

**107. 25. Abnormal Laboratory Values reported as AE and leading to treatment discontinuation (Incidence > placebo) (Safety analyzable population)**

	Valsartan (N=2506)	Placebo (N=2494)
	n (%)	n (%)
Number of patients with lab AE leading to treatment discontinuation	31 (1.2)	9 (0.4)
Blood creatinine increased	13 (0.5)	3 (0.1)
Hyperkalemia	13 (0.5)	2 (0.1)
Hyperbilirubinemia	1 (0.04)	0
Hypokalemia	1 (0.04)	0
Thrombocytopenia	1 (0.04)	0
Anemia NOS	3 (0.1)	1 (0.04)

Source: Volume 35, Table 10.2-7

**Table 107.26. Mean ( $\pm$  SD) Sitting Pulse, Systolic and Diastolic Blood Pressure, and Body Weight Changes by Treatment Group (Safety Analyzable population)**

	Valsartan			Placebo		
	N**	Baseline	Change from baseline to endpoint*	N**	Baseline	Change from baseline to endpoint*
Sitting SBP (mm Hg)	2494	123 (18)	-7 (18)	2482	124	-4 (18)
Sitting DBP (mm Hg)	2494	76 (11)	-5 (11)	2482	76 (11)	-3 (11)
Sitting pulse (bpm)	2493	73 (13)	-0.5 (13)	2481	74 (13)	-0.3 (13)
Body weight (kg)	2491	80 (16)	0.6	2480	79 (15)	-0.1 (6)

\*Endpoint=last observation post-baseline

\*\*=Patients with both baseline and postbaseline observation for that visit except month 0.

Source: Volume 35, Table 10.4-1.

Results for standing vital signs were similar to these values.

**Reviewer's Comments:**

1. There was no survival benefit demonstrated for valsartan.
2. A benefit was demonstrated for valsartan in: prolonging time to first CHF hospitalization, signs and symptoms of CHF, change in EF and LVDD, LHFQ, and neurohormones.
3. Valsartan did not appear to prolong the time to first all-cause hospitalization.
4. Valsartan was associated with an increased treatment-emergent adverse events as well as an increased AE-related discontinuation rate. Dizziness, hypotension, hyperkalemia, diarrhea and renal impairment occurred more frequently in the valsartan group compared to placebo.
5. Explaining the different results of "time to first CHF hospitalization" vs. "time to first 'all-cause' hospitalization" remains an outstanding issue. At least two possible explanations exist: 1. A bias in the adjudication process; 2. No bias in the adjudication process--Valsartan may prolong the time to first CHF hospitalization, but this benefit is "offset" by increased drug (valsartan)-related hospitalizations. Pending requests have been made to the sponsor to explore both possibilities. These include: a detailed explanation of adjudication procedure,

the lists of non-CV first hospitalizations and narratives supplied to the adjudication committee, an analysis of renal failure patients as well as those requiring dialysis by treatment group.

**Study 107 (Substudy 02): Multi-country, randomized, double-blind, placebo controlled trial to assess the effect of valsartan on morbidity and mortality, signs and symptoms, and quality of life in patients with stable, chronic congestive heart failure (NYHA Class II-IV): Six-Minute Walk Substudy. (Phase III) (Protocol date: June 9, 1997)**

Source: NDA Volume 64 (Protocol, Case Report Form, Study Report); electronic database

**Primary Objective:**

- Assess the effect of valsartan, compared to placebo, on exercise capacity as measured by the distance walked in a six-minute walk test in patients with stable, chronic congestive heart failure (NYHA Class II-IV) 4 months following randomization into valsartan Protocol 107.

**Secondary Objective:**

- Assess the relationship of distance walked at baseline with mortality and morbidity endpoints.

Sites: 67 sites in 11 countries; 28 sites in the USA.

Duration: August 8, 1997 (first patient, first visit) to August 17, 1999 (last patient, last visit)

**Study Design:**

This was a substudy of patients enrolled in valsartan Protocol 107. Selected trial sites would utilize the same trial design, randomization, control/comparator, dosing, blinding, inclusion/exclusion criteria as in Study 107. In this substudy, the six-minute walk test was to be performed at Visits 1, 2, 6 and 7 after all other visit procedures in Study 107 were completed (see Study 107 for Visit schedule). Symptoms experienced by patients during the walk were to be recorded on the "Adverse Experience During Six-Minute Walk test" case report form. In addition, at Visits 3, 4, 5, 8, and 9, any continuing adverse experiences that began and did not resolve during the previous six-minute walk test were to be recorded on the "Adverse Experience During Six-Minute Walk Test" case report form provided at each of these visits.

Six-minute walk tests were to be performed up to month 4 (Visit 7), with safety follow-up to month 9 (Visit 9; see Study 107).

**Six-Minute Walk Test:**

As prespecified in the protocol, the six-minute walk test consisted of a measured 20 meter distance in a level enclosed corridor, marked with a chair at either end. The patient was instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the allotted 6 minute time period. A supervisor was to call out the time every 2 minutes and encourage the patient every 30 seconds in a standardized fashion, face the patient and deliver one of two phrases ("you're doing well"; "keep up the good work"). Patients were allowed to stop and rest during the test but were to be instructed to resume walking as soon as they were able. After 6 minutes, patients were instructed to stop walking; total distance (to the nearest half meter) was to be measured and symptoms experienced by the patient were to be recorded.

**Removal of patients from substudy:**

In addition to prespecified events in Study 107, patients were to be removed from the Substudy if they were no longer ambulatory (e.g., broken leg).

**Sample Size Determination:**

A total of 508 patients, 254 per treatment group, who met all admission/randomization criteria and completed all 6-minute walk tests was needed to detect a treatment difference of 30 meters in 6-minute walking distance with 80% power at a 5% significance level, assuming a standard deviation of 120 meters. It was anticipated that approximately 706 patients were to be enrolled into this substudy in order to meet the required size of 508 completed patients.

**Randomization:**

As part of the Val-heft study, patients were stratified, at randomization, according to their use of beta blockers (yes/no). Please see Study 107 for further details.

**Statistics:**

The primary efficacy variable was the change from baseline in 6-minute walking distance. The baseline value used for 6-minute walking distance was the pre-randomization walking distance measurement at Visit 2.

The criterion for efficacy was a statistically significant difference with respect to the primary variable, favoring valsartan (plus background) over placebo (plus background).

The primary analysis was the intent-to-treat analysis of the primary efficacy variable at Endpoint. In addition, all variables were to be analyzed separately at each scheduled measurement time point, based on all randomized patients with baseline and post-baseline evaluations at the corresponding timepoint.

Between-treatment comparisons of valsartan versus placebo were based on the null hypothesis of no treatment difference. All tests were based on two-sided alternative hypotheses. All tests were made at the 5% (0.05) significance level.

A two-factor analysis of covariance was to be performed for the change from baseline in 6-minute walking distance, with center and treatment group as factors and baseline walking distance, baseline ACEI category (y/n), and baseline beta blocker category (y/n) as covariates. Missing walking distance measurements during the double-blind period, because of an inability to walk due to severity of CHF or death, were given a value of zero. Otherwise, no value substitution was made for the missing measurement. After substitution for missing values, the last value was to be the last value carried forward for the terminal visit analysis.

A nonparametric analysis of walking distance ranks was to be performed for robustness purposes. In addition, pooling criteria was prespecified in the protocol.

**Safety Variables:** As noted above, all new or continuing adverse experiences were to be recorded, as well as any exercise-related adverse experiences.

**Amendments to the Protocol:** See Study 107 for five amendments to the protocol. There were no amendments specific to Substudy 02.

**Results:****Patient Disposition:**

According to the electronic database and the study report, 751 patients were enrolled and 71 patients were discontinued prior to randomization. Of those randomized, about 38-39% of patients were from the US, followed by 15-16% from Italy and about 11% from the Netherlands; there were no meaningful differences between the two treatment groups. (Source: walkenr.xpt and vwalk.xpt).

**Table 107.27. Patient Disposition**

	Valsartan n (%)	Placebo n (%)	Total n (%)
Enrolled	--	--	751
Randomized	349 (100)	333 (100)	682 (100)
Permanently discontinued trial treatment prior to Visit 7	23 (7)	8 (2)	31 (5)
Completed (to death or study end)	320 (92)	304(91)	624 (91)
Premature substudy termination*	29 (8)	29(9)	58 (9)
Inability to walk (possible CHF-related)	1(.3)	0	1(.1)
Inability to walk (not CHF-related)	3 (1)	1(.3)	4 (1)
Missing values	25 (7)	28 (8)	53 (8)

Source: electronic database (walkenr.xpt, walk.xpt, walkdisc.xpt) and Table 7.1-2 (Volume 64)

\*Not completing 4 month substudy and no death

**Table 107.28. Analysis Sets**

	Valsartan	Placebo
Intent to treat (ITT)	349	333
Clinically assessable (CAP)	333	326
Safety analyzable (SAP)	347	333

Source: electronic database (walkana.xpt)

**Table 107.29. Baseline Characteristics:**

	Valsartan (N= 349) n (%)	Placebo (N=333) n (%)
Male (%)	278 (80)	256 (77)
Race: Caucasian	307 (88)	299 (90)
Black	36 (10)	28 (8)
Oriental/other	6 (2)	6 (2)
Age < 65 years	186 (53)	182 (55)
Age ≥ 65 years	163 (47)	151 (45)
NYHA Class I	1 (0.3)	0
II	223 (64)	209 (63)
III	116 (33)	117 (35)
IV	9 (3)	7 (2)
Etiology: Coronary disease	183 (52)	191 (57)
Idiopathic cardiomyopathy	121 (35)	101 (30)
Hypertension	21 (6)	23 (7)

Other	24 (7)	18 (5)
Use of CHF-related medications		
ACE inhibitors	327 (94)	313 (94)
Diuretics	307 (88)	291 (87)
Digoxin	232 (67)	225 (68)
Nitrates (short and long-acting)	149 (43)	145 (44)
Beta-blockers	130 (37)	118 (36)
Calcium channel blockers	47 (14)	44 (13)
Antiarrhythmics	40 (12)	36 (11)
Mean ( $\pm$ SD)		
Age (yrs)	62 (11) Range: 21-96	62 (11) Range: 28-87
Height (cm)	170 (9) Range: 141-191	170 (10) Range: 128-198
Weight (kg)	79 (15) Range: 41-131	78 (15) Range: 40-139
CHF Duration (mos)	46 (47) Range: 3-276	51 (54) Range: 2-340

Source: electronic database (walkdeba.xpt, walkdemo.xpt, walkbase.xpt)

**Table 107.30. Baseline walk test**

	Valsartan (N=347)	Placebo (N=333)
Mean ( $\pm$ SD) baseline walking distance	372 (114)	367 (117)
Range	15-780	22-750
Terminated walk test < 6 min	13	18
Reason for termination of walk test		
Dyspnea	9	9
Fatigue	2	6
Angina	1	0
Other	1	3

Source: electronic database (walkeff.xpt) Under the category "patient able to walk" 2 patients (from the total N of 349 in the valsartan group) were listed as "unknown" (listed as not related to CHF) and 347 were listed as "able to walk".

**Table 107.31. Drug Exposure:**

	Valsartan (N=349)	Placebo (N=333)
N	343	331
Mean ( $\pm$ SD) duration of exposure to study medication (days)	109 (34)	114 (30)
Range	1-201	1-219
Mean ( $\pm$ SD) daily dose (mg)	225 (72)	249 (52)
Range	80-289	80-285

Source: Volume 64: Table 8.1-1. Mean daily dose was calculated as: [(number of days on level 1 x 80) + (number of days on level 2 x 160) + (number of days on level 3 x 320)]/ number of days on trial medication.

**Table 107.32. Primary Efficacy results (all randomized patients):**

	N*	Raw Means (m)		Change	LS Mean Change	Difference in LSM change	CI	P value
		Baseline	Endpoint					
Valsartan	320	372.7	385.3	12.6	14.91	1.18	(-11.2, 13.6)	0.85
Placebo	313	373.6	384.8	11.2	13.73			

Source: Volume 64: Table 9.1-1a ANOVA results controlling for pooled center, baseline value, baseline ACEI category, baseline Beta B category and treatment by baseline value interaction.

