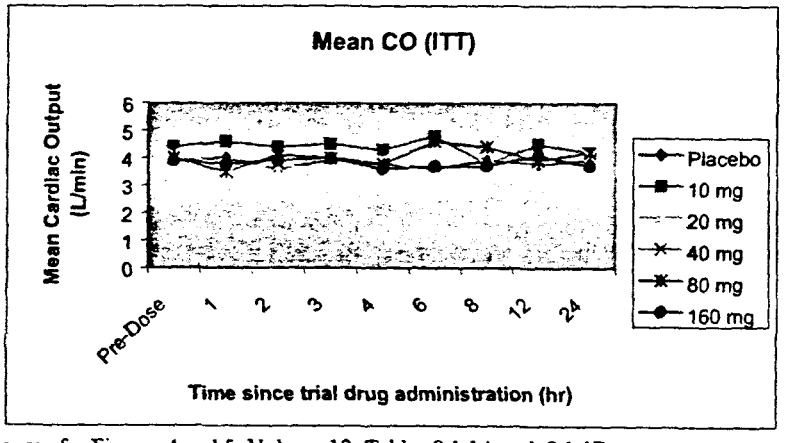


Figure 102.4. Cardiac Output (CO) over Time (ITT)



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

Figure 102.5. Change from baseline in Cardiac Output (ITT)

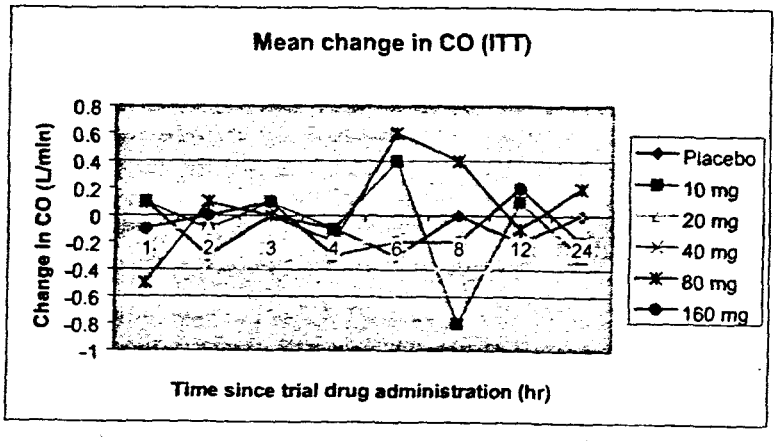


Table102. 4. Primary Efficacy Variables: Change from Baseline at 24 hours (ITT)

	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)

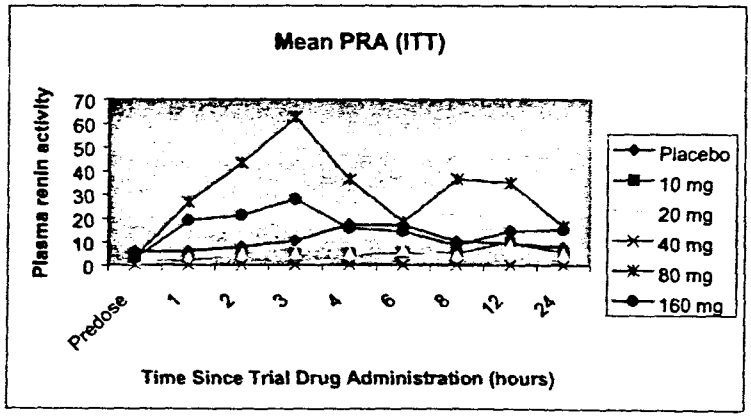
Source: Volume 12: Study Report and Table 8.1:1B * patient 11/507 did not have 24 hour efficacy measurements and was not included in this table.

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.

Table 102.6. Plasma Renin Activity (PRA)



Source for Figures 6 and 7: Volume 12: Table 11.1:2A, 11.1:2B

Figure102. 0-7. Change from baseline in Plasma Renin Activity (PRA)

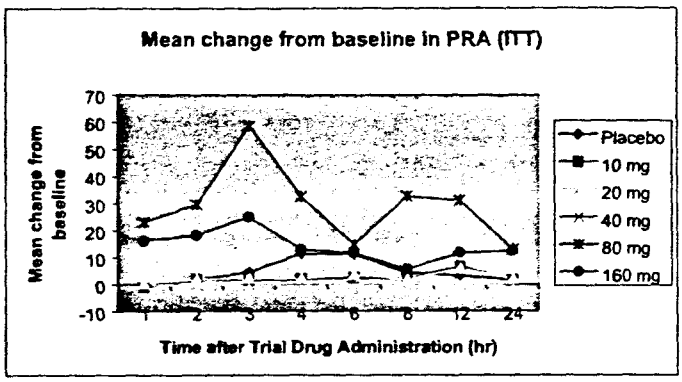


Figure 102.0-8. Plasma Angiotensin II

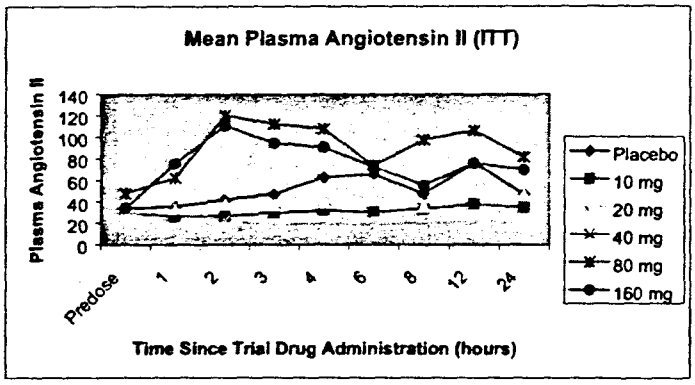
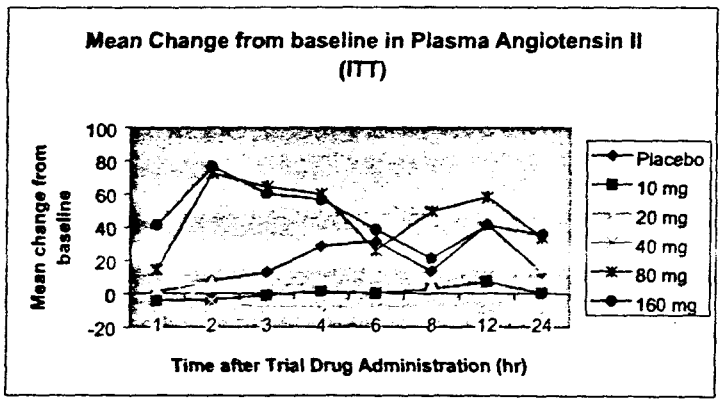


