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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-727

Medical Review(s)

CLINICAL REVIEW

Application Type	NDA, Amendment
Submission Number	20-727
Submission Code	N-000
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Reviewer Name	Salma Lemtouni
Addendum Completion Date	5/12/05
Established Name	Hydralazine HCl and Isosorbide dinitrate
(Proposed) Trade Name	BiDil
Applicant	NitroMed, Inc.
Priority Designation	P
Formulation	Hydralazine 75 mg/Isosorbide dinitrate 40 mg
Dosing Regimen	t.i.d.
Indication	Heart Failure
Intended Population	African American

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Abbreviations

MLWHF:	Minnesota Living with Heart Failure Questionnaire
QOL:	quality of life
HYD:	hydralazine
ISDN:	isosorbide dinitrate
CHF:	congestive heart failure
COPD:	chronic obstructive pulmonary disease
DVT:	deep venous thrombosis
TIA:	transient ischemic attack
AE:	adverse event
EF:	ejection fraction

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Addendum to the A-HeFT review

1 CORRECTIONS

Control-treatment-category headings were reversed in the original review (Tables 2 and 3, page 14)

Table 1. V-HeFT I Data Summary Table¹

	Blacks N = 56			Whites N = 141			Racial Interaction p-Value
	BiDil	Placebo	p-Value	BiDil	Placebo	p-Value	
Annual Mortality Rate (%)	9.7	17.3	0.04	16.9	18.8	ns	0.11
Mortality Risk Ratio	0.341	N/A	0.004	0.746	N/A	0.11	0.074
Change in EF at 12 Months vs. Baseline (%)	0.023	0.0136	0.82	0.081	0.012	0.02	0.23
Change in MVO ₂ at 12 M (mL/kg/min)	1.25	-0.394	0.068	0.681	-0.162	0.12	0.69

Table 2. V-HeFT II Data Summary Table¹

	Blacks N = 215			Whites N = 574			Racial interaction p-value
	BiDil	Enalapril	p-value	BiDil	Enalapril	p-value	
Annual Mortality Rate (%)	12.9	12.8	ns	14.9	11.0	0.02	0.25
Mortality Risk Ratio	0.95	N/A	0.83	1.48	N/A	0.0087	0.10
Change in EF @ 12 M (%)	2.97	1.32	0.34	3.86	2.48	0.12	0.82
Change in MVO ₂ at 12 M (mL/kg/min)	0.79	0.01	0.15	0.24	-0.42	0.058	0.47
Change in QOL at 12 M	-0.67	1.04	0.04	0.24	0.26	0.97	0.09

2 CLARIFICATIONS

The following are missing in the original review

2.1 Blood Pressure Measurement in A-HeFT

Blood pressure was measured at each patient visit; patient study visits were scheduled to occur at times convenient for the patient and clinical site personnel, and did not take into account how recently the patient had taken his/her prior study medication dose.

2.2 Statistical Allocation to the Secondary Endpoints

No statistical weight was allocated to the secondary endpoints.

¹ Analyses completed by the sponsor

2.3 Minnesota Living with Heart Failure Questionnaire

Table 3. The Minnesota Living with Heart Failure (MLWHF) Questionnaire

Did your heart failure prevent you from living as you wanted during the last month by:		No	Very little	2	3	4	Very much
		0	1	2	3	4	5
1	Causing swelling in your ankles, legs etc.?	0	1	2	3	4	5
2P	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3P	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4P	Making your Working Around the house or yard difficult?	0	1	2	3	4	5
5P	Making your going places away from home difficult?	0	1	2	3	4	5
6P	Making your sleeping well at night difficult	0	1	2	3	4	5
7P	Making your sleeping to or doing things with your friend s or family difficult?	0	1	2	3	4	5
8	Making your working to earn a living difficult?	0	1	2	3	4	5
9	Making your recreational pastimes, sports or hobbies difficult	0	1	2	3	4	5
10	Making you sexual activities more difficult?	0	1	2	3	4	5
11	Making you eat less of the foods you like?	0	1	2	3	4	5
12P	Making you short of breath?	0	1	2	3	4	5
13P	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14	Making you stay in a hospital?	0	1	2	3	4	5
15	Costing you money for medical care?	0	1	2	3	4	5
16	Giving you side effects from medications?	0	1	2	3	4	5
17E	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18E	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19E	Making you worry?	0	1	2	3	4	5
20E	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21E	Making you feel depressed?	0	1	2	3	4	5

The QOL questionnaire, per publication consists of four dimensions:
 1. global score (all questions);
 2. physical dimension score (questions # 2-7 and 12 and 13);
 3. emotional dimension (Questions 17-21) and
 4. economic dimension;

Copyright University of Minnesota 1986:

Rector, TS; Kubo, SH and Cohn, JN; " Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire; Heart Failure, 1987; 198-209.

E-Emotional component

P-Physical Dimension

2.4 Other Trials

An Open label, non-controlled extension trial of BiDil (X-A-HeFT) is in progress. All 1050 patients who have participated in A-HeFT were to be offered the option to enroll in X-A-HeFT. The overall objective was to demonstrate continued safety and tolerability, and to assess compliance with treatment for the duration of 12 months. BiDil was to be given to a target dose of 225/120 mg of HYD/ISDN.

3 SAFETY ADDENDUM

3.1 X-A-HeFT Four-Month Safety Update

3.1.1 Background

As of April 8 2005, 187 subjects have continued onto X-A-HeFT and generated the safety data discussed below. The extent of exposure was not provided and only a listing of patients with serious AEs was.

3.1.2 Adverse Events

--two deaths, one cardiac arrest and the other unspecified;

--hospitalization for:

-CHF exacerbation in 2;

-exacerbation of cardiomyopathy in 2;

-pneumonia in 4;

-worsening of COPD in 2;

-other respiratory in 4;

-acute renal failure in 1;

-other: chest pain in 1, TIA in 1, mental in 2, DVT in 1, bone fracture in 1 and acute gastroenteritis in 1;

3.1.3 Comments

This information does not add much to the interpretation of the safety profile of BiDil because there is no comparison group and the population studied is very sick and it is not unlikely to observe the AEs listed above.

3.2 CB-01 and CB-02

Safety summary of these two studies is missing in the original review, and the following summary was taken from Dr. Hinderling's review.

3.2.1 CB-01

A single dose of BiDil given as a fixed combination of 37.5 mg/ 20 mg b.i.d. was compared to the same dose given, in two formulations, as HYD tablet and ISDN tablet , and as HYD capsule and ISDN tablet. Twelve healthy subjects were randomized into the three formulation groups in a three-period crossover design with a 7 day wash out period.

There were two cases of serious postural hypotension, and 9 out of 12 subjects refused to progress to the next treatment period as a result of adverse events. Headache was reported by 10 subjects. The study was terminated early

3.2.2 CB-02

The bioavailability of low and high doses (37.5/10 mg and 75/40 mg tablets) of a fixed combination of HYD and ISDN were compared to HYD 37.5 mg tablet plus ISDN 10 mg tablet and HYD 37.5 mg capsule plus ISDN 10 mg tablet in 149 healthy males and females who have

been initiated on a single dose of HYD HCl 37.5 mg/ISDN 10 mg solution. Of the 88 subjects who were identified as slow acetylators, 75 were randomized to participate in Phase B. In Phase B subjects were randomized into groups A (low fixed dose), B (tablet/tablet formulation), C (capsule/tablet formulation) and D (high fixed dose) with 19 subjects in each group, and with the exception of one, all subjects completed Phase B.

In Phase A, a total of 211 AEs were reported in 110 subjects including one orthostatic hypotension that led to hospitalization. Two subjects experienced severe AEs including hypotension and syncope in one, and dizziness and syncope in the other. Four subjects had a syncopal episode. The most frequent AEs included headache in 62%, dizziness in 17% and nausea in 13% of the subjects.

In Phase B, a total of 96 AEs were reported in 46 subjects. The incidence of any AE was highest in the highest dose (75/40 mg) group of BiDiL. In all treatment groups the most common AEs were headache and dizziness.

Severe AEs included severe headache in a subject in the highest dose group. Eleven subjects had hypotensive episodes, but none had a syncopal episode.

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/s/

Salma Lemtouni
5/17/05 10:58:34 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 20-727
Submission Number	20-727
Submission Code	N-000
Letter Date	December 23, 2004
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Reviewer Name	Salma Lemtouni
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Established Name	Hydralazine HCl and Isosorbide dinitrate
(Proposed) Trade Name	BiDil
Applicant	NitroMed, Inc.
Priority Designation	P
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Indication	Heart Failure
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Abbreviations

AA:	African American
ACE-I:	angiotensin converting enzyme inhibitor
AA:	African American
AE:	adverse event
AICD:	automatic implantable cardiac defibrillator
ARB:	angiotensin receptor blocker
BEST:	Beta-blocker Evaluation of Survival Trial
BNP:	brain natriuretic peptides
bpm:	beat per minute
BSA:	body surface area
BSA:	body surface area
CABG:	coronary artery bypass graft
CAD:	coronary artery disease
CCB	calcium channel blockers
CCB:	calcium channel blocker
CHF:	congestive heart failure
CI:	confidence interval
CKMB:	creatinine kinase
CO:	cardiac output
COPD:	chronic obstructive pulmonary disease
COSTART:	coding symbols for thesaurus of adverse reaction terms
CRF:	case report form
CVA:	cerebrovascular accident
CVD:	cardiovascular disease
D50W:	50% dextrose in water
DBP:	diastolic blood pressure
DSMB:	data and safety monitoring board
DVT:	deep venous thrombosis
EF:	ejection fraction
ER:	emergency room
ETOH:	alcohol
GCP:	good clinical practices
GERD:	gastro-esophageal reflux disease
HF:	heart failure

HR:	heart rate
HYD:	hydralazine
ICAC:	Independent Central Adjudication Committee
ICD:	implantable cardiac defibrillator
ISDN:	isosorbide dinitrate
ITT:	intention-to-treat
LBBB:	left bundle branch block
LOCF:	last observation carried forward
LVEF:	left ventricular ejection fraction
LVEF:	left ventricular ejection fraction
L VH:	left ventricular hypertrophy
LVID:	left ventricular internal diameter
LVIDD:	left ventricular internal diameter in diastolic
MLHF	Minnesota living with heart failure
msec:	millisecond
MVO ₂ :	maximum oxygen consumption
NYHA:	New York heart association
MVO ₂ :	maximum oxygen consumption
NO:	nitric oxide
OL:	open label
PCI:	percutaneous coronary intervention
PTCA:	percutaneous transluminal coronary angioplasty
PVC:	premature ventricular contraction
QOL:	quality of life
q.i.d.:	four times daily
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SLE:	systemic lupus erythematosus
SOLVD:	Studies of Left Ventricular Dysfunction
TIA:	transient ischemic attack
t.i.d.:	three times daily
UTI:	urinary tract infection
V-HeFT:	Vasodilator-Heart Failure Trial
WBC:	white blood count

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The A-HeFT study was prematurely terminated for a significant reduction of mortality on BiDil. Even though less data than planned was collected as a result of early termination, A-HeFT was able to meet its primary endpoint of a significant favorable change in the mean of the composite score of mortality, first hospitalization for HF and QOL on BiDil compared to placebo.

As to the secondary endpoints, changes in the mean of individual scores of mortality and hospitalization were also significantly different between BiDil and placebo.

The incidence of and the time to death and time to first hospitalization for HF were significantly different between the BiDil and the placebo arms.

Except for headache and dizziness, subjects taking BiDil experienced less adverse events than subjects taking placebo. Headache and dizziness are known to be associated with organic nitrates.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

BiDil is a fixed combination of hydralazine (HYD), a drug approved for essential hypertension, and isosorbide dinitrate (ISDN) approved for the prevention of angina pectoris. BiDil was to be taken orally t.i.d which is the equivalent of 225 mg of HYD and 160 mg of ISDN.

A-HeFT was a randomized, placebo-controlled trial that was designed to enroll 1100 African American subjects with NYHA classes III and IV heart failure, and follow them up to 12 months to evaluate the effect of BiDil on all cause mortality, hospitalization and the quality of life and its safety in this ethnic group.

A total of 1050 patients were randomized to BiDil (49%) and placebo (51%), and 71%, 61%, 50%, 42%, 33% and 30% were exposed to the study drug for 3, 6, 9, 12, 15 and ≥ 15 months respectively.

Findings from two other studies, V-HeFT I and V-HeFT II are used as secondary source of the safety assessment and the effect of BiDil in the African American HF sub-population.

1.2.2 Efficacy

The primary endpoint of the A-HeFT trial was the mean change in the composite score of death (-3 or 0), hospitalization (-1 or 0) and QOL (-2 or +2). Secondary endpoints included the mean change in the individual scores of the components, and the rate of and time to event of death and first hospitalization for HF.

The composite score used in this trial was not studied or validated in any population. It weighed the components based on no data that would enable the translation of the differences in individual and/or population scores into clinically meaningful benefits. For instance a subject who was hospitalized and whose QOL deteriorated by > 10 points would contribute as much to the overall score as a patient who died. There is no data that would tell us whether these two outcomes, which are known to have different meanings at the individual

level, are either equivalent at the population level or perceived in a similar way by the medical community.

However, given that BiDil was shown to have an effect on the scores of the main components, the composite score and the weight attributed to its components becomes less critical.

The findings of the A-HeFT study support a beneficial effect of BiDil on all-cause mortality and hospitalization for HF in African American patients.

1.2.3 Safety

The safety of BiDil in the study population was derived from analyses comparing the effect of exposure to BiDil for an average of 6 months in 519 subjects and to placebo in 532 subjects.

