Trends-in-Medicine

June 2005
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Quick Pulse

Trends-in-Medicine
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FDA's CardioRenal Advisory Committee Recommends Approval of NitroMed's BiDil

Gaithersburg, MD
June 16, 2005

The first race-based medication could get FDA approval before the end of June 2005. The FDA's CardioRenal Advisory committee voted unanimously on June 16, 2005, to recommend approval, and the FDA action (PDUFA) date is June 23, 2005.

The committee chair, Dr. Steven Nissen, a cardiologist with the Cleveland Clinic, called this a precedent-setting vote, but FDA officials had a more moderate view. Dr. Robert Temple, who is Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation (CDER), and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology, and cardiac drugs), said, "It is the first drug targeted at a specific race that we know…I think, personally, that (approval in blacks) is reasonable because we have a pretty good idea it doesn't work in the rest of the population (whites)."

NitroMed is seeking to market BiDil "for the treatment of heart failure as an adjunct to standard therapy in black patients to improve survival, prolong time to hospitalization for heart failure, and improve quality of life." The CardioRenal Advisory Committee suggested it be approved for a slightly different indication: ***For the treatment of heart failure in African-Americans with NYHA Class III heart failure as add-on therapy (not monotherapy).***

The panel made five key recommendations about BiDil:

1. **Approval.** The panel voted 9 to 0 in favor of approval.
2. **Race.** The panel recommended 7-2 that BiDil be labeled specifically for African-Americans only – the group of patients in which it was studied. Dr. Temple strongly suggested that this was what the FDA will do.
3. **NYHA Class.** The committee also recommended BiDil be indicated only for NYHA Class III patients. These are heart failure patients who experience symptoms with ***any*** exercise. Dr. Temple said, "They (the panel) pretty much said that the studied population is to whom it should be approved – very severe, symptomatic patients."

   Will the FDA follow this recommendation? Dr. Temple said, "We have to decide. I said (during the panel discussion) that maybe we shouldn't be so restrictive, but they (the panel) said that they wanted it in Class III – not just symptomatic patients which covers all (NYHA) classes. They (the panel) were not persuaded by my arguments to broaden it." This strongly suggests that the final label will say NYHA Class III.

4. **Add-on therapy.** The panel wanted BiDil used as an add-on therapy on top of an ACE inhibitor, diuretic, and perhaps a beta blocker, but not alone – because, again, that was the way it was studied.

5. **Mortality label.** It remains a question whether BiDil will get a mortality claim. Dr. Temple said, "The (mortality) finding is statistically strong. There was a large mortality effect. Even Tom (Dr. Tom Fleming, the biostatistician) found the database pretty strong…We will think about the panel comments and decide…We have a lot of freedom on this."

BiDil is a fixed combination of two generic drugs:

- Isosorbide dinitrate (ISDN) 20 mg
- Hydralazine hydrochloride (HYD) 37.5 mg

In 1997, the FDA issued a not-approvable letter for BiDil to treat heart failure in the general population. The company claims the FDA informed it in 2001 that a positive study in black patients (A-HeFT) would be the basis for approval of BiDil in black patients. In 2004, the A-HeFT trial was stopped for benefit, following the recommendation of the Data Safety Monitoring Board (DSMB) and the Steering Committee .

A NitroMed official and Dr. Jay Cohn of the University of Minnesota outlined the results of the V-HeFT-I and –II trials, which were the basis for the pivotal A-HeFT trial.

V-HeFT Results

Endpoint	Placebo	Prazosin	Hydralazine 75 mg QID + isosorbide dinitrate 40 mg QID
V-HeFT-I			
Survival in all patients	25.6% (p=.053)	49.7% (p=.441)	38.7% (p=.093)
Survival in all patients at 2 years	34.3%	N/A	25.6% (p=.053)
Survival in black patients * (n=128)	---	---	47% risk reduction (p=.04)
Survival in white patients (n=324)	---	---	12% risk reduction (p=.47)
V-HeFT-II			
	No placebo	**Enalapril**	**ISDN/HYD**
Survival in all patients	---	32.8%	38.2% (p=.083)
Survival in all patients at 2 years	---	18%	25% (p=.016)
Survival in black patients * (n=215)	---	---	1% increased risk (p=.96)
Survival in white patients (n=542)	---	---	39% increased risk (p=.02)

* based on self-designated race

NitroMed's Presentation

NitroMed is seeking approval of BiDil based on three clinical trials:

- **V-HeFT-I**, a trial conducted from 1980-1985 in 642 men, which found:
  - 22% lower risk of death overall (p=.09).
  - 12% lower risk of death in white patients (p=.47).
  - 47% lower risk of death in black patients (p=.04).
- **V-HeFT-II**, a trial from 1986-1991 in 804 men, which found:
  - 23% lower mortality overall (p=.08).
  - 39% lower mortality in white patients (p=.02).
  - No difference in mortality in blacks.
- **A-HeFT**, a trial from 2001-2004 in 1,050 black men and women, which found BiDil:
  - Increased survival by 43%.
  - Decreased hospitalization for heart failure.
    - √ Risk for first hospitalization reduced by 39%.
    - √ Number of hospitalizations reduced by 31%.
    - √ Days in the hospital decreased by 42%.
  - Improved quality of life.
  - Had a favorable safety profile for the proposed use.