\*N is the number of patients with observations at both baseline and endpoint. Endpoint is the last available post-baseline observation (LOCF).

Primary Efficacy results are presented above. Improvements in walking distance were seen in both treatment groups; there was no significant difference seen between the two treatment groups. In addition, the number and percent of patients terminating the walk test prior to 6 minutes was similar between the two treatment groups (9 valsartan and 11 placebo patients at month 2; 8 valsartan and 8 placebo patients at month 4; and 8 valsartan and 9 placebo patients at endpoint, respectively). The most common reason for test termination was dyspnea.

A subgroup analysis (below) was submitted by the sponsor. Patients on placebo who were not on a background ACE inhibitor showed a worsening in walking distance compared to baseline; the other groups showed improvements of varying degrees. The differences in baseline walk distances (as in ACEI use, age, gender, LVEF, and LWFQ categories) and differences in sample size (e.g. categories of ACEI use and race) will affect comparisons by and within a subgroup.

**Table 107.33. Subgroup analysis: Change from baseline to endpoint in walking distance by subgroup**

Parameter		Valsartan			Placebo		
		N*	Mean Baseline	Change**	N*	Mean Baseline	Change**
ACEI	Yes	302	375	11	296	378	14
	No	18	335	38	17	306	-37
Beta blocker	Yes	122	384	16	110	388	14
	No	198	366	11	203	366	10
Age	<65	177	396	12	175	395	17
	≥ 65	143	344	13	138	347	4
Gender	Male	253	383	11	242	388	8
	Female	67	333	18	71	323	23
Race	White	282	372	13	281	370	8
	Black	33	376	6	27	418	35
	Oriental/other	5	369	21	5	329	62

LVEF baseline	< median	125	382	8	113	369	1
	≥ median	195	366	16	200	376	17
Overall LWHF score	< median	99	384	13	94	396	6
	≥ median	95	341	10	96	324	4

Source: Sponsor: Table 9-2, 9-3 (Study Report); table 9.1-2, 9.2-3, 9.2-4

N\*=non-missing at Endpoint

\*\*Change from baseline to Endpoint. Endpoint is last observation post baseline.

#### Secondary Efficacy Variable:

Since the primary efficacy endpoint was not met, a correlation with morbid/mortal endpoints was not performed.

#### Safety:

Deaths: There were no deaths during the six-minute walk test. A total of 24 patients randomized into the substudy died during the duration of this study. Please see Study 107 and the Integrated Summary of Safety for further discussion of deaths.

**Table 107.34. Serious adverse experiences during the walk test:**

Treatment	Patient #	Event	Severity	Onset	Duration study drug	Fatal
Valsartan	17/14159	Ventricular flutter	Severe	Day 57	779	No
Placebo	23/1965	Dyspnea	Mild	Day 1	27 days	No
Placebo	11/10118	Intermittent claudication	Moderate	Day 1	13 days	no

Source: Table 10-5. Study Report

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

#### Summary:

This was a four month, 682 patient, 67 site substudy of the Val-heft trial evaluating the effect of background CHF therapy plus valsartan compared to placebo, on the six-minute walk test in patients with chronic stable Class II-IV CHF.

#### Conclusions:

1. Improvements were seen in 6 minute walk test in both placebo and valsartan groups.
2. There was no significant difference in six-minute walk test between the two treatment groups.

**Study 110.** A twelve week, multicenter, randomized, double-blind, active-controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity in patients with stable, moderate, chronic heart failure

Table of Contents Study CVAL4890110  
 Division of Cardio-Renal Drug Products  
 Medical Officer Review

Study # CVAL4890110 (abbreviated here as study 110)

Title of study: A twelve week, multicenter, randomized, double-blind, active-controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity in patients with stable, moderate, chronic heart failure (NYHA II-III)

Investigator and sites: A total of 15 sites were planned, 13 of these sites enrolled subjects. The investigators and sites are shown in table 110.1.

Table 110.1 Investigator and sites:

Center 001 Dr. K. Salden Sahlgren's Hospital, Gothenberg University Gothenburg, Sweden	Center 002 Dr. R. Willenheimer Malmo University Hospital Malmo, Sweden	Center 003 Dr. T. Wallen Vasa Hospital, Gothenburg University Gothenburg, Sweden	Center 004 Dr.K. Schenck-Gustafsson Karolinska Hospital, Karolinska Institute Stockholm, Sweden
Center 005 Dr P. Lofdahl Hjart-mattagningen Helsingborg, Sweden	Center 006 Dr. U. Dalstrom Linkoping university Hospital Linkoping Sweden	Center 007 Dr. E. Panlev Lund University Hospital Lund, Sweden	Center 008 Dr. M. Freitag Blekinge Hospital Karolinska, Sweden
Center 009 Prof Ch. Sylven Huddinge Sjukhus Huddinge, Sweden	Center 010 Dr F. Huhtasaari Subderbyn Hospital Lulea, Sweden	Center 011 Dr. T. Tygesen Boras Hospital Boras, Sweden	Center 012 Dr. M. Edner Danderyd Hospital Karolinska Institute Stolckholm, Sweden
	Center 013 B. Friberg Ostersund Hospital Ostersund, Sweden		

Formulations: Formulations are shown in Table 110.2

Table 110.2 Formulations used in study CVAL4890110

Valsartan 80 mg	B980164, B970033
Valsartan 160 mg	B980068, B980168
Valsartan Placebo	B980004, B980008
Enalapril 5mg	B980228
Enalapril 10 mg	B980229
Enalapril Placebo	B980027

Dates of study:

Protocol Dated: 21 April 1999  
Protocol Amendment 21 June 1999  
First Patient enrolled 31 August 1999  
Last patients entered 31 January 2000  
Statistical Submission: 20 December 2000  
Blind Broken. Not stated.

The statistical report as written after the last patient completed the study. The date at which blind was broken is unclear.

Primary end point: The primary end point of the study was the six-minute walk distance. The primary population of interest was defined as the "Full Set Analysis" population. This population had both baseline and at least one-post baseline measurement. In addition, the population was to satisfy three major enrollment criteria:

1. NYHA Class II/III at visit 1 (baseline).
2. Resting left ventricular ejection fraction at visit 1  $\leq 45\%$ .
3. On ACE inhibitor treatment for at least 3 months prior to randomization.

Subsequently, upon submission of the statistical report (dated 20 December 2000), the sponsor defined the imputation of a "0" walk distance for those unable to walk because of severe CHF or if they were dead. The statistical report was dated well after all patients should have completed the 12-week study (estimated as May 1, 2000).

The primary analysis was an ANCOVA with center and treatment as factors and baseline walking distance as covariate. Treatment by baseline walking distance was also included in the model. A further model with terms for center, baseline walking distance, treatment and baseline interaction, and center by treatment interaction was also assessed. If the interaction term was significant at the 10% level, treatment differences within centers were investigated.

The sponsor analyzed the data first to determine "non-inferiority", which they defined as demonstrating that the lower bound of walking distance was no worse than 45 meters less than enalapril. If the analysis did not violate the 45-meter worsening, a comparison against enalapril for superiority will be performed.

**[Comment: No rationale is defined for indicating why 45 meters in a six-minute constitutes a reasonable bound for non-inferiority. This reviewer knows of no placebo-controlled study that shows an increase in this metric by 90 meters (at the lower confidence interval bound), so that a 45-meter non-inferiority claim would be credible. In fact this reviewer knows of no placebo-controlled studies against ACE-inhibitors that were successful in demonstrating a 6-minute walk benefit of any magnitude for the ACE-inhibitor. The non-inferiority claim, therefore appears to be capricious.]**

Secondary efficacy end points: The four secondary efficacy end points are described below. Each of these end points was analyzed by an ANCOVA with center and treatment as factors and baseline measurement as covariate. Two-sided 95% confidence intervals of Valsartan value – Enalapril value (baseline corrected) were tabulated.

1) The dyspnea fatigue index.

This index consists of measurements that relate to the magnitude of task, the magnitude of pace and the functional impairment. The higher the value the less symptomatic the patient. The specifics of the scale is shown below

Table 110.3 Components and specific characterization of the Dyspnea-Fatigue Index.

Value	Magnitude of Task (at normal pace)	Magnitude of Pace	Functional impairment
4	"Extraordinary". Becomes short of breath or fatigued only with extraordinary activity such as carrying heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks.	"Extraordinary". Essentially all conceivable physical tasks are performed at normal pace.	"None". Can carry out usual activities and occupation (if employed before onset of congestive heart failure) without symptoms.
3	"Major". Becomes symptomatic only with such major activities as walking up a steep hill, climbing more than 3 flights of stairs or carrying a moderate load on the level	"Major". Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Less strenuous tasks can be done at normal pace.	"Slight". Distinct impairment in at least 1 activity but no activities completely abandoned. A change in activity may have occurred at work or in other activities, but change is slight and is not clearly caused by shortness of breath or fatigue.
2	"Moderate". Becomes symptomatic with moderate or average tasks such as walking up a gradual hill, climbing less than 3 flights of stairs or carrying a light load on level ground	"Moderate". Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal pace	"Moderate". Patient has changed jobs or has abandoned at least given up most or all usual activities.
1	"Light". Becomes symptomatic with light activities, such as walking on the level, washing or standing	"Light". Light tasks are done at a reduced pace.	"Severe". Patient is unable to work or has given up most or all usual activities.
0	"None". Symptomatic at rest, while sitting or lying down.	"None". Symptomatic at rest.	"Very Severe". Unable to work and has given up most or all usual activities.

2) Living with heart failure questionnaire:

This questionnaire consisted of 21 questions with value of 0-5. The questions reflect the clinical impairment of heart failure as perceived by the subject. A value of "0" reflect little impairment, a value of "5" reflect substantial impairment. A decrease in the metric reflects improvement.

If < 25% of the values of an individuals assessment were missing, the average value of the reported questions was extrapolated to the questionnaire as a whole. If > 25% of the values were missing, the questionnaire value for that visit was excluded.

3) Atrio-ventricular plane displacement: This is an echocardiographic measurement that reflects the excursion of the A-V plane between the position most remote from the apex. The average of measurements taken in the anterior, lateral, posterior and anterior regions was used as the metric for patients with regular rhythm. For those who had irregular rhythms, eight measurements were taken.

4) Left ventricular end diastolic diameter. This measurement is also an echocardiographic measurement.

Inclusion criteria:

- Patients > 18 years old with stable, moderate chronic heart failure (NYHA II-III) diagnosed at least 3 –months prior to the baseline visit (visit 1). Patients were to be on ACE-inhibitors for at least 3 months.
- An EF ≤ 45% by echocardiography.

- Stable course and stable medication during the two weeks prior to the enrollment visit (week 1).
- Exercise capacity solely limited by CHF.
- Can sign informed consent.

Exclusion criteria:

- Patients with complicated disease including right heart failure due to pulmonary disease, clinically significant valvular lesions or outflow obstruction, infective cardiomyopathy or active peri- or myocarditis.
- Rapidly deteriorating or uncompensated heart failure.
- Recent cardiovascular insult such as MI, cardiac surgery, unstable angina, exercise-induced angina, VT or other arrhythmia, within 3 months of entry or a PTCA within 6 months of entry.
- CAD likely to need intervention during the study period.
- Persistent standing SBP < 90 mm Hg.
- Abnormal serum creatinine (>200 umol/l) and AST (> 3 x upper limit of normal).
- Exercise limited for reasons other than CHF.
- Contraindication to ACE inhibitors or angiotensin II blockers.
- Treatment with angiotensin blockers in the three months prior to visit 1 or during the study.
- Recent (within 30 days) use of investigational new drugs.
- Previous participation in Valsartan CHF trials.
- Other condition that might interfere with efficacy or safety assessment.

