Pooling: Although not prespecified in the protocol or amendment, centers were pooled such that each center and pooled center were to have at least 2 randomized, evaluable patients per treatment group in the primary analyses. Two centers had sufficient patients per treatment group; the other 7 centers were merged into one.

Efficacy—Primary efficacy variable:

Figure 103.0-2. Primary Efficacy Analysis: Change from baseline in mean PCWP
(Source: Volume 65: Table 8.1-2, Exhibit 8.1)

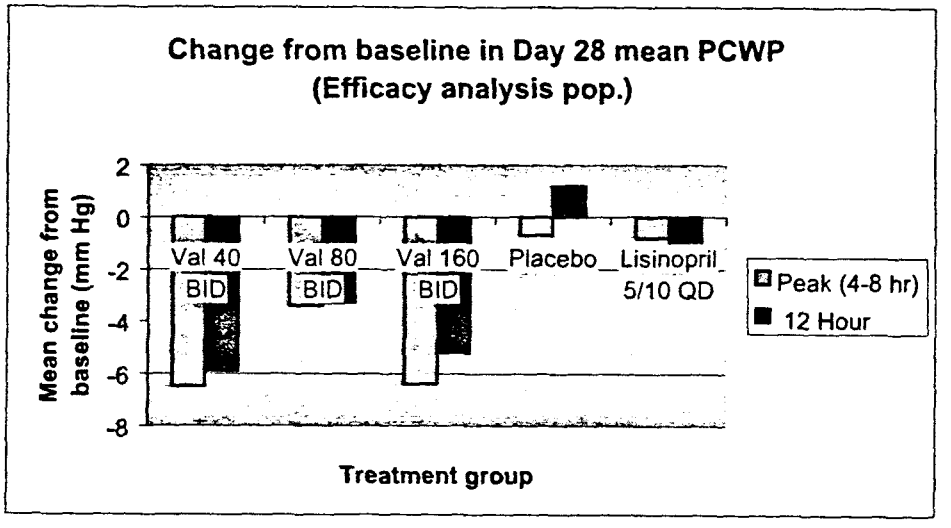


Table 103.9. Statistical Analysis Results : Day 28: Primary Efficacy Analysis (Efficacy Analysis Population)

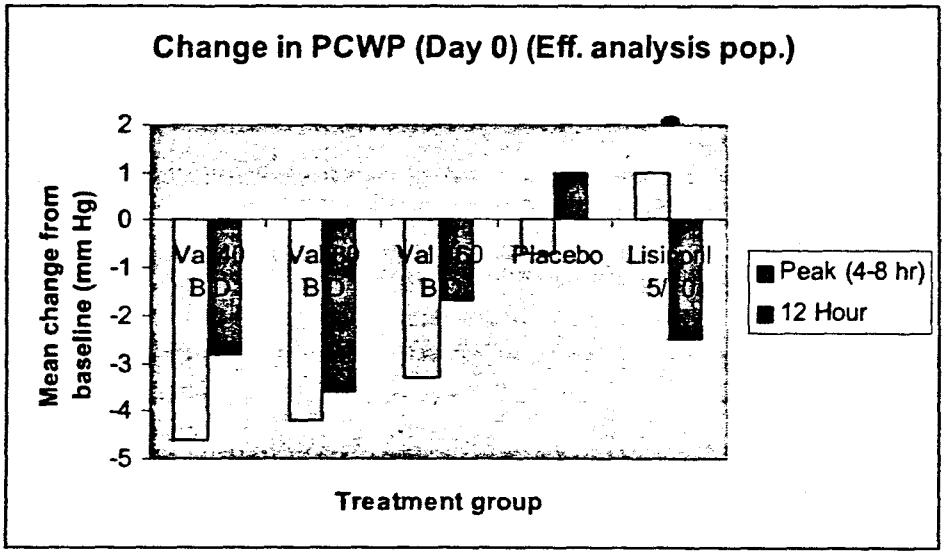
	Peak (4-8 hours after dosing)			Twelve hours after dosing		
	Adjusted mean difference	CI*	p-value	Adjusted mean difference	CI*	p-value
Valsartan 40 mg BID vs. placebo	-6.0	(-11.3, -0.7)	0.007	-7.5	(-13.2, -1.8)	0.002
Valsartan 80 mg vs. placebo	-2.8	(-7.9, 2.4)	0.194	-4.5	(-10.1, 1.1)	0.055
Valsartan 160 mg vs. placebo	-6.9	(-11.8, -1.9)	0.001	-7.5	(-12.8, -2.1)	0.001
Lisinopril 5/10 QD vs. placebo	-2.4	(-7.6, 2.7)	0.352	-5.2	(-10.8, 0.4)	0.071

Source: Volume 65: Study Report, Exhibit 8.1.2
*Confidence Interval=98.3% for valsartan; 95% for lisinopril.
**ANCOVA for change from baseline in mean PCWP. According to the sponsor, no significant treatment-by-baseline or treatment-by-center interactions were observed at either time point.

On Day 0, a dose-response can be seen for valsartan at the 4-8 hour post-dosing time point. The results for valsartan 80 mg BID at Day 28 appear inconsistent with the other valsartan results.

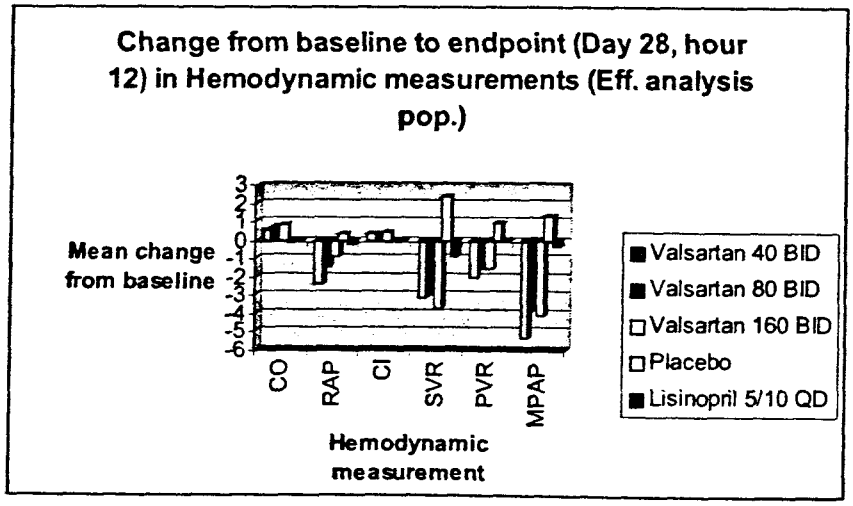
Figure 103-03. Change from baseline in Mean PCWP (Day 0)

Source: Volume 65: Table 8.1-2



Secondary efficacy variables:

Figure 103-04. Selected secondary efficacy variables (Efficacy analysis population). Raw means are presented



Source: Volume 65: Exhibit 8.2.1, 8.3.1, 8.4.1, 8.5.1, 8.6.1, 8.8.1.

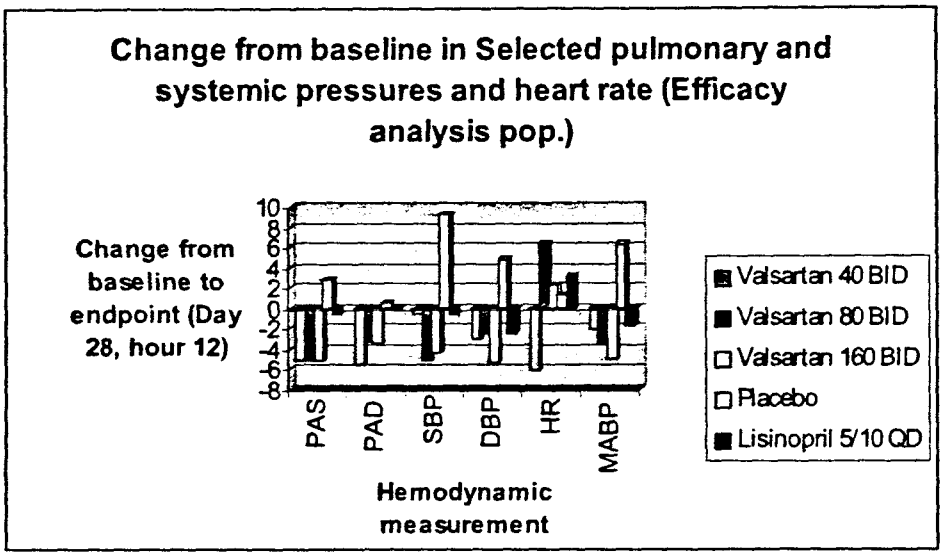
Table 103.10. Statistical analysis of secondary variables (day 28, Visit 5) (Efficacy analysis population): Change from baseline to Endpoint (12 hours post-dose) vs. placebo

	Valsartan			Lisinopril 5/10
	40 mg BID	80 mg BID	160 mg BID	
CO (L/min)				
Adjusted mean difference	0.76	1.04	1.09	0.33
Confidence Interval	(-0.12, 1.64)	(0.16, 1.91)*	(0.25, 1.92)*	(-0.47, 1.13)
RAP (mm Hg)				
Adjusted mean difference	-3.0	-1.9	-1.7	-1.0
Confidence Interval	(-6.1, 0.1)	(-5.0, 1.3)	(-4.6, 1.2)	(-3.8, 1.8)
CI ($L/min/m^2$)				
Adjusted mean difference	0.78	1.09	1.09	0.57
Confidence Interval	(-0.03, 0.95)	(0.05, 1.02)*	(0.20, 1.12)*	(-0.30, 0.60)
SVR (mm Hg/L/min)				
Adjusted mean difference	-5.3	-6.2	-6.2	-4.4
Confidence Interval	(-9.5, -1.0)*	(-10.4, -2.1)*	(-10.1, -2.2)*	(-8.2, -0.6)*
PVR (mm Hg/L/min)				
Adjusted mean difference	-3.11	-2.55	-2.83	-2.75
Confidence Interval	(-5.25, -0.96)*	(-4.65, -0.45)*	(-4.87, -0.78)*	(-4.87, -0.64)*
SVI (L/m^2)				
Adjusted mean difference	0.008	0.004	0.008	0.003
Confidence Interval	(0.001, 0.015)*	(-0.003, 0.011)	(0.001, 0.014)*	(-0.003, 0.010)
MPAP (mm Hg)				
Adjusted mean difference	-6.9	-4.6	-5.5	-4.9
Confidence Interval	(-12.3, -1.6)*	(-9.9, 0.7)	(-10.6, -0.4)*	(-10.8, 1.0)

Results for LS Means were, for the most part, similar to the above means and are not presented here.
Confidence Intervals =98.3% for valsartan, 95% for lisinopril. Adjusted mean difference derived from the analysis of covariance for change from baseline. Source: Volume 65: Exhibits 8.2.2, 8.3.2, 8.4.2, 8.5.2, 8.6.2, 8.7.2 *=Statistically significant

At the prespecified endpoint (Day 28, hour 12), significant increases in CO, CI and SVI and significant decreases in MPAP, SVR and PVR are seen in the valsartan 160 mg BID group compared to placebo. In all active treatment groups, RAP decreased without a dose-response or statistical significance. Results of decreases in DBP, MABP, SVR appear to show a dose-response relationship for valsartan.

Figure 103-5. Selected secondary efficacy parameters (efficacy analysis population)



Source: Volume 65: Exhibit 8.15.1, 8.16.1, 8.17.1

Neurohormone results:

Source: Volume 65: Exhibit 8.15.1, 8.16.1, 8.17.1

Figure 103-6. Neurohormone results (efficacy analysis pop.)

Source: Volume 65: Exhibit 8.9.1, 8.10.1, 8.11.1, 8.12.1, 8.13.1, 8.14.1

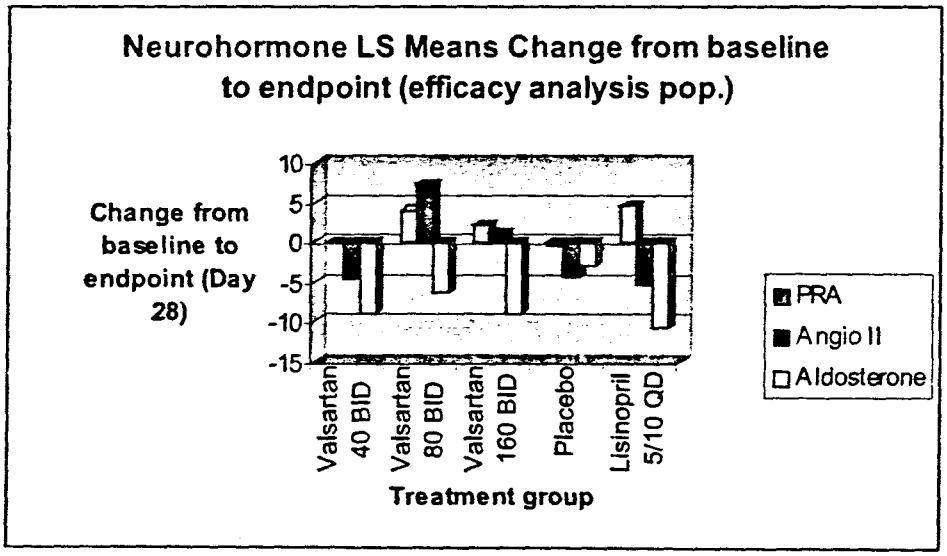


Table 103.11. Statistical Analysis of Neurohormone results (Efficacy analysis pop.): change from baseline to endpoint, Day 28, post-dose hour 12

	Valsartan 40	Valsartan 80	Valsartan 160	Lisinopril 5/10

	BID vs. placebo	mg BID vs. placebo	mg BID vs. placebo	mg QD vs. placebo
PRA (ng/ml/h)				
Adjusted mean difference	0.5	4.5	2.6	5.1
Confidence Interval	(-3.5, 4.6)	(-1.0, 10.0)	(-1.2, 6.5)	(1.4, 8.7)*
Angiotensin II ¶(pmol/ml)				
Adjusted mean difference	-0.4	11.6	5.5	-1.0
Confidence Interval	(-9.8, 9.0)	(0.1, 23.1)*	(-3.2, 14.2)	(-11.9, 10.0)
Aldosterone (ng/dl)				
Adjusted mean difference	-6.0	-3.5	-6.0	-7.9
Confidence Interval	(-12.8, 0.8)	(-10.7, 3.7)	(-13.2, 1.2)	(-13.8, -1.9)*

Adjusted mean differences were derived from the analysis of covariance for change from baseline in the selected measurements.
Confidence Intervals=98.3% for valsartan, 95% for lisinopril
¶ A statistically significant treatment-by-baseline interaction was seen at 12 hours.
*Statistically significant result

Neurohormone results are presented above. PRA appears to increase and aldosterone levels decrease in all active treatment groups compared to placebo; angiotensin II levels appear to increase in the valsartan 80 mg and 160 mg BID group. These results do not seem inconsistent with the known mechanism of action (i.e., angiotensin II-antagonism and converting enzyme inhibition) of these drugs. The results for the valsartan 40 BID group appear inconsistent with the rest of the results; however, the baseline angiotensin II value was highest in this treatment group.