Figure 102.0-9. Change from baseline in Angiotensin II



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

Figure 102.0-10.Plasma Aldosterone

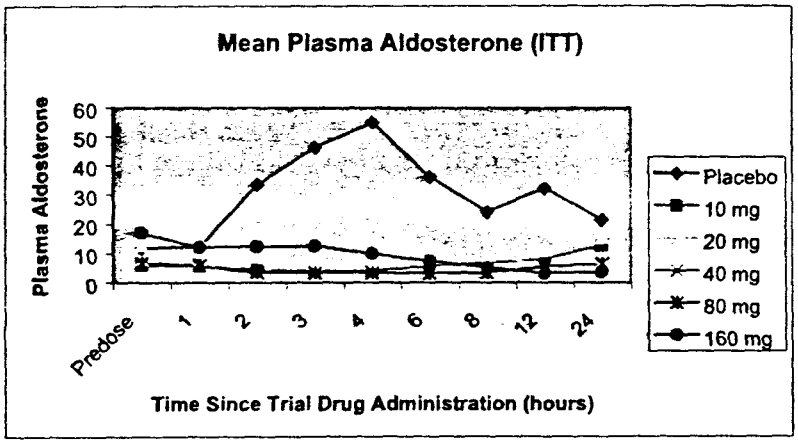
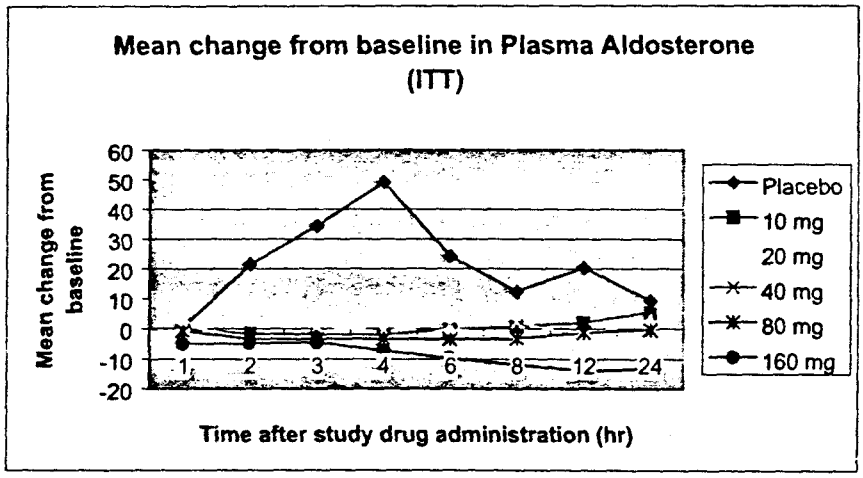


Figure 102.0-11. Change from Baseline in Plasma Aldosterone



Pharmacokinetic/pharmacodynamic results

The pharmacokinetic data are highly variable (see table 102.5). Cmax was reached ~ 3 hours after dosing.

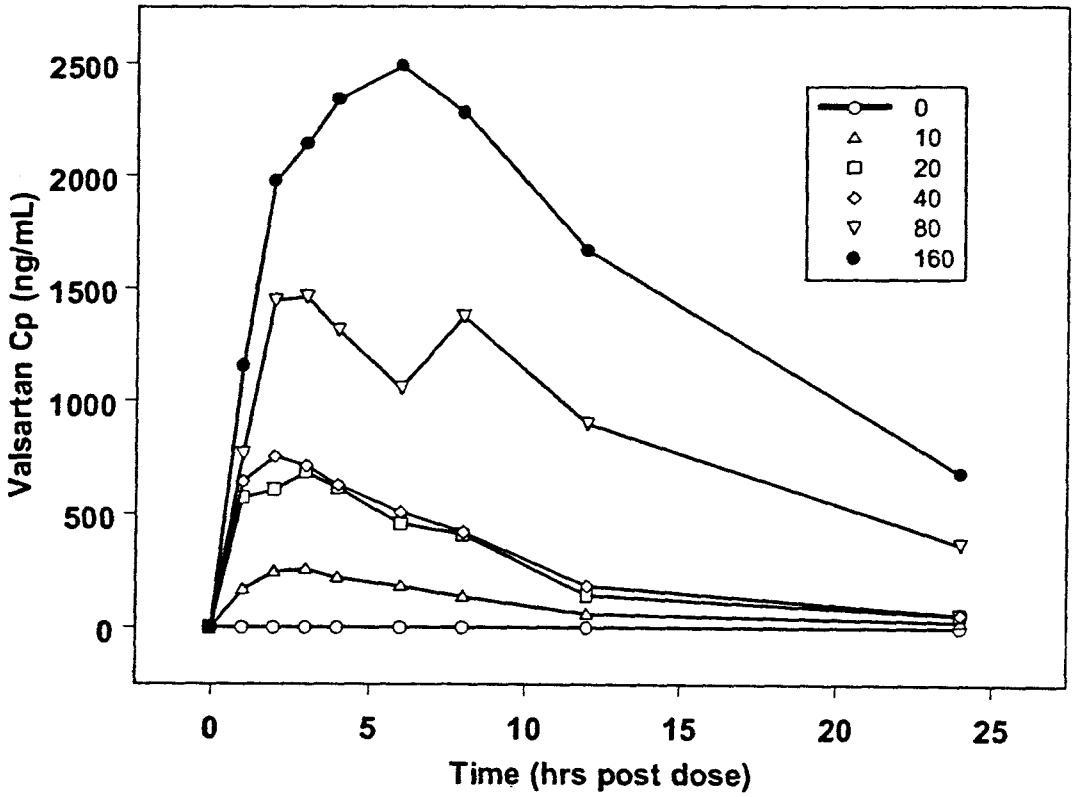
Table 102.5. Mean pharmacokinetic parameters

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 102.012.