Protocol: Subjects were initially enrolled in a 2-week single blind placebo run in period during which they remained on open-labeled ACE- inhibitor. At the end of this period the specific ACE-inhibitor was discontinued and subjects were started on double-blinded medication, either enalapril or valsartan. The specific procedures and timing are shown in table 110.4.

Table 110.4 List of Procedures.

Week	Run-in (14-17 days)	Double-blind Treatment (+ 3 days of specified date) in weeks					
	-2	0	1	2	3	6	12
Visit <sup>a</sup>	1	2	3	4	5	6	7 <sup>b</sup>
<b>Baseline Information</b>							
Medical History and Ongoing medications	X						
12-lead ECG/Pregnancy test (if needed)//consent	X						
<b>Efficacy</b>							
Walking test	X	X				X	X
Signs/symptoms of CHF	X	X				X	X
Dyspnea –fatigue index		X					X
Echocardiography	X	X					X
Quality of life		X					X
<b>Safety</b>							
Vital Signs	X	X	X	X	X	X	X
Routine laboratory			X	X			X
Adverse events		X	X	X	X	X	X
<b>Other</b>							
Concomitant medications		X	X	X	X	X	X
Dispense medications	X	X	X	X	X	X	
Drug accountability		X	X	X	X	X	X
a. Visit 1 took place at the beginning of the run-in visit; visit 2-7 occurred at the end of the relevant weeks.							
b. For subjects withdrawn after randomization. This was their final visit. Only creatinine, BUN, K+, Na+, and Cl-was							

- measured.
- c. Echocardiography was performed at baseline to demonstrate a left ventricular EF < 45%.
  - d. A standard echocardiograph was sent to the central laboratory.

Dosing:

During the open-label period, subjects were left on their stable dose of ACE-inhibitor. After randomization subjects were started on randomized treatments either valsartan 80- mg daily or enalapril 5-mg BID. The medication was administered in a double-dummy format. After one week, assuming that the subject sustained no hypotension and/or no increase in creatinine values (> 50% above baseline), the dose of valsartan was increased to 160 mg daily and the enalapril dose increased to 10 mg BID.

**[Comment: The maximum labeled dose for CHF for enalapril is 40 mg daily. The dose used here was only 20 mg/day.]**

Consequence of amendments:

1. Subjects are to take their stable ACE medication on morning of the day of randomization
2. The criteria for time since PTCA was increased to 6 months. Subjects with persistent symptoms of hypotension (presumable after treatment with either enalapril of valsartan)1 were excluded. The upper reference range for laboratory safety was included
3. If the subject was hypotensive at the attempt to increase dose of either valsartan or enalapril, the patient was dropped from the study. If, however, the patient initially tolerated the dose increase but subsequently developed symptoms of hypotension, the dose increase could be retried up to visit 6. Subjects that do not tolerate up-titration following an adverse event, the subject is to remain on the lower dose.

Oversight:

The protocol and report do not define any standing committees with oversight responsibilities. In the statistical submission refers to a RAP meeting on March 20, 2000, which reviewed the dropouts.

Results:

A total of approximately 200 subjects from 15 sites were to be enrolled with the anticipation of 130 subjects completing. In actuality 146 patients from 13 sites were enrolled and 141 subjects were randomized. The disposition of patients during the study is shown in Table 110.5

Table 110.5 Patient Disposition.

	Total Enrolled =146 D/C during run-in = 5 Randomized = 141	
	Valsartan	Enalapril
Enrolled	70	71
Completed	65	62
Discontinued	5	9
Died	1	5
Adverse Event	2	3
Withdrew consent	2	1

More subjects discontinued from the enalapril than the valsartan group. There were 5 enalapril patients who died and 1 valsartan patient who died.

Baseline demographics:

The baseline demographics are shown in Table 110.6

Table 110.6 Demographic among those enrolled in study 110.

	Valsartan (n=70)	Enalapril (n=71)
Age mean + SD	68.0 + 8.7	67.2 + 9.4
Age > 65 (%)	44 (63%)	6 (65%)
Gender Male (% male)	49 (70%)	56 (79%)
Race (%Caucasian)	70 (100%)	71 (100%)
Weight Mean + SD	82.8 + 15.5	81.0 + 16.6
NYHA Class II/III n (%)	50 (71%)/ 20(29%)	50 (70%) / 21 (30%)
Etiology of CHF		
Ischemic	47 (67%)	39 (55%)
Non-ischemic	23 (33%)	32 (45%)
Idiopathic cardiomyopathy	18 (26%)	26 (37%)
Hypertension	3 (4%)	1 (1%)
Other	2 (3%)	5 (7%)
Clinical signs n (%)		
Paroxysmal nocturnal dyspnea	1 (1%)	4 (6%)
Dyspnea at rest	1 (1%)	0
dyspnea on effort	69 (99%)	71 (100%)
Fatigue	65 (93%)	64 (90%)
Orthopnea	5 (7%)	5 (7%)
Jugular venous distension	8 (11%)	6 (9%)
Edema	8 (11%)	10 (14%)
Rales	2 (3%)	5 (7%)
Third heart sound	5 (7%)	6 (9%)

The groups are well balanced with respect to most demographic characteristics. With respect to CHF etiology, most subjects' CHF was due to ischemic causes. Among the non-ischemic causes the most common etiology was idiopathic cardiomyopathy. Only dyspnea on effort and fatigue were frequently reported symptoms among those enrolled.

Concomitant medications at baseline:

ACE-inhibitors and dose used during open-labeled period. There was a large degree of variation in the use of ACE-inhibitors during the open-labeled period. The median dose of the ACE-inhibitor was, in general less than the maximal dose for the treatment of heart failure. Some of these ACE inhibitors have no CHF indication.

Table 110.7 ACE-inhibitors used during the period prior to randomization

		Captopril	Cilazapril	Enalapril	Lisinopril	Quinapril	Ramipril
Enalapril	# Subjects	17		20	5	1	28
	mean dose	107		17.5	14.0	20	8.3
	min -max	50-150		5-40	10-20	20-20	0.6-10
Valsartan	# Subjects	13	1	26	5		24
	mean dose	86	5.0	17	20.0		8.4
	min -max	2.5-150	5.0-5.0	10-20	20-20		2.5-10

Concomitant medications are shown in Table 110.8. Between 76-84% of those enrolled were on loop diuretics. Beta-blockers were used in 65-70% of those enrolled. Cardiac glycosides were used in 37-49% of those enrolled. More valsartan than enalapril subjects patients were on HMGCOA reductase inhibitors (53 versus 37%).

Table 110.8 Concomitant medications at baseline (&gt; 5 subjects in any treatment) N (%)

Type of Medication	Enalapril (N= 71)	Valsartan (N=70 %)
Biguanides		

Metformin	2 (3%)	6 (9%)
Vitamin K antagonists Warfarin or Warfarin sodium	26 (37%)	32 (36%)
Sulfonylureas Glibenclamide Glipizide	4 (6%)	5 (7%) 1 (1%)
Platelet Aggregation inhibitors Acetylsalicylic Acid Dipyridamole	31 (44%) 1 (1%)	35 (50%)
Cardiac Glycosides Digitoxin Digoxin	1 (1%) 31 (44%)	1 (1%) 25 (36%)
Organic Nitrates Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate	18 (25%) 2 (3%) 10 (14%)	21 (30%) 2 (3%) 10 (14%)
Loop Diuretics Bumetanide Furosemide Torsemide	1 (1%) 53 (75%)	59 (84%) 3 (4%)
Aldosterone antagonists Spironolactone	9 (13%)	4 (6%)
Beta blockers Betaxolol Bisoprolol Metoprolol Carvedolol	8 (11%) 26 (37%) 12 (17%)	1 (1%) 3 (4%) 30 (43%) 14 (20%)
HMG COA Reductase Inhibitors Fluvastatin Pravastatin Simvastatin	4 (6%) 3 (4%) 19 (27%)	3 (4%) 1 (1%) 8 (9%) 27 (39%)
Preparations Inhibiting Uric Acid Production Allopurinol	13 (18%)	12 (17%)
Benzodiazapine related drugs Zolpidem Zopiclone	4 (6%)	5 (7%) 6 (9%)

Six minute walk distance:

The prespecified analysis is unclear. The initial protocol did not pre-specify how dropouts due to death or worsening CHF were to be handled. The statistical report dated 20 December 2000 after all subjects completed the study defines how values for these dropouts would be imputed. Below are the two estimates of the six-minute walk. One estimate treats those who died as a last observation carried forward and the second analysis treats those who died or discontinued due to worsening heart failure by imputing a "0" value for last metric.

The timing of the measurement relative to dosing is not stated.

Table 110.9. Six-minute walk. Patients who died or were unable to exercise due to CHF were not assigned a value of "0".

Week	Treatment	N	Baseline Mean	LS mean change (SE)	Treatment difference
Week 6	Valsartan	64	417	-2.56 ± 5.7	-1.73 ± 7.7
	Enalapril	66	428	-0.83 ± 5.6	
Week 12	Valsartan	65	417	3.4 ± 6.0	-9.3 ± 8.3
	Enalapril	66	432	12.7 ± 6.0	
Endpoint	Valsartan	67	422	1.4 ± 5.9	-10.0 ± 8.0
	Enalapril	67	426	11.5 ± 5.9	

Table 110.10 contains the sponsor's analysis of the change from baseline in 6-minute walk. This analysis imputes a value of 0 for those who discontinue due to death or worsening heart failure.

Table 110.10 Patients who died or were discontinued due to death or were unable to walk due to worsening heart were assigned a value of 0.

Week	Treatment	N	Baseline Mean	LS mean change (SE)	Treatment difference
Week 6	Valsartan	64	417	-2.56 ± 5.7	-1.73 ± 7.7
	Enalapril	66	428	-0.83 ± 5.6	
Week 12	Valsartan	65	417	5.1 ± 8.8	3.4 ± 11.9
	Enalapril	66	429	2.2 ± 8.6	
Endpoint	Valsartan	67	422	3.0 ± 8.5	1.1 ± 11.6
	Enalapril	67	426	1.9 ± 8.5	

In neither analysis was valsartan superior to enalapril. Numerically, applying a last observation carried forth analysis enalapril increases six-minute walk by approximately 10 meters over valsartan. Applying a worse outcome to those, which died or could not exercise due to worsening CHF, valsartan increased walking distance by approximately 1 meter.

Secondary end pointsDyspnea-fatigue index:

The dyspnea fatigue index values are shown below. The higher the value the better the performance. There were essentially no differences between treatments.

Table 110.11 Dyspnea-fatigue index study 110.

	N=	Mean baseline value	LSM change ± SR
Valsartan	67	6.85	0.24 ± 0.16
Enalapril	64	6.73	0.26 ± 0.16

**Minnesota living with heart failure questionnaire**

This metric was listed as the overall score (there were 21 components to the questionnaire, one was excluded since the majority of patients did not answer this question). The maximum value for each question was 5 (worst outcome) and the minimum value was "0". The maximum worse score is therefor 100, the maximum best score was 0. At baseline, the population was only modestly compromised with their CHF. There was a trend for the enalapril group to have fewer symptoms at baseline. There was modest worsening of the score at end of study for both groups.

Table 110.12 Minnesota living with heart failure questionnaire data.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	64	64	64	67	67	67
Mean ± SD	18.2 ± 13	19.4 ± 14.6	1.2 ± 9.9	21.0 ± 16	21.8 ± 16.1	0.71 ± 11.2
Median	15.4	16.5	1.6	17	20	0.0
(min to max)	0 to 57	0 to 56	-28 to 26	1 to 67	(0 to 78)	(-28 to 30)
95% confidence interval treatment difference (-3.78, 3.35)						

The Minnesota living with heart failure questionnaire is divided into several dimensions (physical, emotional, and economic). The sponsor only analyzed the physical and emotional dimension. There were no differences between enalapril and valsartan (data not shown).

Atrio-ventricular plane displacement:

The results of the atrio-ventricular plane changes are shown in Table 110.13. An increase in excursion implies benefit. There was no difference between treatments. [Comment: It should be noted that both treatments are afterload reducers and contraction, therefore was to some extent dependent on the degree of BP drop at the time of measurement.]