Other Results:

Table 103.12. Change from baseline to final visit in NYHA Class (Efficacy analysis population-LOCF)

	Val 40 BID	Val 80 BID	Val 160 BID	Placebo	Lisinopril 5/10 QD
Worse	0	0	0	0	0
Same	13	16	15	15	7
Improved	10	7	12	10	8
Missing	0	0	0	0	0

Source: Volume 65: Exhibit 8.18.1

Results of the change from baseline in NYHA Class , as noted by the sponsor, are shown in Table 103.12. No patient, including those on placebo, was noted to worsen; however, one patient (valsartan group) was discontinued because of worsening CHF.

Mean weights did not increase or decrease by more than 1.4 kg (maximum decrease noted) from baseline to Visit 5

Safety

There were no deaths during the double-blind treatment period. Two patients (1011/85, valsartan 160 mg BID; and 1126/109, placebo) died 8 and 28 days, respectively, after trial completion . No patients were discontinued from the trial due to a laboratory abnormality.

Table 103.13. Number of Patients with Adverse Experience (occurring in more than one patient in any valsartan group)

	Val 40 BID N=24	Val 80 BID N=24	Val 160 BID N=27	Placebo N=26	Lisinopril 5/10 N=15
Total patients with adverse experiences	11	9	15	8	9
Angina pectoris	1	1	8	1	1
Cardiac Failure	0	2	1	1	0
Viral infection	2	2	4	1	0
Dizziness	4	1	2	0	1

Source: Volume 66: Table 9.1-3
Patients with multiple occurrences of the same event are counted only once in each category.

Table 103.14. Serious Adverse Experiences (including deaths)

Patient #/Center	Age	Gender	Treatment	AE	Onset (post-randomization)	Outcome
1011/84/4	48	Male	Val 160 BID	Sudden death	8 days after final visit	Died*
1017/10/4	66	Male	Val 80 BID	Angina; acute deterioration of CHF	Day 28	Recovered
035/74/5	55	Male	Val 80 BID	Orthostatic hypotension	Day 1	Unchanged; not prematurely discontinued
1053/41/4	49	Male	Val 160 BID	Angina; sympt. VT	Day 7	Discontinued; recovered
1076/58/10	39	Male	Val 40 BID	Heart tranplantation	Day 24	Recovered
1125/96/4	68	Male	Val 40 BID	CVA	Day 10	Recovered with sequelae
1126/109/4	55	Male	Placebo	Sudden death	22 days after terminating trial	Died*

*These patients were taking ACE inhibitors after terminating the trial.

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

Medical Reviewer Comments:

1. This was a 4-week, 116 patient study of valsartan 40-160 BID, placebo and lisinopril. The efficacy parameters of this study including hemodynamic and neurohormone measurements.
2. The study design prespecified that these CHF patients were not allowed to take an ACE inhibitor for 6 months prior to the trial. As ACE inhibitors were part of standard CHF therapy, this reviewer is compelled to question whether this study design placed patients in a situation of receiving suboptimal therapy. From documentation supplied by the sponsor, 9 local IRBs (based in Moscow) approved this trial. The makeup of these IRBs and mechanism for study approval is not clear. According to an English translation of the Informed Consent, "listed" alternatives available for the treatment of chronic heart failure are hydralazine and minoxidil. Compensation is not mentioned. Consequently, the ethics of this

trial should be questioned and this reviewer will not entertain the results of this study in decisions involving valsartan.

3. Patients on lisinopril may have been on suboptimal doses. Therefore, no fair comparison can be made between lisinopril and valsartan in this trial.
4. At the highest dose of valsartan (160 mg BID), after 4 weeks of therapy, significant decreases in PCWP, compared to placebo, were seen at peak (4-8 hours post-dosing) and at 12 hours post-dose.
5. Primary efficacy variable results for valsartan 80 mg BID, at 4 weeks post-dosing, were inconsistent with the results of valsartan 40 mg BID and 160 mg BID.
6. Secondary efficacy parameters: results of the other hemodynamic variables showed a significant lowering of PVR, SVR, MPAP, nonsignificant decrease in RAP, and significant increase in CO, CI, and SVI in the valsartan 160 mg BID group compared to placebo.
7. Neurohormonal results appear to be consistent with expected drug effects.

Study 104: A Double-Blind, Placebo-Controlled, Dose Response Trial to Determine the Acute and Chronic Central Hemodynamic Effects of Valsartan in Patients with Symptomatic Congestive Heart Failure. (Phase II) (Dec. 5, 1994)

Source: NDA 20-665, S-016: Volumes 14-17; electronic datasets;

Primary Objective: Evaluate the acute and chronic central hemodynamic effects of valsartan 80 mg bid and 160 mg bid compared to placebo in patients with chronic stable congestive heart failure (New York Heart Association [NYHA] state II-IV) receiving therapeutic doses of an ACE inhibitor.

Secondary Objective: Evaluate safety and tolerability of valsartan administered to patients with chronic stable congestive heart failure (NYHA II-IV) receiving therapeutic doses of an ACE inhibitor.

Sites: 17 centers in the United States.

Duration: March 6, 1995 (first patient in) to June 8, 1996 (last patient out).

Study design: This was a 6 week, multicenter, randomized, double-blind, parallel-group as shown in Figure 104. 1.

Figure 104.1. Study Design

Period		**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
Treatment		Placebo		Valsartan 80 mg BID
				Valsartan 160 mg BID
				Placebo

At randomization, patients were stratified based on the dose of background ACE inhibitor (i.e., predefined high or low dose). As noted in Table 1, patients underwent right heart catheterization at Visits 2 and 5. Hemodynamic measurements were taken at Visits 3 (Day 0) and 6 (Day 28) at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after dosing; neurohormone measurements were also taken at Visits 3 and 6 at 0, 6 and 12 hours after dosing. During Visits 3 and 6, the patients' usual diuretic and ACE inhibitor were withheld until after the 12-hour measurement period. A single, open-label dose of lisinopril was given following each 0-hour hemodynamic measurement, replacing the patient's background ACE inhibitor; the dose of lisinopril was determined by the dose of chronic ACE inhibitor therapy (i.e., patients on low dose ACE inhibitor were given a single dose of lisinopril 10 mg; those on high dose ACE inhibitor were given a single dose of lisinopril 20 mg—per Table 104.1).

Stratification: Patients were stratified based on their Visit 2 dose of ACE inhibitor.

Table 104.1. Stratification chart

ACE inhibitor	Low Dose (total daily dose)	High dose (total daily dose)

Enalapril	≤ 10 mg	> 10 mg
Lisinopril	≤ 10 mg	> 10 mg
Captopril	≤ 75 mg	> 75 mg
Quinapril	≤ 20 mg	> 20 mg

Sample Size: The sample size used was based on time available for patient enrollment. Twenty-five completed patients per arm were to be available for statistical analysis; an estimated 15-18 sites were expected to each provide approximately 6 completed patients. A PCWP treatment difference of at least 3 mm Hg was considered to be clinically relevant. The Bonferroni multiple-comparisons procedure was used to control the family-wise error rate corresponding to the 2 pair-wise between-treatment comparisons of valsartan 80 and 160 mg bid versus placebo.

Inclusion criteria[5]:	Exclusion criteria:
• Males or females 18-80 years at Visit 1. Females must be postmenopausal for one year, surgically sterile, or using effective contraception with negative serum pregnancy tests throughout the trial. • Symptomatic, stable CHF (NYHA Class II-IV) for at least one month prior to Visit 1 while receiving ACE inhibitor therapy. • Able to tolerate right heart catheterization. • Mean pulmonary capillary wedge pressure (PCWP) ≥ 15 mm Hg at rest at Visit 2. • Stable fixed regimen of a therapeutic dose of an ACE inhibitor for at least 4 weeks before Visit 1. If patient also takes digitalis/diuretics, these should be on fixed doses for at least 4 weeks prior to Visit 1. For the purposes of the trial minimum therapeutic doses of the four ACE inhibitors approved for the treatment of CHF are defined as follows: enalapril 2.5-10 mg BID, lisinopril 5-20 mg QD, captopril 25-100 mg TID, quinapril 5-20 mg BID. If a patient is on another ACE inhibitor, permission must be optained from the sponsor. • Provide informed consent.	• Pregnant, nursing or women of childbearing potential not using effective contraception. • History of MI, unstable angina, acute pulmonary edema, or hospitalization for decompensated CHF within 3 months prior to Visit 1. • Angina pectoris requiring more than 5 tablets/week sublingual nitroglycerin prn. • Clinically significant primary obstructive valvular dysfunction (except MR secondary to a dilated LV). • Presence/history of restrictive cardiomyopathy or constrictive pericarditis. • Life-threatening ventricular arrhythmias or episodes of symptomatic sustained VT lasting > 30 seconds at any time during the trial. • Dyspnea of non-cardiac origin within past year. • Hepatic disease: SGOT or SGPT > 2 times the upper limit of normal, past hepatic encephalopathy, esophageal varices, or portocaval shunt. • Insulin dependent diabetes. • Non-insulin dependent diabetes with poor glucose control or neuropathy. • Renal impairment: serum creatinine ≥ 1.5 times upper limit of normal or history of dialysis. • Serum potassium < 3.0 meq/l. • Uncontrolled hypertension (BP ≥ 160/100 mm Hg) or significant hypotension (BP < 80/50 mm Hg). • Stroke or transient ischemic attack within past 6 months. • Gastrointestinal disease which could interfere with drug absorption; • Significant allergies/multiple drug allergies; • Malignancy (except basal cell skin cancer) within past 5 years.

[5] Inclusion and Exclusion criteria are taken from the protocol. Please see Amendments to the Protocol for changes in these criteria.

Table 106.2. Patient Disposition

	Placebo	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID	Total
Enrolled	--	--	--	--	905
Randomized	192	185	195	198	770
Completed	169	151	167	163	650
Discontinued prematurely from double-blind	23	34	28	35	120
Adverse experience	9	22	17	20	68
Abnormal lab value	--	--	--	2	2
Unsatisfactory therapeutic effect	1	--	--	--	1
Does not meet protocol criteria	2	4	5	8	19
Noncompliance	2	2	1	1	6
Consent withdrawn	3	1	1	1	6
Lost to follow-up	1	1	3	--	5
Administrative issues	1	1	--	--	2
Death	4	3	1	3	11

Source: Table 7.1-1, 7.1-2a (Volume 20) and enroll.xpt, vpdisc.xpt

Protocol Deviations:

Of those randomized, 6% (placebo) to 12% (160 BID group) were noted to have protocol violations that led to exclusion from the Clinically Assessable analysis (see below). The major protocol violation of note, ETT duration outside required range for age category, occurred at a rate of 4-8% (8-16 patients), the highest percentage being in the valsartan 160 BID group and the lowest percentage in the placebo group. In addition, more patients in the valsartan 40 mg BID had a visit 1 standing SBP < 100 mm Hg (10.3%) than in the other groups (2.1-3.6%).

Table 106.3. Populations analyzed

	Placebo	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID
All randomized	192 (100)	185 (100)	195 (100)	198 (100)
SAP	192	185	194 (99.5)	197 (99.5)
ITT (ETT endpoint)	179 (93)	168 (91)	180 (92)	182 (92)
ITT (LHFQ endpoint)	172 (90)	166 (90)	175 (90)	177 (89)
CAP (ETT endpoint)	170 (89)	159 (86)	168 (86)	167 (84)
CAP (LHFQ)	161 (84)	156 (84)	164 (84)	161 (81)

Source: Table 7.3-1 (Volume 20).

SAP=Randomized patients who took study medication and had at least one post-baseline assessment for any safety measurement.