Figure 102.012. 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 102.6. 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 %	

1.

Figure 102.013. Observed and predicted AUC at 5 different doses

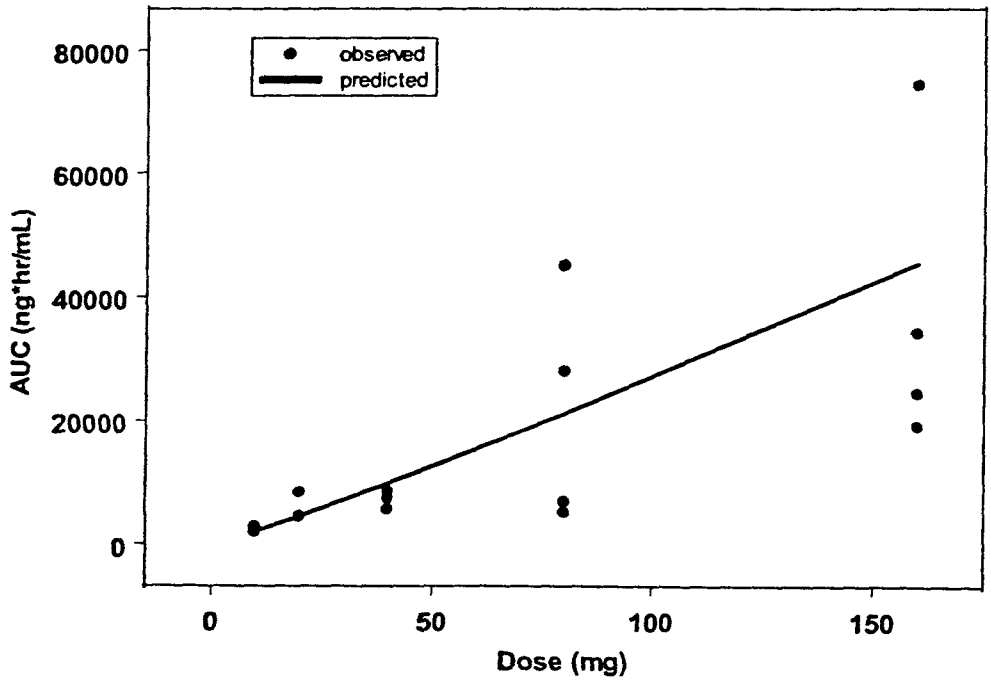
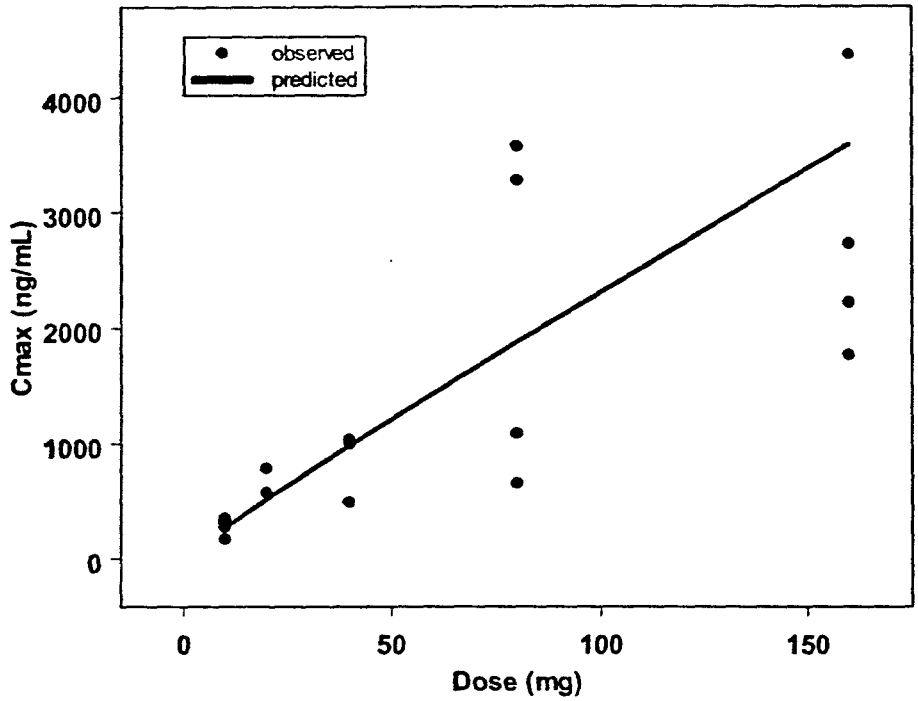