Table 110.13 Atrio-ventricular plane displacement.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	64	64	64	67	67	67
Mean ± SD	8.8 ± 2.2	9.1 ± 2.3	0.31 ± 1.4	8.7 ± 2.3	9.0 ± 2.1	0.33 ± 1.2
Median	8.6	8.8	0.25	8.4	8.9	0.2
(min to max)	4.3 to 16.2	5.5 to 17.9	-3.5 to 3.6	3.0 to 13.2	(4.3 to 13.6)	(-1.8 to 4.3)
95% confidence interval treatment difference (-0.42, + 0.46)						

Left ventricular end-diastolic diameter:

The results of the left ventricular end-diastolic diameter are shown Table 110.14. There was no difference between treatments.

Table 110.14 Left ventricular end-diastolic diameter.

	Enalapril			Valsartan		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
N	63	63	63	67	67	67
Mean ± SD	37 ± 12	34 ± 10	-2.6 ± 11	36 ± 12	32 ± 7	-3.6 ± 13
Median	33.0	32	-1.0	32	31	-1.0
(min to max)	21 to 70	22 to 75	-33 to 33	23 to 83	(24 to 67.5)	(-44 to 33.5)
95% confidence interval treatment difference (-4.90, 0.42)						

Other metrics:

**NYHA Class.** There was little shift in NYHA classification over time.

Table 110.15 NYHA Classification over time

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Class I	0	0	1 (2%)	2 (3%)	2 (3%)
	Class II	50 (75%)	48 (72%)	48 (72%)	47 (73%)	48 (72%)
	Class III	17 (25%)	19 (28%)	18 (27%)	15 (23%)	17 (25%)
valsartan	N	67	67	67	65	67
	Class I	0	0	1 (2%)	3 (5%)	3 (5%)
	Class II	49 (73%)	49 (73%)	48 (74%)	47 (72%)	48 (72%)
	Class III	18 (27%)	18 (27%)	16 (25%)	15 (23%)	16 (24%)

*Jugular venous distension:* Few patients had jugular venous distension at baseline. There were more patients who improved on valsartan relative to enalapril (5 versus 1).

Table 110.16 Jugular venous distension over time.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	60 (90%)	61 (91%)	63 (94%)	59 (92%)	62 (93%)
	Present	7 (10%)	6 (9%)	4 (6%)	5 (8%)	5 (8%)
valsartan	N	67	67	65	65	67
	Absent	65 (97%)	61 (91%)	60 (92%)	64 (99%)	66(99%)
	Present	2 (3%)	6 (9%)	5 (8%)	1 (2%)	1 (2%)

*Edema:* The effect of treatment on edema is shown in Table 110.17. At end of study, there were more enalapril than valsartan patients that had no edema (94 versus 87%).

Table 110.17 Edema over study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	56 (84%)	57 (85%)	58 (84%)	61 (95%)	63 (94%)
	Trace	7 (11%)	5 (8%)	7 (11%)	3 (5%)	4 (6%)
	Feet and ankles	3 (5%)	5 (8%)	2 (3%)	0	0
	Lower legs or thighs	1 (2%)	0	0	0	0
Valsartan	N	67	67	65	65	67
	Absent	57 (85%)	59 (88%)	56 (86%)	56 (86%)	58 (87%)
	Trace	8 (12%)	7 (2%)	6 (9%)	6 (9%)	6 (9%)
	Feet and ankles	2 (3%)	0	2 (3%)	3 (5%)	3 (5%)
	Lower legs or thighs	0	0	1 (2%)	0	0

*Rales:* There were no differences in the distribution of rales at the end of the study.

Table 110.18. Rales during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	62 (93%)	62 (93%)	64 (96%)	61 (95%)	64 (96%)
	Basilar only	4 (6%)	5 (8%)	3 (5%)	3 (5%)	3 (6%)
	> 1/3 lung fields	1 (2%)	0	0	0	1 (2%)
Valsartan	N	67	67	65	65	67
	Absent	65 (97%)	66 (99%)	64 (99%)	63 (97%)	65 (97%)
	Basilar only	2 (3%)	1 (2%)	1 (2%)	2 (3%)	2 (3%)
	> 1/3 lung fields	0	0	0	0	0

*Third heart sound:* More enalapril than valsartan subjects had third heart sounds at baseline. There appeared to be no difference between treatments in altering third heart sounds.

Table 110.19 Third heart sound during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	58 (87%)	61 (91%)	61 (91%)	60 (94%)	62 (93%)
	Present	9 (13%)	6 (9%)	6 (9%)	4 (6%)	5 (8%)
Valsartan	N	67	67	65	65	67
	Absent	64 (96%)	63 (94%)	63 (97%)	64 (99%)	66 (99%)
	Present	3 (5%)	4 (6%)	2 (3%)	1 (2%)	1 (2%)

*Paroxysmal nocturnal dyspnea:* More enalapril than valsartan had paroxysmal nocturnal dyspnea at baseline. There is no strong signal of benefit.

Table 110.20 Paroxysmal nocturnal dyspnea during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	59 (88%)	67 (94%)	64 (96%)	62 (97%)	65 (97%)
	Present	8 (12%)	4 (6%)	3 (5%)	2 (3%)	2 (3%)
Valsartan	N	67	67	65	65	67
	Absent	64 (96%)	67 (99%)	65 (100%)	65 (100%)	67 (100%)
	Present	3 (5%)	1 (2%)	0	0	0

*Dyspnea at rest:* There were too few patients with dyspnea at rest to make any conclusion.

Table 110.21 Dyspnea at rest during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	67 (100%)	67 (100%)	66 (99%)	64 (100%)	67 (100%)
	Present	0	0	1 (2%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	67 (100%)	66 (99%)	65 (100%)	65 (100%)	67 (100%)
	Present	0	1 (2%)	0	0	0

*Dyspnea on effort:* Dyspnea upon effort was common at baseline. There was a general improvement in the enalapril group particularly among those with severe intensity at baseline. There was little change among those treated with valsartan.

Table 110.22 Dyspnea on effort during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	0	0	4 (6%)	2 (3%)	2 (3%)
	Slight	25 (37%)	23 (34%)	24 (36%)	30 (47%)	30 (45%)
	Moderate	30 (45%)	34 (51%)	33 (49%)	30 (47%)	32 (48%)
	Severe	12 (18%)	10 (15%)	5 (8%)	2 (3%)	3 (5%)
	Very severe	0	0	1 (2%)	0	0
valsartan	N	67	67	67	65	67
	Absent	0	1 (2%)	3 (5%)	3 (5%)	3 (5%)
	Slight	24 (35%)	24 (36%)	24 (37%)	27 (42%)	28 (42%)
	Moderate	33 (49%)	35 (52%)	29 (45%)	26 (40%)	26 (39%)
	Severe	9 (13%)	6 (9%)	7 (11%)	9 (14%)	9 (14%)
	Very severe	1 (2%)	1 (2%)	2 (3%)	0	1 (2%)

*Fatigue:* In comparing the two treatments, there is little difference in fatigue.

Table 110.23 Fatigue during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	11 (16%)	7 (10%)	12 (18%)	9 (14%)	9 (13%)
	Slight	27 (40%)	27 (40%)	21 (31%)	24 (38%)	24 (36%)
	Moderate	22 (33%)	26 (39%)	28 (42%)	26 (41%)	28 (42%)
	Severe	7 (1%)	7 (10%)	4 (6%)	5 (8%)	6 (9%)
	Very severe	0	0	2 (3%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	7 (10%)	5 (8%)	5 (8%)	8 (12%)	8 (12%)
	Slight	33 (49%)	29 (43%)	29 (45%)	27 (42%)	28 (42%)
	Moderate	18 (27%)	26 (39%)	25 (39%)	24 (37%)	24 (36%)
	Severe	9 (13%)	6 (9%)	5 (8%)	6 (9%)	6 (9%)
	Very severe	0	1 (2%)	1 (2%)	0	1 (2%)

**Orthopnea:** Most patients did not have orthopnea at baseline. There was no difference in treatment.

Table 110.24 Orthopnea during the study.

		Week -2	Week 0	Week 6	Week 12	Endpoint
Enalapril	N	67	67	67	64	67
	Absent	63 (94%)	62 (93%)	64 (96%)	63 (98%)	66 (99%)
	Lying	3 (5%)	4 (6%)	1 (2%)	1 (2%)	1 (2%)
	0° -4 5°	1 (2%)	1 (2%)	1 (2%)	0	0
	45° - 90°	0	0	1 (2%)	0	0
Valsartan	N	67	67	65	65	67
	Absent	63 (94%)	62 (93%)	62 (95%)	64 (99%)	66 (99%)
	Lying	3 (5%)	4 (6%)	2 (3%)	1 (2%)	1 (2%)
	0° -4 5°	1 (2%)	1 (2%)	1 (2%)	0	0
	45° - 90°	0	0	0	0	0

### Safety:

**Duration of exposure:** There were 71 patients randomized to enalapril and 70 subjects randomized to valsartan. The mean duration of exposure was 78.3 and 78.8 days respectively. The number of patient years were 15.2 and 15.1, respectively.

**Dropouts/discontinuations:** There were a total of 14 patients who discontinued prematurely (see table 110.5). Of these, there were 6 deaths (5 enalapril, 1 valsartan), five adverse events (3 enalapril and 2 valsartan) and 3 patients who withdrew consent (1 enalapril and 2 valsartan).

**Deaths:** There were a total of 6 deaths during the study one in the valsartan and five in the enalapril group. The one valsartan subject who died apparently had worsening status prior to death. Four enalapril subjects had sudden death and one died post-myocardial infarction. Capsular summaries follow:

(Valsartan): Patient # 002/008/116 was a 68 year old Caucasian male NYHA class II who had a history of diabetes mellitus (15 years) and two previous myocardial infarctions, s/p operation for mitral valve prolapse and A-V pacemaker insertion. The patient had deterioration in cardiac function on day 9 and sudden death on day 40.

(Enalapril): Patient # 006/004/203 was a 66 year old Caucasian male (NYHA class III) with a history of MI and hyperlipidemia. On day 57 of the study the patient vomited without other symptoms. The patient was found dead the next morning.

(Enalapril): Patient # 006/011/238 was a 53 year old Caucasian male (NYHA class II) with a history of dilated cardiomyopathy. On day 43 the patient was found dead.

(Enalapril) Patient # 006/015/178 was a 69 year old Caucasian male NYHA Class II with a history of diabetes mellitus, gout and chronic bronchitis. The patient died suddenly on day 51.

(Enalapril) Patient # 007/021/122 was a 68 year old Caucasian male NYHA class II with a history of hypertension died suddenly on day 21. On autopsy the patient had central organ congestion and a dilated left ventricle.

(Enalapril) Patient # 011/003/159 was a 78 year old Caucasian male NYHA Class III with a history of MI and angina. On day 64 the subjects was hospitalized with suspected myocardial infarction (CK-MB =13 ug/l and troponin I =26 ug/l) exacerbation of heart failure and bacterial infection. At the time the patient was hospitalized, the patient had an increase in serum creatinine. The patient died 4 days after admission.

Serious adverse events: There were a total of five valsartan patients and six enalapril patients who had non-lethal serious adverse events. Capsular summaries follow. Those who withdrew are noted.

(Valsartan) Patient # 001/014/244 was an 82-year old Caucasian female NYHA Class II. On day 82 she was hospitalized for worsening heart failure. Her dose of furosemide was increased and she was discharged three days later.

(Valsartan) Patient 002/01/194 was a 75-year old Caucasian male NYHA class II was hospitalized for vertigo, eventually diagnosed as benign positional vertigo.

(Valsartan) Patient 002/021/213 was a 76-year old Caucasian female NYHA III had a syncopal episode. She was hospitalized for three days and treated with furosemide.

(Valsartan) patient # 007/001/133. This was a 75-year old Caucasian female NYHA class III with a history of angina (infrequent). She was hospitalized on day 38 for unstable angina pectoris, treated with low molecular weight heparin and intravenous furosemide. Subsequent to the event, the subject's six-minute walk deteriorated and her X-ray consistent with worsening of CHF status.