Overall serious adverse events were experienced at a similar rate in both-treatment arms, 35% on BiDil and 34.7% on placebo. The following serious adverse events were observed on BiDil at a slightly higher rate than on placebo: ventricular tachycardia 2.7% (14) vs. 1.5% (8), hypotension 1.5% (8) vs. 0.6% (3), dizziness 1.4% (7) vs. 0.0%, cerebral ischemia 1.0% (5) vs. 0.2% (1), syncope 2.1% (11) vs. 1.5% (8), and cellulites 1.2% (6) vs. 0.4% (2).

There were more discontinuations as a result of adverse events on BiDil compared to placebo 21.1% (109) vs. 12.0% (63). More than half the discontinuations on BiDil were accounted for by headache (7.4%) and dizziness (3.7%). Other adverse events that led to discontinuation at a higher rate on BiDil compared to placebo include asthenia 2.3% (12) vs. 0.2% (1), chest pain 1.5% (8) vs. 0.4% (2), nausea 1.5% (8) vs. 0.4% (2), and hypotension 1.4% (7) vs. 0.4% (3).

1.2.4 Dosing Regimen and Administration

The titration schedule of BiDil in the A-HeFT trial seemed to be brisk and as a result, almost twice as many BiDil as placebo patients discontinued the study drug, and more than half of these were due to headache and dizziness, a good proportion of which could have been avoided had the titration proceeded more cautiously.

1.2.5 Drug-Drug Interactions

No formal assessment of interactions of BiDil with other drugs was undertaken. Of concern are some beta-adrenergic antagonists which were found to interact with hydralazine.

1.2.6 Special Populations

The effect of BiDil in heart failure in this study was assessed solely in African American patients. The results of the A-HeFT study will not be generalizable to other ethnic group. Subgroup analyses showed that BiDil was as efficacious and relatively safe in elderly and in female subjects as it was in younger and in male subjects.

BiDil was not studied in pediatric subjects, and a request for a waiver was submitted with this application. The Division abstained from granting the sponsor a waiver until the application is fully reviewed, and instead granted them a deferral.

2 INTRODUCTION AND BACKGROUND

2.1 Rational for the A-HeFT Trial

With respect to medical outcomes, African-American patients are diagnosed with HF at a higher rate than whites. Death rate from cardiovascular disease in AA in the 1990s was estimated to be 353 in males and 226 in females, while that of Caucasians was 244 in males and 135 females per 100,000.

It is hypothesized that in addition to socioeconomic factors, and differences in access to care and disease management, other factors including response to pharmacological therapies contribute to the observed differences. Some of the factors that were either studied or advanced as potential determinant factors in the differences observed include:

- salt sensitivity and low-renin hypertension;
- left ventricular hypertrophy (LVH) disproportionate to afterload;
- microvascular ischemia in the absence of significant epicardial CAD;
- higher prevalence of hypertension and LVH;
- higher incidence of normal coronary arteries in HF despite a high prevalence of risk factors for coronary atherosclerosis;

Secondary post-hoc analyses of SOLVD, VHeFT II and BEST data showed differential effect by race in the following:

- enalapril with regard to HF-related hospitalization in SOLVD, Table 1 page 14, and a change in the QOL in VHeFT II, Table 3 page 14,
- bucindolol with regard to survival in BEST (data not provided).

On the other hand, carvedilol has not been associated with an ethnic effect in HF (data not provided).

The explanation advanced for the difference in response of AA hypertensive subjects to ACE inhibitor therapy, and the observation that AAs fare better with diuretics than with either ACE inhibitors or beta-blockers are suspected to be partially related to nitric oxide (NO) insufficiency in this population. The same explanation is advanced for the apparent reduced responsiveness of AA HF subjects to these medications.

Nitric oxide insufficiency, secondary to either reduced production of NO or its inactivation by overabundant reactive oxygen species as a cause of the reduced responsiveness of AA to the available HF therapies was expected to be addressed by treatment with BiDil which is believed to have both characteristics of an NO donor and an antioxidant.

HYD/ISDN was associated with lower mortality in the study population of the VHeFT I compared to placebo and prazosin but this did not reach statistical significance. In the VHeFT II, HYD/ISDN was shown to be statistically significantly inferior to enalapril in reducing mortality at 2 years. Post-hoc analyses have shown that HYD/ISDN was associated with a reduction of mortality in black patients in V-HeFT I, Table 2 page 14, and mortality trends in the V-HeFT II were reversed in blacks toward no difference between BiDil and enalapril while enalapril was superior to BiDil in whites, Table 3 page 14 and Table 28 page 41.

The following tables summarize the findings of the post-hoc analyses of the SOLVD and VHeFT I and II, and provide the rationale for the conduction of A-HeFT.

Table 1. Ethnic Reanalysis of SOLVD Trial

	Blacks		Whites		Racial Interaction
	Risk Ratio* (CI)	p-Value	Risk Ratio* (CI)	p-Value	p-Value
All-Cause Mortality	0.92 (0.72 - 1.18)	ns	0.95 (0.76 - 1.18)	ns	p=0.7
Cardiovascular Death	0.92 (0.71 - 1.20)	ns	0.96 (0.76 - 1.22)	ns	p=0.6
Hospitalization for CHF	0.95 (0.74 - 1.23)	ns	0.54 (0.41 - 0.71)	p<0.001	p=0.005
Death or Hospitalization for CHF	0.91 (0.75 - 1.12)	ns	0.75 (0.62 - 0.91)	p<0.01	p=0.2

* Enalapril vs. placebo

Table 2. VHeFT I Data Summary Table¹

	Blacks			Whites			Racial Interaction
	BiDil	Enalapril	p-Value	BiDil	Enalapril	p-Value	p-Value
Annual Mortality Rate (%)	9.7	17.3	0.04	16.9	18.8	ns	0.11
Mortality Risk Ratio	0.341	N/A	0.004	0.746	N/A	0.11	0.074
Change in EF at 12 Months vs. Baseline (%)	0.023	0.0136	0.82	0.081	0.012	0.02	0.23
Change in MVO ₂ at 12 M (mL/kg/min)	1.25	-0.394	0.068	0.681	-0.162	0.12	0.69

Table 3. VHeFT II Data Summary Table¹

	Blacks N = 215			Whites N = 574			Racial interaction
	BiDil	Placebo	p-value	BiDil	Placebo	p-value	p-value
Annual Mortality Rate (%)	12.9	12.8	ns	14.9	11.0	0.02	0.25
Mortality Risk Ratio	0.95	N/A	0.83	1.48	N/A	0.0087	0.10
Change in EF @ 12 M (%)	2.97	1.32	0.34	3.86	2.48	0.12	0.82
Change in MVO ₂ at 12 M (mL/kg/min)	0.79	0.01	0.15	0.24	-0.42	0.058	0.47
Change in QOL at 12 M	-0.67	1.04	0.04	0.24	0.26	0.97	0.09

¹ Analyses completed by the sponsor

2.2 Product Information

BiDil is a fixed combination of hydralazine hydrochloride, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, an organic nitrate with a vasodilating action on both arteries and veins. The proposed name is either BiDil or ZiDil. If approved, per the proposed label, BiDil will be indicated for the treatment of chronic heart failure as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE inhibitors .

2.3 Currently Available Treatment for Indication

Medications that have an indication for heart failure treatments in the US include ACE-I, ARBs and beta-adrenergic antagonists. The effect of these drugs in AA subjects has not been evaluated with adequate power, and therefore not quantified in this subpopulation. It is known that these drugs do not have the same effect in the treatment of hypertension in AA as they do in White subjects.

2.4 Availability of Proposed Active Ingredient in the United States

Isosorbide dinitrate is an organic nitrate available in a generic formulation for the prevention of angina pectoris as sustained release capsules of 40 mg.

Hydralazine hydrochloride is also available in a generic formulation for the treatment of essential hypertension alone or as an adjunct therapy as tablets of 10, 25, 50 and 100 mg.

2.5 Pre-submission Regulatory Activity

The original NDA 20-727 was submitted in July of 1996 for BiDil, and the application initially proposed the use of BiDil for a mortality claim in CHF patients who were intolerant to ACE-I. This was later revised to a claim for symptomatic relief for all CHF patients.

In February of 1997 the BiDil application went before Cardiac and Renal Drugs Advisory Committee who voted 9 to 3 to not approve it because the committee did not believe that the data submitted met the regulatory standard for approval.

A non-approvable letter was sent to the sponsor on July 2, 1997. This letter raised chemistry and pharmacokinetics deficiencies, listed pre-approval requirements and responded to requests by the sponsor, and these included:

- the concern that the sponsor has not adequately addressed the possibility of an interaction between the drug substances to form N-nitrosamines, products that have the potential to be carcinogenic;
- the Division's denial of a bioavailability waiver for the 37.5/20 and 75/20 dose strengths because the 37.5/10 strength showed a slower dissolution performance compared to the former strengths;
- the statement that a proposal for inclusion of information regarding food effect on HYD/ISDN based on published literature could not be acceptable, and that a food effect study, using the to-be marketed formulation of BiDil would be required to support any statement relating to the effect of food on administration of BiDil;

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the sponsor's responses to the pharmacokinetic issues, found the responses acceptable except for the response pertaining to the effect of food on BiDil for which the FDA recommended the inclusion in the label of the following text: "No information is currently available regarding the effect of food on BiDil tablets" which was acceptable to the sponsor.

In the minutes of the end-of-phase-II meeting, the Division expressed the concern that the fixed dose combination would produce tolerance because it would deliver ISDN continuously, a regimen that per the ISDN label is to be avoided. The Agency also stated that animal studies showing that hydralazine protected against tolerance to ISDN were not enough and that human data were needed for support.

2.6 Animal Pharmacology/Toxicology

2.6.1 See Dr. Defelice's Review

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

Data used for the evaluation of efficacy and safety came from one main source, the A-HeFT study. Additional material used for the review of this application included Agency medical and statistical reviews of the V-HeFT I and V-HeFT II trials plus subgroup data of these two studies provided by the sponsor as a part of the submission and upon request by the reviewer..

3.2 Tables of Clinical Studies

Table 4. Summary of clinical studies

Study	Design	Type of subjects	Treatment		Duration	Dose	Relevance of Data
			BiDil	Comparator			
A-HeFT	R, DB, PC	AA with HF	518	Placebo 532	6 M	75/40 mg x 3	+++++
V-HeFT I	R, DB, PC	Males with HF	186	Placebo 273	≥ 2 years	75/40 mg x 4	+++
V-HeFT II	R, DB, AC	Males With HF	401	Enalapril 403	62 M	75/40 mg x 4	++
CB-02	R, OL, CO	Healthy males	149	--	[1]	37.5/40 mg	+
CB-01	R, OL, CO	Healthy	12	--	[1]	75/40 mg	-

[1] Single doses interspaced with a washing period;

3.3 Review Strategy

A paper application was submitted and used for review. A-HeFT was reviewed in greater detail than V-HeFT I and II. For efficacy, A-HeFT was the only source of review, but for safety, additional data from the V-HeFT studies were used.

3.4 Data Quality and Integrity

3.5 Compliance with Good Clinical Practices

The study was conducted in the US and per the study report, the sponsor asserts that they had adhered by the guidelines of GCP in conducting A-HeFT.

The protocol violations that occurred during A-HeFT are summarized in Table 7 page 27.

3.6 Financial Disclosures

4 CLINICAL PHARMACOLOGY

4.1 See Reviews of Drs. Hinderling and Velazquez

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The proposed indication for BiDil is the treatment of CHF as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE-Is.

5.1.1 Purpose and Study Objectives

The trial was intended to provide additional data in support of the findings of VHeFT subpopulation analyses and to support an NDA.

Three main objectives were specified:

- To demonstrate that BiDil is superior to placebo with regard to a composite score made up of 3 component scores including the QOL, hospitalizations and all-cause mortality;
- to assess the safety and tolerability of BiDil in AA heart failure patients;
- to demonstrate favorable trends in one or more of the individual components of the primary composite endpoint, the total number of hospitalizations, the duration of hospitalizations, unscheduled office and/or emergency room visits, and the echo parameters of cardiac size and function;

5.1.2 Methods

A-HeFT, the placebo-controlled trial of fixed dose of BiDil added to standard therapy in African-American patients with heart failure, was conducted to assess the effect of BiDil mortality, first-time hospitalization rates, and the quality of life.

V-HeFT I and II used two formulations that are different from the fixed dose used in A-HeFT.

A concern regarding the bioequivalence of the formulations used in V-HeFT to the combination formulation used in A-HeFT was raised in the End-of-Phase-II meeting held in November of 1992. Therefore the post-hoc analysis results of efficacy in the two trials will not be used for support of efficacy.

5.1.3 General Discussion of Endpoints

5.1.3.1 A-HeFT Study Endpoints

5.1.3.1.1 Primary Efficacy Endpoint

This is a composite of three scores, death, hospitalization for heart failure (adjudicated), and change in QOL (MLHF questionnaire) at 6 months or last available assessment.

Death = -3 vs. alive at end of trial = 0

Hospitalization for HF = -1 vs. no hospitalization = 0

Change in QOL

Improvement ≥ 10 units = +2

Improvement ≥ 5 and < 10 units = +1

Improvement < 5 units = 0

Worsening ≥ 10 units = -2

The final score ranged between -6 if a patient's QOL worsened by ≥ 10 units, was hospitalized and died; and +2 in a patient was neither hospitalized nor dead and his QOL improved by ≥ 10 units.

In the primary analysis the worst case scenario was to be assumed for missing data and the secondary analysis was to use only available data with no imputed values.