Dr. Ann Taylor, co-principal investigator in A-HeFT, reviewed the design of the pivotal, six-month, 1,050-patient, Phase III A-HeFT trial in African-Americans with NYHA Class III-IV heart failure who were on standard heart failure therapy. The primary endpoint was the composite of all-cause mortality, first heart failure hospitalization, and change in quality of life at six months (vs. baseline). Secondary endpoints were death from any cause, heart failure hospitalization, and change from baseline in overall quality of life at each time point.

Scoring System for A-HeFT Primary Composite Endpoint

Endpoint	Score
Death (at any time during trial)	-3
Survival to end of trial	0
First hospitalization for heart failure	-1
No hospitalization	0
Change in Quality of Life at 6 months (or at last measurement if earlier than 6 months)	
Improvement by ≥10 units	+2
Improvement by 5-9 units	+1
Change by <5 units	0
Worsening by 5-9 units	-1
Worsening by ≥10 units	-2
Possible Score	**-6 to +2**

18-Month A-HeFT Efficacy Results

Endpoint	BiDil n=518	Placebo n=532	p-value
Primary endpoint			
Primary composite score	-0.1	-0.5	0.016
Composite score with no hospitalization imputed	-.14	-.45	0.14
Composite score with last known QOL measure used	+.03	-.36	0.005
Composite score based on patients randomized prior to April 2004	-.18	-.52	0.15
Components of the primary composite score			
Death from any cause	6.2%	10.2%	0.012
First hospitalization for heart failure	16.4%	24.4%	<0.001
Mean time in hospital for heart failure	13.7 days	15.3 days	0.539
Mean number of hospitalizations per patient	0.3	0.5	0.002
Mean number of days in hospital for heart failure per patient	2.3 days	3.8 days	0.002
All hospitalizations	39.0% (202 days)	41.5% (221 days)	0.41
Hospitalizations for other cardiac causes	15.4% (80 days)	15.9% (90 days)	0.55
Hospitalizations for non-cardiac reasons	21.0%	22.0%	0.75
Marked improvement in quality of life score at 6 months relative to baseline:	38.1%	33.4%	---
Marked worsening in quality of life score at 6 months relative to baseline:	16.9%	23.5%	---
Change in quality of life by ITT (lower is better)	-7.1	-3.1	0.011
Change in quality of life by LOCF	-7.6	-3.4	0.0030
Change in systolic blood pressure	-1.0 mmHg	+1.2 mmHg	0.002
Change in diastolic blood pressure	-2.4 mmHg	+0.9 mmHg	0.001

A-HeFT Adverse Events

Endpoint	BiDil n=518	Placebo n=532	p-value
Adverse events			
Exacerbations of CHF	9.5%	15.2%	0.006
Headache	49.5%	21.1%	<0.0001
Dizziness	31.9%	13.7%	<0.0001
Hypotension	7.9%	4.4%	<0.05
Sinusitis	4.3%	1.7%	<0.05
Serious adverse events			
≥1 serious adverse event	35.0%	34.7%	---
Chest pain	6.4%	5.5%	---
Heart failure exacerbations	3.1%	7.8%	≤0.001
Severe exacerbations of CHF	1.5%	2.5%	---
Discontinuations			
Due to adverse events	21.0%	11.8%	---
Discontinued up to 30 days before event	5.6%	8.8%	---

A member of the DSMB explained in detail the history of the DSMB's consideration of the A-HeFT data and its decision to recommend the trial be stopped for efficacy, even though the efficacy was in a secondary endpoint (all-cause mortality), not the primary endpoint. He said, "Most monitoring committees have guidelines, and you learn they are not always sufficient…You have to be flexible and use common sense." The panel chair agreed that mortality trumps everything, "Common sense tells you that even though mortality is not the primary endpoint, when you see something very strong on mortality, there is an ethical and moral responsibility to make a decision on that…and I completely understand their thinking about that."

Panel Discussion and Questions for NitroMed Officials and Experts

V-HeFT trials

The panel had a lot of questions about the V-HeFT trials, with several panel members characterizing these as Phase II trials that were hypothesis-generating. A panel member said, "My sense is that the V-HeFT trials essentially are hypothesis-generating…and I would love to see two trials…These results have to be highly statistically persuasive since it is a single trial." The FDA's Dr. Robert Temple added, "Hypothesis-generating is not quite right…Those trials (V-HeFT) don't make the case and do suggest perhaps a racial difference…but one implication – and we conspired in this – is that an additional persuasive single trial would do the job…So you are not starting from zero; you are starting part-way there."

