



# Questions

treprostinil  
9 August 2001

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

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The Cardio-Renal Advisory Committee is asked to opine on the benefits and risks of treprostinil, a putative prostacyclin analog, for the treatment of pulmonary hypertension. Reviews of pharmacology, biopharmaceutics, and chemistry present no apparent barriers to its approval.

The Committee is asked if the available data demonstrate clinical benefit and whether the drug merits a role in the treatment of pulmonary hypertension.

1. The two principal effectiveness studies assessed 6-minute walking distance and demonstrated effects favoring treprostinil with p-values of 0.061 and 0.055 individually, and 0.006 pooled. The prospective analysis plan defined a successful program as either both studies with  $p < 0.049$  or one study with  $p < 0.049$  and the pooled  $p < 0.010$ .
  - 1.1 How, if at all, did the following factors make it difficult to show a drug effect?
    - High withdrawal rate?
    - Asymmetrical withdrawal rate?
    - High inter-subject or intra-subject variability?
    - Small effect size?
    - Large placebo effect?
    - Choice of population?
    - Choice of primary end point?
    - Dose too low?
    - Tolerance to study drug?
    - Confounding concurrent medication?
    - Incorrect premise that dyspnea limits exercise?
    - Others?
  - 1.2 How, if at all, did the following exaggerate the apparent drug effect?
    - Withdrawals for progression of symptoms?
    - Rules for imputation of missing data?
    - Others?
  - 1.3 The prospective analysis plan included rules for handling the data from subjects who withdrew prior to the final assessment. Other rules were explored by the sponsor and by the reviewers. Was the prospective rule...
    - 1.3.1 ... the best way to assess effect size?
    - 1.3.2 ... appropriately conservative?
  - 1.4 If these were the only available data, would this result have been "close enough" to have represented substantial evidence of effectiveness? If so, what should have been the prospective standard for a two-study development program?

- 1.5 Six-minute walk was the primary end point in these studies, but there were other measures of clinical benefit. Is it methodologically sound to consider those results in deciding if the development program was successful in distinguishing drug from placebo? If it is reasonable to use secondary end points this way, ...
  - 1.5.1 ... how "close" to winning on the primary end point do you need be to consider other factors?
  - 1.5.2 ... specify an algorithm for the interpretation of secondary end points, taking into account ...
    - ... multiplicity,
    - ... neutral findings, and
    - ... findings indicative of harm?
  - 1.5.3 ... do the effects of treprostinil on the following parameters make a compelling case for benefit:
    - Mortality?
    - Hospitalization?
    - Disease progression?
    - Need for other drugs?
    - Composite or individual assessments of 16 signs and symptoms of pulmonary hypertension?
    - Composite or component scores of the dyspnea fatigue index?
    - Borg dyspnea index?
    - Composite or component scores of Minnesota Living with Heart Failure questionnaire?
    - Hemodynamics?
- 1.6 Do formal retrospective analyses of combinations of the selected primary and secondary end points further support the effectiveness of treprostinil? If so, ...
  - 1.6.1 ... did such an analysis give appropriate weight to its components?
  - 1.6.2 ... how many such analyses were there or were possible?
- 1.7 Considering all pertinent data, is treprostinil an effective treatment for primary pulmonary hypertension?
- 1.8 Over what period of administration are the benefits of treprostinil manifest?
- 1.9 Over what dose range are the benefits of treprostinil manifest?
2. The dose of treprostinil rose steadily during treatment.
  - 2.1 Was this because of ...
    - 2.1.1 ... forced titration?
    - 2.1.2 ... disease progression?
    - 2.1.3 ... changing pharmacokinetics?
    - 2.1.4 ... tolerance to adverse effects of treprostinil?
    - 2.1.5 ... tolerance to beneficial effects of treprostinil?
  - 2.2 Is the rising dose observation an approval issue?
  - 2.3 If treprostinil were approved, how should the label describe how to dose?
3. Infusion-site pain was a problem, often requiring management with opioids.
  - 3.1 Are the long-term data reassuring?
  - 3.2 Is the pain management problem an approval issue?
  - 3.3 If treprostinil were approved, how should the label describe this?
4. Subjects whose disease progressed despite randomized treatment went on to receive another drug. Is it known that the benefits of the follow-on therapy are manifest after treatment with treprostinil?
5. Should treprostinil be approved for the treatment of pulmonary hypertension?