Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, MD

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting for June 16, 2005.

On June 16, 2005, the committee discussed new drug application (NDA) 20-727, proposed trade name BiDil™ (hydralazine hydrochloride/isosorbide dinitrate) Tablets, (37.5 mg hydralazine hydrochloride/20 mg isosorbide dinitrate), NitroMed, Inc., proposed for the indication of heart failure, based on the results from the African American Heart Failure Trial (A-HeFT).

These summary minutes for the June 16, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on June 27, 2005.

I certify that I attended the June 16, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

_____//S//_____
Steven E. Nissen, M.D.
Chair

Quick Minutes
Cardiovascular and Renal Drugs Advisory Committee Meeting
June 16, 2005

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder05.html#cardiovascularRenal.
Slides of the meeting will be available at least 2 days after the meeting.
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
Steven Nissen, MD (Committee Chair)
Susanna Cunningham, PhD
William Hiatt, MD
Frederick Kaskel MD, PhD
Ronald Portman, MD
John Teerlink, MD

Cardiovascular and Renal Drugs Advisory Committee Consultants (voting):
Jonathan Sackner-Bernstein, MD
Thomas Fleming, PhD
Vera Ota Wang, PhD

Patient Representative (voting):
Robert J. Samuels

Anesthetic and Life Support Drugs Advisory Committee Member, Industry Representative (non-voting)
Charles H. McLeskey, MD

Cardio-Renal Advisory Committee Members Absent:
Beverly Lorell, MD
David Demets, PhD
Lynn L. Warner Stevenson, MD
John F. Neylan, MD (IR)
Blasé Carabello, MD
Thomas Pickering, MD, DPhil

FDA Participants:
Robert Temple, MD
Norman Stockbridge, MD

Executive Secretary:
Cathy A. Groupe, RN, BSN

Open Public Hearing Speakers:

Congresswoman Donna M. Christensen, MD
Chair, Congressional Black Caucus

Gary A. Puckrein, PhD
Minority Health Month Foundation

B. Waine Kong, JD, PhD
CEO, American Association of Black Cardiologists

Debra Lee
Patient – AHeFT Trial

Shomarka Keita, MD, PhD

Jonathan Kahn, JD, PhD
Assistant Professor, Hamline University School of Law

Charles L. Curry, MD, FACC, FACP
International Society of Hypertension in Blacks

Basil Halliday, MSc
BDH Clinical Research Services

Charles N. Rotimi, PhD
National Human Genome Center, Howard University

Charmaine Royal, PhD
National Human Genome Center, Howard University

Olivia Carter-Pokras, PhD/Kendrick Gwynn
University of Maryland School of Medicine

Lucille C. Norville Perez, MD
Health Director, National Association for the Advancement of Colored People

Diana Wells
Patient – AHeFT Trial

Quick Minutes
Cardiovascular and Renal Drugs Advisory Committee Meeting
June 16, 2005

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 16, 2005, at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsor.
The meeting was called to order by Steven Nissen, M.D. (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 250 persons in attendance. There were 13 speakers for the Open Public Hearing sessions.

Issue: The Committee is asked to opine on whether V-HeFT I, V-HeFT II, and A-HeFT adequately support a claim that BiDil® (hydralazine plus isorbide dinitrate) improves outcome in patients with heart failure. The Advisory Committee previously reviewed V-HeFT I and II as a possible basis for use of BiDil in the treatment of heart failure.