(Valsartan, withdrew) Patient 013/002/173 was a 53-year old Caucasian male NYHA class III and a previous history of MI. On day 2 of therapy the patient was hospitalized for worsening of heart failure. The patient withdrew from the study.

(Enalapril) Patient # 001/009/108 was a 79-year old Caucasian male NYHA class II. The patient was hospitalized on day 15 due to chest pain. There was no evidence of myocardial infarction. There was however evidence of worsening angina. The patient had worsening in heart failure. The patient recovered and was discharged after two days.

(Enalapril, withdrew) Patient # 001/011/241 was a 68 year old Caucasian male NYHA class II with a history of MI and ischemic heart disease. This patient was hospitalized on day 75 for severe chest pain. CK-MB and troponin T values confirmed the diagnosis of myocardial infarction. The patient was treated with angioplasty and stenting and was withdrawn from the study.

(Enalapril, withdrew) Patient 001/013/243 was an 82-year old Caucasian female NYHA class III with a history of cranial arteritis. She was hospitalized on day 12 with a urinary tract infection. Serum concentration at the time of the event was > 200 umol /L. The study drug was discontinued. The patient recovered three days later.

(Enalapril, withdrew). Patient 002/012/195 was a 75-year old Caucasian female NYHA class II with a history of idiopathic cardiomyopathy. On day 57 the patient developed renal impairment (serum creatinine 491 umol/l) as well as tiredness. Ten days after discontinuation the creatinine decreased to 200 umol/l (baseline creatinine was 132 umol/L) and the tiredness resolved.

(Enalapril) Patient # 001/006/152 was an 80-year old Caucasian male NYHA Class III. This patient had a history of asthma. On day 38 the subject had symptoms that included edema of the lips and tongue. The patient was treated with intravenous adrenaline, hydrocortisone and clemastine. The reaction abated several hours later. The study drug was originally stopped but subsequently restarted. The attribution of the event was to ketoprofen. **[Comment: Gutsy or stupid to attribute this event to other than study drug (ACE-inhibitor or AII blocker)].**

(Enalapril) Patient # 011/012/191 was a 68 year old Caucasian female NYHA class III. The patient was hospitalized on day 32 of the study due to a viral syndrome. The patient also had worsening of CHF and was hospitalized again 8 days later, treated with spironolactone and discharged after one day.

Patients who withdrew due to non serious adverse events:

(Valsartan, withdrew) patient # 002/018/211 was a 65 year old Caucasian male NYHA Class II. The patient had dizziness on day 1 and was withdrawn 7 days later.

(Valsartan, withdrew) patient # 004/007/120 was a 90 year old Caucasian male NYHA class III was withdrawn from the study after 36 days because of pneumonia.

(Enalapril, withdrew) Patient # 006/006/205 was a 72year old Caucasian male NYHA class II who withdrew due to nausea and vomiting.

Patients who had dose reductions:

Those who had their doses reduced and the reason for the reduction are shown below:

Table 110.25 Patients who had dose reductions.

Patient #	Tx	Demographics	Reason
007/002/134	Val	62y/o Caucasian female	Headache and palpitations
007/006/138	ENA	73 y/o Caucasian male	Dizziness
008/007/251	ENA	56 y/o Caucasian male	vertigo
011/014/225	ENA	65 y/o Caucasian male	Bronchitis
012/010/171	ENA	81 y/o Caucasian male	Vertigo

Events classified as "severe" intensity. There were a total of 8 events (not necessarily 8 subjects) whose intensity of the event was classified as "severe". Seven of these events were in the enalapril group and 1 in the valsartan group. The events are tabulated in Table 110.26

Table 110.26 patients who had events categorized as "severe" in intensity.

Event	Enalapril	Valsartan
Myocardial infarction	2	
Ventricular Fibrillation	1	
Sudden Death	2	
Hypersensitivity	1	
Pneumonia	1	1

**Overall adverse events:**

Adverse events that occurred in 2 patients in either group are listed below:

Table 110.27 Overall adverse events which occurred in > 2 subjects in either group.

Event	Enalapril (n=71)	Valsartan (n=70)
Any Adverse event	45 (63%)	35 (50%)
Cardiac failure aggravated	1 (1%)	4 (6%)
Headache	1 (1%)	4 (6%)
Dizziness excluding vertigo	6 (9%)	3 (4%)
Diarrhea	2 (3%)	3 (4%)
Nasopharyngitis	6 (9%)	2 (3%)
Back pain	4 (6%)	1 (1%)

**Chemistry laboratory values (group mean):**

Blood for laboratory tests were drawn on baseline and at the end of study. In addition creatinine, BUN, potassium, sodium, chloride and bicarbonate were measured at visit 3 and 4. The group mean-change from baseline to week 12 is shown below.

Table 110.28. Baseline and change from baseline to final laboratory measurement

Parameter	Enalapril			Valsartan		
	N=	Baseline	Change	N=	Baseline	Change
SGPT (UKAT/L)	63	0.5 + 0.4	0.03 + 0.4	62	0.5 + 0.2	0.03 + 0.2
SGPT (UKAT/L)	62	0.5 + 0.2	-0.03 + 0.1	60	0.4 + 0.1	0.01 + 0.1
Creatinine (Umol/L)	63	100 + 25	3.7 + 26	62	102 + 26	2.9 + 14
Albumin (Umol/L)	60	39 + 3.4	0.6 + 2.3	61	36 + 3.2	-0.3 + 2.5
Uric Acid (Umol/L)	56	417 + 109	4.5 + 58	60	445 + 88	13.2 + 61
Sodium (Mmol/L)	64	140 + 2	-0.1 + 2.3	64	139 + 3	0.6 + 2.8
Potassium (Mmol/L)	63	4.2 + 0.3	0.07 + 0.3	60	4.2 + 0.3	-0.08 + 0.3
Chloride (Mmol/L)	51	104 + 4	-0.3 + 4	54	103 + 4	-0.1 + 4
Bicarbonate (Mmol/L)	46	26 + 3	-0.3 + 2	47	26.3 + 3	-0.1 + 2
Urea (mmol/L)	58	7.7 + 2	0.4 + 2	63	8.4 + 3	0.1 + 1
Cholesterol (mmol/L)	59	5.4 + 1	0.02 + 0.6	63	5.7 + 1.4	-0.4 + 1

**Chemistry values extreme:** The number of subjects who exceeded the extremes in lab values is shown below. Of note, that exceeding the extreme particularly if the baseline measurement is low may not arise to a level of concern.

Table 110.29 Number of subjects and criteria for extremes.

		Decrease		Increase	
		Criteria		Criteria	
SGOT	Valsartan	None	0	>150%	0
	Enalapril		0		2
SGPT	Valsartan	None	0	>150%	0
	Enalapril		0		0
Creatinine	Valsartan	None	0	>50%	1
	Enalapril		0		1
Uric acid	Valsartan	None	0	> 50%	1
	Enalapril		0		0
Sodium	Valsartan	5%	0	>7%	0

Potassium	Enalapril		0		0
	Valsartan	20%	0	> 20%	1
BUN	Enalapril		0		3
	Valsartan	None	0	>50%	1
Creatinine	Enalapril		0		2
	Valsartan	None	0	>50%	1
Sodium	Enalapril		0		1
	Valsartan	>5%	1	>7%	0
Potassium	Enalapril		1		0
	Valsartan	20%	0	>20%	2
BUN	Enalapril		0		5
	Valsartan	None	0	>50%	2
	Enalapril		0		5

Hematologic values group means:

Hematologic values to end of treatment are shown below.

Table 110.30 Baseline and change from baseline of hematologic parameters till end of treatment.

Parameter	N=	Enalapril		N=	Valsartan	
		Baseline	Change		Baseline	Change
Hemoglobin (G/L)	64	140 ± 14	0.3 ± 7	63	143 ± 14	-2.0 ± 8
Hematocrit (%)	63	42 ± 4.0	0 ± 2.0	61	43 ± 4.2	-0.8 ± 2.8
WBC (10 <sup>9</sup> )	64	7.4 ± 1.7	0.3 ± 1.8	63	7.4 ± 1.9	0.11 ± 1.2
Platelets (10 <sup>9</sup> /L)	62	212 ± 53	3.0 ± 27	60	223 ± 47	-2.6 ± 32

Extremes in hematology: Extreme values in hematology are listed in Table 110.31

Table 110.31 Hematologic values as extreme and criteria to define a value as extreme (sponsor's criteria)

		Decrease		Increase	
		Criteria		Criteria	
Hemoglobin	Valsartan	>20%	1	>50%	0
	Enalapril		0		0
Hematocrit	Valsartan	>20%	1	>50%	0
	Enalapril		0		0
WBC	Valsartan	>50%	0	>50%	1
	Enalapril		0		3

Urinalysis:

Positive urine protein increased with both treatments.

Table 110.32 Urinalysis values

Parameter	Baseline	Valsartan		Enalapril	
		# Negative (%)	# Positive (%)	# Negative (%)	# Positive (%)
Glucose	Negative	54 (92%)	1 (2%)	53 (93%)	0
	Positive	1 (2%)	3 (5%)	1 (2%)	3 (5%)
	Total	55 (93%)	4 (7%)	54 (95%)	3 (5%)
Blood	Negative	44 (76%)	5 (9%)	48 (84%)	4 (7%)
	Positive	3 (5%)	6 (10%)	3 (5%)	2 (4%)
	Total	47 (81%)	11 (19%)	51 (90%)	6 (11%)
Protein	Negative	32 (55%)	9 (16%)	28 (49%)	10 (18%)
	Positive	6 (10%)	11 (19%)	4 (7%)	15 (26%)
	Total	38 (66%)	20 (35%)	32 (56%)	25 (44%)

Adverse events that are often reflected in laboratory abnormalities:

Events related to laboratories that either are likely to be reflected in laboratory measurements or are these measurements are shown below.

Table 110.32 Adverse events consistent with laboratory abnormalities.

Valsartan		Enalapril	
Patient Number	Abnormality	Patient Number	Abnormality
002/013/196	UTI	01/013/246	UTI
002/021/213	Hypercholesterolemia	002/001/109	UTI, hematuria
005/003/125	UTI	002/014/195	Renal insufficiency, gout
005/006/130	Hematuria	0089/001/171	Gout
005/008/132	Hyperglycemia		
009/002/142	Gout		

## Laboratory values this reviewer considered noteworthy:

Table 110.33 Noteworthy laboratory values

Treatment	Pt #	Parameter	Normal range*	Value (visit #)
Valsartan	001/010/107	Uric acid	120-480 umol/l	320 (V1); 546 (V7)
Valsartan	002/008/116	Creatinine	60-115umol/l	129 (V1); 163 (V3); 202 (V4)
Valsartan	002/021/216	Sodium	136-147 mmol/l	134 (V1); 127 (V3); 137 (V4)
Valsartan	004/001/117	Potassium	3.4-5.0 mmol/l	4.2 (V1); 4.3 (V3); 4.8 (V4); 5.4 (V7)
Valsartan	008/008/252	Hemoglobin	115-170 g/l	160 (V1); 125 (V7)
Valsartan	008/008/252	Hematocrit	35-48%	49.9 (V1); 37 (V7)
Valsartan	011/013/192	Urea	2-10 mmol/l	7.7 (V1); 7.3 (V3); 10.1 (V4); 10.5 (V7)
Valsartan	011/013/192	Creatinine	60-115umol/l	87 (V1); 103 (V3); 113 (V4); 161 (V7)
Valsartan	004/001/117	Urine Protein	Negative	Neg (V1); 2+ (V7)
Valsartan	005/011/224	Urine Protein	Negative	Neg 9V1); 3+ (V7)
Enalapril	002/012/195	Urea	2-10 mmol/l	11.4 (V1); 15 (V3); 16.6 9V4); 23.1 (V7); 14 (other)
Enalapril	002/012/195	Creatinine	60-115umol/l	132 (V1); 206 (V3); 222 (V4); 319 (V7); 169 (other); 491 (other)
Enalapril	002/027/216	Urea	2-10 mmol/l	5.1 (V1); 6.4 (V3); 5.8 (V4); 9.1 (V7)
Enalapril	002/009/221	Urea	2-10 mmol/l	5.4 (V1); 6.2 (V3); 8.7 (V4); 7.8 (V7)
Enalapril	005/015/234	Urea	2-10 mmol/l	4.1 (V1); 6.6 (V3); 5.2 (V4); 4.2 (V7)
Enalapril	002/027/216	Urea	2-10 mmol/l	5.1 (V1); 6.2 (V3); 8.7 (V4); 7.8 (V7)
Enalapril	005/009/221	Urea	2-10 mmol/l	5.4 (V1); 6.2 (V3); 8.7 (V4); 7.8 (V7)
Enalapril	006/007/206	WBC	3.9-10 x 10 <sup>9</sup>	5.3 (V1); 15 (V7)
Enalapril	008/006/250	SGPT	0.2-0.8 ukat/l	0.32 (V1); 3.34 (V7)
Enalapril	012/007/168	Sodium	136-147 mmol/l	137 (V1); 130 (V3); 132 (V4); 131 (V7)
Enalapril	002/001/109	Urine Blood	Negative	Trace (V1); 2+ (V7)

\* There were several laboratories and a range was constructed by the extremes of laboratories.