Among the key things the panel wanted to know and points they made during the discussion of the V-HeFT trials were:

- **Is there a gene that can explain the differential response in blacks and whites?** Dr. Cohn explained, "The working hypothesis has been that there is evidence for reduced nitric oxide bioactivity in African-American populations, on average, compared to white populations, and that data have been generated in several labs over the past decade. It does appear black people, for reasons we don't know, exhibit, on average, a less robust response to this released nitric oxide (NO)…and that provides the physiologic underpinnings for why we might have expected some differential response to BiDil, which is an NO-enhancing therapy. We believe its action is mediated by NO, which is released by ISDN and preserved by the antioxidant properties of HYD…but the identification of the differential response really came from the mortality data."

➢ **Why was there only one trial, and not two as is usually the case?** Dr. Cohn quipped, "Ask the FDA…They accepted that (V-HeFT-I and –II) as one study for efficacy…in the overall population. We have very little power in subgroups to look at other endpoints. The agency did claim that another mortality trial...another outcome trial would be adequate for registration."

➢ **What are the data on time to first hospitalization, which was an endpoint in the V-HeFT trials?** Dr. Cohn said, "There was a clear trend for delay in V-HeFT-I vs. placebo, and in V-HeFT-II they (Kaplan-Meier curves) are superimposed. We know from other trials that ACE inhibitors do delay hospitalization…so this would support non-inferiority to ACE inhibitors, but there is little statistical power…In blacks, once again, the trend is in favor of ISDN/HYD, with ISDN/HYD more favorable to placebo in V-HeFT-I and to enalapril in V-HeFT-II…It was not statistically significant because of the small sample size, but the trend is in the right direction." The biostatistician on the panel, Dr. Tom Fleming, pointed out that the hospitalization curves showed less dramatic results in the documents in the panel's briefing book than those shown by the company at the meeting.

➢ **Several factors confound the V-HeFT data.** Panel member and company speakers agreed that disease management strategies and reporting procedures (timing and lack of central process) for hospitalizations have changed since the V-HeFT trials were conducted, and this is an ad-hoc analysis.

➢ **Longer-term trial data is less impressive.** A panel member commented, "The data suggest much more interaction by race…and the data should not be looked at just at 1-2 years. The results over a longer period of time are less impressive."

A-HeFT results

Among the key things the panel wanted to know and points they made during the discussion of the A-HeFT trial were:

➢ **Biological markers.** Panel members asked for data on biological markers, but a NitroMed official said the analysis of those (BNP, etc.) is not complete yet. Dr. Fleming (the panel's biostatistician) said, "I would expect much greater sensitivity on biomarkers…and when (the FDA) staff says those are not significant, that sends up a red flag."

➢ **Supporting data.** Dr. Fleming said what will be important to his final decision on BiDil is the strength of the data on things other than mortality."

➢ **Statistical methods in the quality of life analysis.** Questions were raised about whether NitroMed changed the statistical analysis methods after it knew the DSMB was stopping the trial, but a NitroMed official flatly denied that. There was a concern with missing data on quality of life.

- Dr. Fleming said, "We have 81 patients missing…and that is a lot…and it looks like one-third are not fully assessed at six months…Any time that happens there are significant risks of complications in interpreting the results."
- A NitroMed official said, "Many patients didn't make it to six months because of early stopping of the trial."
- Dr. Nissen said he would rather see an area under the curve analysis of quality of life than a single time point.
- The FDA's Dr. Temple said, "I'm sure the six months represented some attempt to be persuasive that it was long enough to matter but not so long that too many patients dropped out. We (FDA) tend to be inclined to believe in the one (time point) that, for better or worse, we picked."

➢ **Quality of life data.** Despite the concerns with the statistical method, Dr. Nissen was reassured by the trends across the time points. He said, "What reassures me is there are consistent differences regardless of p-values…The bar for BiDil is better than for placebo."

➢ **Components of each drug.** Normally, a sponsor who wants to get approval for a combination product must do a trial that compares the combination to each individual component as well as placebo. Dr. Temple explained why that has not been required for BiDil: "We have grappled with this over the years…and we are working on a new combination policy rule…But we worry about data that makes us uncomfortable, at the least, to explore which of the two components makes the contribution (in this case). You would have to do a trial to find out on which drug patients die, but do you really want to tell people they have to do a study in which you will discover which component saves lives by showing that people who don't get one component die more frequently? …We think we have to be reasonable. This (thinking) doesn't apply to a minor symptomatic benefit, but if the event is major, you have to consider whether you can do the study."

➢ **P-value on the primary endpoint.** Three different values for the p-value of the primary endpoint have been proposed: 0.021, 0.022, and 0.016. A NitroMed official argued the 0.016 is appropriate, the FDA briefing documents indicate 0.021 is more appropriate, but the panel's biostatistician said he doesn't accept any of them.