Figure 102.0-14. Observed and predicted Cmax at 5 different doses



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

Figure 102-0.15. Mean PCWP and valsartan concentration relationship

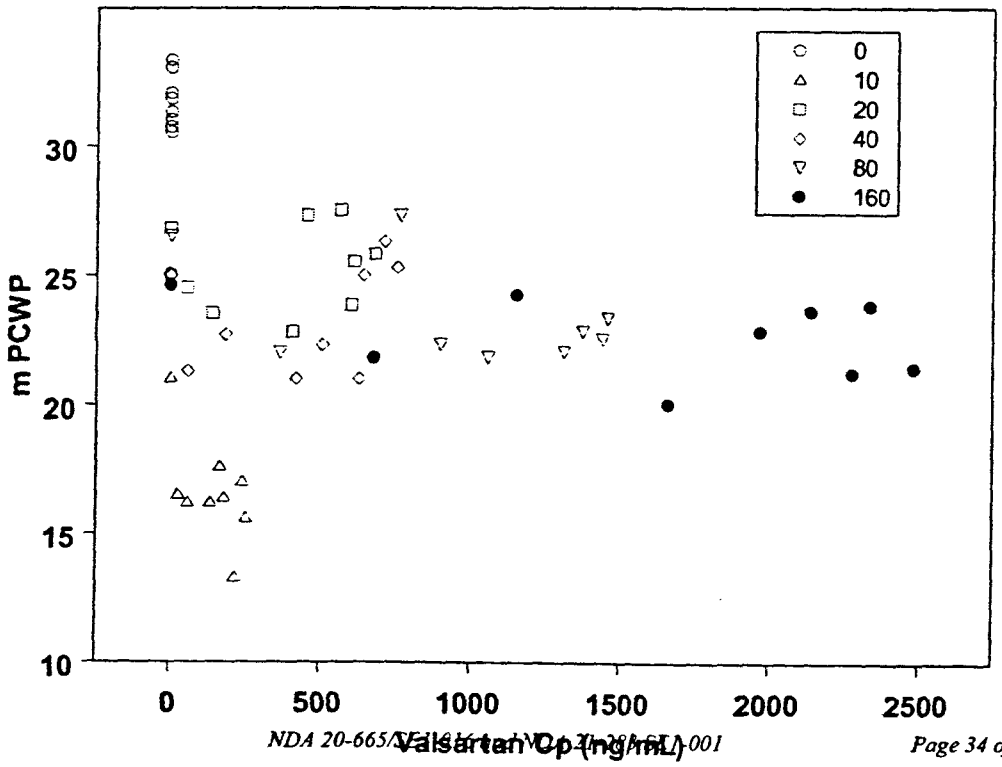
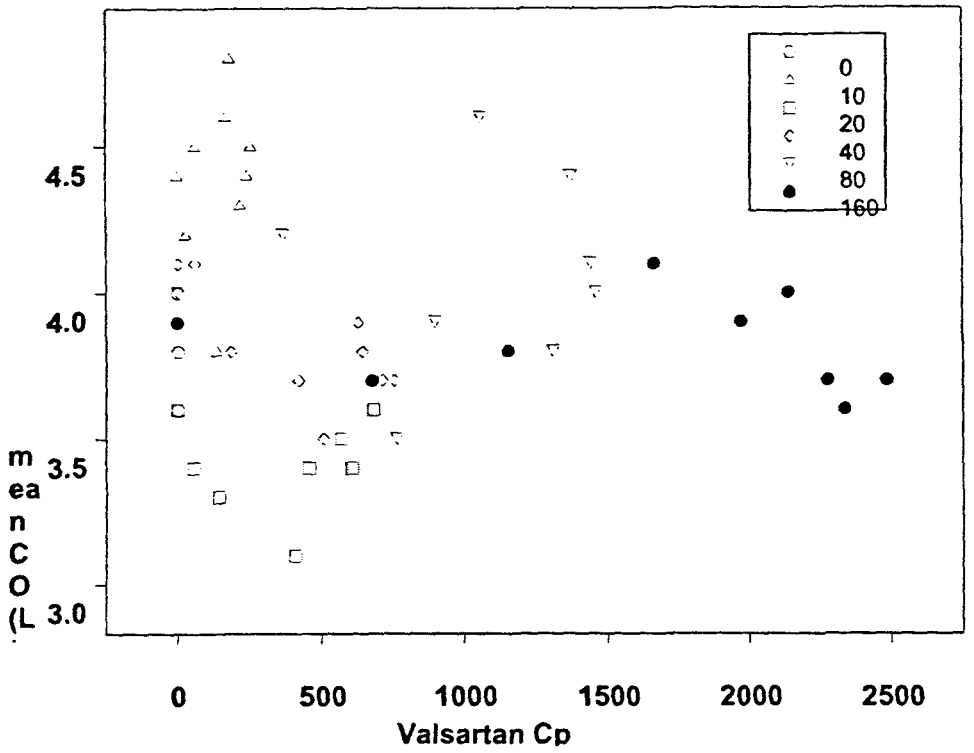


Figure 102.0.16. Mean CO and valsartan concentration relationship



There was a slight trend in the placebo-adjusted change from baseline PRA, aldosterone and angiotensin II (see figures 102.0-17, 18, and 19).

Figure 102.0-17

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.

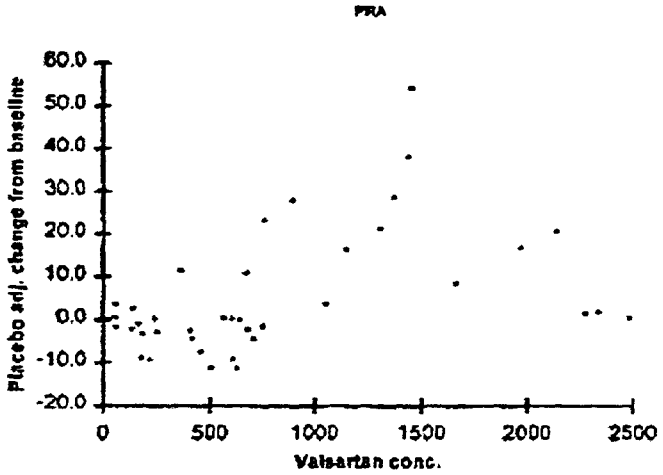


Figure 102.0-18.

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.