ITT=Randomized patients who took study medication and had baseline and at least one post-baseline efficacy measurement for a given variable. CAP=Clinically assessable population

Other Patients Excluded from Analyses:

- Two patients (#1498/0143 and 1535/0158) were assigned to valsartan 80 mg BID and 160 mg BID groups, respectively, but did not take study drug medication; therefore, both patients were excluded from the SAP and CAP populations.
- Sixty-one randomized patients were excluded from the ITT population for the primary ETT endpoint analysis: 15 of these patients were unable to walk for reasons other than CHF and the rest did not have post-randomization ETT information (either recorded or imputed).
- Eighty randomized patients were excluded from the ITT population for the primary overall LHFQ analysis, including 53 Argentinian patients who did not participate (the questionnaire was not validated in non-English speaking patients) and 27 patients who either did not participate for the same language reason or had no post-baseline measurements with $\geq$ 75% of the questions answered.
- A total of 106 and 128 randomized patients were excluded from CAP for ETT and LHFQ, respectively.

Baseline Characteristics:

The randomized population was mostly (79-83%) male and over 80% Caucasian; the valsartan 80 mg BID group appeared to have a slightly higher percentage of Caucasian and a smaller percent of Black patients. Otherwise, there appeared to be no meaningful differences between the treatment groups.

Table 106.4. Baseline Demographics (ITT)

	Placebo (N=192) n (%)	Valsartan 40 mg BID (N=185) n (%)	Valsartan 80 mg BID (N=195) n (%)	Valsartan 160 mg BID (N=198) n (%)
Gender:				
Male	154 (80)	146 (79)	161 (83)	158 (80)
Female	38 (20)	39 (21)	34 (17)	40 (20)
Race:				
Caucasian	156 (81)	156 (84)	171 (88)	159(80)
Black	25 (13)	22 (12)	18 (9)	30 (15)
Oriental	2 (1)	--	2 (1)	--
Hispanic	4 (2)	6 (3)	2 (1)	7 (4)
Other	5 (3)	1 (0.5)	2 (1)	2 (1)
Age:				
< 65	100 (52)	98 (53)	105 (54)	97 (49)
$\geq$ 65	92 (48)	87 (47)	90 (46)	101 (51)

Source: Table 7.4-1a, 7.4.1-b (Volume 20)

About 53-57% and about 42-46% of randomized patients, respectively, fell into NYHA Class II and Class III CHF; less than 3% of patients were in NYHA Class I or IV. Prior to randomization, about 63-73% of patients used background digoxin, 79-85% of patients used diuretics, 85-90% of patients used ACE inhibitors, 24-31% of patients were on background beta-blockers (higher use in the valsartan 40 BID group), 9-17% were on antiarrhythmics (higher use in the valsartan 80 BID group) and 8-11% were on calcium channel blockers. About 6% of placebo patients and about 2-5% of valsartan patients were on alpha-adrenergic blockers (the sponsor noted a statistically significant difference). About 54-57% carried an etiologic diagnosis of coronary

heart disease, 21-34% idiopathic cardiomyopathy, 7-12% hypertension, and 5-9% other. About 59-63% had no previous hospitalization for CHF. There were no differences between the treatment groups in NYHA Class, etiology of CHF, or prior CHF hospitalization.

The mean baseline LV ejection fraction was 25-27%. About 36-42% had a baseline LV ejection fraction < 25%; about 58-64% had a corresponding baseline LV ejection fraction ≥ 25%.
Mean age was about 62-64 years. Mean height was 172-173 cm and mean weight was 84-86 kg. Mean duration of CHF was 4.0-4.4 years (range (0.1-26.6 years)). No meaningful differences were seen across treatment groups.

Mean baseline LHFQ scores were 38 (±24) for the overall score, 17 (±10) for the physical score, and 8 (± 7) for the emotional score. Overall mean baseline ETT times were 434-438 (±135-143) sec; mean baseline ETT times by age were 813 (±38) seconds for the 18-29 year age group (N=2); 520 (±156) seconds for the 30-50 year age group (N=113); and 422 (±135) seconds for the > 50 age group. There appeared to be no differences by age across treatment groups.

In terms of CHF signs and symptoms, 83-91% of patients had no paroxysmal nocturnal dyspnea, 89-91% of patients had no dyspnea at rest, 92-97% had no jugular venous distension, and 76 to 83% exhibited no third heart sound. Rales were absent in 87-90% (10-12% had basilar rales only) and edema was absent in 74-77% (11-17% had trace edema). The majority of this population had dyspnea on effort (absent in 3-7%) and fatigue (absent in 8-12%). About 58-66% had no orthopnea.
Baseline mean sitting systolic blood pressure was 121-124 (±17-18) mm Hg, sitting diastolic blood pressure was 73-75 (± 10-11) mm Hg and sitting pulse rate was 76-77 (±12-14) bpm. Baseline standing pulse rate was slightly higher (80-81 ±14-15 bpm); otherwise, results for standing vital signs were similar. Baseline CHF signs and symptoms as well as vital signs were similar across treatment groups.

At baseline, about 47-50% of those randomized were on low-dose and about 37-40% were on high-dose ACE inhibitors. Throughout the study, there appeared to be minor changes in frequency but no striking differences between the treatment groups.

Drug Exposure:
The mean and median exposures were similar across treatment groups. Drug exposure was consistent between Weeks 0 and 1, and Week 1 to 16.

Table 106.5. Patient exposure to drug (ITT:all randomized patients)

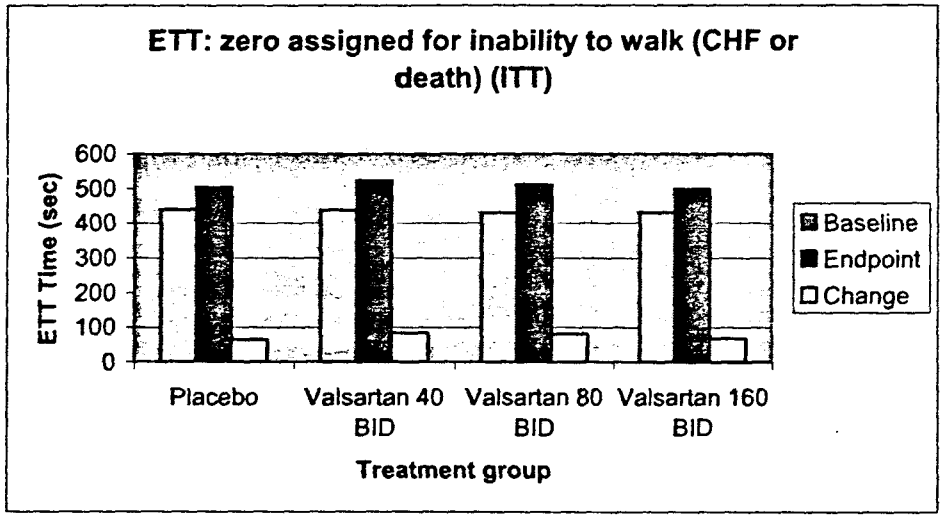
Exposure (days)	Placebo	Valsartan		
Week 0 to 16		40 mg BID	80 mg BID	160 mg BID
N	192	185	195	198
Mean (SD)	107.5 (26.7)	103.9 (31.4)	105.9 (30.9)	105.3 (29.3)
range	8-160	3-188	1-154	2-163

Efficacy:
Primary Efficacy Variables:

Over the course of this study, at least 92% of patients were able to walk. There appeared to be no meaningful differences across treatment groups in deaths or patients alive and unable to walk. Mean ETT times in all treatment groups, including placebo, improved over the course of the study.

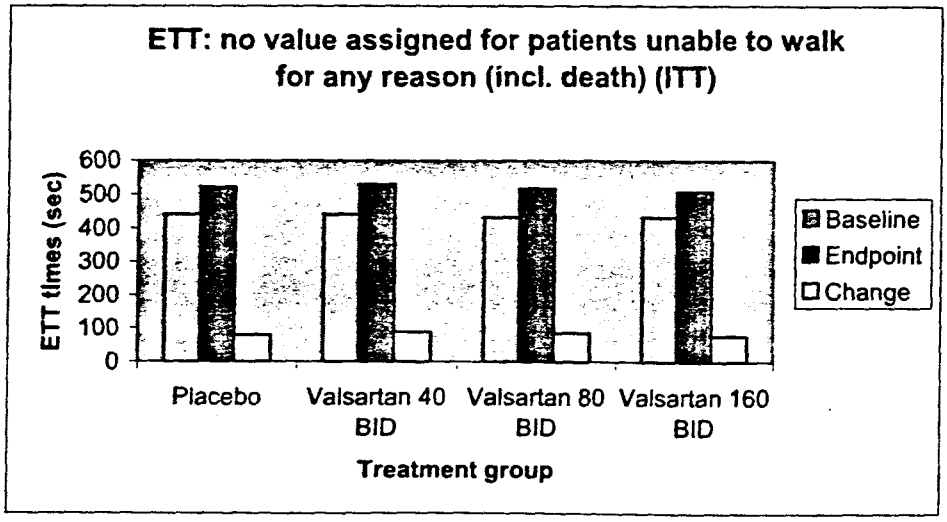
ETT: The sponsor presented the prespecified analysis, with zero assignment for inability to walk due to CHF or death, for both ITT and CAP groups. Results for the CAP were consistent with that seen in the ITT population. In addition, the sponsor presented analyses where zero was assigned for inability to walk for any reason, as well as an analysis where there was no zero assignment. Results were consistent across analyses.

Figure 106-3. ETT result: zero assigned for inability to walk due to CHF/death



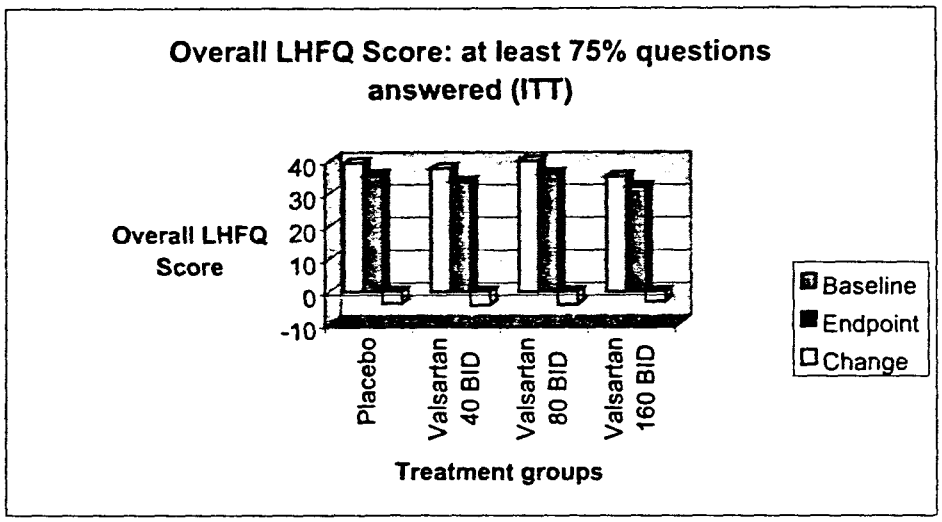
All groups, including placebo, showed statistically significant improvements in ETT time compared to baseline.

Figure 106-4. ETT result: no zero assignment



LHFQ:
Results for the overall LHFQ score are presented below, with change from baseline to endpoint. The highest baseline score was seen in the Valsartan 80 mg BID group; the largest change from baseline was seen in the Valsartan 40 mg BID group.
Results of mean change from baseline values for overall LHFQ were similar for patients with at least 1 of 21 questions answered. Results for the CAP were consistent with the ITT analysis.

Figure 106-5. Overall LHFQ Score:



Source: Volume 20, Table 9.1-5a

Table 106.6 Primary Efficacy Variable:

ANCOVA results for ETT (0 assigned for patients unable to walk due to CHF or death) and LHFQ Overall Score (≥ 75% of 21 questions answered): ITT

Between Treatment Comparison	Difference in LS means (SE of difference)	95% CI for Difference	Adjusted p value
ETT:			
40 BID vs. Placebo	19.35 (16.1)	(-12.25 50.95)	0.48
80 BID vs. Placebo	19.72 (15.8)	(-11.27, 50.71)	0.45
160 BID vs. Placebo	2.92 (15.7)	(-27.99, 33.83)	0.99
Overall LHFQ:			
40 BID vs. Placebo	-1.24 (1.5)	(-4.25, 1,78)	0.75
80 BID vs. Placebo	0 (1.5)	(-2.97, 2.97)	>0.99
160 BID vs. Placebo	-0.17 (1.5)	(-3.13, 2.80)	0.99

Source: Sponsor: Volume 20: Table 9.1-7a. Adjusted p-value based on Dunnett's procedure for multiple comparisons vs. a control.

ETT:
Results for Hochberg's step-up procedure at endpoint also showed no statistical significance. Results for CAP were consistent with the ITT analysis (ie, no significant difference for valsartan vs. placebo); it should be noted that, in the CAP analysis the placebo group did slightly better (ie, longer ETT time) than the 160 BID group at Week 12; thus, it cannot be said that valsartan group at all times showed better ETT times compared with placebo. ANCOVA results by week showed no statistically significant difference compared with placebo.

