



# **DRAFT**

## **Questions**

Hvdralazine /ISDN

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

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The Advisory Committee is asked to opine on whether the A-HeFT study supports a claim that BiDil (hydralazine plus isorbide dinitrate) improves outcome in patients with heart failure.

1. By the sponsor's and the statistical reviewer's intent-to-treat analyses, BiDil was associated with an improved composite risk score ( $p=0.021$  by the reviewer). However, the sponsor's pre-specified per-protocol analysis is not significant ( $p=0.46$ ).
  - 1.1. Why are these results so discrepant?
  - 1.2. Why were 60% of subjects excluded from the pre-specified per-protocol analysis?
2. Subjects enrolled prior to the second interim analysis, when sample size was re-estimated, comprised 30% of the total patients and 42% of the events, and they showed a nominal 7% lower risk of death on BiDil. Subjects enrolled after the second interim analysis had a nominal 62% lower risk of death on BiDil. Why do you think that was?
3. Ordinarily, one expects to understand the role of each component in a combination product, and one does not in this case.
  - 3.1. How important would that be...
    - 3.1.1. ...if you believed there was an effect on mortality?
    - 3.1.2. ...if you believed there was only an effect on hospitalization?
    - 3.1.3. ...if you believed there was only an effect on symptoms?
    - 3.1.4. ...if there had been more than two active ingredients?
    - 3.1.5. ...if you suspected one component is subject to tolerance effects?
  - 3.2. What is the evidence that both components of BiDil have hemodynamic effects when used together...
    - 3.2.1. ...short-term?
    - 3.2.2. ...long-term?
4. Ordinarily, one expects to know something about the effect of dose, and one does not in this case, for either component.
  - 4.1. How does the importance of information on dose change...
    - 4.1.1. ...with the end point?
    - 4.1.2. ...with the number of active ingredients?
  - 4.2. What instructions do you give for patients who do not tolerate one component?

5. A-HeFT enrolled only the subgroup in which BiDil appeared to work in V-HeFT I. The strength of evidence is fairly strong that BiDil works in that subgroup. How strong is the evidence that BiDil does not work in the subgroup excluded from A-HeFT?
6. Subjects randomized to BiDil had lower blood pressure than those randomized to placebo.
  - 6.1. Is this a plausible explanation for the differences in outcome?
  - 6.2. What should labeling say about observed differences in blood pressure?
7. In A-HeFT, the difference in time to first hospitalization for heart failure was large and statistically significant, while the difference in total days in hospital for heart failure or for other cardiovascular causes was small and statistically insignificant.
  - 7.1. For patients with heart failure, is time to (next) hospitalization a measure of overall hospitalization?
  - 7.2. Is postponing hospitalization a clinical benefit if one does not also shorten the total duration of hospitalization?
8. Should BiDil be approved for the treatment of heart failure? If so, ...
  - 8.1. ...what are the benefits of treatment?
  - 8.2. ...to what NYHA Classes do these benefits apply?
  - 8.3. ...in whom should it be indicated?
  - 8.4. ...what advice should be given to patients who are intolerant...
    - 8.4.1. ...because of headache?
    - 8.4.2. ...because of hypotension?