Death: All cause mortality was to be used in the primary efficacy analysis. Death was to be adjudicated by an Independent Central Adjudication Committee (ICAC) and classified by cause including HF and other cardiac or non-cardiac cause, and as sudden or non-sudden death.

Hospitalization: Occurrence of the first hospitalization for HF was to be counted, and like death, the cause was to be adjudicated;

Hospitalization for HF: was defined as such if it lasted more than one calendar day, and the primary reason was worsening of signs or symptoms of HF and the patient required IV medications or other non-parenteral medication given specifically for HF;

QOL: the MLHF questionnaire administered at 6 months or last available measurement if the 6-month one was not;

5.1.3.1.2 Secondary efficacy parameters

They consist of:

- Individual components of the primary composite;
- Death:
 - from any cause;
 - from HF;
 - from cardiac causes other than HF;
 - sudden vs. non-sudden;
- Total number of hospitalizations
 - for HF;

- for any cause;
- Total days in hospital;
- Overall QOL throughout the trial;
- Number of unscheduled emergency room and/or office/clinic visits (cause adjudicated by ICAC);
- Echocardiogram parameters including LVEF, LVIDD, and LV wall thickness. Echocardiograms were to be inspected for readability by a core laboratory and read by a blinded external expert;
- BNP levels;
- Newly recognized need for cardiac transplantation; this was to be adjudicated by the ICAC and data from patients undergoing transplant during the trial were to be censored;

5.1.3.1.3 Discussion of A-HeFT Endpoints

A-HeFT was the first study to ever use the composite score (discussed in 5.1.3.1.1 page 17), and because of the lack of an estimate of its variability in the intended study or any other population, criteria were built in the design to allow for interim analyses to adjust the sample size.

The primary endpoint would have been difficult to defend had the study not won on the main components of the composite endpoint because it would be difficult to interpret the meaning of a score in terms of a clinical benefit. The other issue would have been whether the components were weighted proportionally to the clinical weight each one has in the study population.

Secondary endpoints included components of the primary composite endpoint, endpoints that revolve around death and hospitalization, unscheduled visits to the ER and/or office/clinic, echocardiographic parameters and markers of deterioration most of which are clinically relevant to heart failure patients.

The endpoints that were planned to be adjudicated are cause of death, all hospitalizations, unscheduled ER or Office visits and new heart transplant listing.

5.1.3.2 V-HeFT Study Endpoints

See 5.1.5.2 page 22 and 5.1.5.3 page 22;

5.1.4 Study Population

5.1.4.1 A-HeFT Study Population

Eleven hundred patients with NYHA class III-IV and stable chronic heart failure were required to meet the primary objective of A-HeFT.

They were to have a resting LVEF $\leq 35\%$ or LVIDD ≥ 2.9 cm/m² BSA (or > 6.5 cm) plus LVEF $< 45\%$ (by echocardiogram obtained within 6 months), and to be, per the investigator, symptomatically stable for at least 3 months and on a stable treatment regimen for at least 2 weeks (at least 3 months for beta-blockers)

To be excluded were subjects with significant valvular disease, hypertrophic obstructive cardiomyopathy, active myocarditis, uncontrolled hypertension or symptomatic hypotension;

subjects who have had unstable angina, MI, cardiac surgery or PTCA, cardiac arrest, life threatening sustained ventricular tachycardia requiring intervention unless treated with an ICD, or stroke within 3 months of screening; subjects who have CAD likely to require CABG or PTCA; subjects who have rapidly deteriorating or uncompensated HF that render cardiac transplantation likely during the ensuing year; subjects who received parenteral inotropic therapy within one month; or subjects who have significant hepatic, renal or other condition that might limit survival over the ensuing one year;

5.1.4.2 V-HeFT Study Populations

See 5.1.5.2 page 22 and 5.1.5.3 page 22;

5.1.5 Study Design

5.1.5.1 Pivotal Trial: "A-HeFT (African-American Heart Failure Trial), a Placebo-Controlled Trial of BiDil Added to Standard Therapy in African-American Patients with Heart Failure"

This is a multicenter, randomized, double-blind, placebo-controlled parallel group study in AA patients in which eligible subjects were to be randomized after a 2-week run-in period to t.i.d. BiDil or identical appearing placebo within strata of beta- or no beta-blocker therapy.

The original protocol of A-HeFT (reviewed under IND 41816) was completed on 3/15/01, and after a little over 3 years and ten amendments, the final A-HeFT protocol was completed (06/08/04, date of the last amendment), just one month before termination of the trial.

Mortality was the main endpoint. Other endpoints were adjudicated by an Independent Central Adjudicated Committee.

The investigational therapy, BiDil was supplied as a fixed-dose combination of ISDN 20 mg plus HYD 37.5 mg (referred to as BiDil 20 Tablets). One tablet of BiDil was to be initiated t.i.d. and if tolerated 3 to 5 days later the dose is to be increased to 2 tablets t.i.d thus delivering an initial dose of 60/112.5 mg/day and maintenance dose of 225/160 mg/day of ISDN/HYD. If not well tolerated, either BiDil or background medication could be adjusted as appropriate. BiDil could be administered as ½ and 1 ½ tablets t.i.d. as well.

BiDil could be titrated down to avert adverse events. For symptomatic hypotension, it was suggested to adjust other anti-hypertensive therapies before altering the dose of BiDil.

Following a dose adjustment, another dose titration was to be attempted and if the target dose was not tolerated, the maximally tolerated dose was to be administered.

The plan was to follow patients up to a maximum of 18 months or until the last randomized patient has completed 6 months post-randomization, but because the study was terminated early as a result of a statistically significant difference in mortality between the two treatment arms, 38.7% and 36.8% of the BiDil and placebo groups had less than 6 months exposure.

Study design is shown schematically in figure below

Figure 1. Schematic of Study Design (sponsor's schema)

	Screening	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3*	4+ & Final Visit*
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.

* All patients seen every 3 months until either a maximum of 18 months or until the last patient completes visit No. 2.

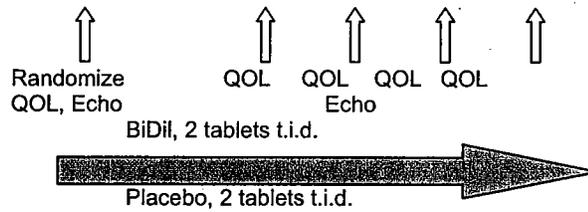


Table 5. Study flow chart (Sponsor's chart)

	Screen	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3	4+ & Final Visit
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
Informed consent	X						
Incl./Excl. criteria	X	X					
Medical history	X						
Complete physical exam	X				X		
Review qualifying LVEF & LVDD	X						
Serum or urine pregnancy	X						
NYHA class	X	X		X	X	X	X
Concomitant medications	X	X		X	X	X	X
Adjust background therapy	X		X	X	X	X	X
Interim history		X	X	X	X	X	X
Brief physical exam		X		X	X	X	X
Confirm stability		X					
ECG		X					
Clinical chemistry		X					
Hematology		X					
Urinalysis		X					
Echocardiogram ¹		X			X		

	Screen	Baseline	Titration	Treatment & Follow-up			
				Visit No.	1	2	3
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
BNP		X			X		
QOL		X		X	X	X	X
Randomize & start study medication		X					
Dispense study medication		X		X	X	X	X
Titrate study medication ²			X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X
Document Adverse Events		X	X	X	X	X	X

¹ Obtain in all patients for baseline and follow-up LVEF and LVIDD. Baseline results not used for "qualifying".

² May repeat titration visit as needed and may adjust study medication and background therapy anytime as needed.

5.1.5.2 V-HeFT I "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure"

This was a controlled parallel group, placebo, ISDN/HYD and prazosin, multicenter trial that randomized 642 patients with chronic CHF, NYHA class II and III who were on a background therapy of digitalis and diuretics.

The study randomized only male patients who had a history and physical consistent with left ventricular failure and with a limitation of exercise tolerance because of dyspnea and/or fatigue beginning at least 3 months prior to screening. Excluded were patients with hypertrophic cardiomyopathy, hypertensive patients requiring treatment with drugs other than diuretics, chronic beta blocker therapy, and therapy with vasodilator drugs. The double blind treatment period was to last at least 2 years. Major endpoints included two-year mortality, the number and duration of hospitalization for cardiovascular causes, maximum oxygen consumption during peak exercise, maximum treadmill exercise time on graded test, and duration of exercise on submaximal test.

5.1.5.3 V-HeFT II "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure"

IND 16-960 submitted on 11/25/85 described the study in a protocol as a multicenter, randomized, double-blind, parallel, active-controlled trial in patients with CHF. Patients were randomized to either HYD/ISDN or enalapril and the duration of the study was projected to be of 62 months with a minimum of 6 months.

Inclusion criteria were similar to those of V-HeFT I with additional specifications including EF < 0.45 by radionuclide method, LVID > 2.7 cm/m² at diastole on echocardiography, cardiothoracic ratio ≥ 0.55, and reduced exercise tolerance. Exclusion criteria were similar to

those of V-HeFT I plus diastolic blood pressure ≥ 105 mmHg or hypertension requiring non-diuretic therapy and dependence on chronic therapy with calcium channel blocker.

Major study endpoints were similar to the V-HeFT I study plus changes in the QOL and oxygen consumption at the anaerobic threshold.

Four hundred and one patients were randomized to HYD/ISDN and 403 to enalapril.

5.1.5.4 Adequacy of Study Design

The design of the pivotal trial was not the required design of a combination product which is usually factorial and compares the combination product to each of the components and placebo. The A-HeFT trial compared BiDil to placebo only. Therefore, we will not be able to know for sure whether the combination is necessary for treatment of the studied condition in the studied population, or either component would have been as effective as and somewhat safer than the combination.

5.1.6 Treatment Plan

In A-HeFT, a target maintenance dose of 120 mg/day of ISDN and 225 mg/day of HYD was to be achieved through 2 BiDil tablets taken t.i.d. If the target maintenance dose was not tolerated, the maximally tolerated dose was to be given by adjusting the number of tablets and/or the portion of a tablet to be taken t.i.d. Background medication was to be adjusted as clinically indicated to increase the likelihood of study drug toleration. Another attempt to titrate the dose to target level in subjects who failed to reach it was to be made within the first month of treatment.

5.1.7 Concomitant Medication

Study subjects were to be symptomatically stable and receiving a stable treatment regimen for at least 2 weeks prior to randomization. The treatment regimens of these patients may include spironolactone, digitalis, or other at the investigator's discretion. Beta blockers were to have been taken for at least 3 months.

Except for patients on phosphodiesterase-5 inhibitors, patients on other medications especially those with potentially significant hemodynamic effects maybe enrolled as long as the regimen of administration was to remain stable for the duration of the trial.

5.1.8 Statistical Methods

The following hypothesis was the basis for the test of superiority of BiDil over placebo:

$$H_0: \mu_B = \mu_P \quad \text{versus} \quad H_a: \mu_B \neq \mu_P$$

μ_B and μ_P are mean composite scores for BiDil and placebo.

5.1.8.1 Primary Efficacy Analyses

The primary analysis was to consist of a comparison of the mean composite score on BiDil to that on placebo using a 2-sample t-test, and constructing a two-sided 95% CI.

ANCOVA was to be used to test for the effect of BiDil controlling for baseline characteristics. The covariates that were to be considered were age (< 65 and ≥ 65), sex, and beta-blocker and ACE inhibitors categories (yes/no). Because the centers were numerous and the number of subjects per center was small, treatment effect was to be examined across centers using descriptive statistics only.

Summary tables and figures were to include summary statistics of the composite score by treatment groups, and by age, sex, center, and beta-blocker and ACE inhibitors intake.

BiDil was to be considered superior to placebo and to have a treatment effect on the composite score if the null hypothesis above was rejected.

5.1.8.2 Secondary Efficacy Analyses

The consistence and robustness of the treatment effect was to be tested using secondary outcome measures. Two sample t-tests and ANCOVA modeling were to be used for continuous parameters, and Fisher's Exact tests (or Chi-Square tests where appropriate) and logistic regression models were to be used for binary parameters.

5.1.8.3 Analyses Populations

Intent to treat population or full analysis set of patients that consisted of all randomized patients was to be used as the primary efficacy population.

Analyses using the per-Protocol population were to be used for sensitivity analysis. Included were patients who have taken at least one dose of study drug, were still taking at least ½ tablet per day, have completed at least 3 months of treatment, have an QOL assessment without any major deviation from the protocol, and who's compliance $\geq 60\%$ (compliance is computed as 100 times the ratio of tablets consumed to the required number prescribed).

For safety, all patients who were randomized and have at least one post baseline safety measure were to be included in the safety analysis.

5.1.8.4 Analysis Time Points

Analysis of the composite score was to use component scores at endpoint, the latter been defined as "death" or "no death" any time after randomization, "first hospitalization" or "no hospitalization" any time after randomization, and QOL at 6 months (or last measurement available if earlier than 6 months).

5.1.8.5 Handling of Missing Data

For the primary analysis, a worst score was to be assigned to components of the composite endpoint with missing values. Patients who were lost to follow-up were to be assumed to have died with a score of -3, to have been hospitalized (if they have not already being before loss to follow-up) with a score of -1, and their QOL to have worsened by ≥ 10 units and scored as -2 if they had no post randomization QOL measurement.

For secondary analyses, only available data was to be used with no imputation for missing data. Characteristics of drop-outs were to be compared between treatments, and characteristics that significantly differentiate drop-outs from completers were to be controlled in ANCOVA models.