Vital signs: Vital signs were measured at each visit. The protocol stipulates that the timing of the measurements was to be the same at each visit. The timing relative to dose is not stated.

Sitting diastolic and systolic blood pressures are shown below. Figure 110.1 and 110.2, pulse in figure 110.3 With the exception of week 12 for valsartan both diastolic and systolic blood pressures decreased. The week 2 systolic blood pressure for the valsartan group shows an excessive and unexplainable drop.

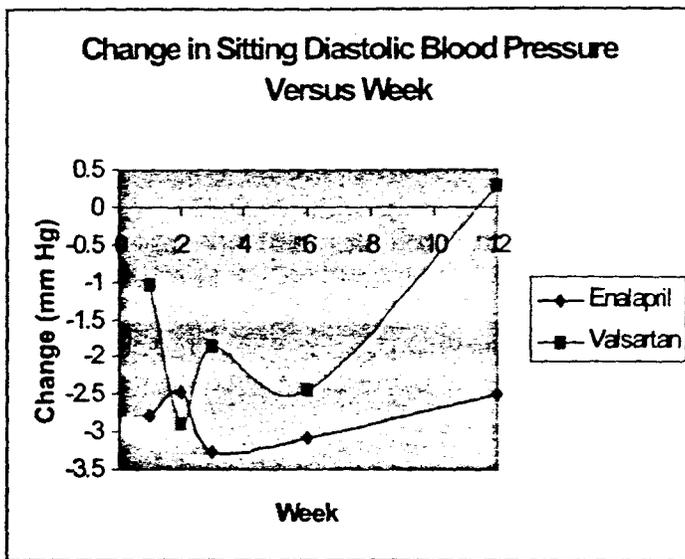


Figure 110.1 Diastolic blood pressure

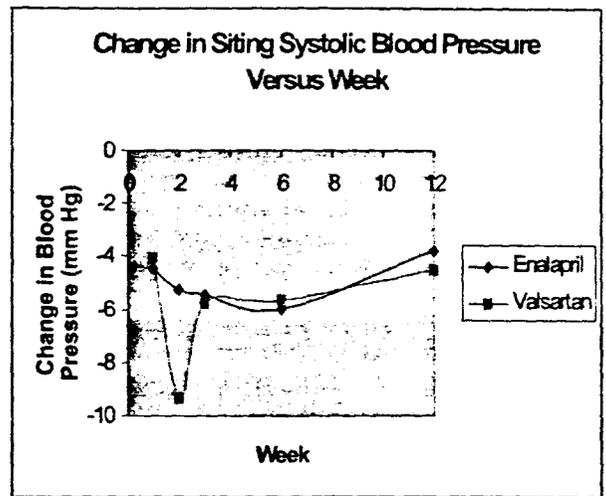
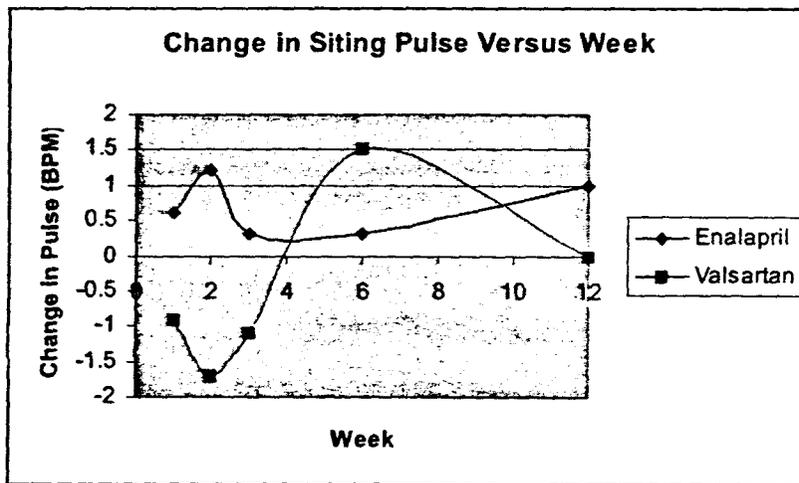


Figure 110.2 Systolic blood Pressure

With respect to pulse, there is a small increase throughout the observation period for enalapril and no consistent pattern for the valsartan.

Figure 110.3 Sitting Pulse



Orthostatic measurements: Orthostatic measurements were not taken

ECGs:

ECGs were only collected at baseline.

Discussion:

This was a decent sized study comparing enalapril at a maximum dose of 10-mg BID to Valsartan at a dose of 160-mg daily. The maximal dose of enalapril based on current labeling is, however, 40 mg/day. Subjects who entered the study were NYHA class II-III patients who were on some dose of ACE-inhibitors for at least 3 months and stable doses for > 2 weeks before entry.

Baseline ACE inhibition may not have been adequate (that is the drug may not be optimum drug and the dose may not have the optimum dose).

The primary metric of interest was six-minute walk. Baseline distance walked was approximately 420 meters. Any large increases in this metric would, therefore, be unlikely (assuming that a healthy subject could walk a mile in 20 minutes, the distance walked in six minutes would be approximately 483 meters). A reasonable maximal increase for any individual would therefore be about 60 meters.

This study should be considered a randomized withdrawal study. That is going from some dose of ACE-inhibitor to either similar or different therapy. The time course of deterioration in exercise performance after the withdrawal of ACE-inhibitors in CHF subjects is not known. Since there was no measurement of walk distance prior to the start of the ACE-inhibitor, the benefit of ACE-inhibitors on six-minute walk for those enrolled is also unknown and the consequence of their discontinuation is uncertain.

The original protocol was silent as to how to impute data for those who discontinue during the study. The first specific plan was submitted on 20 December 2000, well after all patients completed the study. This plan imputed a worst outcome for those who died or were too symptomatic to exercise. There were more of these patients treated with enalapril who died during the course of the study and imputing a worst outcome favors valsartan. The deaths of the m enalapril-treated patients were in general, sudden in nature and did not therefore reflect the deterioration in pump function. Imputing a zero value for exercise under these circumstances is not an obvious choice as to how to handle missing data. Imputing a last value carried forth is equivalently valid for the study.

If one imputes a last value carried forth for the study the enalapril group had a least square mean change of 10 meter increase in 6-minute walk when compared to valsartan. If one imputes a worse outcome for those who died or were unable walk due to worsening heart failure valsartan had a 1-meter increase in walk distance relative to enalapril. Neither analysis shows a difference between groups.

There were four secondary end points measured within the study, dyspnea fatigue index, Minnesota Living with heart failure questionnaire, atrio-ventricular plane displacement and left ventricular end diastolic diameter, none of these parameters differed between the two treatment groups.

There were in addition a total of 10 additional metrics collected (NYHA classification, jugular venous distension, edema, rales, 3<sup>rd</sup> heart sound, paroxysmal nocturnal dyspnea, dyspnea at rest, dyspnea on effort, fatigue and orthopnea), none of these were preferentially altered by either treatment.

With respect to safety, there were five deaths among those treated with enalapril and one death among those treated with valsartan. Capsular summaries do not suggest a relationship to treatment. Overall adverse events are not unusual.

Conclusion:

This study does not support a benefit of valsartan on six-minute walk.

This study does not support a claim of non-inferiority.  
There were no safety issues.

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Shari Targum  
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MEDICAL OFFICER

please sign ASAP

James Hung  
9/13/01 02:34:18 PM  
BIOMETRICS

Abraham Karkowsky  
9/13/01 02:44:20 PM  
MEDICAL OFFICER  
Only study 110 reviewed.

George Chi  
9/13/01 04:10:53 PM  
BIOMETRICS

**NDA 20-665, S-016: 120 day Safety Update:**

**Drug:** Valsartan

**Sponsor:** Novartis

**Medical Reviewer:** Shari L. Targum, MD

**Date of Review (120 day Safety Update):** October, 10, 2001

Most of the information from the 120-day safety update appeared to be related to Study 109. Overall conclusions will appear at the end of this review.

**Table 1. Ongoing trials:**

Protocol #	Study Design	Efficacy parameters	Sample size	Treatment groups	Status/results
107 ext.	See Review. Treatment exposure 26 weeks	See Review	2021	Val 40, 80, 160 BID or Placebo	ongoing
108 (VALIANT)	Randomized, DB, AC, forced titration, parallel-group, Class II-III CHF post-MI. Exposure: 4 years	Time to death, hospitalization, SD with resuscitation, MI, CV procedures, QOL	Total 14,500 planned.	Valsartan monotherapy 20>40>80>160 mg PO BID (4833 patients planned); Captopril monotherapy 6.25>12.5>25>50 mg PO TID (4833 pts planned); Combination valsartan- captopril (4833 planned):	ongoing
CH01	Open label, post MI, EF< 40%. Exposure: 26 weeks	Echo, treadmill, MRI, PFT, muscle strength	Total 40 planned	Valsartan + basic training program; valsartan + basic training program + strength training	ongoing
CH02	DB, crossover, AC, NYHA IIb-III. Exposure: 26 weeks	LVEF, NE, biopsy, central hemodynamic	Total: 40 planned	Benazepril 20 mg QD; valsartan (? Dose); benazepril +valsartan	ongoing
US12	Multicenter, open- label, forced titration, NYHA I- IV. Exposure: 13 weeks.	24-hour Holter (HRV) and neurohormones	Total: 68 planned	Valsartan 80>160 mg PO BID	ongoing
US06	Open-label, multicenter, forced titration, NYHA II- IV, effect on coronary reserve flow. Exposure: 14 weeks.	Cine MRI, brachial artery ultrasound	Total: 21	Valsartan 80>160 mg PO BID	Study cancelled due to administrative reasons; 21 patients enrolled so far.

**Table 2. Deaths and SAEs from ongoing trials (between October 2, 2000 and June 1, 2001)**

Study	Number randomized patients		Patients with SAE	Deaths
	Planned	Estimated		
107 ext	2021	1589	97	23
108 (VALIANT)*	14,500	14,781	--	--
CH02	40	16	1	0
US06	54	21	1	0
US12	68	69	3	1
CH01	40	6	0	0

This study has a DSMB. Serious, unexpected, drug-related events were reported for one patient (9097/008, rhabdomyolysis) during this time frame.

Study 109: Multicenter, randomized, double-blind, active-controlled parallel group trial to assess the 16-week effect of valsartan capsules (40-160 mg o.d.), compared with lisinopril, on autonomic nervous system activity, evaluated by means of heart rate variability and neuro-humoral measurements, in patients with stable chronic congestive heart failure (NYHA Class II-IV). (Phase IIIb) (Protocol date: Oct 12, 1998, signed January 20, 1999 and March 11, 1999)

Source: NDA 20-665, S-016:120 day safety update;

Primary Objective: Determine in patients with stable CHF the effect of treatment with valsartan, in comparison with lisinopril, on HRV measures.

