



Questions

valsartan for heart failure

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiac and Renal Drugs Advisory Committee

The Cardio-Renal Advisory Committee is asked to give counsel regarding the use of valsartan for the treatment of chronic congestive heart failure. Pre-clinical pharmacology, biopharmaceutics, and chemistry present no barriers to its approval.

The development program randomized a total of 6,120 patients in 5 clinical trials. There were 2 studies of acute hemodynamics and 3 studies of clinical benefit. An effect on acute hemodynamics is not an appropriate basis for approval of a treatment for chronic heart failure. In ascending order of size, the studies of clinical benefit were:

- Study 110 (N=141) showed very little difference in 6-minute walking distance between valsartan and enalapril at 12 weeks.
- Study 106 (N=770) failed to distinguish valsartan from placebo for effects on primary end points of treadmill exercise tolerance and quality of life.
- Study 107 (Val-HeFT; N=5010) compared placebo to valsartan, titrated as tolerated to 160 mg b.i.d., given in a background of ACE inhibitors and beta-blockers, for two primary endpoints, (1) time-to-all cause mortality, and (2) time-to-first occurrence of (a) all cause mortality, (b) sudden death with resuscitation, (c) hospitalization for congestive heart failure, or (d) need for at least 4 hours of treatment with an intravenous inotropic or vasodilating agent for the treatment of congestive heart failure. In order to preserve an overall trial alpha ≤ 0.05 (2-sided), either of the primary endpoints needed to achieve a $p \leq 0.02532$ to deny the null hypothesis. The final analysis of mortality included all 5010 patients randomized and found no difference between the two groups ($p = 0.80$). For time-to-first occurrence of a mortal or morbid event, the hazard ratio was 0.87, and the corresponding p-value of 0.009 is less than the alpha value of 0.025.

- 1 Consider the exercise tolerance studies 110 and 106.
 - 1.1 In study 110, all subjects were on ACE inhibitor for at least 3 months prior to enrollment. Thus, subjects randomized to valsartan were withdrawn from ACE inhibitor. What is known about the time course for the loss of effects of an ACE inhibitor on exercise tolerance?
 - 1.2 In study 110, subjects walked 420 meters in 6 minutes at baseline. What degree of impairment does this represent?
 - 1.3 What is known about effects of valsartan and enalapril on exercise can be summarized as follows:

	Treadmill	6-minute
Enalapril vs. placebo	Improved	No data
Valsartan vs placebo	Unaffected	No data
Valsartan vs enalapril	No data	Similar

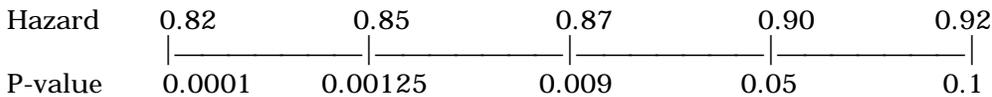
What is the effect of valsartan on exercise tolerance?

- 2 Ignoring Val-HeFT, ...
 - 2.1 ...what role do the 2 studies of hemodynamics and 2 studies of exercise ability and quality of life have in the case for approval?
 - Contribute to demonstration of clinical benefit?
 - Contribute to understanding of mechanism for clinical benefit?
 - Contribute to safety database?
 - 2.2 ...how important are these 4 studies in the case for approval?
 - Adequate, even without Val-HeFT?
 - Critically important?
 - Helpful?
 - Largely irrelevant?
 - Would have been better not having them?