➢ **Lupus side effect.** A panel member worried that women could be at a four-times higher risk of lupus with BiDil – but that this wouldn't be shown in the trial because it doesn't manifest in six months.

The race issue

A panel member brought up the issue of race and how it was identified in A-HeFT – self-identification. A NitroMed official defended the use of self-identification, saying, "That is consistent with the U.S. Census…It is consistent with FDA guidelines on collecting ethnicity and race in clinical trials." But the panel member responded, "If we talk about racial classifications, it is often based on what people look like – skin tone – and I don't think skin tone is a great proxy for a

biological effect. I'm a little wary because I don't know what you mean by black."

Dr. Temple explained why the FDA allowed the A-HeFT to be conducted only in self-identified African-Americans: "There is tremendous interest in individualization of therapy, and when you try to identify the people in which the drug will be effective, then there is a question of how much information is needed in the on-off population. If the drug works less well in that population, providing convincing evidence would require a massive study…We have not worked that out. For example, with Lotrenox (GlaxoSmithKline, alosetron) for IBS (irritable bowel syndrome) in women, there was some evidence it didn't work well in men, but I think if we asked gastroenterologists, I'm not sure they would say it doesn't work in men…This (race) may be a matter of sensitivity, and everyone wants to stay away from it, but it is clear the white subset is larger than the black, and doesn't look like much is going on (from the drug in whites)...That is why we thought it was reasonable to consider only the black population. We don't have a firm policy yet on what you do if a sponsor is going for something in only one population and doesn't care about the other population. We never said that is out of the question, but it obviously makes you uncomfortable. So we expect some kind of evidence on the other populations, and one of the questions here is how persuasive that is."

Testing for responders

The panel chair asked if it is possible to test for nitric oxide deficiencies. He wanted to know if there are some white Americans who have this (NO) response and fall into the same (responder) group? A company official said, "The company is working on direct assays for nitric oxide. There are no predictors or assay available right now…We are committed to expanding the population by looking at various physiology, function, and genomic markers that would expand the population." An NIH geneticist on the panel said, "When we talk of genetic markers, we need to talk about what you mean, especially when you are talking about markers that are more social (skin tone)…I think there is a presumption here that a self-identified social identifier is identical to a biologic process, and I'm not sure it is."

Gender

Dr. Jonathan Sackner-Bernstein, a cardiologist at St. Luke's-Roosevelt Hospital Center in New York, said, "I'm concerned about African-American women…You have a study with >300 women randomized to combination therapy who were followed >6 months. The point estimate was favorable…So, if we are looking for subgroups, like skin, then it is appropriate for us to look at the persuasiveness for women…Are there data to look at efficacy and safety in women?…I think the label for this should be for black men…We are looking for surrogates for biological differences and paying less attention to real biological difference. If this were all in my hands…I would approve it just for black men." *(There was no support for this idea among other panel members.)*

Other issues

The panel chair summarized some of the panel opinions:

- "The consensus is (use should be limited to NYHA) Class III."
- "We aren't so persuaded by V-HeFT in our thinking process, and the FDA may want to factor that in…No one here thinks it tells us much." Dr. Temple responded, "V-HeFT gives some reason to think that you might not want to limit use to Class III, but I hear you."

PUBLIC WITNESSES

More than a dozen people spoke in favor of approval of BiDil, but they were divided on whether the drug should be approved for use in African-Americans specifically.

In favor of a race-based label:

➢ **Cong. Donna Christiansen, Chair of the Congressional Black Caucus,** urged the panel to recommend approval of BiDil for African-Americans. She said, "You have an unprecedented opportunity to significantly reduce one of the major health disparities afflicting African-Americans…The drugs in BiDil are not new medications. It is the specific combination of these medications that is before the committee, so I think we can assume it is not the safety of the medications that is in question. Neither would our concern be the A-HeFT trial because I think it could be considered a model trial, and it was stopped after 18 months because of higher mortality in the placebo group…Today, we are asking for your approval for a drug that will save countless lives…So, why hesitate? This drug would likely not be approved for a large population because it was not shown to be positive in a larger white population…But neither does it cast a negative stigma on African-Americans because it would be labeled for us…Would you deny life rather than do what the evidence says can and should be done? The Congressional Black Caucus believes it (BiDil) should be approved and indicated for use in African-Americans."

➢ **Lucille Norville Perez, National Health Director of the NAACP,** urged approval in African-Americans. She said, "The results of (A-HeFT) should not be invalidated by perceived political objections. Given the disproportionate impact of cardiovascular disease…anything short of BiDil in this population cannot be justified and would be tantamount to the FDA disavowing its commitment (to minorities)."