Secondary Objectives (listed as "optional" in protocol): Determine in the same patient population the effect of short-term treatment with valsartan, in comparison with lisinopril, on neuro-hormonal indicators of left ventricular dysfunction.

Sites: 1 center in Italy (3 were planned).

Duration: May 17, 1999 (first patient in) to September 29, 2000 (last patient out).

Study design: This was a 18 week (16 weeks of active treatment), multicenter, randomized, double-blind, forced titration, parallel-group, active-controlled trial as shown in Figure 1.

Figure 1. Study Design (109)

Period	Period 1: Single-blind placebo run-in (2 weeks)	Period 2: Double-blind forced-titration (6 weeks)	Period 3: Double-blind treatment maintenance (10 weeks)
		Randomization ↓	
Visit	1	2      3      4	5      6      7
Week	-2	0      2      4	6      10      16
Treatment	Placebo	Valsartan 40→80→160 mg QD  Lisinopril 5→10→20 mg QD	Continue same dose (after titration) of randomized drug

In the original protocol (section 3.2) it was stated that "twice daily dosing of valsartan with forced titration was chosen..."; however, in the rest of the protocol and study report "once daily dosing" is written. The medical reviewer assumes that this study used once daily dosing of valsartan and lisinopril.

After a 2 week placebo run-in period, patients with stable CHF were randomized to valsartan or lisinopril (starting dose 40 or 5 mg QD, respectively); at visits 3 and 4 the doses were uptitrated as per Figure 1.

No ACE-inhibitors, Ang II receptor antagonists or beta-blockers were allowed during the double-blind portion of the trial. Allowed treatment including: diuretics, digoxin, hydralazine, nitrates and antiarrhythmics except for amiodarone and Class IC agents (as per exclusion criteria).

Criteria for titration:

At Visits 3 and 4, patients were titrated to the next higher dose level if all three of the following criteria were met:

1. Persistent standing SBP > 100 mm Hg.
2. No symptoms of hypotension (syncope, faintness, orthostatic dizziness) were reported on current dose.
3. No increase in serum creatinine > 50% from baseline (Visit 2) to a value > 2.0 mg/dL.

Stratification: None

Inclusion criteria <sup>1</sup> :	Exclusion criteria:
<ul style="list-style-type: none"> <li>• Males or females outpatients, 18-80 years, inclusive.</li> <li>• Suffering from CHF (NYHA Class II-IV) for at least 3 months prior to Visit 1.</li> <li>• With sinus rhythm and echocardiographically measured ejection fraction &lt; 40% within two weeks prior to Visit 1 or during the placebo run-in.</li> <li>• Not having received an ACE-inhibitor or an Ang II receptor antagonist or a beta-blocker during the last 9 months before Visit 1. <i>(please see Protocol amendment for change in this criterion)</i></li> <li>• With CHF medication at a stable dosage regimen for two weeks prior to Visit 1 and during the placebo run-in period. <i>(please see Protocol amendment for change in this criterion)</i></li> <li>• With clinical conditions stable in the last two weeks prior to Visit 1 and during the placebo run-in period. <i>(please see Protocol amendment for change in this criterion)</i></li> <li>• Provide informed consent.</li> </ul>	<ul style="list-style-type: none"> <li>• History of heart transplant or who are on a transplant list.</li> <li>• History of MI or cardiac surgery within past 3 months prior.</li> <li>• Unstable angina or coronary artery disease likely to require coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA).</li> <li>• Constrictive pericarditis or active myocarditis.</li> <li>• Sustained ventricular arrhythmia with syncopal episodes within past 3 months.</li> <li>• Hemodynamically significant mitral stenosis or mitral regurgitation, except mitral regurgitation secondary to left ventricular dilatation.</li> <li>• Hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic stenosis.</li> <li>• Persistent standing SBP &lt; 100 mm Hg.</li> <li>• Right heart failure due to pulmonary disease</li> <li>• Diagnosis of postpartum cardiomyopathy.</li> <li>• Stroke or TIA within the past 6 months.</li> <li>• Primary liver disease considered to be life-threatening.</li> <li>• Renal disease likely to be life-threatening or serum creatinine &gt; 2.5 mg/dL.</li> <li>• Pregnancy, nursing or women of childbearing potential not practising effective contraception.</li> <li>• Evidence/history of drug or alcohol abuse within past 3 years.</li> <li>• Mental impairment limiting ability to comply with study requirements.</li> <li>• Previous participation in a valsartan clinical trial.</li> <li>• Who, for any reason, are unable to complete the study.</li> </ul>

<sup>1</sup> Inclusion and Exclusion criteria are taken from the protocol. Please see Amendments to the Protocol for changes in these criteria.

	<ul style="list-style-type: none"> <li>• Taking or planning to take other investigational drugs during the study or prior participation in any investigational drug study within past 30 days.</li> <li>• Previous treatment with class IC antiarrhythmic agents (such as flecainide and propafenone) or an intravenous inotropic or vasodilator agent within last 3 months prior to Visit 1 as well as during the trial.</li> <li>• Treatment with amiodarone within 6 months prior to Visit 1 as well as during the trial.</li> <li>• Known hypersensitivity or contraindication to Ang II receptor antagonist or ACE inhibitor.</li> </ul>
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**Criteria for withdrawal:**

Patients were to be removed from trial treatment if, after alteration of the lowest dose level of trial treatment and background treatment, any of the following criteria were met:

1. Persistent standing SBP < 90 mm Hg;
2. Symptoms of hypotension (syncope, faintness, orthostatic dizziness);
3. Increase in serum creatinine > 50% from baseline (Visit 2) to a value > 2.0 mg/dL.

**Table 3. Schedule of procedures (109)**

period	Single-blind placebo run-in	Double-blind treatment					
		↓ Randomization					
Visit	1	2	3	4	5	6	7
Week	-2	0	2	4	6	10	16
Personal data	X						
Physical exam	X	X	X	X	X	X	X
LVEF	X						
BP, HR, body weight	X	X	X	X	X	X	X
Signs/symptoms CHF	X	X	X	X	X	X	X
HRV study		X					X
24-hour Holter monitor		X					X
Laboratory tests	X	X	X	X	X		X
Neurohormone measurements (optional)					X		X
Trial treatment	X	X	X	X	X	X	
Concomitant medication	As needed	→					
Medical history	X						
Adverse events	As needed	→					
Informed consent	X						

Assessments of heart rate variability (HRV) were to be derived via time-domain and frequency-domain measurements. Time-domain measurements would be taken from 24-hour ECG monitoring, including measurements of mean normal-to-normal (NN) intervals, standard deviation of normal RR intervals (SDNN), and root mean square successive difference of normal RR intervals (rMSSD). Frequency-domain HRV evaluations would include ECG evaluations during spontaneous breathing (BS), breathing paced to a metronome (CR), passive head-up tilt-test, and recovery (10 minutes supine).

**Primary Efficacy Variables:**

1. 24-hour SDNN (ms), variable of the time-domain power.
  2. Total LF power (in normalized units), component of the frequency-domain total power.
  3. Baroreflex sensitivity: evaluated by HRV/BP spectral analysis as  $\alpha$  index (msec/mmHg).
- These variables will be measured on the 24-hour Holter recordings made after randomization (Visit 2) and on the last day of the trial (Visit 7).

**Secondary Efficacy Variables:**

**For HRV assessment:**

1. 24-hour NN (ms), variable of the time-domain power.
2. Day-time NN (ms): variable to the time-domain power.
3. Night-time NN (ms): variable of the time-domain power.
4. Day-time SDNN (ms): variable of the time-domain power.
5. Night-time SDNN (ms): variable of the time-domain power.
6. 24-hour rMSSD (ms): variable of the time-domain power.
7. Day-time rMSSD (ms): variable of the time-domain power.
8. Night-time rMSSD (ms): variable of the time-domain power.
9. 24-hour SDANN (ms) (standard deviation of the average NN intervals in all 5-minute segments): variable of the time-domain power.
10. 24-hour SDNN index (ms) (mean of standard deviations of all NN intervals for all 5-minute segments): variable of the time-domain power.
11. HF power (in normalized units), component of the frequency-domain total power.

**For neurohormonal assessments (optional):**

12. Plasma Ang II (mol/ml).
13. Plasma norepinephrine (ng/ml).
14. Plasma aldosterone (ng/ml).
15. Plasma endothelin-1 (pg/ml)
16. Plasma BNF (pg/ml).
17. Plasma BARK1 (pg/ml).

**Statistical analyses:**

The stated goal was to show superiority of valsartan over enalapril with respect to the three primary efficacy variables.

The three predefined analysis populations were: all randomized patients (regardless of trial medication intake), intent-to-treat (all randomized patients who received trial medication and underwent at least one post-baseline assessment), and per protocol population (all patients who completed the study without any major protocol deviation).

Between treatment of valsartan and enalapril was based on a null hypothesis of no treatment difference; all tests were to be two-sided.

The primary analysis was performed on the last measured value using fixed-effects ANCOVA model with center and treatment groups as factors and baseline visit 2 values as covariates. Treatment by baseline interaction was also included in the main model. Mean differences were estimated together with 95% confidence intervals. In adjusting for multiplicity of three primary endpoints, each primary variable was to be analyzed following the Holm's stepdown procedure (to achieve an overall significance level of 0.05).

**Sample Size:** The study was designed to show that valsartan was different from lisinopril in effects on HRV. On the basis of HRV-related literature, it was calculated that 95 patients must be randomized to show, with 80% power and an overall significance level of 0.05 (0.0167 for each contrast, two-tail test) to detect a difference of 10 ms (SD=15) in 24-hour SDNN and a difference of 0.20 normalized unit (SD=0.30) in LF total power and a difference of 2 msec/mmHg (SD=3) in the  $\alpha$  index of baroreflex sensitivity between valsartan and enalapril. Given a drop-out or protocol violation rate of 25%, the sample size calculation prespecified that 118 patients were to be randomized.

**Safety analysis:**

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

**Drug Supply:**

**Table 4. Drug supply**

Drug	Batch number
Lisinopril 5 mg capsules	X0800299
Lisinopril 10 mg capsules	X0810299
Lisinopril 20 mg capsules	X082 0299
Placebo-matched valsartan capsules	B980004
Valsartan 40 mg capsules	B980162
Valsartan 80 mg capsules	B980001
Valsartan 160 mg capsules	B980002

**Amendments to the Protocol:**

1. Amendment #1 (dated July 21, 1999, signed July 22-28, 1999): A. Changed the inclusion/exclusion criteria so that patients could not receive an ACE-inhibitor, Ang II antagonist or beta blocker during the 4 weeks prior to Visit 1 and were to be on stable CHF medications/dosages with stable clinical conditions for 4 weekss prior to Visit 1 and during the placebo run-in period; B. Changed primary efficacy variables to 24-hour SDNN (ms) and shifted the other two primary efficacy variables to secondary efficacy variables. The sample size was recalculated to 88 randomized and 70 patients who will have completed the trial.

**Results:**

**Patient Disposition:**

Table 5 lists patient disposition. In the valsartan group, one patient was discontinued because of abnormal lab (anemia, high creatinine/urea) and two were discontinued because of adverse events (cough and worsening chronic renal failure, respectively). In the lisinopril group, 4 patients were discontinued because of adverse events (two developed cough, one developed hypotension with high creatinine/urea, and one developed worsening of chronic renal failure). The ITT population consisted of 40 patients in each treatment group; the per protocol population consisted of 38 patients in valsartan and 37 in the lisinopril group. Five patients in each treatment arm were excluded from both ITT and per protocol analyses because of lack of post-randomization 24-hour SDNN values and failure to complete the study; these patients, however, were included in the safety analysis. In addition, 2 patients on valsartan and 1 on lisinopril were noted to have major protocol deviations (overall protocol deviations were seen in 4 valsartan and 12 lisinopril patients).