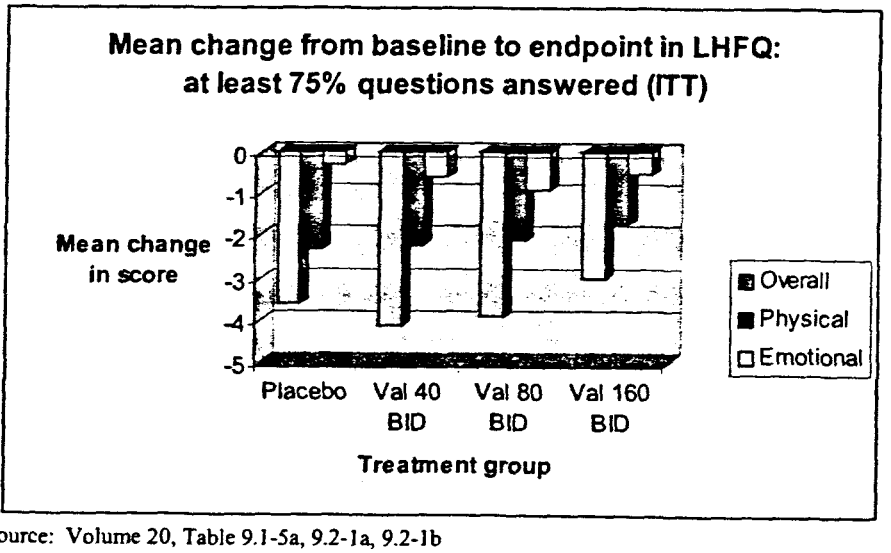
In an analysis where zero was assigned for patients unable to walk for any reason, including death, there was a trend toward statistical signficance only in the valsartan 80 BID group (adjusted p value =.056); however, this result was not seen in the higher dose group (valsartan 160 BID, adjusted p value =0.90). A pairwise-treatment-comparison for ranked ETT (residuals after baseline adjustment), controlling for background use of ACE inhibitors, showed trends toward statistical signficance in the valsartan 40 BID vs. placebo (p=0.09) and in the valsartan 80 BID vs. placebo (p=0.06) in favor of valsartan; however, the favorable trend was much smaller in the valsartan 160 BID vs. placebo group(p=0.74).

A subgroup analysis of ETT results by background ACE (y/n), beta blockers (y/n), age <65 vs. 65 years and older, gender and CHF etiology was presented by the sponsor. However, because of the differences in sample size (for example, the N per each treatment group for females=32-38 compared to the N for males=133-148; the N not taking ACEI =19-28 and the N on ACE=149-156) as well as baseline ETT differences make subgroup interpretation difficult.

Secondary Efficacy Variables:

Change from baseline in emotional and physical scores of the LHFQ:
Results are shown below (see Figure). Greater decreases with valsartan, compared to placebo, can be seen with the changes in emotional score, but not overall or physical score.

Figure 106.6. Change in LHFQ Scores from baseline to endpoint (ITT)



Source: Volume 20, Table 9.1-5a, 9.2-1a, 9.2-1b

Change from baseline in EF:
A statistically significant increase in ejection fraction from baseline to endpoint can be seen (Table 106.7) for valsartan vs. placebo.

Table 106.7. ANCOVA pairwise-treatment comparison results for change from baseline at endpoint in LV EF (ITT)

Treatment group	N	LS mean	LS mean difference (SE) from placebo	95% Confidence Interval for LS mean difference from placebo	p-value
Placebo	169	1.31	--	--	--
Val 40 mg BID	150	3.02	1.71 (0.85)	(0.05, 3.38)	0.0437*
Val 80 mg BID	168	2.72	1.41 (0.82)	(-0.20, 3.01)	0.0856
Val 160 mg BID	167	3.90	2.59 (0.82)	(0.97, 4.20)	0.0017*

Source: Sponsor, Volume 20, Table 9.5. N=number of patients with values at baseline and endpoint.
*=statistically signficiant at the 0.05 level

NYHA Class and Signs/Symptoms of CHF are listed in Table 8 as % improved and worsened from baseline to endpoint. For NYHA Class, the trends in improvement and worsening favored valsartan; however, pairwise treatment comparisons, controlling for baseline values and background use of ACE inhibitors, showed no statistically significant differences between valsartan and placebo at endpoint.
The results of changes in signs/symptoms of CHF were inconsistent.
Dyspnea on effort and fatigue, the two most prevalent signs and symptoms in this study population, showed greater improvement in the valsartan groups; dyspnea on effort also showed the highest percent worsening in the valsartan 80 BID group. For PND, edema, third heart sound and rest dyspnea, the placebo group showed the greatest improvement; for PND and rest dyspnea, the highest dose of valsartan showed the greatest worsening. No statistically significant differences were noted at endpoint (when analyzed as pairwise treatment comparisons, controlling for baseline values and background ACE inhibitor use).

Table 106.8. NYHA Class and Signs/Symptoms: Percent ITT who improved/worsened (at endpoint)

	Placebo N=192 %N	Val 40 BID N=185 %N	Val 80 BID N=195 %N	Val 160 BID N=196 %N
NYHA:				
Improved	19.8	20.5	24.1	21.9
Worsened	8.3	4.9	5.6	5.6
PND:				
Improved	11.5	8.1	9.2	6.6
Worsened	3.1	2.2	3.6	5.1
Dyspnea at rest:				
Improved	7.3	7	7.7	5.6
Worsened	4.7	4.3	4.6	5.6
Dyspnea on effort:				
Improved	33.8	37.8	36.9	35.2
Worsened	15.1	15.7	17.4	15.8
Fatigue:				
Improved	33.3	32.4	35.4	36.2
Worsened	21.9	20.5	18.5	20.9

Orthopnea:				
Improved	13.5	16.8	19	18.4
Worsened	6.8	8.6	6.2	8.2
JVD:				
Improved	4.2	4.3	4.1	1.5
Worsened	4.2	1.6	2.1	1.5
Edema:				
Improved	13.5	13.0	12.8	13.3
Worsened	12.5	9.7	13.8	8.2
Rales:				
Improved	5.7	7.0	5.1	6.6
Worsened	6.3	5.4	6.7	1.5
Third heart sound				
Improved	10.4	9.7	8.2	8.6
Worsened	6.8	4.9	4.6	3.5

Source: Volume 20: Table 9-6

Safety:

Table 106.9. Number (%) of patients who died, had other serious or clinically significant AE or discontinued due to AE (Safety analyzable population)

	Placebo N=192	Val 40 BID N=185	Val 80 BID N=194	Val 160 BID N=197
Deaths	6 (3.1)	2 (2.2)	2 (2.1)	5 (2.5)
All SAE	30 (15.6)	27 (14.6)	27 (13.9)	21 (10.7)
Discontinued due to AE	9 (4.7)	20 (10.8)	17 (8.8)	21 (10.7)
Discontinued due to SAE	5 (2.6)	6 (3.2)	8 (4.1)	7 (3.5)
Discontinued due to lab abnormality	0	0	0	2 (1.0)

Source: Volume 20: Table 10-8. Deaths include patients who died during double-blind, and those who died within 30 days after completing or discontinuing study.

Deaths:

A total of 20 patients died: one patient died during the placebo run-in, 11 patients died during the double-blind period, and 8 patients died either after premature discontinuation or within 30 days after completing the study.

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

Conclusions:

1. There were no significant improvements in baseline ETT or overall MHFQ to endpoint with valsartan compared to placebo.
2. Compared to placebo, there was a significant increase in LV ejection fraction in the valsartan groups.

Study 107: Multicountry, randomized, double-blind, parallel, placebo-controlled trial to assess the effect of valsartan on morbidity and mortality, signs and sympbtoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV) (Phase III)

Source: NDA 20-665, S-016: Volume 57 (Protocol); Volume 28 (Study Report); electronic database.

Sites: 302 centers in 16 countries (Europe, South Africa, Australia, and USA).

Study Duration: March 27, 1997 (first patient enrolled) to October 5, 2000 (last patient completed).

Objective: To assess the effect of valsartan, in comparison with placebo, on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV).

Primary Efficacy Variables: 1. Time to death; and 2. Time to first occurrence of a morbid event (morbid event: death, sudden death with resuscitation, need for therapeutic doses of an intravenous intropic or vasodilating agent for congestive heart failure (CHF) for at least 4 hours, or hospitalization for CHF).

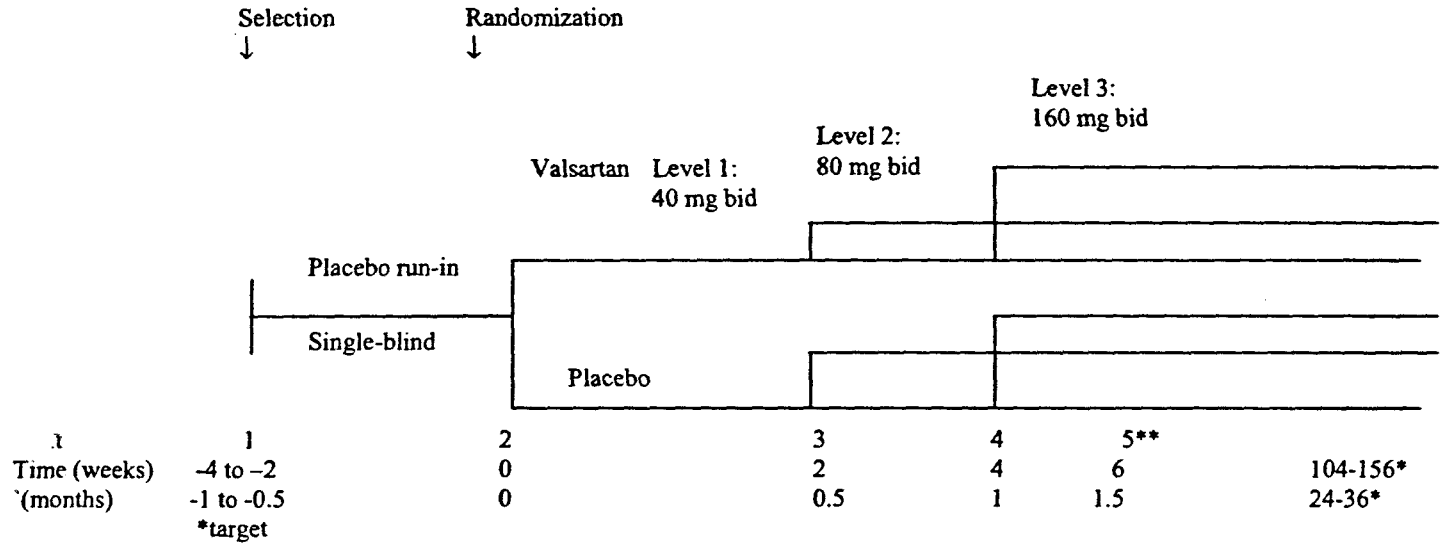
Secondary Efficacy Variables: 1. Time to first occurrence of a morbid event other than death (morbid event defined as above); 2. Time to hospitalization for CHF (first occurrence); 3. Time to cardiovascular-related death; 4. NYHA classification; 5. Signs/symptoms of CHF (paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea on effort, othopnea, jugular venous distension -45°, rales, third heart sound); 6. Change from baseline in ejection fraction; 7. Change from baseline in LV internal diastolic diameter (LVIDD); 8. Change from baseline in overall, physical, and emotional scores for the Minnesota Living with Heart Failure quality of life questionnaire.

Design: This was a randomized, double-blind, forced titration, event-driven, parallel, placebo-controlled trial. Patients were to receive valsartan or placebo, as shown in Figure 1, in addition to standard CHF background therapy. Randomized patients were stratified according to their use of beta blockers.
The trial was to continue, with all randomized patients remaining in the trial, until 906 deaths occurred or statistically significant results were observed for either of the two interim analyses (see Protocol Amendment #3 regarding modification of interim analysis). The scheduled time for enrollment was 12 months and the targeted duration of double-blind treatment was 24-36 months.

At Visit 2, patients were stratified according to their use of beta blockers and randomized to receive either valsartan 40 mg bid or matching placebo. Patients were then up-titrated at Visits 3 and 4. Those who could not tolerate the highest dose of valsartan were to be titrated down to the next lower dose after 2 weeks of treatment (Visit 5). The criteria for titration (Visits 3, 4, 5) were: persistent standing systolic BP $\geq$ 90 mm Hg AND no symptoms of hypotension (i.e. syncope, faintness, orthostatic dizziness) AND no increase in serum creatinine > 50% from baseline to a value > 2.0 mg/dl (see Protocol Amendment #2). If patients did not meet all three

criteria, they were either down-titrated to the previous dose level or discontinued from trial treatment from lowest possible dose level. If up-titration could not be performed due to a temporary medical condition, an attempt to reach the highest tolerated dose level was made, if medically acceptable, after Visit 5. When a patient was up-titrated after Visit 5, laboratory testing was done after 2 weeks of exposure to the higher dose level.

Figure 107-1. Study Design (107)



**Visits continue past Visit 5. Please see Table 1 (Schedule of Procedures) below

Inclusion Criteria:

1. Males or females; minimum 18 years old, with CHF (NYHA Class II-IV) beginning at least 3 months prior to Visit 1. Females of childbearing potential were to use effective forms of contraception with negative preganancy tests throughout the study.
2. Ejection fraction < 40% on echocardiography and left ventricular internal diameter in diastole > 2.9 cm/m^2 on echocardiography within one week prior to Visit 1 or during the placebo run-in period.
3. Stable dosage regimen of CHF medication for two weeks prior to Visit 1 and during the placebo run-in period.
4. Willingness to provide informed consent.

Exclusion Criteria:

1. Pregnant, nursing or women of childbearing potential not practicing effective contraception.
2. Right heart failure due to pulmonary disease.
3. Postpartum cardiomyopathy.
4. Rapidly deteriorating heart failure.
5. Unstable angina, stroke, myocardial infarction or cardiac surgery, including percutaneous transluminal coronary angioplasty (PTCA) within past 3 months.