In favor of a broad label:

➢ **Gary Puckrein PhD, National Minority Health Month Foundation** – which has a research grant from NitroMed – supported approval in all populations, not just African-Americans. He said, "I support approval because it will improve the life of African-American patients…A-HeFT doesn't show it won't be effective in other population groups. The results of the trials cannot be meant to read that it works

only in African-Americans and won't work in other racial groups…Access to BiDil will improve mortality and improve quality of life. Lack of access to BiDil has the potential to create unavoidable resource demands on the healthcare delivery system and to unnecessarily compromise the health status of Americans…BiDil must be part of the treatment modalities available to doctors who treat heart failure…Our position is…that this be made available to all."

➢ **Dr. Shomara Omar Keita** argued in favor of approval – but for all people, not just African-Americans. He said, "The African-American group does not consist of individuals who are biologically the same…It has not been shown that the clinical phenotype that responded to BiDil is exclusive to African-Americans."

➢ **Jonathan Kahn JD PhD, of Hamline University School of Law,** urged approval but in the general population, without regard to race. He said, "There are no data from A-HeFT supporting a claim that it works differently or better in African-Americans than any other racial group. There was no comparison population, so there is no scientific basis for race …Approving this as a race-based drug would say race is an acceptable variable…Any use in non-African-Americans would be off-label use…Most drugs on the market today were approved on trials primarily in whites. The proper assumption by the FDA was that the category white didn't differ from human beings…If a drug tested in a white population is good enough for everyone, then a drug tested in a black population should be good enough for everyone as well."

➢ **Dr. Charles Currey, President of the International Society of Hypertension in Blacks,** 'vigorously" supported approval of BiDil but for everyone, not just African-Americans. He called BiDil "the most important advance in the care of black Americans in my lifetime." However, he said he doubted a statin trial conducted in Scandinavian people would be limited to use in only Scandinavian people…I think it would be unfortunate if this drug were not approved and even more unfortunate if whites and other ethnic groups were not allowed the advantages this drug offers."

➢ **Charles Rotimi, PhD, National Human Genome Center, Howard University,** urged broad approval of BiDil. He said, "It would be tragic not to approve this drug, and it would also be tragic to approve it for just African-Americans…We advocate that if it is approved, it should be approved for everybody. It should not be approved as an African-American only drug."

➢ **Charmaine Royal, National Human Genome Center,** also urged broad approval, noting that the cost of BiDil is expected to be three to four times the cost of the components. She wondered, "Will the African-Americans, the target group, be able to afford this drug? And what about other groups for whom it might work? Will we deny them the benefit of this drug? And how are we going to identify African-Americans?"

No position on race:

➢ **B. Wayne Kong, CEO, American Association of Black Cardiologists (ABC),** supported approval of BiDil, without taking a position on the race label.

➢ **Two patients** from the A-HeFT trial urged approval – Deborah Lee and Dianna Wells.

➢ **B. Basil Halliday, President/CEO of BDH Clinical Research Services** (which ran the A-HeFT trial), supported approval of BiDil, but his real message was that more minorities need to be enrolled in clinical trials. He urged the FDA to mandate minority participation in trials. On BiDil, he said, "BiDil demonstrates that race does matter in pharmacological treatment…BiDil will save African-American lives and reduce health disparities…NitroMed's successful attempt to recruit African-Americans in A-HeFT should be a model for recruiting minorities in clinical trials."

THE FDA'S QUESTIONS AND THE PANEL'S VOTES

The Advisory Committee was asked to opine on whether the A-HeFT study supports a claim that BiDil improves outcomes in patients with heart failure.

CLAIMS BASED ON A-HEFT

1. Primary endpoint. The primary endpoint was a composite of all-cause mortality, hospitalization 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). Why are these results so discrepant, and why were 60% of subjects excluded from the pre-specified per protocol analysis?

The general consensus of the panel appeared to be that the p-value on the composite primary endpoint of all-cause mortality, first heart failure hospitalization, and change in quality of life at six months was statistically significant, though it was not clear whether it was 0.016, 0.021, 0.044, or some other figure. The per protocol analysis had so many missing numbers because of exclusions and because of the early termination of the trial that panel members mostly dismissed it. Dr. Fleming said, "With the substantial exclusions, it makes analysis uninterpretable…I wonder why the sponsor proposed it initially…The bottom line, I think, is that this is not a key issue…I think the per protocol analysis is essentially uninterpretable." Panel chair Dr. Nissen said, "I'm not terribly interested in the per protocol analysis here. The intent-to-treat analysis is the appropriate analysis to focus on. We recognize sensitivity analyses are sometimes useful, but this one is particularly colored by the 60% exclusion which gives it very little power."

2. Mortality findings. 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:

a. More continuous analyses of mortality by time in study?

b. Analyses of CHF hospitalization among early and late enrollees?