Other analyses deviating from the original worst case scenario assignment to missing data were planned post-hoc and these include three types:

- The first analysis was to use the LOCF for QOL (up to 6 months), HF hospitalization and survival, and the worst score imputation to be used only for QOL, and only when a post-baseline value is unavailable.

The second analysis is similar to the first except that the LOCF value is not limited by the 6-month QOL.

The third analysis was to be conducted on a subset of the ITT population, 951 subjects who were randomized on or before April 19, 2004 and who have had the opportunity for a three-month QOL assessment.

5.1.8.6 Background and Demographic Characteristics

They were to be compared between treatment groups. It was stated that in the case an imbalance in baseline characteristics occurred, the treatment effect might be reassessed including the unbalanced characteristics in an ANCOVA model to increase the precision of its estimate.

5.1.8.7 Interim Analyses

No formal analyses were planned, but they were incorporated to determine whether the sample size was adequate. Two interim analyses were to be conducted, the first when 25% (150) and the second when 50% (300) of the patients have completed 6-month follow-up. The generated results were to be reviewed by the DSMB only. The sample size was to be re-estimated, using the Cui, et al. method, to provide an 80% power to detect an effect at a two-sided significance level of 0.02. It was decided that the sample size was to be formally adjusted only after the second interim analysis. The same method used to estimate the standard deviation for sample size calculations (described below) was to be used for sample size re-estimation.

The study was to be treated as a group sequential design (with K=3 Looks total) since the analyses were to be used for sample re-estimation and not to stop early for efficacy. Using the O'Brien-Fleming Boundaries, the two-sided p-values required for statistical significance were 0.00001 at Look 1, 0.0052 at Look 2, and 0.048 at the final Look.

5.1.8.8 Sample Size

For lack of data regarding the variability of the composite score, the estimation of the sample size relied on previous data from studies including VHeFT II that was designed to detect (with 80% power and a two-sided alpha of 0.05) a difference equivalent to 22.8% of a standard deviation of similar measures with 300 patients in each arm.

Using similar measures, the standard deviation of the proposed composite score was estimated to range between 1 and 2 units, and it was assumed that the study had adequate power to detect a difference of less than $\frac{1}{2}$ a unit.

5.1.9 Protocol Amendments

There were ten amendments to the protocol most of which concerned the inclusion/exclusion criteria, for detail of the amendments, see 9.1. Some of these included a change in the cutoff of the LVEF, in the duration of pre-randomization beta-blocker intake, in the requirement of length of time the patient was in NYHA class III-VI before screening; the addition of a LVEF criteria if LVIDD was to be used as an inclusion criteria; the elimination of the requirement of prior hospitalization; and forbidding current use of phosphodiesterase-5 inhibitors.

LV wall thickness assessment was added to echocardiographic measurements of LVEF and LVIDD; Echocardiographic measurements were to be done only at baseline and at 6- months instead of every three months; and reading of echocardiographic assessments were to be completed by an external expert instead of a core laboratory;

5.1.10 Post Hoc Changes

After the termination of the study the sponsor requested the addition of analyses termed “sensitivity analyses” in which missing data were to be handled differently than originally planned. The worst score was no longer to be imputed for survival and hospitalization and it was to be imputed for the QOL only if a post-baseline value was missing.

5.1.11 Results

5.1.11.1 Study Conduct

5.1.11.1.1 Interim Analyses

There were six DSMB meetings held. The first on March 19, 2002 after 221 subjects have been randomized. During this meeting the DSMB charter was discussed and it was agreed upon that the DSMB was to remain blinded until a decision was imminent. An overview of the sample size reassessment plan was presented, and it was decided that the first DSMB interim analysis was to be conducted when the first 150 patients have completed six-months of follow-up, and that an interim analyses assessing the sample size was to be conducted for the second, August 23, 2002 meeting. The new QOL scoring system was also discussed and it was decided that QOL analyses would be performed first using all participants who had 6-month QOL assessments, and they would be repeated using participants who have at least a 3-month QOL assessment.

At the second, August 23, 2002 DSMB meeting, only 137 participants had 6-month follow-up data. Results of an interim analysis were presented to the DSMB for a first look at the data. It was decided that next meeting would be scheduled when 300 patients have completed six-month visit.

The third DSMB meeting of March 3, 2003, the committee unexpectedly unblinded itself for a second look at the second interim analysis results, and it was concluded that the treatment difference was small but favorable for BiDil. During this meeting, the committee recommended an increase in the sample size.

The fourth DSMB meeting of March 13, 2004, at this meeting the committee formally unblinded itself, reviewed the third interim analysis results and noted that the mortality trend was getting stronger. The DSMB recommended another safety interim analysis in mid summer of 2004 to review mortality data again, and decided to establish monitoring boundaries for mortality since this was not determined early in the trial. The O’Brien-Fleming type group sequential boundary using the Lan-DeMets alpha spending function was chosen to be constructed for 5 interim analyses including the two that were to take place later on. The spending computation showed that the logrank test comparison of treatment groups fell just below the O’Brien-Fleming boundary value. An estimate of when the logrank z statistic or nominal p-value would cross the boundary values was generated and these were 2.24 for the logrank z statistic and 0.0126 for the p-value. These triggered a discussion by the DSMB about early termination of the trial.

In the meeting of June 9, 2004 with mortality data available on 1014 patients, it was noted that the trend of mortality strongly favoring the active treatment over the placebo group had continued. The boundary for this analysis was crossed with a logrank z statistic of 2.47 and a logrank two-sided p-value of 0.0132 (less than the required nominal p-value for the interim analysis). The committee recommended that the A-HeFT trial be terminated due to a statistically significant favorable mortality benefit on treatment when compared to control.

5.1.11.1.2 Statistical Issues

The statistical analysis plan was modified as a result of early termination of the trial and most of the changes concerned the way missing data were to be handled, see 5.1.8.5 page 24. For detailed description of the statistical method and changes, refer to Dr. Hung's review.

5.1.11.1.3 Protocol Violations

A total of 216 (20.6%) patients had deviations related to inclusion and exclusion criteria, with similar proportions on both BiDil and placebo.

The majority, ten percent and a half in each group, violated the LV dysfunction criteria. More subjects on BiDil had one or more of the conditions that were to be excluded compared to placebo, 2.1% (11) vs. 1.1% (6) respectively. Similar proportions on both treatment arms were exposed to forbidden medications during the trial, see Table 7 page 27.

5.1.11.2 Patient Disposition

5.1.11.2.1 A-HeFT

Table 6. A-HeFT Patient disposition (primary analysis population)

	BiDil (N=518) n (%)	Placebo (N=532) n (%)
Number of patients randomized	518	532
Completers	469 (91%)	457 (86%)
discontinued study drug prematurely	153 (30%)	101 (19%)
Withdrawal for adverse events	109 (21.1)	63 (12.0)
Discontinued from study prematurely	49 (9%)	75 (14%)
Investigator decision	9 (2%)	13 (2%)
Patient withdrew consent	5 (1%)	3 (1%)
Lost to follow-up	2 (0%)	0 (0%)
Cardiac transplantation	3 (1%)	3 (1%)
Death	30 (6%)	54 (10%)
Not reported	0	2 (0%)
Final status for assessment of the composite endpoint		
Vital status known at study completion	518 (100%)	532 (100%)
Hospitalization status known at study completion	505 (98%)	521 (98%)
QOL assessment done at or before six-month visit	472 (91%)	497 (93%)

Source: Sponsor's report;

¹ Two deaths occurred after completion of patient participation in the study and were not captured on the Study Completion CRF and thus are not captured in this table (112-001 and 231-002).

Very few people were lost to follow-up. Nine more percents of the subjects on BiDil discontinued as a result of adverse events, while 5% more of the subjects on placebo withdrew from the study prematurely.

Table 7. Protocol violations

	BiDil (N=518)	Placebo (N=532)
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	BiDil (N=518)	Placebo (N=532)
Number took prohibited medication	71 (14%)	90 (17%)
Hydralazine	14 (3%)	15 (3%)
Long-acting nitrate	65 (13%)	78 (15%)
Phosphodiesterase-5 inhibitor	3 (1%)	4 (1%)

5.1.11.2 V-HeFT

Table 8. Patient disposition in V-HeFT I (Sponsor's analysis)

	HYD/ISDN	Placebo	All
Randomized	186	273	642
Completed	92	134	
Deaths	72	120	283
Discontinuations	22	19	

Table 9. Patient disposition in V-HeFT II

	HYD/ISDN	Enalapril	All
Randomized	401	403	
Completed	199 (49.6)	233 (57.8)	432
Deaths	153 (38.2)	132 (32.8)	285
Discontinuations	49 (12.2)	38 (9.4)	87

5.1.11.3 Demographics

5.1.11.3.1 A-HeFT

Table 10. Baseline demographic, medical and therapeutic characteristics of the A-HeFT population (Dr. Hung's analysis)

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Gender						
Male	59.2%	66.5%	54.5%	62.9%	56.0%	63.9%
Female	40.8%	33.5%	45.5%	37.1%	44.0%	36.1%
Age (mean ± sd)	56±12	56±14	57±13	57±13	57±13	57±13
< 65	73.2%	74.3%	68.4%	70.3%	69.9%	71.4%
≥ 65	26.8%	25.7%	31.6%	29.7%	30.1%	28.6%
Weight (kg)	91±27	94±25	92±25	94±26	92±26	94±25
Blood pressure						
Systolic	126±20	121±26	128±18	125±22	128±19	124±24
Diastolic	76±19	71±24	77±11	75±14	77±14	74±17
Heart rate	75±12	72±18	74±11	75±11	74±11	74±14
EF (%)	23.6±7.2	23.8±7.3	24.1±7.4	24.3±7.6	23.9±7.3	24.2±7.5
Hypertension	86.0%	86.8%	93.5%	88.4%	91.1%	88.0%
Arrhythmias	33.5%	35.5%	32.2%	34.2%	32.6%	34.6%
Diabetes Mellitus	40.2%	36.2%	46.9%	37.4%	44.8%	37.0%
Hyperlipidemia	45.7%	41.5%	60.5%	52.6%	55.8%	49.4%
Cerebrovascular disease	17.7%	17.1%	14.1%	12.6%	15.3%	13.9%

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Peripheral vascular disease	12.8%	13.2%	10.5%	13.4%	11.2%	13.4%
COPD	20.1%	25.7%	16.4%	18.7%	17.6%	20.7%
Chronic renal insufficiency	15.9%	18.4%	16.4%	18.2%	16.2%	18.2%
Valvular disease	29.3%	30.3%	39.0%	39.0%	35.9%	36.5%
Previous implantable pacemaker or ICD	14.6%	14.5%	17.5%	18.4%	16.6%	17.3%
Previous MI	28.7%	25.7%	29.7%	29.7%	29.3%	28.6%
Angina	0.6%	0.0%	0.6%	0.3%	0.6%	0.2%
Unstable angina in the past 3 months	0.0%	0.0%	0.3%	0.0%	0.2%	0.0%
Cigarette smoking during the past year	31.7%	25.7%	25.7%	26.6%	27.6%	26.3%
Previous cigarette smoking	62.8%	66.5%	57.1%	61.8%	58.9%	63.2%
Stroke	11.0%	11.2%	11.3%	10.0%	11.2%	10.3%
Atrial Fibrillation	18.9%	19.7%	13.8%	16.8%	15.4%	17.7%
TIA	6.7%	6.6%	3.4%	3.4%	4.4%	4.3%
Etiology of HF						
Ischemic	22.6%	22.4%	23.7%	22.9%	23.4%	22.7%
Idiopathic	25.0%	29.0%	24.3%	27.1%	24.5%	27.6%
Hypertensive	39.0%	36.2%	40.4%	37.9%	40.0%	37.4%
Valvular	3.7%	4.0%	2.0%	2.9%	2.5%	3.2%
others	9.8%	8.6%	9.6%	9.2%	9.7%	9.0%
Dyspnea						
Mild	25.6%	30.3%	26.8%	30.0%	26.5%	30.1%
Moderate	64.0%	57.2%	62.2%	55.5%	62.7%	56.0%
Severe	7.3%	7.9%	5.4%	8.4%	6.0%	8.3%
None	3.1%	4.6%	5.7%	6.1%	4.8%	5.6%
Orthopnea						
Mild	24.4%	32.9%	32.8%	34.5%	30.1%	34.0%
Moderate	37.2%	38.2%	38.1%	35.8%	37.8%	36.5%
Severe	11.6%	9.2%	7.3%	6.1%	8.7%	7.0%
None	26.8%	19.7%	21.5%	23.7%	23.2%	22.6%
Fatigue						
Mild	26.2%	23.0%	27.4%	29.8%	27.0%	27.8%
Moderate	61.6%	61.2%	57.6%	53.4%	58.9%	55.6%
Severe	8.5%	12.5%	11.0%	11.8%	10.2%	12.0%
None	3.1%	3.3%	4.0%	5.0%	3.7%	4.5%
Hospitalized in the past year for HF	92.7%	96.7%	61.3%	67.6%	71.2%	75.9%
NYHA class						
I	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
II	0.6%	0.0%	0.0%	0.0%	0.2%	0.0%
III	95.7%	92.8%	97.2%	95.5%	96.7%	94.7%
IV	3.7%	7.2%	2.8%	4.5%	3.1%	5.3%
ACE	79.9%	77.0%	72.0%	74.5%	74.5%	75.2%
ARB	14.6%	16.5%	28.3%	22.9%	23.9%	21.1%
Beta blockers	76.2%	76.3%	87.3%	84.5%	83.8%	82.1%
Calcium blockers	18.3%	17.1%	22.3%	20.5%	21.0%	19.6%
Non-aldosterone antagonist diuretics	91.5%	95.4%	91.2%	91.8%	91.3%	92.9%

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Aldosterone antagonist	40.2%	33.6%	40.1%	39.5%	40.2%	37.8%
Digitalis glycosides	70.1%	73.7%	53.4%	55.8%	58.7%	60.9%
Insulin					97 (18.7)*	67 (12.6)
Oral hypoglycemic drugs					156 (30.1)*	119 (22.4)
Potassium supplement					256 (49.4)	271 (50.9)

* p < 0.05

As can be seen from the table above, there were more males on placebo.