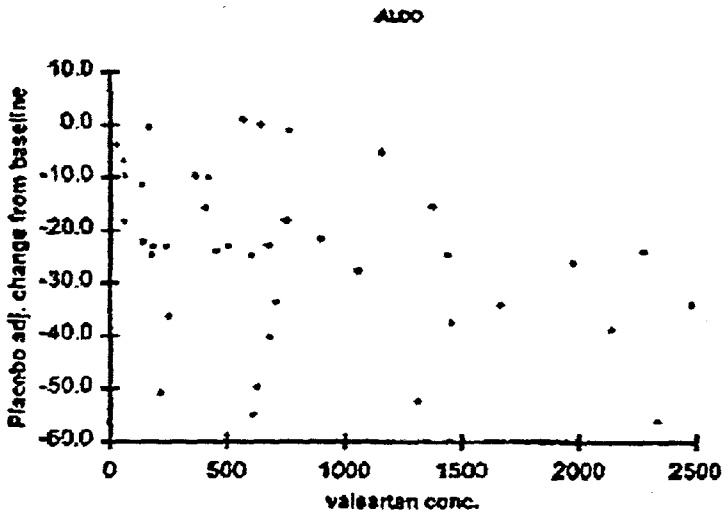
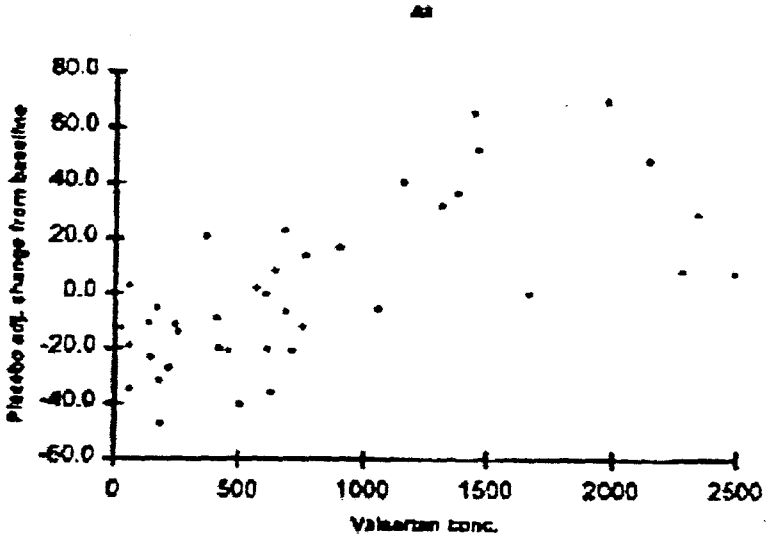


Figure 102.0-19

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 102.7. 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.

Study 103. A multicenter, double-blind, randomized, placebo- and active-controlled, between patient trial to assess the cardiac hemodynamic effects of valsartan 40 mg, 80 mg and 160 mg, all twice daily, in patients with chronic stable congestive heart failure NYHA stage II-IV treated for four weeks (Phase II) (Protocol date: January 25, 1995

Source: NDA Volume 65 (Study Report and Tables), 67 (Protocol); electronic (.xpt) datasets.

Primary Objective (listed as "aim" in the protocol):

- Assess the cardiac hemodynamic effects of valsartan 40 mg, 80 mg and 160 mg, all twice daily, in patients with chronic stable congestive heart failure NYHA stage II-IV after four weeks of treatment.

Secondary Objective (listed as "aim" in the protocol):

- Evaluate safety and tolerability of valsartan administered to patients with stable chronic congestive heart failure.

Sites: This 9 site study was conducted in Russia. The principal investigator was Dr. Vladimir Mazayev, MD, DMSc.

Duration: April 14, 1995 (first patient, first visit) to March 38, 1996 (last patient, last visit)

Study Design:
This was a multicenter, double-blind, randomized study in patients with chronic stable Class II-IV CHF. After a 2-4 week drug-free run-in period, eligible patients were randomly assigned, with a ratio of 2:2:2:2:1 to receive either valsartan 40 mg, 80 mg, 160 mg, placebo (all BID) for 4 weeks or lisinopril 5 mg QD (1 week) followed by lisinopril 10 mg QD (3 weeks) to complete 4 weeks of treatment. Treatments were matched to look identical in size and color; lisinopril was given as active treatment in the morning with a matching placebo in the evening for a twice daily regimen.

Figure 103.0-1. Study design

	Enrollment	Randomization Valsartan 40 mg BID Valsartan 80 mg BID Valsartan 160 mg BID Placebo Lisinopril 5 mg ⇒10 mg QD (Visit 3) ⇓ ⇓			
Visit	1	2	3	4	5 (Final)
Day	-28 or –14	-1to 1	7	14	27-28
Hour			0		

On Day –1 (Visit 2) patients were admitted for right heart catheterization. Patients were eligible for randomization if the initial two mean pulmonary capillary wedge pressures (PCWP) were both ≥ 18 mm Hg. A maximum of 5 sets of measurements (each set containing two

measurements) was to be done. If the fifth mean PCWP was not within 10% of the fourth, the patient was to be discontinued from the trial. The same procedures were to be followed for Visit 5 (day 27-28). Hemodynamic measurements were to be taken at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose.