FDA officials appeared convinced there was a mortality benefit shown in A-HeFT, and panel members generally agreed, but they were not convinced this was strongly proven. Dr. Fleming said, "My best attempt to recreate a proper adjustment in mortality, comes up ~0.04. What is the impact of this? It is not huge, but it is not irrelevant…I would say this benefit is in the range of the boundary."

The panel chairman was willing to cut NitroMed some slack on this point, but an FDA official appeared less willing to do so. Dr. Nissen said, "A trial that reduced mortality by 15% would be a blockbuster, but this trial was under-powered…The fact is they were working on the margins for an adequately powered study…That is the problem of a small company with limited resources…I would think it is not unreasonable to make (analyses) adjustments sometimes… When you get information that is potentially very valuable about a group that can be difficult to treat, you have to give a sponsor points for going after that." The FDA's Dr. Temple commented, "I don't think there is problem finding a suitable number of blacks for a study like this…So, it ought to be good data, and we shouldn't make allowance for that here…I don't think that is the issue here."

3. Hospitalization data. 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.

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

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

The panel skipped these questions, concluding that the company had adequately addressed them in its presentation.

4. Quality of life data. 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 LOCF (last observation carried forward)?

Using a single time point (six months) for the quality of life data may not have been the best approach, panel members suggested, but the panel chair was convinced of the benefit because quality of life improved over time with BiDil and worsened with placebo. He said, "The question speaks to the robustness of the data…Clearly, it was harmed significantly by the early termination (of A-HeFT)…There are several things that help me with the data…I liked the time point data. It is very helpful that you see that, at virtually every assessment, things are going in the right direction and by about the same amount…So, I consider LOCF vs. ITT to be a sensitivity analysis. No matter how you slice and dice it, you end up with a p-value. For future trials, I'm not sure I'd pick a single point in time to do this (measure quality of life)...I think it could be very distorting in another trial…but the consistency of the effect, I felt was convincing…The endpoints are good, and this is a feel-good endpoint, and I value it." Dr. Fleming said, "I largely agree…though I would have preferred hospital-free survival (as an endpoint)."

POLICY ISSUES

5a. Secondary endpoints. Ordinarily, one expects to understand the role of each component in a combination product, and one does not in this case. How important would that be…

- **If you believed there was an effect on mortality?**
- **If you believed there was only an effect on hospitalization?**
- **If you believed there was only an effect on symptoms?**
- **If there had been more than two active ingredients?**
- **If you suspected one component is subject to tolerance effects?**

The panel generally agreed that it would be impossible now to do a study to find out whether it is a single agent in BiDil or the combination that provides the benefit or to find out whether the benefit is only in a particular component of the composite endpoint, but the panel did not want BiDil to set a precedent for other combination products that would permit them to get approval without having to show a benefit from each component – and the FDA does not plan to relax its combination drug requirements as a result of BiDil. Dr. Nissen said, "Is the evidence of mortality persuasive enough? A 43% reduction in mortality is a pretty good effect. In order to find out if it is from one component, you would have to expose patients to a pretty substantial risk. If the effect were on hospitalization, then it would be very difficult. You will always have a placebo effect, so the question is where the boundary lies…and that is a very, very difficult question. I am not necessarily prepared to answer it in the abstract. In this specific case, I think that, given the fact that we are dealing with legacy (generic) products always given together, there is prior evidence that influences our thinking. I guess I think the fact that the sponsor has a positive trial pretty much precludes taking it apart and finding out which aspect provides protec-

tion." Another panel member said, "I support that. I was concerned about the lack of information on the components and doses…but your (Dr. Nissen's) argument trumps that."

A panel member raised a question about a potential link between BiDil and lupus, but other panel members did not share that concern. He said, "If this were to go forward, I really think it is imperative that the potentially rare toxicities be formally and rigorously evaluated and not left to just an open reporting system. The issue is: Is there a potential toxicity (lupus), and how are we going to detect that?…I'm worried because hydralazine was given a lot a long time ago and not much now…and it would be given to a lot of new patients…and more women might get it who would be at higher risk of lupus…There may be a small signal not detected in this small trial (A-HeFT)." Dr. Nissen responded, "We are talking about a disease (SLE) that is not as serious (as heart failure)."

An FDA official asked, "What am I supposed to tell the next one (combination product)...Do they have an obligation to work up the contributions of the individual components, or do we wait and see if it (the combination) affects something you care about?" Dr. Fleming responded, "I've been thinking about that…(With BiDil, it is a discussion that should have been held before the trial." The FDA's Dr. Temple added, "I don't think the combination rule is in danger, but there are special cases."

Dr. Nissen pointed out that it may be more problematic with combinations that involve three or more components. Dr. Temple responded, "We've had people come with 20 components, and we told them, 'Show us a survival benefit, and we'll talk.'" The industry representative on the panel said, "Industry is pleased that factorial designs are not absolutely mandated but will be judged on their needs on a case-by-case basis. That is refreshing to us." Dr. Temple quickly added, "Don't over-refresh. We would ordinarily expect factorial designs – unless it is obvious."