There were more diabetic patients on BiDil which explains the excess of diabetic drugs in this treatment group.

BiDil subjects had on average higher systolic and diastolic blood pressure;

Subjects on BiDil were more likely to be hypertensive;

Hypertensive as an etiology of HF was more prevalent on BiDil;

5.1.11.3.2 V-HeFT

Table 11. Demographics and other baseline characteristics of the V-HeFT I population

Characteristics	HYD/ISDN	Placebo
Age (yr.)	58.3	58.5
Heart Failure Symptoms (%)		
< 6 mo.	18.9	19.5
6 mo. – 1.5 yr.	23.2	27.2
1.5 – 4.0 yr.	25.4	22.4
> 4 yr.	32.4	30.9
Race (%)		
White	71	70
Black	27	29
Other	2	1
Etiology		
CAD	44.1	44.3
Previous MI	40.3	42.3
Alcohol excess	43.0	38.2
Hypertension	39.7	42.6
Diabetes	17.2	24.5
Previous Surgery		
Coronary Bypass	11.8	13.6
Valve Replacement	4.9	4.0
Previous Therapy*(%)		
Vasodilators	41.9	36.3
Antiarrhythmics	27.4	26.7
Sublingual Nitroglycerin	20.4	19.5
Anticoagulants	17.7	17.6

Characteristics	HYD/ISDN	Placebo
Clinical data		
Symptom Score	5.6	5.6
Arterial Pressure (mmHg)	119.6/75.0	118.9/76.1
Heart Rate (beats/min.)	83.1	81.5
Cardiothoracic Ratio (%)	52.8	52.9
EF (%)	30.3	30.4
LVIDD (cm/m ²)	3.5	3.5
Exercise Duration (min.)	9.7	9.8
Oxygen Consumption (ml/kg/min.)	14.4	15.0

Previous 6 months;

Table 12. Demographics and other baseline characteristics of the V-HeFT II population

Characteristics	HYD/ISDN N = 401	Enalapril N = 403
Age		
Mean (SD)	60.55 (8.52)	60.62 (8.25)
Race		
White	282 (70.32)	292 (72.46)
Black	109 (27.18)	106 (26.30)
Other	10 (2.29)	5 (1.24)
Duration of CHF (months)		
N	387	383
Mean (SD)	40.15 (48.64)	31.20 (37.84)
NYHA class		
I	22 (5.49)	24 (5.96)
II	210 (52.37)	200 (49.63)
III	167 (41.65)	178 (44.17)
IV	2 (0.50)	1 (0.25)
CAD	213 (53.25)	220 (54.59)
Previous MI	189 (47.13)	197 (48.88)
CVA (n, %)	38 (9.48)	46 (11.41)
Coronary Bypass Surgery	87 (21.70)	85 (21.09)
Hypertension (n, %)	182 (45.39)	199 (49.62)
Diabetes	80 (19.95)	84 (20.84)
Excessive use of alcohol	147 (36.65)	135 (33.50)
Tobacco Use (n, %)	132 (32.92)	135 (33.50)
Previous Therapy*(%)		
Vasodilators	247 (61.60)	250 (62.03)
Antiarrhythmics	106 (26.43)	100 (24.81)
Sublingual Nitroglycerin	67 (16.71)	64 (15.88)
Anticoagulants	88 (21.95)	84 (20.84)
Clinical Assessment		
Arterial Pressure (mmHg)		
Mean systolic/diastolic	126.98/78.44	125.53/77.97
EF (%)		
Mean (SD)	29.42 (11.53)	28.61 (10.87)
Oxygen consumption (ml/kg/min)		
Mean (SD)	13.54 (3.52)	13.84 (3.46)
Heart Rate (beats/min.)		
Mean (SD)	77.25 (11.93)	78.35 (12.06)
Cardiothoracic Ratio (%)		
Mean (SD)	53.0 (6.2)	53.7 (6.0)
LVIDD (cm/m ²)		
Mean (SD)	3.23 (1.22)	3.58 (1.42)

Characteristics	HYD/ISDN N = 401	Enalapril N = 403
Plasma Norepinephrine (pg/ml) Mean (SD)	543.79 (226.78)	592.59 (388.12)
Plasma rennin activity (ng/ml/hr) Mean (SD)	15.65 (28.09)	19.86 (52.64)
Atrial fibrillation (n, %)	63 (15.71)	46 (11.41)
S, Gallop (n, %)	69 (17.21)	89 (17.21)

5.1.11.4 Efficacy Findings

5.1.11.4.1 A-HeFT

5.1.11.4.1.1 Primary Efficacy Endpoint

5.1.11.4.1.1.1 Composite Score of All-Cause Mortality, First Hospitalization for HF and QOL

Table 13. Scoring of the components of the primary endpoint

Component	Score	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)
Death			
Yes	-3	32 (6.2)	54 (10.2)
No	0	486 (93.8)	478 (89.8)
Missing	-3	0 (0.0)	0 (0.0)
First hospitalization for heart failure			
Yes	-1	85 (16.4)	130 (24.4)
No	0	420 (81.1)	391 (73.5)
Missing	-1	13 (2.5)	11 (2.1)
Change from baseline in QOL at 6 months			
Improvement ≥10 units	2	180 (38.1)	166 (33.4)
Improvement ≥5 and <10 units	1	49 (10.4)	56 (11.3)
Change <5 units	0	117 (22.6)	126 (23.7)
Worsening ≥5 and <10 units	-1	46 (8.9)	32 (6.4)
Worsening ≥10 units	-2	80 (16.9)	117 (23.5)
Missing	-2	46 (8.9)	35 (6.6)

Table 14. Mean change in composite score of Mortality, Hospitalization for HF, and QOL

Composite score	BiDil (N = 518)	Placebo (N = 532)	p-value
Mean change	-0.16	-0.47	0.011 ¹ 0.016 ² 0.021 ³
Median	0	0	
Range	-6 to 2	-6 to 2	

¹ unadjusted two-sample t test

² sponsor's calculation using adaptive two-sample t test of Cui, Hung and Wang incorrectly

³ Dr. Hung's calculation using adaptive two-sample t test of Cui, Hung and Wang

Table 15. Mean change in composite score before and after sample size re-estimation at the 2d interim analysis (analyses completed by Dr. Hung)

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	Difference (B - P)	BiDil (N=354)	Placebo (N=380)	Difference (B - P)
Composite score	-0.23	-0.47	0.24	-0.07	-0.38	0.31

5.1.11.4.1.2 Secondary Efficacy Endpoints

5.1.11.4.1.2.1 Individual Scores of the Components of the Primary Composite

Table 16. Change in the mean of individual scores of the components of the composite endpoint (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	p-value
Death	-0.19	-0.30	0.019
First hospitalization for heart failure	-0.19	-0.27	0.003
Change from baseline in QOL at 6 months	0.21	0.10	0.24

¹ two-sample analysis

As can be seen from the table above, the significant change in the composite score was driven by mortality and hospitalization. The QOL score changed in the right direction but not significantly.

Table 17. Event rate and time to event analysis for deaths and first hospitalization for heart failure (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	Hazard ratio (95% CI)	p-value ¹
Death	32 ² (6.2%)	54 (10.2%)	0.47 (0.37, 0.89)	0.012
First hospitalization for heart failure	86 (18.4%)	130 (24.4%)	0.61 (0.46, 0.80)	< 0.001

¹ Cox regression analysis

² Two of these deaths were not included in the sponsor's primary analysis because they occurred one and five days post study closure.

Table 18. Mean change in the composite score at the 2d interim analysis or Look 2 (analyses completed by Dr. Hung)

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	HR (95% CI)	BiDil (N=354)	Placebo (N=380)	HR (95% CI)
Death	18 (11.0%)	18 (11.8%)	0.93 (0.49, 1.79)	14 (4.0%)	36 (9.5%)	0.38 (0.21, 0.71)
First HF hospitalization	35 (21.3%)	48 (31.6%)	0.66 (0.42, 1.01)	50 (14.1%)	82 (21.6%)	0.58 (0.41, 0.82)

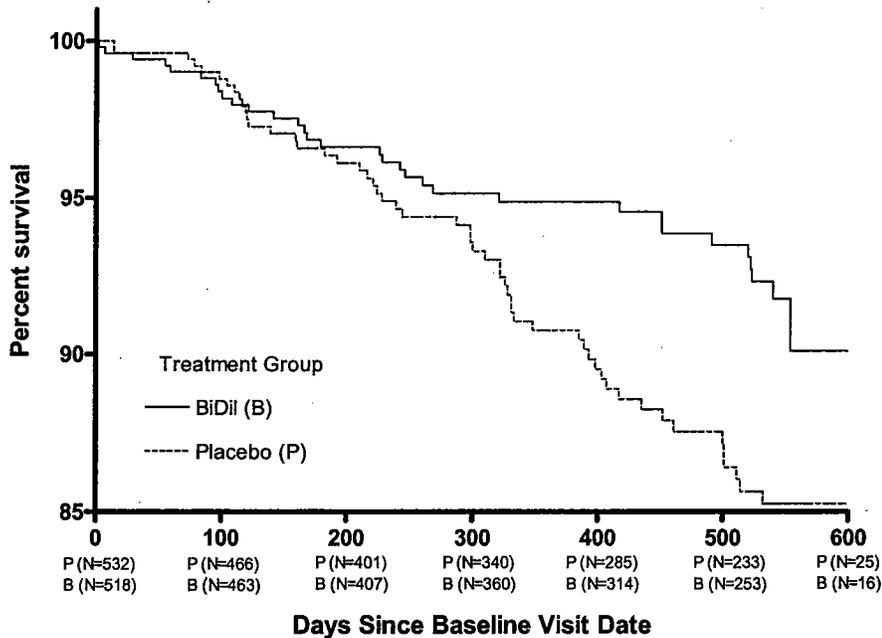
5.1.11.4.1.2.2 Death from Any Cause

Table 19. Tabulation of causes of death as adjudicated by ICAC (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)
All-cause mortality	32 (6.2%)	54 (10.2%)	0.47 (0.37, 0.89)
Heart failure deaths	21 (4.1%)	42 (7.9%)	0.61 (0.46, 0.80)
Sudden cardiac death	17 (3.3%)	24 (4.5%)	
Pump failure death	4 (0.8%)	16 (3.0%)	
MI-related death	0 (0.0%)	2 (0.4%)	
Cardiac procedure-related death	0 (0.0%)	0 (0.0%)	
Other cardiac cause-related death	0 (0.0%)	0 (0.0%)	
Non-heart failure (vascular death)	5 (1.0%)	3 (0.6%)	
Cerebrovascular accident death	4 (0.8%)	3 (0.6%)	
Vascular-related death	1 (0.2%)	0 (0.0%)	
Pulmonary embolism-related death	0 (0.0%)	0 (0.0%)	
Other vascular cause-related death	0 (0.0%)	0 (0.0%)	
Non-cardiovascular death	6 (1.2%)	9 (1.7%)	
Non-cardiovascular cause death	3 (0.6%)	5 (0.9%)	
Unknown cause death	3 (0.6%)	4 (0.8%)	

The reduction in all cause mortality was mainly due the reduction in cardiac failure deaths. The risk of sudden death is slightly higher on placebo, but not significantly different. One case on BiDil and three cases on placebo were classified by the investigator as due to cardiovascular causes, but due to non-cardiovascular causes by the ICAC, Table 49 page 72.

Figure 2. Kaplan-Meier estimates for all-cause mortality by treatment (Sponsor's analysis)



5.1.11.4.1.2.3 Number of Hospitalizations and Total Days in Hospital

Table 20. Hospitalization event rate and total days in hospital (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value
Event rate for hospitalization			
HF hospitalization	85 (16.4%)	130 (24.4%)	< 0.001 [#]
All cause hospitalization	202 (39.0%)	221 (41.5%)	0.41 ^{\$}
Other cardiac cause hospitalization	80 (15.4%)	90 (16.9%)	0.56 ^{\$}
Non-cardiac cause hospitalization	109 (21.0%)	117 (22.0%)	0.76 ^{\$}
Days in hospital (days/patient)			
HF hospitalization			
Mean (SD)	13.7 (16.6)	15.3 (20.2)	0.54 [*]
Range	2 - 122	2 - 164	
All cause hospitalization			
Mean (SD)	13.0 (15.6)	17.7 (21.6)	0.012 [*]
Range	2 - 135	2 - 196	
Other cardiac cause hospitalization			
Mean (SD)	7.2 (10.0)	7.4 (5.7)	0.90 [*]
Range	2 - 84	2 - 26	
Non-cardiac cause hospitalization			
Mean (SD)	8.1 (6.8)	10.6 (11.8)	0.051 [*]
Range	2 - 34	2 - 65	

Table compiled by Dr. Hung

log-rank test \$ Fisher's exact test * two-sample t test

Hospitalization for all causes, for other cardiac causes and for non-cardiac causes was not different between the treatment arms.