Inclusion Criteria[2]	Exclusion Criteria
• Male or female patients 18 to 80 years, inclusive. • Symptomatic chronic stable CHF, present for at least one month prior to Visit 1, NYHA Class II, III or IV. • Mean PCWP $\geq$ 18 mm Hg[3] at rest at Visit 2 (Day -1) • Written informed consent to participate in the trial and to attending the examinations laid out in the protocol.	• Pregnancy, nursing, or women of childbearing potential without an effective method of birth control. • History of acute MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 3 months prior to Visit 1. • Angina pectoris requiring more than 15 tablets/week of prn sublingual nitroglycerin. • Clinically significant primary valvular dysfunction (except mitral regurgitation secondary to a dilated failing LV). • Presence or history of restrictive cardiomyopathy, constrictive pericarditis. • Dyspnea of non-cardiac origin within the past year. • Gastrointestinal disease or surgery which would impair drug absorption, any condition/lab abnormality which would interfere with this study. • Life-threatening ventricular arrhythmias including arrhythmias requiring cardioversion or AICD or episodes of symptomatic sustained VT lasting longer than 30 seconds at any time previous to or during the trial, or requirement of antiarrhythmic agents affecting myocardial performance at usual doses (eg calcium antagonists, beta blockers, flecainide, disopyramide). • Hepatic disease as determined by: SGOT or SGPT > two times ULN, history of hepatic encephalopathy, esophageal varices, portocaval shunt. • Renal impairment as determined by: serum creatinine $\geq$ 1.5 times ULN or history of dialysis. • Uncontrolled hypertension (BP $\geq$ 160/100 mm Hg) or malignant hypertensive or Keith-Wagner Grade III or IV hypertensive retinopathy. • Hypotension (BP < 80/50 mm Hg). • Hypertensive encephalopathy or CVA within past 6 months. • Clinically significant allergies or multiple drug allergies.

[2] Taken from Protocol. Please see Amendments to the Protocol for changes in Inclusion/Exclusion criteria.
[3] Please see Protocol amendment: this criteria was lowered to $\geq$ 15 mm Hg.

	• IDDM. • NIDDM with poor glucose control, peripheral neuropathy or autonomic neuropathy. • Malignancy (exc. for basal cell CA) within past 5 years. • History of any other severe life-threatening disease. • Administration of ACE inhibitors 6 months prior to Visit 1. • Drug/alcohol abuse within the past 2 years. • Participation in any investigational drug trial within 30 days prior to Visit 1. • Those persons directly involved in the execution of this protocol.

Allowed Concomitant medications:

- Digitalis (administered prior to 12 hour hemodynamic measurement, where applicable)
- Diuretics
- Long-term oral anticoagulant therapy
- Acute use of medications (e.g., antibiotic or analgesic use)

Excluded medications:

- Daily doses of diuretic greater than 80 mg furosemide or equivalent.
- Administration of diuretic on Days –1, 0, 27 and 28.
- Administration of nitroglycerine 12 hours prior to hemodynamic measurements.
- Antihypertensive agents except for diuretics.
- Vasodilator drugs (e.g. hydralazine and long-acting nitrates).
- Calcium antagonists.
- Tricyclic antidepressants.
- MAO inhibitors.
- Phenothiazines.
- Anti-inflammatory drugs, both steroidal or nonsteroidal. Topical steroids were allowed.
- Thyroid medication unless this has been a stable maintenance replacement dose for the preceeding 6 months.
- Over the counter diet preparations.
- Common cold preparations taken chronically.
- Amphetamine and its derivatives.

Table 103.1 . Schedule of Procedures

Period	Drug-free run-in period	Double-blind treatment period			
Visit	1	2	3	4	Final
Day	-28 (-14)	-1 to 1	7	14	27-28
History/ECG/CXR/Informed consent	X				
Physical exam/signs and symptoms of CHF/weight/pulse/BP	X	X	X	X	X
Inclusion/Exclusion criteria	X	X			
Routine laboratory tests	X	X		X	X
Right heart catheterization; 12 h hemodynamics		X			X
Withhold diuretics		X (day-1, day 0)			X (day 27, 28)
Withhold NTG 12 hours prior to hemodynamic measures		X (day-1, day 0)			X (day 27, 28)
Neurohormonal measurements *		X			X
Adverse experiences/concomitant meds		X	X	X	X

*PRA, angiotensin II, aldosterone

Criteria for Discontinuation from Trial:

1) When the patient decides that it is in his/her best interest.
2) When the investigator considers it advisable.
3) Intolerable adverse experiences.
4) Lack of therapeutic response resulting in intolerable symptoms.
5) Major protocol violation.
6) Noncompliance of the patient.
7) Deterioration in NYHA class starting at Visit 1 and throughout the trial.
8) Persistent SBP < 70 mm Hg after randomization and throughout the trial.
9) Persistent DBP < 50 mm Hg after randomization and throughout the trial.
10) Development of hypokalemia (< 3 mmol/l) or hyperkalemia (> 5.5 mmol/l) refractory to treatment.
11) Deterioration of renal function: > 40% change from baseline in serum creatinine.
12) Persistent PCWP < 5 mm Hg.
13) Development of any exclusion criteria (see Above).
14) Development of an arrhythmia requiring cardioversion, AICD or pharmacologic therapy during the course of the trial.

Primary Efficacy Variable:

The primary efficacy variable was the change from baseline in pulmonary capillary wedge pressure (PCWP).

Secondary Efficacy Variables:

Change from baseline to endpoint in the following:

1. Cardiac output (CO).
2. Right atrial pressure (RAP).
3. Cardiac Index (CI).
4. Systemic vascular resistance (SVR).
5. Pulmonary vascular resistance (PVR).
6. Stroke volume index (SVI).
7. Mean pulmonary artery pressure (MPAP).
8. Systolic pulmonary artery pressure (SPAP).
9. Diastolic pulmonary artery pressure (DPAP).
10. Heart rate.
11. Systolic (systemic) BP.
12. Diastolic (systemic) BP.
13. Mean arterial BP (MAP).
14. Plasma renin activity.
15. Angiotensin II.
16. Aldosterone

CO was determined by taking 5 measurements, excluding highest and lowest values, and averaging the remaining 3 values.
CI, MAP, SVR, SVI, and PVR were calculated from formulas that were prespecified in the protocol.