5b. Hemodynamic effects. Is the evidence that both components of BiDil have hemodynamic effects when used together…

- **Short-term?**
- **Long-term?**

Dr. Nissen explained that historically, ISDN and HYD have been combined, and when they were combined, there has been a hemodynamic effect.

5c. Advice to patients. What instructions do you give for patients who do not tolerate one component of BiDil?

Panel members declined to offer any advice to the FDA on this point. This panel member pretty much summed up the panel thinking: "There is an issue with oral nitrates…Nitrates have first pass fatty metabolism…So the range of doses where you see toxicity is very broad…There may be clinicians who may choose not to use body weight – to use them individually and individually titrate them – and we are not precluding anyone from doing that…If I have an idea that giving half as much ISDN with HYD is a good decision, it might not meet the strength of regulatory evidence, but it might reach the strength of an individual patient…You can always go back to the old way of doing things (two separately titrated drugs)…I don't think you can be very specific in this area in clinical practice. A lot of the drugs we give can cause hypertension… Physicians will have to decide what component to down-titrate if the patient gets side effects, and I am hesitant to advise on that."

6. Dosing. Ordinarily, one expects to know something about the effect of dose, and one does not in this case, for either component. How does the importance of information on dose change…

a. with the end point?

b. with the number of active ingredients?

The panel was not concerned with this issue, noting that this information is often missing for a drug.

POPULATION

7. African-Americans. 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? If it is approved, what should labeling say about:

a. Excluded subgroups?

b. The underlying genetic or cultural bases for the observed differences?

The panel recommend 7-2 that BiDil be labeled specifically for African-Americans – the group of patients in which it was studied. Among the comments on this issue were:

In favor of a broad label

➢ *Dr. Ronald Portman, a pediatric nephrologist at the University of Texas-Houston Medical School:* "I see the differences every day in clinical practice. I don't know if they are genetic, social, or economic. I do applaud the FDA for requiring the study be done in this population…and I do think this should be approved, but not in one population. I think it should be approved in general…And perhaps we should ask for post-marketing surveillance in whites."

➢ *Vivian Ota Wang PhD, of NIH's National Human Genome Research Institute:* "If we are moving to genomic sciences, we need to carefully look at self-identified racial categories…If we are going to look at SNPs, that will be a biological basis and consistent with the assumptions we are

making about a population. That would make me more comfortable than self-reference. I hear we are using self-reference as a surrogate for a biological process. You may be satisfied with that, but I am not. In a clinical setting, that reference will be assumed by clinicians…That inconsistency gives the false notion that race has a biological basis." *(This comment brought applause from the audience.)*

In favor of an African-American-only label

➢ *Dr. Nissen:* "I recognize the passion and the emotion, and I respect both views…Drugs are not racist; people are racist. The overwhelming evidence comes from a defined population…We are moving toward an era of genomic-based medicine…In 10-15 years we will have the ability to look at which group will benefit…What we are doing (with BiDil) is using a self-identified race as a surrogate for genomic-based medicine. I don't think that is unreasonable. I wish we had the gene chip and could do it on a genetic basis…but in absence of that, we know that African-Americans get a pretty robust response to the drug…I'm not uncomfortable with knowing that we aren't there technologically (with genetic testing). In the absence of genetic markers, we have to use the best evidence available today…They (NitroMed) did everything in a state-of-the-art trial, and that is a compelling argument for this population (blacks), but only this population."

➢ *The FDA's Dr. Temple:* "If we had no information about the white population and just knew it worked in blacks, you could argue it (whites are) an under-served population…But we have V-HeFT-I and V-HeFT-II, and that is not such shabby data…They make it look like the response to BiDil is quite different in the two groups (blacks and whites). It certainly doesn't look close to the A-HeFT data…I thought V-HeFT-I and –II showed it is not very promising in the white population…The V-HeFT-II black subset is ambiguous, but in the white subset it is not ambiguous – they were 40% worse. I thought that was pretty strong evidence in whites."

➢ *Dr. Fleming:* "I would call it a surrogate that we are in essence trying to target in an enriched population that there is some reason to believe would have the most enhanced benefit-to-risk. I don't know that it is precedent-setting to say we will use parameters more rapidly measurable – age, disease stage, race – that might not precisely characterize factors that lead to a more favorable benefit-to-risk…I am not sure it is novel to say we define as best we can who we think and what we think are effective modifiers…What is the evidence in whites? If you exclude patients and target a particular group (blacks), that is where your label should be."