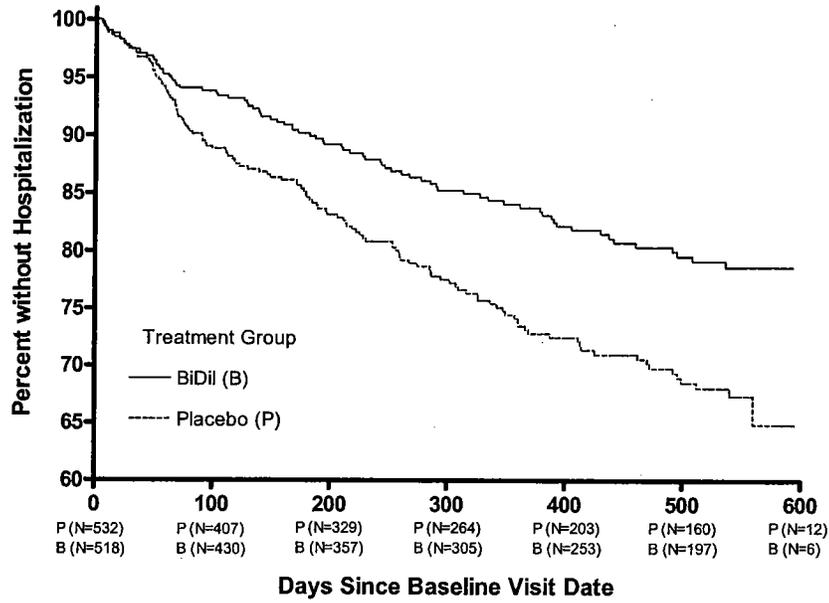
Days in hospital for HF were slightly different between BiDil and placebo, but not statistically significant. This is in contrast of a significant reduction in the rate of first HF hospitalization on BiDil. The lack of a significant difference in days spent in the hospital in the face of a significant difference in the rate of hospitalization for HF could be explained by a competing increased mortality on placebo.

Days in hospital for all causes were significantly reduced on BiDil and days in hospital for non-cardiac causes were of borderline significance.

Table 21. Event rate and time to event analysis for all-cause deaths and hospitalization (post hoc added secondary efficacy analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)	p-value ⁽¹⁾
First hospitalization for heart failure or all-cause mortality	108 (20.8%)	158 (29.7%)	0.63 (0.49, 0.81)	< 0.001
All-cause hospitalization or all-cause mortality	215 (41.5%)	237 (44.5%)	0.86 (0.72, 1.04)	0.12

Figure 3. Kaplan-Meier estimate for first heart failure hospitalization by treatment as adjudicated by the ICAC (Sponsor's analyses)



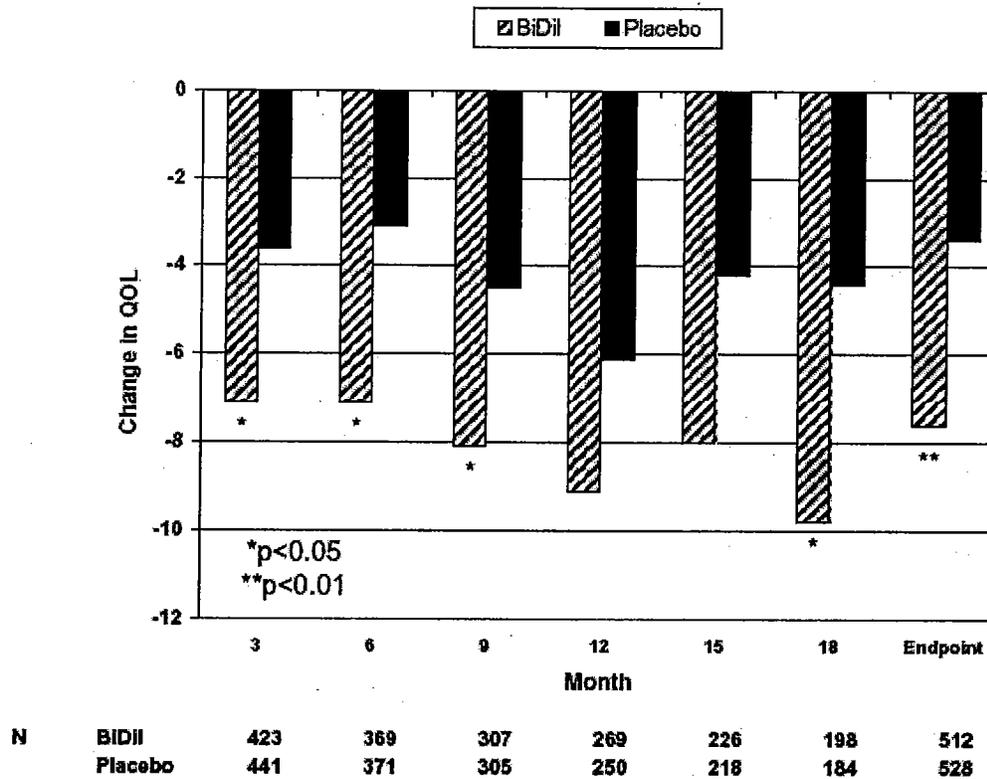
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5.1.11.4.1.2.4 Overall Quality Of Life throughout the Trial

Table 22. Quality of Life scores by treatment (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value[1]
Overall score			
Mean baseline	50.9	50.8	
Mean change (SD)	-7.6 (22.6)	-3.4 (22.7)	0.003
Range of change	-91 – 68	-105 – 70	
Physical score			
Mean baseline	22.1	22.0	
Mean change (SD)	-3.5 (10.5)	-1.4 (10.6)	0.002
Range of change	-40 – 29	-401 – 30	
Emotional score			
Mean baseline	10.4	10.4	
Mean change (SD)	-1.3 (6.8)	-0.7 (6.5)	0.13
Range of change	-25 – 22	-25 – 17	

Figure 4. Mean change from baseline in MLHF overall score throughout the trial (Sponsor's analysis)



5.1.11.4.1.2.5 Number of Unscheduled Emergency Room and Office/Clinic Visits

Table 23. Number (%) of patients with unscheduled emergency room or office/clinic visits by cause (Sponsor's analysis)

	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)	p-value ¹
Unscheduled ER visits for any reason			
0	379 (73.2)	385 (72.4)	0.782
1	88 (17.0)	87 (16.4)	
2	27 (5.2)	29 (5.5)	
3	10 (1.9)	17 (3.2)	
≥4	14 (2.7)	14 (2.3)	
Unscheduled ER visits for HF			
0	500 (96.5)	502 (94.4)	0.105
1	14 (2.7)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	1 (0.2)	4 (0.8)	
Unscheduled ER visits for other cardiac cause			
0	486 (93.8)	505 (94.9)	0.503
1	27 (5.2)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	2 (0.4)	1 (0.2)	
Unscheduled ER visits for non-cardiac cause			
0	401 (77.4)	416 (78.2)	0.767
1	80 (15.4)	77 (14.5)	
2	23 (4.4)	21 (3.9)	
3	7 (1.4)	6 (1.1)	
≥4	7 (1.4)	12 (2.3)	
Unscheduled office/clinic visits for HF			
0	511 (98.6)	528 (99.2)	0.379
1	6 (1.2)	4 (0.8)	
2	0 (0.0)	0 (0.0)	
3	1 (0.2)	0 (0.0)	

¹Fisher's exact test

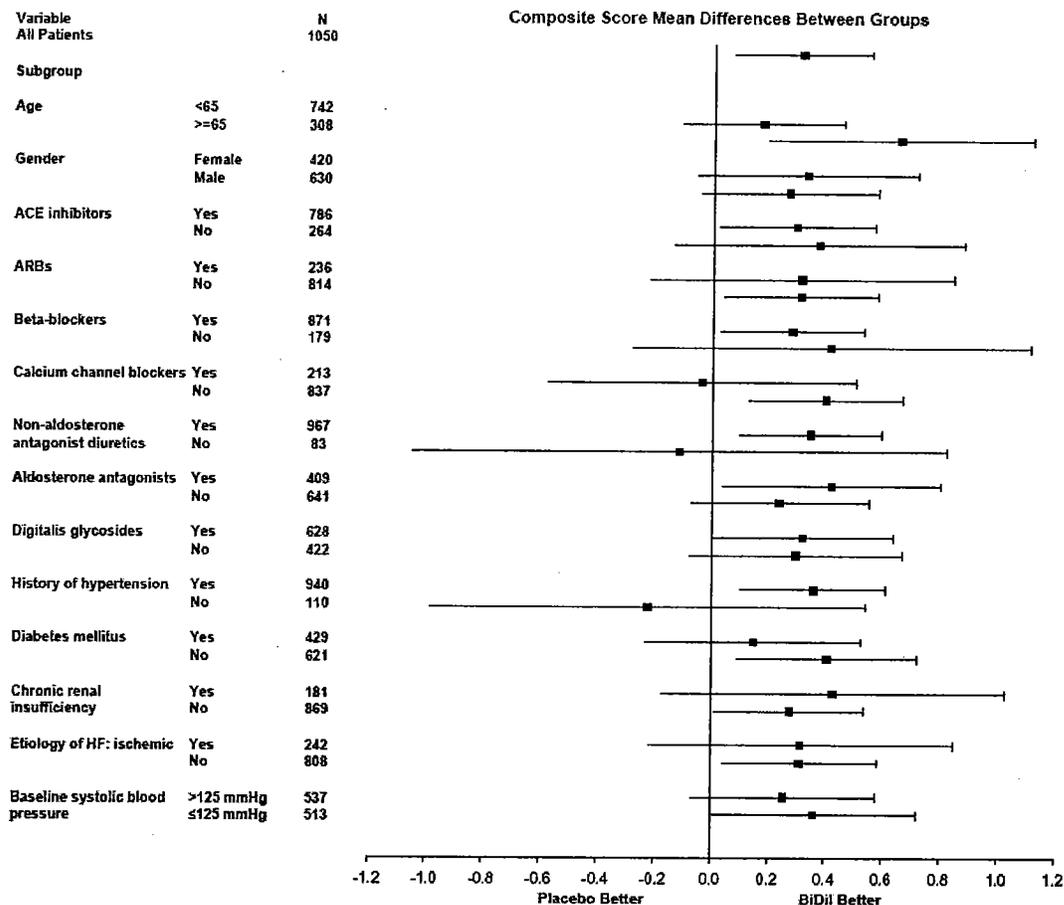
There were no differences between the two treatment groups with regard unscheduled visits for any cause. This may be due to the competing cause of mortality with subjects that would likely have had an unscheduled visit having died.

5.1.11.4.1.2.6 LVEF, LVIDD And LV Wall Thickness

Request to omit these findings from the submission were granted by the Division.

5.1.11.4.1.2.7 Composite Score Mean Differences by Baseline Demographic, Clinical and Therapeutic Characteristics

Figure 5. Composite score mean change by baseline characteristics (Sponsor's analysis)



All subgroup categories seem to have benefited in their score, except for three categories and these are subjects on calcium channel blockers, patients not receiving non-aldosterone antagonist diuretics, and patients with a non-hypertensive etiology of CHF.

5.1.11.4.1.3 Potential Confounding Factors Of Efficacy

Gender -A predominance of males in the placebo group with a difference of 8% between the two groups was observed. Gender being a significant risk factor of cardiovascular disease and death could have put the placebo group at a disadvantage with regard to HF outcomes.

Blood pressure –the BiDil group had higher systolic (+4 mmHg) and diastolic (+3 mmHg) blood pressure readings at baseline. If this difference stemmed from a high prevalence of hypotension in the placebo group this could have put this group at a disadvantage given that hypotension is not a desirable risk factor for HF..

Diabetes mellitus –almost 8% more of the BiDil group had DM at baseline. DM is a significant factor of cardiovascular disease progression and mortality, and it could have put the BiDil group at a disadvantage.

Hyperlipidemia –a little over 5% more of the BiDil group had hyperlipidemia at baseline. Hyperlipidemia a significant risk factor of cardiovascular diseases, and apart from its indirect prediction of the incidence of HF and its progression, it is not known what direct effect this has on the outcome of HF.

Etiology of HF -2.5% more of the placebo group had a non-hypertensive etiology, and 3% more has an idiopathic etiology of HF. The findings of A-HeFT show that BiDil was more effective in the subgroup with a hypertensive etiology.

COPD –a predominance (+3%) of COPD was observed in the placebo group. Given pulmonary edema is a complication of CHF, COPD could have played a role in the deterioration and possibly fatal outcomes of CHF and put the placebo group at a disadvantage.

Other baseline imbalances include 4% more of the placebo patients had a history of previous smoking, 2% more had peripheral vascular disease even if there were less diabetics on placebo, 2% more had arrhythmia, and 2% less each were on concomitant ARBs and aldosterone antagonists known to be beneficial in HF disease.