The agenda was as follows:

Call to Order and Introductions	Steven E. Nissen, M.D. (Chair)
Conflict of Interest Statement	**LT Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Welcome and Comments	**Norman Stockbridge, M.D., Ph.D. (Acting) Director** Division of Cardiovascular and Renal Drug Products
Sponsor Presentation	
BiDil® (isosorbide dinitrate/ hydralazine HCl): Regulatory Background and Introductions	**Manual Worcel, M.D.** Chief Medical Officer NitroMed, Inc.
V-HeFT I and V-HeFT II Trials: The Path to A-HeFT	**Jay N. Cohn, M.D.** Professor University of Minnesota
A-HeFT: Design and Study Population	**Anne Taylor, M.D.** Professor University of Minnesota
A-HeFT: Outcomes	Clyde Yancy, M.D. Professor University of Texas Southwestern Medical School
Conclusions: From V-HeFT I To A-HeFT	Milton Packer, M.D. Professor University of Texas Southwestern Medical School
Questions and Answers	**Michael Sabolinski, M.D.** Senior Vice President of Clinical Development and Regulatory Affairs NitroMed, Inc.

Questions to the Committee: Of the four questions brought before the committee, only **Question 4** required a vote, as directed by the Agency, along with any additional considerations the committee had on subparts 4.1 and 4.2. All other questions and subparts were discussed amongst committee members. A few key points that were identified are provided below. For a complete review of the discussion, however, please see the transcripts.

1. Claims based on A-HeFT
   1.1. The primary end point was a composite of all-cause mortality, hospitalizations for heart failure, and response to the Minnesota Living with Heart Failure questionnaire. 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).
      1.1.1. Why are these results so discrepant?
      1.1.2. Why were 60% of subjects excluded from the pre-specified per-protocol analysis?

   The committee discussed this discrepancy, specifically the per protocol analysis exclusion of 60% of the intent-to-treat (ITT) population, as earlier discussed by NitroMed, which clearly confirmed that these exclusions were not at random. In general, the ITT analysis is thought to be less biased, but, in this case, most of the exclusions had to do with the early termination of the study, not likely to favor one treatment group. The ITT analysis better used the available data by imputing with last observation carried forward, so, even though this was not the primary analysis, everyone agreed it was more sensible. Questions were raised as to the validity of such analysis, under these conditions, leaving the per protocol analysis uninterpretable with very little power. The committee added that, especially from a clinician standpoint, the intent-to-treat analysis is more valuable and is the one that should be used. ***(See transcripts for detailed discussion)***

   1.2. 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. How troubling is that difference? How comforted are you by…
      1.2.1. …more continuous analyses of mortality by time in study?
      1.2.2. …analyses of CHF hospitalization among early and late enrollees?

   The committee discussed decisions made by the Data Safety Monitoring Board [DSMB], during various meetings throughout the course of the study, and unblinding decisions made during the adjustment of samples sizes. Members felt that, essentially, there is considerable risk of interpreting statistical strength of evidence when the data is used, part way through the course of the trial, to refine the hypothesis and questions were raised about the percentage of weights given to different portions of the sample sizes. Concern was also raised about the potential bias of the DSMB during the various unblinding looks at the data, and the decision to stop the trial prematurely. Prejudgment of early results that may occur threatened to impact the integrity of the trial.

   Recognition was given for the fact that very few trials have been done in a solely African American population and considerations, such as these, should be recognized, specifically the challenges that presented to the sponsor, in enrolling an adequate sample of this population. Compromises such as those in question, while impacting the strength of evidence, may need to be made, in light of the exigency of doing such a trial in a small population, with a small company with limited resources. Other committee participants disagreed, citing concern about lowering the bar on strength of evidence minority. The committee consultant Patient Representative provided an additional patient perspective of the advantages that such a trial provided to the African American population and the possible need for the adjustments cited in the discussion, in this population, while appreciating the in depth statistical analysis being considered. ***(See transcripts for detailed discussion).***

   1.3. 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.

1.3.1. For patients with heart failure, is time to (next) hospitalization a measure of overall hospitalization?

1.3.2. Is postponing hospitalization a clinical benefit if one does not also shorten the total duration of hospitalization?

The chair along with the Agency, agreed that these issues were addressed adequately by the sponsor, during earlier discussions. ***(See transcripts for detailed discussion)***

1.4. Interpretation of the quality of life data is rendered difficult because of the early termination of the study. How persuasive is the retrospective analysis with last observation carried forward?