6. History of heart transplant or those patients who are on transplant list.
7. Coronary artery disease likely to require coronary artery bypass graft (CABG) or PTCA.
8. Sustained ventricular arrhythmia with syncopal episodes within past 3 months that is untreated.
9. Hemodynamically significant mitral stenosis or mitral regurgitation (MR), except MR secondary to left venticular (LV) dilatation.
10. Hemodynamically significant obstructive lesions of LV outflow, including aortic stenosis.
11. Persistent standing systolic blood pressure < 90 mm Hg.
12. Primary liver disease considered to be life threatening.
13. Renal disease likely to be life threatening or serum creatinine > 2.5 mg/dl.
14. Malignancies likely to limit 5 year survival.
15. History or presence of any other disease with a life expectancy of < 5 years.
16. Contraindication to the use of angiotensin II receptor antagonists.
17. Prior or current double-blind treatment in valsartan CHF trials.
18. Participation in an investigational drug study within the past 30 days.
19. Any condition that would jeopardize evaluation of efficacy or safety.
20. History of noncompliance/considered potentially unreliable.
21. Treatment with any of the following within the past 3 months prior to Visit 1: Class IC antiarrhythmic agents (such as flecainide and propafenone), chronic intermittent intravenous inotrope or intravenous vasodilator therapy, angiotensin II receptor antagonists (including valsartan).

Concomitant medications:
As noted above, patients were to be on stable doses of medications for CHF for at least 2 weeks prior to Visit 1. Medications for CHF that were allowed as background therapy included diuretics, ACE inhibitors, digoxin, hydralazine, nitrates, and antiarrhythmics (except Class IC agents).

Table 107.1. Schedule of Procedures (107)

Visit	1	2	3*	4*	5	6	7	8	9	10	11	12	13	14-18†
Month	-1 to -0.5	0	0.5	1	1.5	2	4	6	9	12	15	18	21	24-36
Physical Exam/Sympt. review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X									X				X
LVEF/LVIDD	X						X			X		X		X
ECG	X	X					X			X				X
Heart Failure QoL questionn.‡	X	X		X			X	X	X	X	X	X	X	X
Morbid event		X	X	X	X	X	X	X	X	X	X	X	X	X
AE/ con med	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoecon.		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory**	X	X	X	X	X		X			X		X		X
Neurohormones		X					X***			X***				X***
Trial medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X■

*Up-titration visits **hematology, blood chemistry, urinalysis, pregnancy test ***only norepinephrine
■except at final visit.
† Visits at 3 month intervals; procedures for Visits 15 and 17 are same as Visit 11; procedures at Visit 16 as for Visit 12; procedures at Visit 18 as for Visit 10.
‡The Minnesota Living with Heart Failure Questionnaire was used in selected countries.

Withdrawal criteria:

Patients were withdrawn from the trial:

- Whenever the patient or investigator decided that it was in the patient's best interest.
- Intolerable adverse experiences
- Life-threatening laboratory abnormality despite manipulation of trial therapy and/or background treatment
- Positive pregnancy-test results in a patient who decides to carry pregnancy to term.

Patients were to be removed from trial treatment if, after alteration of dose level and background treatment, the persistent standing systolic BP < 80 mm Hg, or there were symptoms of hypotension. Patients still alive at the time of premature discontinuation from double-blind treatment were to continue to visit the investigator according to the protocol until trial end.

Statistical Methods:

Two primary efficacy endpoints were analyzed for this trial: time to death and time to first occurrence of a morbid event. To achieve an overall significance level ≤ 0.05 (two-sided), an adjustment for two primary endpoints was made, with each primary endpoint tested at a 2-sided significance level of 0.02532 based on Dunn-Sidak inequality. The null hypothesis tested was that median survival time to the primary endpoint of death is the same for valsartan and placebo. The alternative hypothesis was that the median suvival time for valsartan is different from that of placebo.

Three analyses of the primary endpoint time to death were initially planned: two interim and one final analysis. The Lan-DeMets alpha-spending function with a O'Brien-Fleming group-boundary was used. It was assumed that these three analyses were to be equally spaced (based on the accumulated total number of patient deaths prior to permanent discontinuation from treatment for both treatment groups). The interim analyses, according to the protocol, were planned to occur when a total of 302 and 604 deaths (prior to permanent discontinuation from trial treatment) occurred.

A total of 906 patient deaths for both treatment groups combined was needed for the primary efficacy analysis, except in the case of significant interim findings. The number of patient deaths is calculated to have statistical power of 90% (or more) for each primary endpoint, assuming an annual death rate for placebo of 12% (i.e., median survival time of 5422 years) and an annual rate of 9.6% for valsartan (i.e., median survival time of 6868 years). The annual event rate of 9.6% for valsartan was based on detecting a 20% reduction from the annual event rate for placebo. The sample size was determined by the number required to achieve 906 patient deaths. It was estimated that approximately 3660 completed patients, 1830 per treatment arm, would be required. Assuming a discontinuation rate of 15%, it was estimated that 4310 patients, 2155 per treatment arm, would be required. Since death is a component of morbid events, the sample size planned was also to be adequate for the analysis of time to morbid event.

According to the protocol, comparability among treatment groups was to be examined for the following:

- Race (White, Black, Other)
- Gender
- Significant medical history/concomitant diagnosis (yes or no)
- CHF etiology (ischemic/non-ischemic)
- Background Antiarrhythmic treatment at baseline (yes or no)

- Background uses of digoxin at baseline (yes or no)
- Background use of diuretics at baseline (yes or no)
- Background use of beta-blockers at baseline (yes or no)
- Background ACE inhibitor therapy at baseline (yes or no)
- Previous hospitalization for CHF (yes or no)

The Cochran-Mantel-Haenszel chi-square test was to be used for this analysis.

Comparability among treatment groups for all randomized patients was to be examined using the F-test for the baseline values of: age, height, weight at Visit 1, duration of CHF

The log rank test was to be performed as the primary for the survival analysis of time to death and time to morbid event. A supplementary Cox-regression analysis of the primary endpoints was also to be performed for robustness purposes and to explore potential prognostic factors. Major prognostic factors for the Cox regression analysis was to be determined prior to data analysis. Prognostic factors to be considered for this analysis include country, baseline NYHA classification, use (yes/no) of beta-blocker at baseline, CHF etiology (ischemic/non-ischemic), baseline neurohormone levels, and age (or age group).

Safety Evaluation: included adverse event monitoring, laboratory measurements, and vital signs.

Protocol amendments: (The original protocol was dated 8-5-96.)

1. Amendment #1: (dated 1-14-97): modified 2 exclusion criteria, established procedures for titration to the highest possible dose if not possible between visits 2 to 5, included triglycerides as part of routine laboratory testing, included measurements of BNP (brain natriuretic peptide) at Visits 7, 10, and annually thereafter, and to permit recording of signs/symptoms of CHF as a scoring system.
2. Amendment #2: (dated 11-17-97): modified creatinine titration criterion for valsartan, adding the phrase "to a value > 2.0 mg/dl.
3. Amendment #3: (dated 2-23-98) modified the interim analysis to include both primary variables; in addition, interim analyses were changed from 3 equally spaced to approximately every 6 months, beginning around March, 1998, allowing modifications when warranted, based on trial progress and DSMB meetings. The interim analysis was to be performed by a Novartis statistician who is independent of the trial. In addition, the requirement for patient death to occur "prior to discontinuation from double-blind medication" was eliminated.
4. Amendment #4: (dated 3-27-00) modified procedures for the final study visit, clarified definition of trial completion date, and defined analysis of morbid/mortal events after occurrence of the 906th patient death.
5. Amendment #5: (dated 4-10-2000) offered patients who completed the final visit of the core study the opportunity to continue double-blind treatment for another 4-6 months until the database was complete and unblinded. This was conducted on a compassionate use basis with no planned efficacy analyses.

Monitoring committees:

- Data and Safety Monitoring Board (DSMB):

  Committee Members:
  William Parmley, MD (USA)
  Jonathan Abrams, MD (USA)
  Marco Bobbio, MD (Italy)
  David DeMets, Ph.D (USA)
  Dirk van Veldhuisen, MD (Netherlands)

Reviewer's Comment: DSMB minutes were requested by the Agency. According to the Sponsor, minutes were not kept and there are no available notes. According to the Study report, the DSMB was to review serious adverse events and other safety parameters in a "semi-blinded fashion." According to the sponsor, the independent Novartis statistician (who was responsible for performing and reporting the interim analyses to the DSMB) physically attended one meeting and was available by phone for the other meetings. This independent statistician was the only person with access to the randomization codes.
The medical reviewer is unable to verify the DSMB process or extent of unblinding.

- Endpoint committee: According to the sponsor, this committee provided independent, blinded assessment of efficacy endpoints (all cause mortality, sudden death with resuscitation, need for therapeutic doses of an intravenous inotropic or vasodilating agent for CHF for at least 4 hours, cardiovascular-related deaths) as defined in the protocol, based on standardized classifications and definitions.
  Endpoint Committee Members:
  Peter Carson, MD (USA)
  Christopher O'Conner (USA)
  Cristina Opasich, MD (Italy)
  Ileana Pina, MD (USA)
  Marino Scherillo, MD (Italy)
  Gianfranco Sinagra, MD (Italy)
  Felix E. Tristani, MD (USA)
  Alberto Volpi, MD (Italy)
  Lynne Warner Stevenson, MD (USA)

Dr. Volpi was also responsible for one of the three echocardiogram laboratories (see below). According to the Endpoint Committee Manual (dated December 6, 1998), each potential endpoint was to be independently assessed by two members (from the US and Europe, respectively). The results of these assessments was to be presented to the full committee by one of the evaluators and a final decision was to be made by majority vote. The sponsor provided a package of information regarding efficacy endpoints with documentation in English.

- **The sponsor screened all hospitalization endpoints; hospitalizations that did not meet endpoint criteria (i.e., scheduled, elective, or clearly non-cardiovascular) were not submitted to adjudication. For non-scheduled hospitalizations with clearly non-cardiovascular conditions, the sponsor provided only a narrative summary to the committee chair.**
- "Hospitalization" was defined as an overnight stay even if the total duration of time was < 24 hours; overnight stays in emergency rooms or observation units were included in this category. Hospitalizations for CHF treatment-related complications were not included in this category.
- In an addendum to the Endpoint Committee Manual, dated April 4, 2001, it was defined that an admission due to overdiuresis or drug toxicity was to be classified as a "hospitalization for reasons other than heart failure"; also listed in this category was cardiac decompensation that did not meet the heart failure definition. Hospitalizations that were clearly less than 24 hours were not submitted as events. If it could not be clearly determined that a patient was hospitalized for less than 24 hours, and there was a change in days, the case was adjudicated.

- The Endpoint Committee was supplied with the SAE report, hospitalization records as available, investigator narratives when applicable and CRF printout. The Endpoint Committee did not make determination of CV relation.
- The Endpoint Committee met 15 times. A planning meeting was held in March, 1997. The first adjudication meeting was held in December, 1997. Three meetings were held in 1998, five during 1999, and five meetings in 2000.

Reviewer's comments:
1. The diagnoses of "overdiuresis" and "drug toxicity" were not further defined in the Endpoint committee manual.
2. From two to four representatives of the sponsor attended the Endpoint Committee meetings. According to the sponsor, the role of these representatives was to handle logistics and record adjudications issued by the committee.
3. In a meeting with the sponsor, the sponsor claimed that "all endpoints" were adjudicated. Since the written definition appears to be different, the Agency requested written clarification as to the exact adjudication process, i.e., what information from the first hospitalization endpoint was sent to the Endpoint Committee.

- Steering committee: ethical, scientific and policy decisions regarding conduct of the trial; act upon recommendations of the Endpoint Committee and DSMB. One or more Novartis staff members attended all meetings.

Members: Jay Cohn, MD (Study Chairman) (Minneapolis, MN, USA)
Gianni Tognoni, MD (Italy)
Inder Anand, MD (USA)
Antoni Bayès de Luna, MD (Spain)
Csaba Farsang, MD (Hungary)
Torben Haghfelt, MD (Denmark)
Christer Höglund, MD (Sweden)
Niklas Holwerda, MD (Netherlands)
Henry Krum, MD (Australia)
Phillippe Lechat, MD (France)
Silja Majahalme, MD (Finland)
Lionel Opie, MD (South Africa)
Klaus Stumpe, MD (Germany)
Lip Bun Tan, MD (Great Britain)
Luigi Tavazzi, MD (Italy)
Johan Vanhaecke, MD (Belgium)
Arne Westheim, MD (Norway)
Jiri Widimsky, MD (Czech Republic)

Drs. Widimsky, Vanhaecke, Haghfeldt, Majahalme, Krum, Farsang, Tavazzi, Holwerda, Westheim, Bayes de Luna, Hoglund, Tan and Anand are also Investigators for 107.

- Executive committee

Members: Jay Cohn, MD (USA)
Gianni Tognoni, MD (Italy)
Robert Glazer, MD (Novartis; USA)
Dirk Spormann, Ph.D. (Novartis; Switzerland)

- Echo laboratories:

Alberto Volpi, MD (Italy)
Christer Hoglund, MD (Sweden)
Maylene Wong, MD (USA)

Dr. Hoglund was one of the Investigators. Dr. Volpi was a member of the Endpoint Committee.

Interim Analyses Results:

Five interim analyses were performed biannually. More precisely, the total number of deaths at the interim analyses were 38, 141, 368, 595, and 748, respectively. Table 107.2 presented the interim results. Clearly, there was no statistical evidence for the valsartan effect on mortality. The trial end date was May 3, 2000 which was determined as the date by which 906 deaths were recorded and a letter was sent out to declare and document the trial end as soon as 906 deaths were observed on May 3, 2000. There were 979 deaths between May 3, 2000 and locking the database. In the final analysis of time to death at the trial end, the significance level was adjusted according to the planned Lan-DeMets spending function, using the information times based on 38, 141, 368, 595, 748, and 979 deaths. Thus, the primary analysis at trial end was performed at a two-sided significance level of 0.02.