5.1.11.4.2 V-HeFT

5.1.11.4.2.1 V-HeFT I Efficacy Findings

Table 24. Crude mortality rate and cause of death in the V-HeFT I trial²

	BiDil (N = 186)	Placebo (N = 273)	Prazosin (N = 183)
# of deaths	72	120	91
Crude mortality rate	38.7%	44.0 %	49.7%
Cause of death	n (%)	n (%)	n (%)
Pump failure	22 (31)	38 (32)	33 (36)
Primary arrhythmia	27 (37)	45 (38)	32 (35)
Other	6 (8)	4 (3)	6 (7)
Unknown	5 (7)	4 (3)	3 (3)
Cardiac	1 (1)	-	-
Suspected cardiac	10 (14)	20 (17)	-
Not specified	1 (1)	9 (7)	17 (19)

Table 25. Crude mortality and 95% CI for population subgroups²

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
CAD						
Yes	82	41.5	121	50.4	-8.9	-22.8, 5.0
No	84	36.5	152	38.8	-2.3	-14.4, 9.8
Race						
Black	49	30.6	79	44.3	-13.7	-30.6, 3.2
Non-black	136	41.9	194	43.8	-1.9	-12.7, 8.9
Baseline EF						

² Dr. Hung’s review of V-HeFT I

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
> median	88	29.5	123	33.3	-3.8	-16.5, 8.9
< median	88	48.9	131	51.9	-3.0	-16.5, 10.5
Baseline Max O ₂						
> median	93	33.3	139	32.4	-1.0	-11.3, 13.3
< median	92	44.6	133	55.6	-11.1	-24.3, 2.1

5.1.11.4.2.2 V-HeFT II Efficacy Findings

Table 26. Crude mortality rate in the V-HeFT II Trial³

Crude mortality	BiDil N = 401 n (%)	Enalapril N = 403 n (%)
2-year mortality	95 (23.7)	68 (16.9)
5-year mortality	153 (38.2)	132 (32.8)

Table 27. Cumulative mortality from Life Table Analysis³

Year	Number alive at start		Cumulative mortality (%)	
	BiDil	Enalapril	BiDil	Enalapril
1	401	4.3	13.0	09.0
2	329	344	25.0	18.0
3	239	262	36.0	31.0
4	152	165	47.0	42.0
5	84	85	54.0	48.0

p (logrank for survival) 0.019 (2 years), 0.083 (overall)

Table 28. Crude mortality rates based on race and alcohol use³

	N	BiDil: Enalapril	BiDil - Enalapril	95% CI	95% CI Hazard Ratio
Black	109	0.36 : 0.37	-0.010	-0.14, 0.12	0.65, 1.58
Non-black	292	0.39 : 0.31	0.077	0.00, 0.15	1.01, 1.74
Alcohol use	147	0.37 : 0.39	-0.011	-0.12, 0.10	0.78, 1.66
No alcohol use	254	0.39 : 0.30	0.087	0.01, 0.17	0.97, 1.75

5.1.11.4.2.3 V-HeFT Trial Analyses Findings by Race

Post-hoc analyses of the V-HeFT I and V-HeFT II study data were used to promote the benefit of BiDil in African-American CHF patients. See Table 2 and Table 3 in 2.1, page 13.

5.1.11.4.3 Efficacy Conclusions

In the pivotal trial, the primary composite endpoint score was shown to be statistically significantly different between the BiDil and placebo treatment arms. The effect on all-cause mortality and first hospitalization for heart failure, two components of the composite endpoint, was shown to be substantial and statistically significant. The score of the third component of this composite, the QOL was shown not to be statistically significantly different between the treatment arms, but a trend of an effect was observed. This does not carry as much weight because it is not as robust in predicting the progression of HF as the other two components of the primary endpoint.

³ Dr. Hung's review of V-HeFT II

From the supportive trials in the overall study populations, the difference in mortality rates was either not statistically significant when BiDil was compared to placebo (V-HeFT I), Table 24, page 40, or it was higher on BiDil compared to enalapril (V-HeFT II), Table 26, page 41 and Table 27, page 41. Subgroup analyses have shown that crude mortality rates in Blacks on BiDil were either substantially reduced compared to placebo (V-HeFT I), Table 25 page 40, or trending toward a reduction compared to enalapril, Table 28 page 41.

5.1.11.4.3.1 Could Lowering Blood Pressure Have Accounted for the Difference Observed in Effect?

Blood pressure on BiDil was consistently and statistically significantly reduced at all visits including the 6-month time point; Table 42, page 56.

Additionally, subgroup analysis showed that BiDil had more effect in subjects with a history of hypertension than those without, Figure 5 page 39.

In the V-HeFT II trial, systolic and diastolic blood pressure on enalapril decreased to a greater degree compared to BiDil (-3-4 mmHg vs. -1-1.5 mmHg) at 12 months.

A meta-analysis investigating whether pharmacological properties of antihypertensive drugs or reduction of systolic pressure accounted for cardiovascular outcome in hypertensive or high-risk patients was conducted⁴. The authors' conclusion was that the effect of anti-hypertensive drugs, ACE inhibitors and betablockers had an effect on the prognosis of cardiovascular diseases through their anti-hypertensive effects.⁵

5.1.11.4.3.2 The Effect Of Other Covariates

Analyses conducted by Dr. Hung adjusting for baseline characteristics (discussed in 5.1.11.4.3.2 page 42) that are believed to be associated with HF outcomes, did not change the magnitude or the significance of the effect of BiDil on the primary endpoint.

5.1.11.4.3.3 Is It a Difference of Race?

To think in terms of a difference in effect of a biopharmaceutical substance one can't help thinking in terms of a difference in the pathophysiology of the condition intended for treatment. This was the hypothesis that the Sponsor put forward to explain the failure of the V-HeFT trials in demonstrating the effect of BiDil in a population that was predominantly Caucasian, the V-HeFT post-hoc analysis findings by race, and the success of A-HeFT in preventing undesirable HF outcomes in an African-American population.

What is problematic in relating the effect observed in A-HeFT to race and interpreting it at the pathophysiological or molecular level is the definition used, an old-fashioned way of determining race which relies on one's perception of one's race.

The difference by race in the response of hypertension to ACE inhibitors was determined as a result of consistent findings from many ACE inhibitors hypertension trials even though a difference in response at the physiological level was demonstrated only in small numbers of patients and using only surrogate markers.

⁴ Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; 358: 1305-15

⁵ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903-13

Given that Caucasians respond favorably to ACE inhibitors for the treatment of both hypertension and heart failure and that AA do not respond well to ACE inhibitors for the treatment of hypertension, one would expect that AA would not respond well to ACE inhibitors for the treatment of heart failure either.

Hypertension is a well-established determinant of incident heart failure and of its prognosis. Racial differences in patients with heart failure were reported to be in the mean age, prevalence of hypertension, left ventricular hypertrophy and ejection fraction. It is also reported that hypertension is more prevalent as an etiologic factor of HF in African Americans than in Caucasians. The characteristics (cited above) of the average African American failing heart are telling of a prevalent pathophysiology of systemic resistance as a cause of and/or a precipitating factor of HF. Common sense dictates that the reduction of this resistance would not only prevent HF, but its deleterious outcomes as well.

The reviewer's argument is that finally a drug is probably able to efficiently control blood pressure in AAs and prevent the consequences of both hypertension and HF. Facts that support and those that do not support the reviewer's argument follow:

--Facts NOT supporting:

- Lack of data that the HYD/ISDN combination is effective in the treatment of hypertension in AAs;
- Lack of data that the combination is superior to ACE-Is, ARBs and/or beta-blockers in the treatment of hypertension in AAs;
- Lack of data from well-conducted clinical trials that lowering BP is the mechanism by which the above therapies reduce and/or delay the outcomes of HF;

--Facts supporting:

- Anti-hypertensive therapies are well documented therapies for HF;
- Most medications that were shown to be effective in HF including ACE-Is, beta-blockers, ARBs, aldosterone antagonists and now BiDil have a strong feature in common, lowering blood pressure;
- Findings of the V-HeFT trials: in the V-HeFT I, BiDil seems⁶ to be superior to placebo in AAs, and in the V-HeFT II, BiDil seems to be "non-inferior"⁷ to enalapril in AA patients, especially that enalapril was shown to be clearly superior to BiDil in the overall population;
- In A-HeFT:
 - the group of patients on BiDil had a higher prevalence of hypertension at baseline and a higher prevalence of hypertension as an etiologic factor of HF;
 - the mean BP at baseline of the subjects on BiDil was higher than that of subjects on placebo;

⁶ the term "seem" is used because the analyses were not pre-specified, and the findings are result of post-hoc analysis

⁷ the design was not a non-inferiority design, but the trend was shifted toward no difference between AA on BiDil and AA on enalapril

-the mean change from baseline in trough blood was significantly greater on BiDil compared to placebo;

-In V-HeFT II enalapril lowered BP to a greater extent than BiDil;

-Data from two meta-analyses concluding that lowering blood pressure in HF wards off its undesirable outcomes (see selected figures from these publications: Figure 6 page, Figure 7 page 81, Figure 8 page 82 and Figure 9 page 83):

- Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15.
- Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

In the pivotal trial, assessment of safety was to consist of monitoring and recording all adverse events, SAEs, measurements of vital signs, and findings of physical examinations.

It was assumed that the safety profile of BiDil was known, therefore, there was to be no routine laboratory monitoring. Abnormal laboratory values or test results were considered as adverse events only if they induced clinical signs or symptoms or required change in therapy.

Hospitalization for HF, worsening of HF, and unscheduled office or emergency room visits for HF were not to be reported as adverse events because they were to be assessed as efficacy endpoints.

An independent Data and Safety Monitoring Board was to monitor the conduct of the study, review periodic reports of safety data by blinded treatment group, and make recommendations to the Steering Committee.

In addition, data from the V-HeFT I and V-HeFT II studies and from the CB-01 and CB-02 were reviewed for safety.

CB-01 “The 36-Hour Relative Bioavailability of BiDil, a Fixed Combination of Hydralazine/Isosorbide dinitrate, compared to Equivalent Doses of Reference Products (Pilot Study)”. In this study 12 subjects received one dose of BiDil.

CB-02 “The Relative Bioavailability of Low and High dose BiDil, a fixed combination of Hydralazine HCL and isosorbide dinitrate, compared to an Oral Solution, Tablet, and Capsule of Hydralazine HCL and ISDN (Pivotal Bioequivalence Study)”

6.1.1 Overview of Adverse Events

Table 29. Summary of overall adverse events (Sponsor’s summary)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Patients with at least one adverse event	475 (91.9)	432 (82.0)
Patients with at least one drug-related adverse event ¹	350 (67.7)	167 (31.7)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Patients with at least one serious adverse event ²	181 (35.0)	183 (34.7)
Patients with at least one drug-related serious adverse event ^{1,2}	13 (2.5)	15 (2.8)
Patients who died ³	32 (6.2)	54 (10.2)
Patients who permanently discontinued study drug due to adverse events ⁴	109 (21.1)	63 (12.0)

¹ Assessed by the investigator as being possibly, probably, or definitely related to study drug.

² Serious adverse events exclude clinical endpoint HF hospitalization and adverse event death.

³ Adjudicated by the ICAC includes two patients (112-001 and 231-002) who died post-study.

⁴ As recorded on the adverse event CRF, includes patients who completed the study and those who did not complete the study, may include patients who temporarily stopped study drug as well as permanent discontinuations.

6.1.2 Deaths

Deaths are summarized under the efficacy section because all cause mortality is a component of the primary endpoint and stands on its own as a secondary endpoint.

6.1.3 Other Serious Adverse Events

6.1.3.1 Serious Adverse Events that led to Discontinuation

Table 30. Serious adverse events that led to discontinuation, overall incidence

AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)	AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Any AE N (%)	29 (5.6)	32 (6.1)			
Chest pain	3 (0.6)	1 (0.2)	CVA	1 (0.2)	3 (0.6)
Heart arrest	3 (0.6)	3 (0.6)	Syncope	1 (0.2)	0.0
Heart failure	3 (0.6)	4 (0.8)	Gastroenteritis	1 (0.2)	1 (0.2)
Hypotension	3 (0.6)	1 (0.2)	Myasthenia	1 (0.2)	0.0
Kidney failure	3 (0.6)	1 (0.2)	Dyspnea	1 (0.2)	2 (0.4)
Infection	2 (0.4)	0.0	Edema of the lung	1 (0.2)	0.0
Ventricular fibrillation	2 (0.4)	0.0	Angioedema	1 (0.2)	0.0
Dizziness	2 (0.4)	0.0	Carcinoma of the breast	1 (0.2)	0.0
Arrhythmia	1 (0.2)	0.0	Uremia	1 (0.2)	0.0

As can be seen from the table above, the numbers are very small but more events, the ones expected to be observed, on BiDil were serious and led to discontinuation including hypotension, dizziness and chest pain. Of note are 3 cases of kidney failure vs. 1, and 2 cases of ventricular fibrillation vs. none on BiDil and placebo respectively.

