



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

ADDENDUM #2

Clinical Studies

NDA #/Serial #: 20-727
DRUG NAME: Bidil (hydralazine HCl and isosorbide dinitrate)
INDICATION: Treatment of heart failure in black patients
APPLICANT: NitroMed, Inc.
DATE: December 23, 2004
DATE OF COMPLETION: May 18, 2005
REVIEW PRIORITY: P
BIOMETRICS DIVISION: Division of Biometrics I
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KEY WORDS: NYHA, DSMB, early stopping

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This addendum pertains to the following two subjects: mortality and heart failure hospitalization by NYHA class, DSMB's recommendation of early stopping of A-HeFT.

Mortality and heart failure hospitalization by NYHA class

Numerically, the Bidil group had a larger mortality rate than the placebo group in NYHA IV patients, but the sample size is very small.

Table 19a. Mortality by NYHA Class

[Source: reviewer's analysis]

	Bidil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)
NYHA Class			
II	1/1	0/0	-----
III	29/501 (5.8%)	50/504 (9.9%)	0.55 (0.35, 0.86)
IV	3/16 (18.8%)	4/28 (14.3%)	1.23 (0.28, 5.49)

Table 20a. Heart failure hospitalization by NYHA Class

[Source: Reviewer's analysis]

	Bidil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)
NYHA			
II	1/1	0/0	-----
III	81/501 (16.2%)	122/504(24.2%)	0.61 (0.46, 0.80)
IV	4/16 (25.0%)	8/28 (28.6%)	0.78 (0.23, 2.61)

DSMB's Recommendation of Early Stopping of A-HeFT

According to the DSMB meeting minutes for the July 7, 2004 teleconference, the DSMB does not address any plan for a possible survival difference; mortality is a major component of the composite endpoint but a significant difference was not anticipated in that component alone. At the previous DSMB meeting, the DSMB recommended that an O'Brien-Fleming group sequential boundary for a two sided 0.05 alpha be used to guide the DSMB in interpreting the results. The DSMB recognized that mortality is not the primary outcome and that no stopping guidelines are provided for a mortality benefit (although the DSMB implemented O'Brien-Fleming boundaries at the previous meeting). Based on the report discussed on July 7, 2004 that mortality results favor active treatment and worsening heart failure type SAEs also favor active treatment, the DSMB asked the statistical center to quickly conduct additional analyses on the A-HeFT composite endpoint as well as for other standard composite outcomes for heart failure trials (death plus hospitalization, death plus heart failure hospitalization). On June 9, 2004, based on the updated analysis provided by Dr. D'Agostino, the following results were discussed:

1) Outcomes	A	B	p-value
Composite	-0.39	.13	0.0001
Mortality	48 (10.6%)	27 (6.0%)	0.012
Hospitalization	103 (22.6%)	64 (14.2%)	0.001
QOL	-2.47	-7.46	0.002
2) CHF Worsening	94 (20.3%)	66 (14.6%)	0.023
SAEs	70 (15.2%)	47 (10.4%)	0.03

The DSMB concluded that these results re-enforced the previous mortality results and all of the data are internally consistent and significant in their own right. The unanimous recommendation of the DSMB is to terminate the A-HeFT trial due to a favorable effect of the treatment on mortality, consistent with the A-HeFT primary composite endpoint and consistent with the components.