Table 107.2 . Interim results

Interim Analysis No.	Hazard ratio (95% CI)	Value of log rank test	Value of rejection boundary for valsartan efficacy
1	0.60 (0.31, 1.16)	1.53	5.00
2	0.93 (0.67, 1.30)	0.42	5.00
3	0.97 (0.79, 1.19)	0.32	3.75
4	0.99 (0.84, 1.16)	0.15	2.87
5	0.95 (0.83, 1.10)	0.65	2.55

Source: Sponsor's results

Interim analyses of time to first morbid event were performed concurrently with interim analyses for time to death. However, no upper boundary was considered for time to first morbid event because interim analysis results for this variable were not used to claim efficacy, but were only used to aid in determining whether to terminate the trial due to lack of efficacy with valsartan (the same lower boundary as that using the opposite of the upper boundary for time to death was used). Therefore, no further statistical adjustment was made for this variable and the final analysis of time to first morbid event was performed at the significance level of 0.02532.

Primary and secondary variable, treatment group comparability with respect to demographics, background medication and baseline data, serious adverse events, specified laboratory variables, blood pressure, and reasons for discontinuation.

Results:

Of those randomized, 43-44% of each treatment group were from sites in the United States; after the United States, 14% of patients in each group were entered from sites in Italy, and 11% in each group from sites in the Netherlands.

Table 107.3. Patient Disposition (107)

	Valsartan n (%)		Placebo n (%)		Total n (%)	
Enrolled					5984	
Randomized	2511	(100)	2499	(100)	5010	(100)
Completed (to death or trial end)	2487	(99)	2466	(99)	4953	(99)
Discontinued:	24	(1.0)	33	(1.3)	57	(1.1)
Heart transplant	18	(0.7)	23	(0.9)	41	(0.8)
Other	6	(0.2)	10	(0.4)	16	(0.3)
Lost to f/u	3	(0.1)	4	(0.2)	7	(0.1)
Permanently discontinued from study treatment	448	(18)	339	(14)	787	(16)
Adverse experience	215	(9)	136	(5)	351	
Life-threatening lab abnormality	34	(1.4)	10	(0.4)	44	
Persistent SSBP < 80 mm Hg or signs of hypotension	30	(1.2)	11	(0.4)	41	
Other	169	(7)	182	(7)	351	(7)
Discontinued from run-in	--		--		974	(16)
Death	--		--		21	(0.4)
Heart transplant	--		--		2	(<0.1)
other	--		--		947	(16)
Reason missing					4	(0.1)

Source: Sponsor—Volume 28, Section 7

Of the 2511 patients in the valsartan arm and the 2499 patients in the placebo arm, 23% and 24%, respectively, were noted to have protocol violations. Of these, 3% were considered to be major protocol violations and 21% were minor protocol violations; there were no meaningful differences between the two treatment groups.

Three patient populations were identified: the intent-to–treat (ITT) group; the Safety Analyzable Population (SAP), or those who received drug and for whom safety data are available; and the Clinically Assessable Population, or the ITT group excluding major protocol violators.

Table 107.4. Patient populations (107)

	Valsartan		Placebo		Total	
Patients randomized	n 2511	% 100.0	n 2499	% 100.0	n 5010	% 100.0
ITT	2511	100.0	2499	100.0	5010	100.0
SAP	2506	99.8	2494	99.8	5000	99.8
CAP	2441	97.2	2419	96.8	4860	97.0

Source: Sponsor—Volume 28, Section 7

Baseline Characteristics:
The randomized population was 80% male and 20% female, about 90-91% Caucasian, 7% Black and 3% Oriental; about 52-52% were below 65 and 46-48% were 65 and older. Mean age was 62-63 (± 11) years old; the ages ranged from 18 to 96 years old. Mean height was 171 (± 9 cm), mean weight was 79-80 (± 15-16) kg and mean duration of CHF was 51 months (with a median of 36 and range from 1 to 660 months). Mean sitting systolic Blood Pressure (SBP) was 124 (± 18-19) mm Hg , mean sitting diastolic BP was 76 (± 11) mm Hg and sitting pulse rate was 73-74 (±13) beats/minute. Standing blood pressures and pulse rates yielded similar results. There were no meaningful differences between the two treatment groups.

The most common baseline symptoms reported were dyspnea on effort (absent in only 5%) and fatigue (absent in 16-17%). Most patients (> 70 %) had no jugular venous distention, orthopnea, paroxysmal nocturnal dyspnea, dyspnea at rest, rales, or a third heart sound. Edema was absent in 82-83% of patients. No differences between the two treatment groups were noted.

Over 90% of the randomized patients were on baseline ACE inhibitors and about 85-86% were on diuretics. A little over one-third were on baseline beta blockers and less than half were on nitrates. A review of the individual beta blockers, diuretics, ACE inhibitors, calcium channel blockers and nitrates at baseline revealed no difference in use between the two treatment groups.

Table 107.5. Baseline characteristics (all randomized patients) (107)

		Valsartan		Placebo	
		n	%	n	%
Randomized		2511	100	2499	100
NYHA Class	I	2	0.1	3	0.1
	II	1560	62	1535	61
	III	907	36	906	36
	IV	42	2	55	2
Background treatment	Amiodarone	322	13	332	13
	Digoxin	1685	67	1689	68
	Diuretics	2154	86	2128	85
	Beta-blockers	867	35	883	35
	ACE inhibitors (ACEI)	2326	93	2318	93
	Nitrates*	986	39	957	38
	Calcium channel blockers	289	12	320	13
ACEI/beta blocker (BB) at baseline	BB and ACEI	794	32	816	33
	Neither BB nor ACEI	112	5	114	5
	ACEI but no BB	1532	61	1502	60
	BB but no ACEI	73	3	67	3
Etiology	Ischemic	1446	58	1419	57
	Idiopathic cardiomyopathy	780	31	780	31
	Hypertension	154	6	183	7
	Other	131	5	117	5

Source: Sponsor: Volume 28: 7.4.2 *Long and short-acting

Baseline LV measurements (ITT) revealed the following: mean (and median) ejection fraction (EF) of 27% (±7) with a range of approx. 4-55%; mean LV internal diastolic diameter (LVIDD) of 6.9 (± 0.9) and mean LVIDD/BSA of 3.6-3.7 (±0.5) cm/m^2. Approximately 48% and 47% of all randomized patients in the valsartan and placebo groups, respectively, had baseline LV EF meaurements less than the median value. The Minnesota Living with Heart Failure questionnaire (LHFQ) baseline results revealed a mean overall score of 32-33 (± 23), mean physical score of 14-15 (±11), and mean emotional score of 6.8 (± 7). There were no meaningful differences between the two treatment groups.

Of the baseline neurohormone measurements, only mean aldosterone levels showed a statistically significantly different ($p < 0.05$), higher in the placebo group.

Table 107.6. Baseline neurohormone measurements (all randomized patients):

Neurohormone		Valsartan (N=2511)	Placebo (N=2499)
Norepinephrine (pg/ml)	N (non-missing)	2141	2160
	Mean (±SD)	456 (270)	472 (368)
Brain natriuretic peptide (pg/ml)	N (non-missing)	2145	2160
	Mean (±SD)	184 (231)	178 (230)
Aldosterone (pg/ml)	N(non-missing)	2114	2126
	Mean (±SD)	132 (118)	140 (137)
Plasma renin activity (ng/mL/h)	N(non-missing)	2141	2150
	Mean (±SD)	15 (24)	14 (24)
Endothelin I (fmol/mL—US patients)	N(non-missing)	964	970
	Mean (±SD)	2 (1.7)	1.9 (1.6)
Big endothelin (fmol/ml) –non-US patients	N(non-missing)	1180	1179
	Mean (±SD)	1 (0.7)	1 (0.6)

Source: volume 28, Table 7.4-9

Patient Exposure:
Tables 107.7 and 8 summarize exposure to valsartan monotherapy:

Table 107.7. Minimum exposure to therapy by Total Daily Dose of Valsartan (all randomized)

Exposure to Valsartan (days)	Valsartan (mg/d)				
	0	80	160	320	Any dose>0
>1	1170	2508	2345	2120	2508
>30	533	449	526	1947	2412
>60	358	310	396	1900	2325
>90	221	276	343	1852	2268
>180	67	223	268	1693	2156
>360	9	162	199	1544	1968
>720		69	78	724	1063

Source: Sponsor: Volume 28: section 8, Table 8.1-1a

Table 107.8. Patient exposure (Summary)

Total number of patients on Valsartan	2511
Range of Duration on Valsartan (days)	1 to 1203
Mean Duration on Valsartan (days)	604
Mean daily dose of valsartan (mg)	254

Between Months 1 and 30, at least 70% of randomized patients were on a total daily dose of 320 mg.

EFFICACY RESULTS

Time to event variables were derived from the event date on the Endpoint Committee Form and not from investigators' event dates. Censoring times were determined from CRF page 106 (heart transplant, lost to f/u), page 105 (date of last medication taken=date of treatment discontinuation) or from analysis cut-off date of May 3, 2000. For time to event variables, endpoint was determined as the last available value before the cutoff of May 3, 2000 (whether or not event occurred before or after permanent discontinuation of study treatment). The time to event was considered censored for: patients discontinued from the trial due to heart transplant with no events observed prior to heart transplant (time from randomization to date of heart transplantation (if known) or date of final visit (if heart transplantation date unknown); patients completing trial with no observed events; or patients lost to follow-up with no events observed. In those patients, time to censoring was the time from randomization to completion, or analysis cut-off date, or date of lost to follow-up. There was no adjudication on mortality/morbidity endpoints at trial end (May 3, 2000); all patient deaths and dates from trial end to trial completion (last patient, last visit) were recorded by the investigators.

For the two primary endpoints, the sponsor presented the p-value of logrank test and the hazard ratio and its confidence interval based on the analysis adjusted for various covariates (e.g., NYHA Class III vs. (II & I), NYHA Class IV vs (II & I), LVEF < median value, ACE inhibitor at baseline, beta blocker at baseline, etiology, age category). Thus, in some instances the 95% confidence interval of hazard ratio contained one but the logrank p-value is much less than 0.05. Such presentation is not desirable. For secondary endpoints, the sponsor presented the results of analyses adjusting for various baseline covariates, pooled centers, and treatment by covariate interactions.

In this review we presented the results with no adjustment for covariates in all endpoints. For secondary endpoints, the results in our tables were based on the analysis using last available post-randomization value to compute the change from baseline. Our results and the sponsor's results are qualitatively similar.

As summarized in Tables 107.9 and 107.10, the time to censoring for the primary adjudicated morbid events and for the non-fatal morbid events appeared to be balanced between the two treatment groups.

Table 107.9. Distribution of time to censoring for primary morbid events

		Valsartan (N=2511)	Placebo (N=2499)
# of events		723 (28.8%)	801 (32.1%)
# censored		1788 (71.2%)	1698 (67.9%)
IN DAYS	Max	1112	1108
	95th-tile	1028	1031
	90th	981	980
	75th	891	888
	Median	758	751
	Mean	743	742
	25th	575	574
	10th	499	500
	5th	478	479
	Min	68	26

Primary morbid events: death, sudden death with resuscitation, therapies for CHF, CHF hospitalizations

Table 107.10. Days at risk for non-fatal morbid events

		Valsartan (N=2511)	Placebo (N=2499)
IN DAYS	Max	1111	1118
	95th-tile	1022	1023
	90th	965	965
	75th	870	866
	Median	715	719
	Mean	681	680
	25th	518	527
	10th	384	378
	5th	195	179
	Min	2	1

Days at risk = time to death for deaths and time to last follow-up for survivors.

It can be seen from Table 107.11 that there was no survival benefit in the valsartan group, either for all-cause or CV deaths. In fact, the frequency and hazard ratios trend slightly in favor of the placebo group. For non-fatal morbid events, results significantly favor the valsartan group. This composite endpoint appears to be "driven by" the results of CHF hospitalization, where the data significantly favor the valsartan group (the effect size of the category "Sudden Death with

Resuscitation" may also contribute to the favorable valsartan effect; however, the event rates are relatively small). From Figures 38 and 39, the log(-log(time-to-event)) curves were parallel during the most part of study duration, except that the curves appeared to cross at an early time (this may be due to random variations because of very small number of events early on). The figures suggested that the valsartan effects in terms of hazards on the primary adjudicated morbid events and 1st CHF hospitalization appeared to be constant in the most part of study duration.

Table 107.11. Adjudicated Mortality and morbidity endpoints(all randomized patients)

	Valsartan N=2511	Placebo N=2499	Hazard ratio (95% CI)	p-value*
Primary endpoints				
All cause deaths	495 (19.7%)	484 (19.4%)	1.02 (0.90, 1.15)	0.80
Morbid events	723 (28.8%)	801 (32.1%)	0.87 (0.79, 0.97)	0.009
Secondary endpoints				
CV deaths	427 (17.0%)	419 (16.8%)	1.01 (0.89, 1.16)	0.86
Non-fatal morbid events	367 (14.6%)	486 (19.5%)	0.73 (0.64, 0.84)	< 0.0001
Sudden death with Resuscitation	20 (0.8%)	30 (1.2%)	0.66 (0.38, 1.17)	0.15
CHF therapy	7 (0.3%)	8 (0.3%)	0.87 (0.32, 2.40)	0.79
CHF hospitalization	349 (13.9%)	463 (18.5%)	0.73 (0.64, 0.84)	< 0.0001

Source: Reviewers.