APPROVAL

8. Approval. Should BiDil be approved for the treatment of heart failure? Unanimously YES

Among the comments the nine panel members made as they cast their votes were:

➢ *Dr. Tom Fleming, a biostatistician from the University of Washington:* "A-HeFT was an appropriate design…It leaves me with approval resting on how persuasive we view the A-HeFT trial to be…The hospitalization data are the strongest, but…balancing that are the sponsor's data on time in-hospital…So, I think CHF is the clearest signal. Overall, hospitalization is disappointingly dampened…I didn't want more, just the same …In quality of life, I found it difficult to interpret, as I often do, but it was important information nonetheless…And safety, while not totally pristine, is relatively favorable…This isn't an analgesic…In essence, there is considerable consistency there…It is a close call, but in my view it meets the general fundamental principle. What I couldn't support is a label for improved mortality or improved overall hospitalization or a label for improved overall quality of life. I would believe one could justify a label for improved heart failure hospitalization."

➢ *Dr. John Teerlink, a cardiologist at the University of California, San Francisco:* "V-HeFT-I is basically a negative trial…so I've been torn…I am extraordinarily reticent to have claims on efficacy on the basis of those trials…It could be a play of chance, especially when you are dealing with small numbers. And that applies to V-HeFT-II…So, then we are pretty much left with A-HeFT, and the decisions on who to treat is based on A-HeFT…Just (NYHA) Class III…I also think it is a very close call…Having, for me personally, discounted V-HeFT-I and -II, we are left with A-HeFT, which, on a mortality basis, I am convinced is showing a positive trend. It doesn't provide the usual force of evidence that it clearly saves lives, but there is a consistent effect across the board."

➢ *Dr. Jonathan Sackner-Bernstein, a cardiologist at St. Luke's-Roosevelt Hospital Center in New York:* "I have trouble as well with the composite endpoint, but looking at the individual components – not only in heart failure hospitalization and days in the hospital for heart failure – but also data for all days in the hospital for all hospitalizations, quality of life, as presented, are very reassuring that the drug is having a favorable impact. And the mortality benefit is one that you can't ignore, no matter what your concerns. The safety issues I'm concerned with can be watched easily."

➢ *Dr. Steven Nissen, a cardiologist at the Cleveland Clinic:* "There are times when you need to adjust your thinking for clinical factors. I think this (A-HeFT) was a courageous thing to do – to develop a drug for this population (blacks)…There are issues about how much power the trial had. The trial was stopped early, and that hurts its interpretability….What is compelling for me is how high the bar was set. This trial set the bar about as high as you can set it. They used beta

blockers and ACE/ARBs at rates that are almost unprecedented in other trials, and then they asked the question. When you give the best therapy today to a population and then test on top of that, you are putting yourself through a very, very rigorous test…And that has to be considered in weighing the significance. You won't get p=0.001 in that setting. It turns out the therapy was powerful, but the point estimates showed large benefits…I said a 15% reduction was a home run, and this is 43%."

- *Robert Samuels, the patient representative:* "I was impressed by the mortality (data)."

- *Dr. William Hiatt, a vascular medicine expert at the University of Colorado Health Sciences Center:* "The sponsor (provided) a single study. In that contest, the study seemed underpowered. I guess I would say to future people: Don't do that. The power issue was a problem for me. And the conduct of the DSMB was a problem. If you are going to look at the data and are underpowered, then you need to be careful about multiple looks. In the end, I agree clinically: The data are convincing. But, in retrospect, there are conduct issues that could have been avoided and been cleaner."

- *Susanna Cunningham PhD, the consumer advocate and a Professor of Nursing at the University of Washington:* "The need for an effective treatment…is very important."

- *Vivian Ota Wang PhD, of NIH's National Human Genome Research Institute:* "Overall, I think my decision is based on a combination of statistical discussion and the data…I think some of the design issues and statistical analysis make me uncomfortable…but the quality of the discussion on quality of life was very persuasive…So, on that basis, I vote to approve – but I don't agree on an African-American label."

- *Dr. Ronald Portman, a pediatric nephrologist at the University of Texas-Houston Medical School* had to leave early, but he cast his vote before departing – for approval, but for a broad population, not just African-Americans.

FDA COMMENTS

After the vote, Dr. Temple spoke with reporters. He offered comments on several issues:

- **Timing.** He would not comment on the BiDil PDUFA date, which the company has said is June 23, 2005, but he suggested the FDA can and will make its decision by that date.

- **Other drugs.** The FDA is unlikely to re-label the individual drugs that make up BiDil. But a BiDil approval will not necessarily open the door very wide for other race-based drugs. Dr. Temple said, "If a product came out of the blue and wanted to study blacks, we would need data on whites. If someone did a study only in EGFR positive patients, is that okay? Or do you need EGFR negative patients as well? We are working on a policy on that – but it isn't coming soon."

- **Effect on other combination therapy approvals.** Dr. Temple insisted it would not set a precedent for approval of other combination therapies. He commented, "Most people don't get a mortality benefit...There is no arterial dilation in heart failure (with prazosin, etc.), so there is a lot of reason to think you need both arterial and venous sides."

- **BiDil affordability.** This is not an issue that the FDA can or does consider.

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