3 Consider the components of the morbidity and mortality end point of Val-HeFT.

	Events	Hazard^a	P
All-cause mortality	979	1.02	0.80
CHF hospitalizations	812	0.73	<0.0001
Resuscitations	50	0.66	0.15
CHF therapy	15	0.87	0.79
^a Valsartan:placebo			

- 3.1 What role do each of the components have in the case for approval?
 - Contribute independently to demonstration of clinical benefit?
 - Contribute to understanding of mechanism for clinical benefit?
 - Undermine the case for approval?
 - 3.2 How do you reconcile large effects on CHF hospitalization with post-hoc analyses that show little or no effect on...
 - ... all-cause hospitalization or death?
 - ... number of days in hospital?
 - ... total days alive and out of the hospital?
- 4 If more Val-HeFT patients on valsartan had had events, the hazard ratio and the p-value would both have been larger. If fewer patients on valsartan had had events the hazard ratio and p-value would both have been smaller. The actual study result is in the middle of the scale below. If Val-HeFT had had no secondary end points other than components of its primary end point, but all other aspects of this development program were unchanged, what value for the hazard ratio would be necessary to conclude the development program was successful? Why do you pick the value you do?



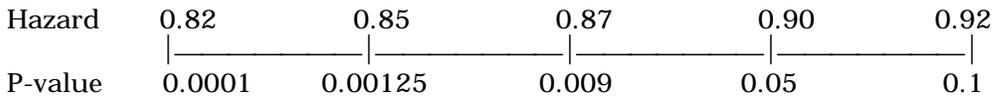
5 Consider other end points that were not individual components of the morbidity-mortality primary end point of Val-HeFT.

	Favors	P		Favors	P	
Cardiovascular mortality	Placebo	0.86	Signs & symptoms Paroxysmal nocturnal dyspnea Fatigue Edema Dyspnea at rest Dyspnea on effort Orthopnea Jugular venous distension Rales Third heart sound			
NYHA class	Valsart	0.001		Valsart	0.001	
Ejection fraction	Valsart	0.001		Valsart	0.010	
Left ventricular diastolic diameter	Valsart	0.0001		Valsart	0.003	
Quality of life questionnaire				Valsart	0.037	
	Overall	Valsart		0.004	Valsart	0.003
	Physical	Valsart		0.009	Valsart	0.2
	Emotional	Valsart		0.029	Valsart	0.001
				Valsart	0.001	
				Valsart	0.22	

What role do each of these secondary end points have in the case for approval?

- Contribute independently to demonstration of clinical benefit?
- Contribute to understanding of mechanism for clinical benefit?
- Undermine the case for approval?

6 If all other aspects of this development program were unchanged, including what you know about all of Val-HeFT's secondary end points, what value for the hazard ratio would be necessary to conclude the development program was successful? Why do you pick the value you do?



7 Consider the effects on mortality and morbidity end points by (non-randomized) use of ACE inhibitors and beta-blockers:

		Mortality ^a			Morbidity ^a		
		Beta-blocker			Beta-blocker		
		Yes	No	All	Yes	No	All
ACEI	Yes	1.09, 1.85	0.81, 1.11	0.93, 1.21	0.97, 1.45	0.73, 0.93	0.82, 1.03
	No	0.37, 1.74	0.28, 0.86	0.37, 0.91	0.26, 0.97	0.34, 0.81	0.35, 0.73
	All	1.05, 1.73	0.79, 1.06		0.91, 1.33	0.71, 0.90	

^a95% confidence limits for hazard ratio (valsartan : placebo)

With which of the following hypotheses are these data most consistent?

- Valsartan is an effective treatment added to ACE inhibitor and beta-blocker.
- Valsartan is an effective treatment as an alternative to ACE inhibitor or beta-blocker.

8 Evaluate the following findings with respect to whether they are considerations related to approval, or to labeling:

- The lack of apparent treatment effect in Blacks.
- The very small apparent treatment effect in patients taking ACE inhibitors.
- The lack of apparent treatment effect in patients taking beta-blockers.

9 Has adequate information been obtained to describe instructions for the use of valsartan in heart failure?

- 10 Should valsartan be approved for use in the treatment of patients with chronic congestive heart failure? If so, what should labeling say about ...
 - 10.1 ... patients also receiving ACE inhibitors?
 - Alternative to ACE inhibitor.
 - Second-line to ACE inhibitor.
 - 10.2 ... patients also receiving beta-blockers?
 - Alternative to beta-blocker.
 - Second-line to beta-blocker.
 - 10.3 ... use in Blacks?
 - 10.4 ... any other issues?