There was discussion about how important this data was, although including this in the composite endpoint may not have been the wisest choice, as opposed to making it a secondary endpoint. The robustness of the data is clearly harmed by early termination, citing concerns about the exact circumstances under which termination was decided. Members commented that early termination takes away important endpoints, although important point estimates were identified in the 6 month, 12 month, 18 month time points, which were very helpful. However, there was concern about using a single point in time, to make this assessment. A committee suggestion was made to use heart failure hospitalization free survival, as an additional endpoint.

Additional comments included concerns about reviewing a therapy based on biological differences between blacks and non-blacks, while there is more physiology known about the difference between men and women, yet little data was collected when being treated with this drug. ***(See transcripts for detailed discussion)***

2. Policy issues

2.1. Ordinarily, one expects to understand the role of each component in a combination product, as noted in 21 CFR 300.5.

2.1.1. How important would that be…

2.1.1.1. …if you believed there was an effect on mortality?

2.1.1.2. …if you believed there was only an effect on hospitalization?

2.1.1.3. …if you believed there was only an effect on symptoms?

2.1.1.4. …if there had been more than two active ingredients?

2.1.1.5. …if you suspected one component is subject to tolerance effects?

The committee agreed that it is difficult to understand what all of the components are contributing, although some conclusions can be drawn regarding toxicity (drug-induced lupus development) as it relates to hydralazine. While recognizing that all the components are not clearly understood, it was identified that the clinician threshold of worry may be decreased, given this situation presents non-fatal side effects to a fatal disease (congestive heart failure). It was pointed out that historical data regarding safety and efficacy for these components does exist and could be considered.

There was discussion about Agency challenges with 21 CFR 300.5, when considering applications with 3-5 combination drugs and the obligation to work up each single drug versus waiting for something to happen.

The committee seemed satisfied that, while additional post marketing surveillance into the role of the components is important, if a combination drug, such as this, creates a significant benefit, there is more willingness to accept the data. If there is a reasonable basis for combining agents, then we should use a case-by-case assessment to make a decision. ***(See transcripts for detailed discussion).***

2.1.2. What is the evidence that both components of BiDil have hemodynamic effects when used together…

2.1.2.1. …short-term?

2.1.2.2. …long-term?

The committee had limited discussion on this issue, given hemodynamic effects are not the basis for approval. There was additional discussion of the pathophysiological differences that these drugs have on the arterial versus venous systems and the rationale for the combination effect. *(See transcripts for detailed discussion).*

2.1.3. What instructions do you give for patients who do not tolerate one component of BiDil?
The committee discussed the challenge in determining, with few exceptions, which component caused certain effects and had limited advice on labeling, in terms of these instructions, given the trial utilized a 'fixed dose' combination. *(See transcripts for detailed discussion).*

2.2. Ordinarily, one expects to know something about the effect of dose, and one does not in this case, for either component.
2.2.1. How does the importance of information on dose change…
2.2.1.1. …with the end point?
2.2.1.2. …with the number of active ingredients?
The committee agreed on the importance of dose information, while recognizing, it is wonderful to have but sometimes, unfortunate if you do not. They cited similar examples of this challenge, specifically in current heart failure drugs, stating, it is a confounder physicians have to deal with every day. The committee agreed that this challenge increases as the number of components added increase. *(See transcripts for detailed discussion).*

2.3. Subjects randomized to BiDil had lower blood pressure than those randomized to placebo.
2.3.1. Is this a plausible explanation for the differences in outcome?
2.3.2. What should labeling say about observed differences in blood pressure?
The committee discussed the obvious dissociation of lowering blood pressure and the effects on heart failure – although there are some differences, how much is the anti-hypertensive is uncertain? This question is difficult to answer definitively. There was further discussion on the hydralazine effect on cardiac output and systemic vascular resistance. *(See transcripts for detailed discussion)*