Sample size: The sample size was based on time available for patient enrollment. Twenty to 24 completed patients in each valsartan group and placebo, with 10-12 completed patients in the lisinopril group, were targeted for statistical analysis. A treatment difference of at least 6 mm Hg

for PCWP was considered by the sponsor to be clinically relevant. Given a standard deviation of 6 mm, and an overall significance level of 0.05 (with 0.017 significance for pair-wise treatment comparison), a treatment difference in PCWP of 6 mm Hg was expected to have a statistical power of 82.4%.

Data set analysis: According to the protocol, all randomized patients with a baseline and at least one non-missing post-randomization measurement for a particular variable were to be included in the analysis of that variable. The safety analysis was prespecified to include all randomized patients.

Although not prespecified in the protocol or amendment, three patients (one each in valsartan 40 BID, 80 BID and placebo) were excluded from the efficacy analysis population because of the use of excluded concomitant medications. These three patients were discontinued from the study and did not undergo Day 28 hemodynamic measurements. According to the sponsor, these patients were excluded prior to database lock. The patients analyzed are referred to as the "efficacy analysis population."

Statistical Plan:
The primary analyses was mean change from baseline (Day 0 Hour 0) in PCWP over 4 to 8 hours on Day 28 and at 12 hours on Day 28.

For the PCWP and other right heart pressures between-treatment analyses of change from baseline were to be performed at each individual time point at which data were collected. In addition, change from baseline over 4, 6, and 8 hours and mean change from baseline over 0 to 12 hours were to be performed. The mean change from baseline over 4 to 8 hours was expected to provide information about peak drug effect.

Mean change from baseline over 4, 6, and 8 hours was to be calculated using equal weights for each time point, based on the equal time intervals between measurements. Mean change from baseline over 0 to 12 hours was to be calculated from weights based on the trapezoidal-rule principle and the unequal time intervals between measurements; weighting was prespecified in the protocol.

Summary statistics only were to be provided for the secondary variables related to changes in pulmonary and systemic blood pressures and heart rate.

Between-treatment comparisons were based on a null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. Testing for between-treatment differences were made at a 5% overall significance level, using Bonferroni adjustments for valsartan 160 mg BID vs. placebo, valsartan 80 mg BID vs. placebo, and valsartan 40 mg BID vs. placebo; each individual pair-wise comparison was to be tested at the 1.7% (5% divided by 3) significance level. Lisinopril 10 mg was to be compared to placebo at the 5% significance level.

A two-way analysis of covariance was to be performed on change from baseline; the baseline value was to be used as the covariate and treatment and center were to be used as factors. This model was also to include all two-way interactions with treatment.

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

Amendment to the Protocol:
3. (signed, April 27, 1995):
   A) PCWP inclusion criterion lowered to patients with mean PCWP $\geq$15 mm Hg at rest on Visit 2 (day –1);
   B) Exclusion criterion for acute pulmonary edema or hospital admission for CHF changed from "within 3 months prior to Visit 1" to "within one month prior to Visit 1."
   C) In case of premature discontinuation, all procedures and CRF pages should be completed as appropriate. Right heart catheterization should only be performed at the final visit if this visit is at least two weeks after visit 2 (day 0).
   D) If PCWP was unable to be measured at some timepoint, then the pulmonary artery diastolic pressure (PAD) was to be taken instead if the PCWP and PAD have been the same during previous measurements and the field for mean PAP in the CRF will be empty.
   E) The unit in the CRF for angiotensin II was to be changed from pmol/ml to pmol/L.
   F) In addition to PRA, angiotensin II and aldosterone, norepinephrine concentrations were to be determined at visits 2 and 5 at baseline, and at 2, 4, 8 and 12 hours post-dosing.

Neurohormone analysis:
- PRA, angiotensin II and aldosterone were to be analyzed at the laboratory of Moscow Medical Academy, B. Pirogovskaya 6, Moscow 119435.
- Plasma norepinephrine was to be analyzed by Hazleton, Otely Road, Harrogate, North Yorkshire HG31PY, England.

Batch and formulation numbers follow (Table 103.2):

Table 103.2 . Drug Supply

Treatment group	Batch Number	Formulation Number
Valsartan 40 mg	1051/6	F.1
Valsartan 80 mg	1052/6	F.1
Valsartan 160 mg	1059/4	F.1
Lisinopril 5 mg	1126/1	F.1
Lisinopril 10 mg	1127/1	F.1
Placebo	1070/13	F.1

Source: Sponsor: Volume 65 (Study report)

Administrative Issues:
1. According to the sponsor, it was noted that "a few patients had PCWP > MPAP at certain time points." Since the prespecified formula for PVR used the calculation of (MPAP-PCWP)/CO, PVR was instead calculated using the formula Total PVR = MPAP/CO.
2. For results of norepinephrine levels, 2 of 3 batches could not be analyzed because 90% of the samples were below the lower limit of detection. The third batch was discarded without being analyzed.

3. According to the Moscow Medical Academy, four neurohormonal samples for three patients (Patient 1028/22, visit 2; patient 1029/23, visit 2; patient 1075/57, visits 2 and 5) were "unreliable" and therefore excluded from analysis.
4. All calcium values from laboratory #2 measured before 10/1/95, from laboratory #4 before 11/23/95, and all values from laboratory #6 were excluded from laboratory data analysis because ionized calcium was measured instead of total calcium.

Medical Reviewer's Comments:
1) This study did not require documentation, via echocardiogram or MUGA, of extent and type of LV dysfunction.
2) It is unclear why the lisinopril doses (5/10 mg) were chosen. The effective dose range for CHF is from 5 to 40 mg once daily.[4] Patients on lisinopril may have been receiving suboptimal therapy.
3) Patients were not allowed to receive ACE inhibitors 6 months prior to Visit 1 and throughout the trial. During the period when this study was conducted, ACE inhibitors were part of standard US therapy for the treatment of CHF. Indeed, captopril was approved in the early 1980s for hypertension and was in common use, by the mid-1980s, for CHF. Captopril was apparently available in Russia as well; one patient (7/ Rand. #28) was discontinued because he was taking captopril for CHF (Source: Table 6.1-2: Premature Discontinuations).