Figure 107.2. log(-log(survival)) vs. logarithm of time to primary adjudicated morbid events

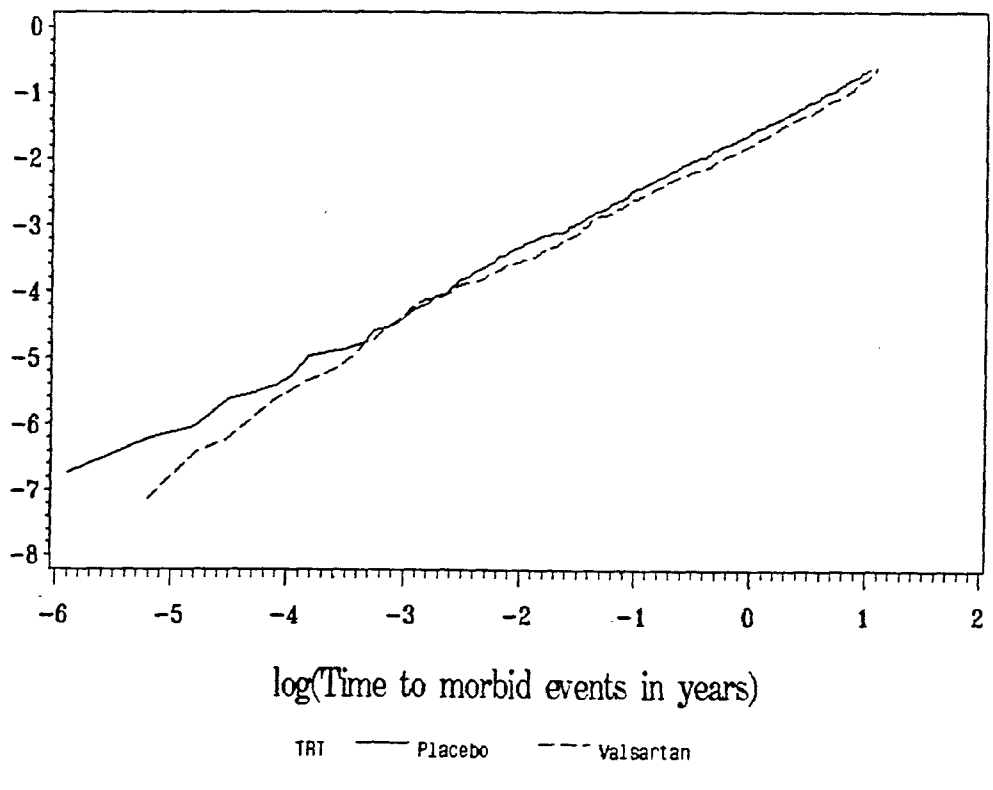
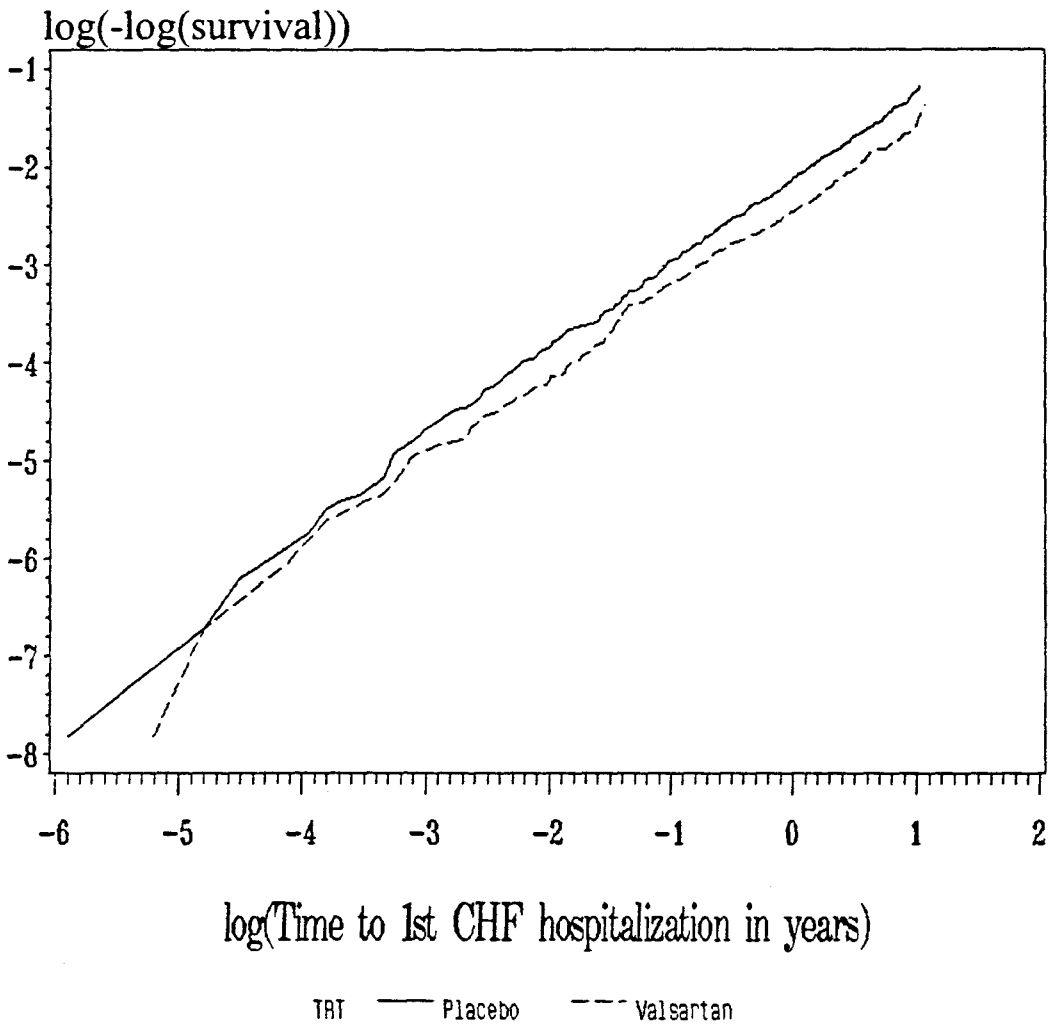


Figure 107.3. log(-log(survival)) vs. logarithm of time to 1st CHF hospitalization



Analysis by censoring those events that occurred after permanent discontinuation of study medication showed the results consistent with the primary analysis (Table 107.12).

Table 107.12. Additional analyses on primary efficacy endpoints

	Valsartan N=2511	Placebo N=2499	Hazard ratio (95% CI)	p-value*
All cause deaths[$]	372 (14.8%)	411 (16.5%)	0.93 (0.81, 1.08)	0.34
Morbid events[$]	585 (23.3%)	720 (28.8%)	0.82 (0.73, 0.91)	0.0003
All cause deaths (until patients last visit)	505 (20.1%)	499 (20.0%)	1.01 (0.89, 1.14)	0.93

[$] Censoring those events that occurred after permanent discontinuation of study medication
Source: Reviewers

At the Agency's request, results were further analyzed for 1. Time to All-cause hospitalization or death; 2. Time to CV-related hospitalization or death; 3. Days Alive and Out of the Hospital. The following analyses were reported:

Table 107.13. Time to death or first hospitalization:

Endpoint*	Valsartan (N=2511)		Placebo (N=2499)		Comparison		
	n	%	n	%	Risk ratio**	95% CI	Log Rank Test p-value
All-cause hospitalization or death	1365	54	1398	56	0.97	(0.90, 1.05)	0.39
CV-related hospitalization or death	1076	43	1145	46	0.91	(0.84, 0.99)	0.02

*cutoff date is May 3, 2000, with non-censoring of events occurring after permanent treatment discontinuation (randomized patients). Time to first hospitalization was based on investigator assessment. **adjusted for NYHA class, LVEF, baseline ACEI category, baseline beta blocker category, etiology, and age group.
Source: Sponsor

Table 107.14. Summary of All-cause Hospitalization Days

All-cause Hospitalizations *	Valsartan (N=2511)		Placebo (N=2499)	
# days alive/out of hospital	Mean 689.5	SD 246.1	Mean 687.7	SD 246.9
# of days in hospital	9.8	22.1	11.0	22.2

*based on investigator assessment. All hospitalizations during the entire core trial were included. Source: Sponsor

In response to further requests from the Agency, the sponsor supplied the following tables for Time to First CHF hospitalization (Endpoint Committee vs. Investigator Assessment), total number of hospitalizations, and frequency distribution of number of patients with hospitalization. The results appear to be consistent with the above findings.

Table 107.15. Analysis results: Time to first CHF hospitalization

Time to First Event	Valsartan N=2511		Placebo N=2499		Comparison (V vs. P)		
CHF Hospitalization	N	%	N	%	Risk Ratio**	95% CI	p-value*
Endpoint Committee***	349	13.9	463	18.5	0.725	(0.631, 0.833)	0.00001
Investigator Assessment***	525	20.9	613	24.5	0.832	(0.740, 0.935)	0.00236

Source: Sponsor. *P-value for both are statistically significant (log rank test). **Cox regression model adjusted for NYHA class, LVEF, baseline ACE categroy, baseline beta blocker category, etiology, age group.
***cut-off date is May 3, 2000 with noncensoring of events occurring after permanent treatment discontinuation (randomized patients).

Table 107.16. Total Number of Hospitalizations (Investigator Assessment)

Cause	Valsartan	Placebo	Difference	Percent difference	p-value*
All-cause	2856	3106	-250	-8.0	0.1445
CHF	923	1189	-266	-22.4	0.0017
Non-CHF	1933	1917	16	0.8	0.8867

Source: Sponsor. *p-value: CMH test for number of hospitalizations stratified for beta blocker (y/n), ACE (y/n) and NYHA (I/II vs. III/IV) as appropriate, using modified Ridit scores.

In an analysis of US vs non-US results, it appears that there is less benefit of valsartan in the US in reducing CHF hospitalization and non-fatal morbid events.

Table 107.17. Mortality and morbidity endpoints (all randomized patients)

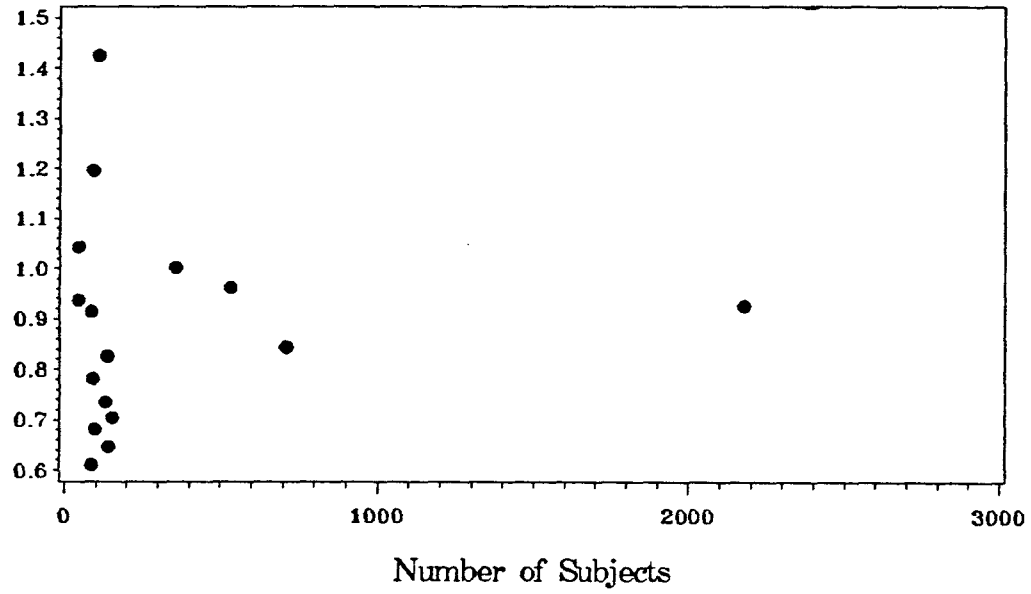
	Valsartan	Placebo	Hazard ratio (95% CI)
US	**(N=1093)**	**(N=1085)**	
All cause deaths	227 (20.8%)	222 (20.5%)	1.02 (0.85, 1.22)
Morbid events	350 (32.0%)	375 (34.6%)	0.91 (0.79, 1.06)
CV deaths	191 (17.5%)	185 (17.1%)	1.03 (0.84, 1.26)
Non-fatal morbid events	194 (17.8%)	231 (21.3%)	0.82 (0.68, 1.00)
Sudden death with Resuscitation	12 (1.1%)	13 (1.2%)	0.92 (0.42, 2.01)
CHF therapy	7 (0.6%)	8 (0.7%)	0.87 (0.32, 2.41)
CHF hospitalization	183 (16.4%)	222 (20.5%)	0.81 (0.66, 0.98)
Non-US	**(N=1418)**	**(N=1414)**	
All cause deaths	268 (18.9%)	262 (18.5%)	1.02 (0.86, 1.20)
Morbid events	373 (26.3%)	426 (30.1%)	0.84 (0.73, 0.97)
CV deaths	236 (16.6%)	234 (16.6%)	1.00 (0.84, 1.20)

Non-fatal morbid events	173 (12.2%)	255 (18.0%)	0.65 (0.54, 0.79)
Sudden death with Resuscitation	8 (0.6%)	17 (1.2%)	0.47 (0.20, 1.08)
CHF therapy	0	0	----
CHF hospitalization	166 (11.7%)	241 (17.0%)	0.67 (0.55, 0.81)

Source: Reviewers

As illustrated in Figure 107.4, there were no surprising treatment by country interactions on the primary adjudicated morbid events.