3. Population
3.1. A-HeFT enrolled only the subgroup in which BiDil appeared to work in V-HeFT I and II, namely self-identified African-Americans. How strong is the evidence that BiDil does not work in patients excluded from A-HeFT? If it were approved, what should labeling say about…
3.1.1. …excluded subgroups?
3.1.2. …the underlying genetic or cultural bases for the observed differences?
Committee discussion recognized important points identified by many Open Public Hearing speakers, that the black population in the U.S. is heterogeneous. It is unclear whether these differences are genetic, social, economic or health delivery-related. The Agency was applauded for their request for this study in the African American population. Many committee members agreed that labeling should include information about the study being done in an African American population.

There was some committee disagreement about generalities that can be made, across all populations, based on the results of A-HeFT, citing the importance of looking for evidence of effectiveness during the drug approval process, along with the population for which the drug will benefit. Members expressed that, when the evidence of effectiveness comes from a population that we can define, albeit self-identified race, it is significant. There was some discussion about the future of the genomic-based medicine and the hopeful science that this era will bring, along with compromising self-identified race utilization, as a surrogate for genomic-based medicine.

Discussions cited that there is additional information about the white population, through V-HeFT I and II, and illustrates quite a different response between the two groups (white and black population). Some members were less impressed by that data, given the timeframe of the V-HeFT

trials was 20 years ago. From a statistical standpoint, there was discussion about the unfavorable results in the white population in V-HeFT, coupled with proactive exclusion of whites in A-HeFT, leading to the reasonable conclusion that there was less benefit to risk in this population. *(See transcripts for detailed discussion).*

3.2. Bearing in mind experience in V-HeFT I and II, to what NYHA classes do the benefits of BiDil apply?
3.3. Are there other population-specific differences apparent?
There is considerable agreement amongst committee members, that A-HeFT included a more advanced disease patient population. There was consensus that benefits associated with BiDil apply to the NYHA Class 3.

Additional discussion on other population-specific differences included comments about the lack of studies in African American women, again citing gender as a known and recognized biological factor, as opposed to self-identified race. *(See transcripts for detailed discussion).*

4. Should BiDil be approved for the treatment of heart failure? If so, ...
4.1. …what should labeling say about concomitant therapy to be used with BiDil?
4.2. … what advice should be given to patients who are intolerant of BiDil?
The Agency requested that the committee vote on Question #4, with additional comments encouraged, in response to Subparts 4.1 and 4.2.
The committee voted unanimously
9 yes
0 no
in favor of BiDil's approval for the treatment of heart failure.
One of the nine voting committee participants added that BiDil's approval should extend to the general population. A second member expressed concern about labeling that specified this subgroup without persuasive evidence about the self-designation of race and the challenges that exist in defining the heterogeneity among this population.

Other members were not as conflicted about the differentiation of this subgroup, in approval of the drug, citing the disproportionate population of African Americans with heart failure and the challenges of clinical trials with this subgroup. Other comments included the necessity of effective treatment in the black population, in light of disparities in healthcare, challenges in representation of ethnic groups.

There was additional discussion about the persuasiveness of A-HeFT, from a statistical standpoint, with general agreement about the limitations of interpreting the individual components (heart failure hospitalizations, quality of life and mortality). Despite these concerns, however, from a single trial perspective, the committee felt that primary endpoints were favorable.

Further recommendations from the committee included encouragement for the Agency to emphasize, in labeling, the self-identification of black patients, along with the trial being done in the context of ace inhibitors and beta blockers, in order to clearly provide directives that treatment should be 'an adjunct to standard therapy.' *(See transcripts for detailed discussion).*

Due to his early departure from the meeting, and subsequent limited participation in the complete afternoon discussion, committee member Dr. Frederick Kaskel was excluded from vote inclusion in this question.

The meeting adjourned at 5:00 PM.

See transcript for detailed discussion