Results:

Patient Disposition:

One hundred forty-five patients were enrolled at Visit 1; a total of 116 patients were randomized at Visit 2 and 103 patients completed the study.

Table 103.3. Patient disposition

	Valsartan			Lisinopril	Placebo	Total
	40 mgBID	80 mg BID	160 mg BID	5/10 mg		
Enrolled						145
Randomized	24*	24*	27	15	26*	116
Completed	20	21	24	14	24	103
Discontinuations from Double-Blind						
Adverse Event	1	--	1			2
Withdrew consent	1**	--	1	1	1	4
Lack of Therapeutic Effect		1***				1
Did not meet Protocol criteria	1	2			1	4
Administrative	1		1			2

*One patient in each of these groups did not have a valid hemodynamic measurement for at least one time point.
Source: Volume 65: Table 6.1-1
**This patient underwent heart transplantation; consent was withdrawn because a donor was found.
***Deterioration of CHF

[4] Source: Zestril labeling.

Protocol violations:
There were a total of 6, 8, 2 and 9 protocol violations noted in the valsartan 40 BID, 80 BID, 160 BID and placebo groups, respectively; no protocol violations were seen in the lisinopril group. As noted above, 3 patients were excluded from the efficacy analysis because of the use of excluded medications.

Drug Exposure:

Table 103.4. Duration of Drug Exposure (All Randomized Patients)

	Placebo	Valsartan			Lisinopril
		40 mg BID	80 mg BID	160 mg BID	5/10 mg
N	26	24	24	27	15
Median (days)	28	28	28	28	28
Range (days)	16-32	8-35	10-31	13-29	27-29

Source: Volume 65: Table 6.4-1

Baseline characteristics:
The randomized study population was 100% Caucasian. Mean age was 53-59 (±9-14) years. Most patients had a baseline abnormal CXR; except for 2 patients with a normal ECG, most patients had ECGs that were "abnormal but compatible." Mean heights and weights were about 168-173 (±7-8) cm and 79-85 (± 15-18) kg, respectively Mean sitting pulse rate was about 77-82 (± 9-13) bpm. Mean baseline SBP was 121-134 (± 15-20) mm Hg, mean DBP was 78-85 (± 9-11) mm Hg; baseline mean PCWP was about 20-21 (± 6-10) mm Hg and mean CO was 4.84-4.97 (±1.4-1.8) L/min. There is a higher percentage of elderly in the 40 BID group, and longer mean duration of CHF in the 160 BID group.

Table 103.5. Selected baseline characteristics

	Placebo N=26 n (%)	Valsartan			Lisinopril 5/10 mg N=15 n (%)
		40 BID N=24 n (%)	80 BID N=24 n (%)	160 BID N=27 n (%)	
Male (%)	23(89)	18 (75)	23 (96)	22(82)	10 (67)
Age ≥ 65	5 (19)	9 (38)	4 (17)	5 (22)	5 (33)
Mean duration CHF (yrs)	2.8(2)	2.6(3)	1.9 (2)	4.1(5)	2.1 (2)
Etiology*: Ischemic	16 (62)	18 (75)	20 (83)	26 (96)	11 (73)
Idiopathic	11 (42)	7 (29)	2 (8)	2 (7)	3 (20)
Hypertensive	9 (35)	10 (42)	6 (25)	11 (41)	5 (33)
Other	0	0	1 (4)	0	0

Source: Volume 65:Tables 7.1-1, 7.1-2, 7.1-3 *Note: these numbers do not add up to the total N.

Table 103.6. Visit 2 NYHA Class (Efficacy analysis population)

NYHA Class	Placebo N=25	Valsartan			Lisinopril 5/10 mg N=15
		40 BID N=23	80 BID N=23	160 BID N=27	
II	8	11	12	13	6
III	12	10	8	11	6
IV	5	2	3	3	3

Source: Volume 66: Table 8.18-1

Table 103.7. Baseline mean (±SD) neurohormone levels (Visit 2, Day 0) (Efficacy analysis population)

	Placebo	Val 40 BID	Val 80 BID	Val 160 BID	Lisinopril 5/10
N	24	19	21	24	14
Angiotensin II (pmol/ml)	11.8 (19.9)	19.2 (40.7)	6.5 (5.3)	12.8 (33.0)	7.2 (5.4)
Aldosterone (ng/ml)	27.4 (33.5)*	23.1 (22.0)	13.9 (8.1)	13.7 (8.9)	20.1 (16.8)
PRA (ng/ml/h)	1.6 (3.1)	1.4 (2.5)	0.7 (0.8)	2.2 (7.1)	1.6 (2.1)

*N=22 for this group.
Source: Volume 65: Table 8.15-1 and Volume 66: Table 8.16-1, 8.17-1

Concomitant Medications:
About 53-71% of patients were taking concomitant digoxin at trial entry. About 22-29% were on Dyazide, and about 83-93% were on furosemide. Of the beta blockers, propranolol use is listed in Table 103.8; 0-1 patients per treatment group were on atenolol. Three to four patients per treatment group were on concomitant amiodarone. The most common concomitant analgesic was aspirin; only two patients (in valsartan 160 BID and lisinopril group, respectively) were on indomethacin.

Table 103.8. Selected Concomitant Medications at Trial Entry

	Placebo N=26 n (%)	Valsartan			Lisinopril 5/10 mg N=15 n (%)
		40 BID N=24 n (%)	80 BID N=24 n (%)	160 BID N=27 n (%)	
Digitalis *	19	17	13	17	8
Furosemide	22	20	22	23	14
Digitalis *	19	17	13	17	8
Acetylsalicylic Acid	12	13	12	13	5
Propranolol**	4	4	2	2	0

*This category combines digitalis and digoxin
**This category combines propranolol and propranolol hydrochloride