Figure 107.4. Relative Risk of Adjudicated Morbid Events by Country



The following tables show results of other secondary endpoints. Except for the category, "Third heart sound", most of the signs and symptoms and NYHA category favor valsartan. The results of the change in LV ejection fraction, LHFQ, norepinephrine, and BNP appeared to significantly favor valsartan.

Table107.18. Changes at the last available visit in NYHA class and in clinical signs and symptoms

	Valsartan (N=2511)	Placebo (N=2499)	p-value
NYHA			0.001
Improved	580 (23.1%)	518 (20.7%)	
Worsened	252 (10.0%)	319 (12.8%)	
Paroxysmal nocturnal dyspnea			0.002
Improved	169 (6.7%)	148 (5.9%)	
Worsened	121 (4.8%)	173 (6.9%)	
Dyspnea at rest			0.037
Improved	113 (4.5%)	95 (3.8%)	
Worsened	159 (6.3%)	183 (7.3%)	
Dyspnea on effort			0.003
Improved	858 (34.2%)	791 (31.7%)	
Worsened	470 (18.7%)	528 (21.1%)	
Fatigue			0.010
Improved	795 (31.7%)	736 (29.5%)	
Worsened	539 (21.5%)	628 (25.1%)	
Orthopnea			0.20
Improved	358 (14.3%)	348 (13.9%)	
Worsened	265 (10.6%)	286 (11.4%)	
Jugular venous distension			0.001
Improved	204 (8.1%)	195 (7.8%)	
Worsened	137 (5.5%)	179 (7.2%)	
Edema			0.003
Improved	299 (11.9%)	247 (9.9%)	
Worsened	253 (10.1%)	305 (12.2%)	
Rales			0.001
Improved	181 (7.2%)	166 (6.6%)	
Worsened	152 (6.1%)	206 (8.2%)	
Third heart sound			0.22
Improved	337 (13.4%)	303 (12.1%)	
Worsened	139 (5.5%)	139 (5.6%)	

Source: Reviewers

LHFQ was assessed only in patients in the USA, UK, Australia and Italy (specific countries were not prespecified in the protocol or amendments). The LHFQ sample size was 1587 for valsartan and 1573 for placebo; missing values were < 5%.

Table 107.19. Change at last available visit in secondary efficacy parameters

	Valsartan		Placebo		V minus P (95% CI)	p-value
	N	Δ	N	Δ		
LVEF (%)	2300	4.37	2336	3.57	0.80 (0.31, 1.29)	0.0014
LVIDD/BSA (cm/m2)	2294	-0.09	2331	-0.04	-0.05 (-0.07, -0.03)	< 0.0001

LHFQ score – Overall	1508	1.46	1512	3.26	-1.80 (-3.02, -0.58)	0.004
LHFQ score – Physical	1507	0.79	1511	1.55	-0.77 (-1.34, -0.19)	0.009
LHFQ score – Emotional	1505	0.16	1512	0.55	-0.39 (-0.75, -0.04)	0.029
Norepinephrine (pg/mL)	1951	-8.08	1987	20.62	-28.7 (-44.9, -12.5)	0.0005
Brain natriuretic peptide (pg/mL)	1950	-18.97	1987	25.61	-44.6 (-57.2, -32.0)	< 0.0001

Source: Reviewers

An analysis of morbid and mortal events by subgroup is presented below. No subgroup showed (very) inconsistent results. The valsartan appeared to have little favorable, or even adverse effect on morbid events in the patients who receiving ACE inhibitors or beta blockers or both, compared to the patients who did not receive either.

Table 107.20. Adjudicated Morbidity endpoint in subgroups (all randomized patients)

	Valsartan (N=2511)	Placebo (N=2499)	Hazard ratio (95% CI)
Age			
< 65	330 (24.1%)	348 (26.9%)	0.88 (0.76, 1.02)
≥ 65	393 (34.4%)	453 (37.6%)	0.88 (0.77, 1.01)
Gender			
Male	590 (29.4%)	641 (32.1%)	0.90 (0.80, 1.00)
Female	133 (26.4%)	160 (32.1%)	0.79 (0.63, 0.99)
Race			
Caucasian	635 (28.2%)	715 (31.5%)	0.87 (0.78, 0.97)
Black	68 (37.4%)	52 (32.1%)	1.21 (0.84, 1.74)
Oriental/Other	20 (27.0%)	34 (51.5%)	0.44 (0.26, 0.77)
NYHA Class			
I	0	0	--
II	350 (22.4%)	378 (24.6%)	0.91 (0.78, 1.05)
III	347 (38.3%)	387 (42.7%)	0.85 (0.73, 0.98)
IV	26 (61.9%)	36 (65.5%)	0.81 (0.49, 1.35)
LVEF			
< baseline median	400 (33.0%)	449 (38.2%)	0.83 (0.72, 0.95)
≥ baseline median	323 (24.9%)	352 (26.6%)	0.92 (0.79, 1.07)
CHF etiology			
Ischemic	471 (32.6%)	476 (33.5%)	0.96 (0.84, 1.08)
Non-ischemic	252 (23.7%)	325 (30.1%)	0.76 (0.64, 0.89)
ACEI use			
No	46 (24.9%)	77 (42.5%)	0.51 (0.35, 0.73)
Yes	677 (29.1%)	724 (31.2%)	0.92 (0.82, 1.02)
Beta-blocker use			
No	506 (30.8%)	599 (37.1%)	0.80 (0.71, 0.90)
Yes	217 (25.0%)	202 (22.9%)	1.10 (0.91, 1.33)

ACE=no/beta=no	31 (27.6%)	54 (47.4%)	0.52 (0.34, 0.81)
ACE=yes/beta=no	475 (31.0%)	545 (36.3%)	0.82 (0.73, 0.93)
ACE=no/beta=yes	15 (20.5%)	23 (34.3%)	0.51 (0.26, 0.97)
ACE=yes/beta=yes	202 (25.4%)	179 (21.9%)	1.18 (0.97, 1.45)

Source: Reviewers

Table 107.21. All-Cause mortality endpoint in subgroups (all randomized patients)

	Valsartan (N=2511)	Placebo (N=2499)	Hazard ratio (95% CI)
Age			
< 65	208 (15.2%)	194 (15.0%)	1.02 (0.84, 1.24)
≥ 65	287 (25.1%)	290 (24.0%)	1.04 (0.88, 1.22)
Gender			
Male	415 (20.7%)	401 (20.1%)	1.04 (0.90, 1.19)
Female	80 (15.9%)	83 (16.6%)	0.93 (0.68, 1.27)
Race			
Caucasian	444 (19.7%)	444 (19.6%)	1.00 (0.88, 1.15)
Black	37 (20.3%)	23 (14.2%)	1.50 (0.89, 2.52)
Oriental/Other	14 (18.9%)	17 (25.8%)	0.72 (0.36, 1.46)
NYHA Class			
I	0	0	--
II	242 (15.5%)	222 (14.5%)	1.09 (0.91, 1.31)
III	233 (25.7%)	238 (26.3%)	0.95 (0.79, 1.14)
IV	20 (47.6%)	24 (43.6%)	1.04 (0.58, 1.89)
LVEF			
< baseline median	267 (22.0%)	286 (24.4%)	0.90 (0.76, 1.06)
≥ baseline median	228 (17.6%)	198 (14.9%)	1.18 (0.98, 1.43)
CHF etiology			
Ischemic	339 (23.4%)	304 (21.4%)	1.10 (0.94, 1.28)
Non-ischemic	156 (14.6%)	180 (16.7%)	0.87 (0.70, 1.08)
ACEI use			
No	32 (17.3%)	49 (27.1%)	0.59 (0.37, 0.91)
Yes	463 (19.9%)	435 (18.8%)	1.07 (0.93, 1.21)
Beta-blocker use			
No	353 (21.5%)	374 (23.1%)	0.92 (0.79, 1.06)
Yes	142 (16.4%)	110 (12.5%)	1.35 (1.05, 1.73)
ACE=no/beta=no	19 (17.0%)	36 (31.6%)	0.50 (0.28, 0.86)
ACE=yes/beta=no	334 (21.8%)	338 (22.5%)	0.96 (0.82, 1.11)
ACE=no/beta=yes	13 (17.8%)	13 (19.4%)	0.80 (0.37, 1.74)
ACE=yes/beta=yes	129 (16.2%)	97 (11.9%)	1.42 (1.09, 1.85)

Source: Reviewers

Safety:

Safety results are presented below and in the Integrated Summary of Safety.

Table 107.22. Number (%) of patients with adverse experience by Treatment group (Safety analyzable patients) with incidence > 1.0% and greater than Placebo (in descending order for Valsartan)

Adverse Experience—Primary Term	Valsartan (N=2506)		Placebo (N=2494)	
Patients with an adverse experience	2295	91.6	2235	89.6
Dizziness (exc vertigo)**	627	25.0	451	18.1
Hypotension NOS*	347	13.9	201	8.1
Nasopharyngitis	250	10.0	229	9.2
Diarrhea NOS**	238	9.5	193	7.7
Arthralgia**	195	7.8	172	6.9
Influenza	184	7.3	173	6.9
Hyperkalemia¶	163	6.5	81	3.3
Limb pain	154	6.2	146	5.9
Back pain***	145	5.8	122	4.9
Renal impairment NOS	135	5.4	76	3.1
Ventricular tachycardia	125	5.0	119	4.8
Gout	125	5.0	113	4.5
Anemia NOS	119	4.8	110	4.4
Fatigue*	117	4.7	106	4.2
Postural hypotension	95	3.8	48	1.9
Dizziness postural	92	3.7	54	2.2
Myocardial Infarction	89	3.6	78	3.1
Dehydration	84	3.4	65	2.6
Dyspepsia***	79	3.2	78	3.1
Vertigo NEC***	78	3.1	51	2.0
Hyperglycemia NOS	62	2.5	55	2.2
Pruritis NOS***	59	2.4	57	2.3
Paresthesia NEC***	55	2.2	41	1.6
Renal failure NOS@	54	2.2	31	1.2
Vision blurred	55	2.2	22	0.9
Blood creatinine increased	54	2.2	27	1.1
Weight increased	45	1.8	38	1.5
Anorexia	45	1.8	39	1.6
Renal failure acute	46	1.8	43	1.7
Gastroenteritis NOS	43	1.7	25	1.0
Hyperlipidemia NOS	42	1.7	29	1.2
Ventricular fibrillation	39	1.6	37	1.5
Arrhythmia NOS	39	1.6	31	1.2
Neck pain	38	1.5	35	1.4
Intermittent claudication	35	1.4	19	0.8
Digoxin toxicity	35	1.4	30	1.2
Inguinal hernia NOS	33	1.3	26	1.0
Abdominal distension	33	1.3	29	1.2
Diabetes mellitus aggravated	29	1.2	18	0.7
Nasal congestion	30	1.2	28	1.1
Hypothyroidism	27	1.1	24	1.0
Ventricular extrasystoles	27	1.1	22	0.9
Herpes zoster	27	1.1	22	0.9

Infection NOS	28	1.1	20	0.8
Hyperuricemia	27	1.1	18	0.7
Contusion	27	1.1	26	1.0
Wheezing	26	1.0	13	0.5

Safety analyzable= patients who received drug and for whom safety data are available.
Source: Volume 29: Table 10.1-1
*Noted in current Valsartan (Diovan) labeling: Hypotension in Volume and/or Salt-Depleted Patients is listed under Warnings. Fatigue is listed as having occurred in at least 1% of patients and at a higher incidence than placebo (Placebo-controlled clinical trials).
**Noted in current Valsartan labeling: listed as having occurred in more than 1% of patients but at about the same incidence in placebo and valsartan patients.
***Noted in current Valsartan labeling: listed as an adverse experience that occurred in >0.2% of valsartan patients, without determination of causality.
¶Noted in labeling under Clinical Laboratory Test Findings and Post-Marketing experience.
@Noted in labeling under Post-Marketing Experience.

Table 107.23. Serious Adverse Experiences by Primary term (incidence > 1.0% for Valsartan and occurring at higher rate than placebo) (Safety Analyzable)

	Valsartan (N=2506)		Placebo (N=2494)	
Patients with a serious adverse experience	N 1282	% 51.2	N 1342	% 53.8
Angina pectoris	63	2.5	49	2.0
Myocardial infarction	83	3.3	73	2.9
Ventricular tachycardia	84	3.4	77	3.1
Dehydration	49	2.0	33	1.3
Hyperkalemia	40	1.6	23	0.9
Dizziness (exc. Vertigo)	39	1.6	36	1.4
Syncope	62	2.5	60	2.4
Renal impairment	44	1.8	20	0.8
Renal failure acute	30	1.2	27	1.1
Renal failure NOS	25	1.0	15	0.6
Hypotension NOS	55	2.2	48	1.9

Source: Volume 35: Table 10.2-3

Table 107.24. Adverse Experiences Leading to Study Discontinuation (Incidence > 1.0% in Valsartan and Greater than placebo) (Safety analyzable population)

	Valsartan (N=2506)	Placebo (N=2494)
	n (%)	n (%)
Patients with an adverse experience	249 (9.9)	181 (7.3)
Dizziness (exc vertigo)	41 (1.6)	11 (0.4)
Hypotension NOS	32 (1.3)	20 (0.8)
Renal impairment NOS	27 (1.1)	6 (0.2)

Source: Volume 35, Table 10.2-5a