**Table 5. Patient Disposition**

	Valsartan	Lisinopril	Total
Enrolled	--	--	95
Discontinued during placebo run-in			5
Randomized	45	45	90
Completed double-blind	41	38	79
Discontinued double-blind (total)	4	7	11
For adverse experience	2	4	6
Abnormal lab	1	0	1
For death	1	0	1
Withdrew consent	0	2	2
Lost to follow-up	0	1	1

Source: Safety Update Table 7-1, 7.1-1, 7.1-2

**Table 6. Drug Exposure (all randomized patients)**

	Valsartan	lisinopril
N	45	45
Mean ( $\pm$ SD) days on trial drug	111.67 (17.96)	104.4 (31.76)
Median (days)	116	115
Range (days)	48-139	1-133

Source: Table 8.1-3. Duration of exposure calculated as last intake date-start treatment date +1 day.

Baseline characteristics are shown below. The study population was 100% Caucasian and a majority were male (higher percentage in valsartan); Mean age was 61 years with 40% over 65 years of age. About 69% were classified as NYHA Class II and 31% were judged to be Class III. About 29% carried a diagnosis of coronary artery disease. Mean baseline sitting blood pressure was 131-133 mm Hg (systolic) and 82-84 mm Hg (diastolic); mean sitting pulse rate was 76 to 78 bpm. Baseline ejection fraction was 30-31%. Of those randomized, about 88% were on diuretics, 73% on digitalis, 48% on nitrates, 37% on calcium channel blockers.

**Table 7. Baseline characteristics (all randomized patients)**

	Valsartan (N=45) n (%)	Lisinopril (N=45) n (%)
Males	32 (71)	26(58)
Females	13 (29)	19 (42)
Previous MI	15 (33)	13 (29)
Previous cardiac revascularization	5 (11)	10 (22)
Mean (SD) Body weight visit 2 (kg)	71.5 (15.7)	76.5 (13)

Source: Table 7-4.

Primary Efficacy Variable: Results are shown in Table 8. No significant differences were demonstrated between valsartan and lisinopril.

**Table 8. Primary Efficacy Variable**

Patient population	Treatment (n)	Baseline mean	Endpoint actual mean	Endpoint adjusted mean	Estimated difference valsartan-lisinopril (95% CI)	Significance level (p)
ITT	Valsartan (40)	114.7	114.9	114.4	-8.16 (-19.1, 2.77)	0.14
	Lisinopril (40)	113.5	122.1	122.6		
Per protocol	Valsartan (38)	114.0	115.4	115.9	-7.37 (-18.76, 4.02)	0.20
	Lisinopril (37)	115.1	123.7	123.2		

Source: Table 9-1

Secondary Efficacy Variables:

**Table 9. Selected Secondary Efficacy Variables (ITT)**

Variable	Treatment (n)	Baseline mean	Endpoint mean	Estimated difference valsartan-lisinopril (95% CI)	Significance level (p)
LF power (NU)	Valsartan (17)	32.7	31.5	11.63 (-1.94, 21.98)	0.11
	Lisinopril (21)	29.3	22.7		
Alpha index (ms/mmHg)	Valsartan (17)	4.8	5.7	-0.51 (-2.45, 2.28)	0.59
	Lisinopril (21)	5.0	5.3		

Source: Table 9-2

Other secondary efficacy variables related to HRV are shown in Table 11. No significant differences can be seen between valsartan and lisinopril. In several instances (eg, 24 hour NN, 24 hour SDANN, HF power, daytime and nighttime SDNN) the confidence intervals are fairly wide.

**Table 10. Secondary efficacy variables (ITT)**

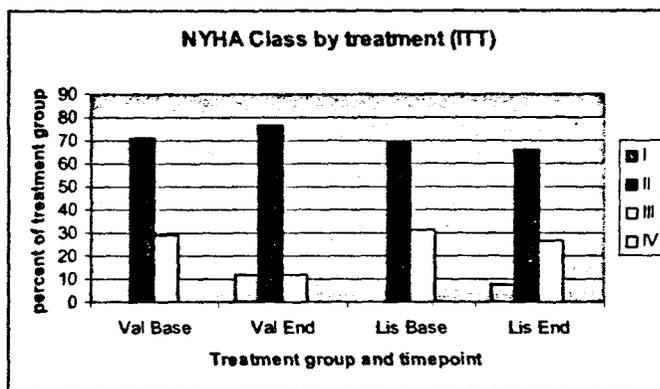
Variable	Treatment (n)	Baseline mean	Endpoint mean	Endpoint adjusted mean	Estimated difference valsartan-lisinopril (95% CI)	P value
24-hr NN (ms)	Valsartan (40)	746.9	771.0	779.7	21.44 (-10.01, 52.91)	0.18
	Lisinopril (40)	766.8	765	758.6		
Daytime NN (ms)	Valsartan (40)	682.8	717.1	726.1	30.62 (-2.71, 64.35)	0.07
	Lisinopril (40)	704.8	702	695.3		
Nighttime NN (ms)	Valsartan (40)	856.2	865.2	870.1	-10.71 (-54.35, 32.93)	0.63
	Lisinopril (40)	867.9	885.5	881.2		
Daytime SDNN (ms)	Valsartan (40)	78.9	80.4	80.3	-2.94 (-13.44, 7.56)	0.58
	Lisinopril (40)	78.7	83.2	83.3		
Night time SDNN (ms)	Valsartan (40)	85.7	96.7	97.2	5.09 (-7.73, 17.91)	0.43
	Lisinopril (40)	87.1	92.7	92.1		
24-hour RMSSC (ms)	Valsartan (38)	36.5	34.4	33.3	0.92 (0.78, 1.08)	0.32
	Lisinopril (36)	32.7	34.8	36.1		
Daytime RMSSD (ms)	Valsartan (38)	33.4	29.1	27.9	0.9 (0.75, 1.07)	0.23
	Lisinopril (36)	29	30.1	31.3		

Nighttime RMSSD (ms)	Valsartan (38)	38.2	37.9	37.6	0.95 (0.79, 1.15)	0.6
	Lisinopril (36)	37	38.8	39.2		
24-h SDANN	Valsartan (40)	101.6	103.3	102.5	-9.31 (-21.2, 2.58)	0.12
	Lisinopril (40)	99.4	110.6	111.6		
SDNN index (ms)	Valsartan (40)	44.3	46	46.1	1.00 (0.89, 1.13)	0.98
	Lisinopril (40)	44.5	46.1	46		
HF power (NU)	Valsartan (17)	39.1	35.5	--	-3.01 (-17.93, 6.69)	0.56

Source: Tables 9-3, 9-4, 9-5, 9-69-7, 9-8.

**NYHA Classification:** Results of NYHA Class are presented below. There is an increase in Class I and decrease in Class III CHF with both treatments. It should be reiterated that most patients were in Class II; at week 16, five valsartan and ten lisinopril patients were in Class III CHF.

Figure 2. NYHA Class



Source: Table 9.2-15

**Neurohormones:** Neurohormone measurements, listed as “optional” in the protocol, were measured at rest, during the tilt test, and at recovery.

At rest, plasma norepinephrine and aldosterone decreased in both treatment groups from baseline to the final value. The sample size for angiotensin II (less than 10 patients per treatment group) was fairly small compared to the total; reported results showed an increase in the valsartan group from baseline and no meaningful change in the lisinopril group. Plasma BNP appeared unchanged in the valsartan group and decreased in the lisinopril group. Plasma endothelin-1 did not appear to show meaningful changes in the two treatment groups.

Of the measured neurohormones, only plasma BARK-1 showed a statistically significant difference between the treatment groups (ie, valsartan (N=24) significantly decreased mean BARK-1 while an increase was seen in the lisinopril group (N=22) (p=.004)).

#### Safety:

##### Deaths:

There was one death in the valsartan group (Patient 102). This patient was a 72 year old Caucasian male who had sudden death at the end of the 7<sup>th</sup> week of treatment.

Another patient had sudden death (Pt rand #70) apparently prior to randomization. During the double blind treatment period, 25 valsartan patients developed 54 adverse events and 29 lisinopril patients developed 71 adverse experiences.

Seven patients on valsartan (including the death) and 2 on lisinopril developed serious adverse events.

Treatment-emergent adverse experiences are summarized below.

**Table 11. Treatment-emergent adverse experiences by preferred term occurring in (N<sub>≥</sub>2) in valsartan group, regardless of drug relationship (safety analyzable population)**

Preferred term	Valsartan (N=45) n (%)	Lisinopril (N=45) n (%)
Total patients with adverse experience	25 (56)	29 (64)
Anemia NOS	3 (7)	1 (2)
Asthenia	2 (4)	8 (18)
Chest pain NEC	3 (7)	2 (4)
Pyrexia	2 (4)	0
Viral infection	2 (4)	0
Blood creatinine increased	3 (7)	4 (9)
Hypercholesterolemia	2 (4)	1 (2)
Headache NOS	2 (4)	2 (4)
Renal failure chronic aggravated	2 (4)	2 (4)
Cough	6 (13)	7 (16)

Source: Table 10.1-2

**Table 12. Nonfatal serious adverse experiences**

Valsartan

Patient #	SAE	Date randomized	Date of onset	Outcome
106	Dyspnea NOS Asthenia	Oct. 21 1999	Oct. 24, 1999	Hospitalized.
113	Asthenia Hypotension	Jan. 22, 2000	Jan. 27, 2000	Study drug dosage adjusted/interrupted; hospitalized.
119	Basal cell carcinoma	Mar. 7, 2000	Apr. 20, 2000	Hospitalized.
122	Angina pectoris	Mar 12, 2000	May 28, 2000	Hospitalized/meds given.
137	Atrial fibrillation	April 19, 2000	Aug. 2, 2000	Study drug dosage adjusted/interrupted; hospitalized.
176	Chest pain NEC	May 31, 2000	June 3, 2000	Meds given/hospitalized.

Lisinopril

107	Hypotension NOS Influenza Blood creatinine increased Blood urea increased	Nov 20, 1999	Jan 3, 2000	Discontinued due to AE; hospitalized.
112	Atrial fibrillation	Jan 21, 2000	May 17, 2000	Meds

121	Diarrhea NOS Weight decreased	Mar 11, 2000	May 10, 2000	given/hospitalized. Discontinued due to AE; hospitalized.
163	Cough Dyspnea NOS Chest pain NEC Pleural effusion	May 19, 2000	June 16, 2000 June 16, 2000 Aug 30, 2000 Aug 30, 2000	Meds given/hospitalized.
174	Vomiting NOS	May 30, 2000	Aug 23, 2000	Meds given/hospitalized.

Source: 10.2-2

**Laboratory changes:**

In one valsartan and two lisinopril patients, the serum creatinine increased more than 50% from baseline or exceed 2 mg/dl throughout the trial. Otherwise, there appeared to be no clinically meaningful change in laboratory parameters in this trial.

**Vital signs:**

No clinically important changes in heart rate or body weight were noted.

As expected, there was a mean decrease of 11.2/7.4 mm Hg sitting BP for valsartan and a respective decrease of 11.8/7.6 mm Hg for lisinopril.

**Comments:**

This was an active control trial of valsartan and lisinopril, evaluating effects on parameters of heart rate variability. No significant differences were seen between the two treatment groups in terms of the primary efficacy variable, as well as secondary efficacy variables related to heart rate variability.

The only significant difference was seen in measurement of BARK-1.

**Conclusions:**

No significant differences were seen between valsartan and lisinopril regarding measurements of heart rate variability.

No significant differences were seen between valsartan and lisinopril regarding most neurohormone measurements (except for BARK-1).

**Findings from Other Sources:**

Valsartan is not currently approved in other countries for the treatment of CHF. Two drug-related spontaneous reports were noted in CHF patients on valsartan (tachycardia/diarrhea/flushing and pruritis/generalized rash). There was also a report in the literature of two instances of angioedema in one patient.

**Reviewer Comments:**

The safety profile as seen in the 120-day safety update, including study 109, appears to be consistent with the safety profile in the overall submission (NDA 20-665, S-016).

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MEDICAL OFFICER