6.1.3.2 Serious Adverse Events

Table 31. Serious adverse events, overall incidence

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
Number (%) of patients with at least one SAE	181 (35.0)	183 (34.7)	1.0
Chest pain	33 (6.4)	29 (5.5)	1.2
Heart failure	16 (3.1)	41 (7.8)	0.4
Ventricular tachycardia	14 (2.7)	8 (1.5)	1.8
Pneumonia	12 (2.3)	8 (1.5)	1.5
Syncope	11 (2.1)	8 (1.5)	1.4
Dyspnea	10 (1.9)	12 (2.3)	0.8
Arrhythmia	9 (1.7)	7 (1.3)	1.3
Hypotension	8 (1.5)	3 (0.6)	2.5
Heart arrest	7 (1.4)	9 (1.7)	0.8
CVA	7 (1.4)	13 (2.5)	0.6
Dizziness	7 (1.4)	0.0	NA
Cellulites	6 (1.2)	2 (0.4)	3.0
DM	6 (1.2)	5 (0.9)	1.3
Cerebral ischemia	5 (1.0)	1 (0.2)	5.0
Coronary artery disease	5 (1.0)	2 (0.4)	2.5
Anemia	5 (1.0)	3 (0.6)	1.7
Bronchitis	5 (1.0)	3 (0.6)	1.7
Dehydration	5 (1.0)	4 (0.8)	1.3
Angina pectoris	5 (1.0)	5 (0.9)	1.1
Hyperglycemia	5 (1.0)	5 (0.9)	1.1
Hypoglycemia	5 (1.0)	5 (0.9)	1.1
Infection	5 (1.0)	5 (0.9)	1.1
Acute kidney failure	5 (1.0)	8 (1.5)	0.7
Neoplasm/carcinoma	4 (0.8)	1 (0.2)	4.0
Gout	4 (0.8)	3 (0.6)	1.3
Atrial fibrillation	4 (0.8)	3 (0.6)	1.3
GI hemorrhage	4 (0.8)	5 (0.9)	0.9
Kidney failure	4 (0.8)	5 (0.9)	0.9
Myocardial infarct	4 (0.8)	9 (1.7)	0.5
Sepsis	3 (0.6)	1 (0.2)	3.0
Asthma	3 (0.6)	2 (0.4)	1.5
Injury, accidental	3 (0.6)	8 (1.5)	0.4
Cholecystitis	3 (0.6)	0.0	NA
Cholelithiasis	3 (0.6)	0.0	NA
Supraventricular tachycardia	3 (0.6)	0.0	NA
Esophagitis	2 (0.4)	1 (0.2)	2.0
Edema of the lung	2 (0.4)	1 (0.2)	2.0
Headache	2 (0.4)	2 (0.4)	1.0
Osteomyelitis	2 (0.4)	2 (0.4)	1.0
Peripheral vascular disease	2 (0.4)	2 (0.4)	1.0
Bradycardia	2 (0.4)	3 (0.6)	0.7
Digitalis intoxication	2 (0.4)	4 (0.8)	0.5
Gastroenteritis	2 (0.4)	4 (0.8)	0.5
Hyperkalemia	2 (0.4)	5 (0.9)	0.4
Hemorrhage, cerebral+	2 (0.4)	0.0	NA

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
subarachnoid			
Thrombophlebitis, deep	2 (0.4)	0.0	NA
Angioedema	2 (0.4)	0.0	NA
Ascites	2 (0.4)	0.0	NA
Infection viral/fungal	2 (0.4)	0.0	NA
Fibrillation, ventricular	2 (0.4)	0.0	NA
Anomaly Vascular	1 (0.2)	1 (0.2)	1.0
Coagulation disorder	1 (0.2)	1 (0.2)	1.0
Creatinine increased	1 (0.2)	1 (0.2)	1.0
Hyponatremia	1 (0.2)	1 (0.2)	1.0
Diarrhea	1 (0.2)	1 (0.2)	1.0
Liver failure	1 (0.2)	1 (0.2)	1.0
Neoplasm of the prostate	1 (0.2)	1 (0.2)	1.0
Myasthenia	1 (0.2)	1 (0.2)	1.0
Palpitations	1 (0.2)	1 (0.2)	1.0
UTI	1 (0.2)	1 (0.2)	1.0
Dyspepsia	1 (0.2)	2 (0.4)	0.5
Kidney function abnormal	1 (0.2)	4 (0.8)	0.3
Anemia, iron deficiency	1 (0.2)	0.0	NA
Alkalosis	1 (0.2)	0.0	NA
Arrhythmia NOD	1 (0.2)	0.0	NA
Arthralgia	1 (0.2)	0.0	NA
Carcinoma of the breast	1 (0.2)	0.0	NA
Hypokalemia	1 (0.2)	0.0	NA
Ketosis	1 (0.2)	0.0	NA
Cerebral infarct	1 (0.2)	0.0	NA
Emotional lability	1 (0.2)	0.0	NA
Edema of the face	1 (0.2)	0.0	NA
Gastritis, hemorrhagic	1 (0.2)	0.0	NA
Gait abnormal	1 (0.2)	0.0	NA
Hematemesis	1 (0.2)	0.0	NA
Herpes Zoster	1 (0.2)	0.0	NA
Uremia	1 (0.2)	0.0	NA
Leucopenia	1 (0.2)	0.0	NA
Thrombocytopenia	1 (0.2)	0.0	NA
Necrosis	1 (0.2)	0.0	NA
Ophthalmitis	1 (0.2)	0.0	NA
Parathyroid disease	1 (0.2)	0.0	NA
Respiratory distress	1 (0.2)	0.0	NA
Skin ulcer	1 (0.2)	0.0	NA
Thinking abnormal	1 (0.2)	0.0	NA
Vascular disease	1 (0.2)	0.0	NA
Wrist drop	1 (0.2)	0.0	NA
Gastritis	1 (0.2)	2 (0.4)	0.5

As can be seen from the table above, some of the adverse events that were expected to be observed were reported as serious in excess on BiDil including hypotension, dizziness and syncope. Other serious adverse events were also reported in excess on BiDil compared to placebo and these are ventricular tachycardia, pneumonia, cellulites, cerebral ischemia, CAD, anemia and bronchitis.

6.1.4 Other Significant Adverse Events

6.1.4.1 Overall Profile of Dropouts

Forty nine (9.5%) of the subjects on BiDil and 75 (14%) of the subjects on placebo discontinued the study prematurely. One hundred and nine (21%) of the subjects on BiDil and 63 (12%) of the placebo patients discontinued the study medication as a result of adverse events. Five BiDil and 3 placebo subjects withdrew consent, 2 BiDil subjects were lost to follow-up, 9 (1.7%) BiDil and 13 (2.4%) placebo patients discontinued per investigator decision, 3 in each study group discontinued for cardiac transplant and 32 BiDil and 54 placebo patients died.

6.1.4.2 Adverse Events Associated with Permanent Discontinuation

Twenty one percent (109) on BiDil and 12% (63) on placebo permanently discontinued the study drug as a result of adverse events. Using the number of events, 5.9% (170 of all events) compared to placebo 3.3% (91 of all events) led to permanent discontinuation.

Table 32. Adverse events leading to treatment discontinuation (number and % of subjects)

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
Any AE N (%)	109 (21.1)	63 (12.0)	1.8				
Asthenia	12 (2.3)	1 (0.2)	11.5	Ventricular fibrillation	2 (0.4)	0.0	NA
Headache	38 (7.4)	4 (0.8)	9.3	Angioedema	1 (0.2)	0.0	NA
Dizziness	19 (3.7)	4 (0.8)	4.6	Amblyopia	1 (0.2)	0.0	NA
Pain	4 (0.8)	1 (0.2)	4.0	Anorexia	1 (0.2)	0.0	NA
Chest pain	8 (1.5)	2 (0.4)	3.8	Neck pain	1 (0.2)	0.0	NA
Nausea	8 (1.5)	2 (0.4)	3.8	Carcinoma	1 (0.2)	0.0	NA
Hypotension	7 (1.4)	3 (0.6)	2.3	Carcinoma of the breast	1 (0.2)	0.0	NA
Abdominal pain	2 (0.4)	1 (0.2)	2.0	Dehydration	1 (0.2)	0.0	NA
Chills	2 (0.4)	1 (0.2)	2.0	Edema of the face	1 (0.2)	0.0	NA
Kidney failure	2 (0.4)	1 (0.2)	2.0	Edema peripheral	1 (0.2)	0.0	NA
Malaise	2 (0.4)	1 (0.2)	2.0	Edema of the lung	1 (0.2)	0.0	NA
Heart arrest	3 (0.6)	3 (0.6)	1.0	Fever	1 (0.2)	0.0	NA
Confusion	2 (0.4)	2 (0.4)	1.0	Hyperglycemia	1 (0.2)	0.0	NA
Diarrhea	2 (0.4)	2 (0.4)	1.0	Hypertension	1 (0.2)	0.0	NA
Gastroenteritis	1 (0.2)	1 (0.2)	1.0	Infection	1 (0.2)	0.0	NA
Back pain	1 (0.2)	1 (0.2)	1.0	Infection fungal	1 (0.2)	0.0	NA
Acute kidney failure	1 (0.2)	1 (0.2)	1.0	Impotence	1 (0.2)	0.0	NA
Myasthenia	1 (0.2)	1 (0.2)	1.0	Ketosis	1 (0.2)	0.0	NA
Nervousness	1 (0.2)	1 (0.2)	1.0	Breast neoplasm	1 (0.2)	0.0	NA
Pruritus	1 (0.2)	1 (0.2)	1.0	Lab tests abnormal	1 (0.2)	0.0	NA
Heart failure	3 (0.6)	4 (0.8)	0.8	Myalgia	1 (0.2)	0.0	NA
Dyspepsia	1 (0.2)	2 (0.4)	0.5	Photophobia	1 (0.2)	0.0	NA
Cerebrovascular accident	1 (0.2)	3 (0.6)	0.3	Pleural effusion	1 (0.2)	0.0	NA
Constipation	1 (0.2)	3 (0.6)	0.3	Somnolence	1 (0.2)	0.0	NA
CVA	1 (0.2)	3 (0.6)	0.3	Sweat	1 (0.2)	0.0	NA
Dyspnea	1 (0.2)	4 (0.8)	0.3	Vasodilatation	1 (0.2)	0.0	NA
Nausea vomiting	3 (0.6)	0.0	NA	Weight decrease	1 (0.2)	0.0	NA
Paresthesia	3 (0.6)	0.0	NA	Uremia	1 (0.2)	0.0	NA
Abnormal kidney function	2 (0.4)	0.0	NA	Hypoglycemia	0.0	2 (0.4)	NA
Kidney function	2 (0.4)	0.0	NA	Myocardial infarction	0.0	4 (0.8)	NA

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
abnormal							
Palpitations	2 (0.4)	0.0	NA	Rash	0.0	3 (0.6)	NA
Syncope	2 (0.4)	0.0	NA	Rectal hemorrhage	0.0	2 (0.4)	NA

Table excludes hospitalization for HF and death. A patient can have more than one event or type of event; each patient is counted only once in each category.

Discontinuation of study drug due to adverse events was observed in excess (80% excess in risk) on BiDil, and headache alone accounted for a third of these. Headache, dizziness, asthenia, chest pain, nausea, and hypotension accounted for 84% of the discontinuations on BiDil and only 25% of the discontinuations on placebo.

Of note are two cases of ventricular fibrillation, and two cases of syncope on BiDil vs. none on placebo.

6.1.4.3 Adverse Events Associated with Temporary Discontinuation or Dose Adjustment

Dose adjustment or temporary study drug discontinuation occurred at a higher incidence in patients on BiDil 42.2% (218) compared to those on placebo 25.2% (133), and of these 19.3% (42) and 26.3% (35) returned to pre-event dose level.

Twenty percent (570) and 13% (341) of the events led to temporary discontinuation or dose level adjustment in BiDil and placebo respectively.

6.1.5 Other Search Strategies

The clinical and statistical results of the V-HeFT studies reported here are those summarized by the Division's review of the original NDA (Doctors Hung, Chen and Ganley, 1997).

6.1.6 Common Adverse Events

6.1.6.1 Eliciting Adverse Events Data in The Development Program

Investigators were instructed to report all adverse events that occur before, during or within 14 days following the cessation of treatment whether or not believed to be related to the study drug. Patients were assessed every three months when they returned for a study visit.

There were no plans to assess of the effect of BiDil on laboratory parameters, QT interval and the immune system because it was assumed that its safety profile was known.

6.1.6.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse events were summarized by body system and using the COSTART preferred term. This categorization and the preferred term used were used in other trials and deemed acceptable.

6.1.6.3 Incidence of Common Adverse Events in the A-Heft Trial

Table 33. Common adverse events, overall incidence by treatment ($\geq 0.4\%$, and where in excess on BiDil)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR		BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
N (%) with at least one AE	475 (91.9)	432 (82.0)	1.1				

	BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR		BiDil N = 517 n (%)	Placebo N = 527 n (%)	RR
Headache	256 (49.5)**	111 (21.1)	2.3	Infection, viral	7 (1.4)	3 (0.6)	2.3
Dizziness	165 (31.9)**	72 (13.7)	2.3	Myalgia	7 (1.4)	3 (0.6)	2.3
Asthenia	70 (13.5)	59 (11.2)	1.2	Rectal disease	7 (1.4)	4 (0.8)	1.8
Nausea	50 (9.7)*	32 (6.1)	1.6	Abscess peridontal	6 (1.2)	4 (0.8)	1.5
Bronchitis	43 (8.3)	34 (6.5)	1.3	Angioedema	6 (1.2)	1 (0.2)	6.0
Hypotension	41 (7.9)*	23 (4.4)	1.8	Cerebral ischemia + infarct	6 (1.2)	2 (0.4)	3.0
Syncope	23 (4.4)	20 (3.8)	1.2	Infection, sepsis	6 (1.2)	1 (0.2)	6.0
Sinusitis	22 (4.3)*	9 (1.7)	2.5	Malaise	6 (1.2)	1 (0.2)	6.0
Ventricular tachycardia	21 (4.1)	14 (2.7)	1.5	Cardiovascular disease	5 (1.0)	0.0	
GI disorder	20 (3.9)	14 (2.7)	1.4	Hernia	5 (1.0)	0.0	
				Melena	5 (1.0)	3 (0.6)	1.7
Palpitations	20 (3.9)	14 (2.7)	1.4	Tendon disease	5 (1.0)	2 (0.4)	2.5
Rhinitis	19 (3.7)	14 (2.7)	1.3	Cholelithiasis	4 (0.8)	1 (0.2)	4.0
Paresthesia	18 (3.5)	12 (2.3)	1.5	Hypotension, postural	4 (0.8)	2 (0.4)	2.0
Vomiting	18 (3.5)	10 (1.9)	1.8	Respiratory disease	4 (0.8)	2 (0.4)	2.0
Amblyopia	16 (3.1)	7 (1.3)	2.4	Tachycardia, supraventricular	4 (0.8)	0.0	
Hyperlipidemia	15 (2.9)	10 (1.9)	1.5	Vascular, anomaly	4 (0.8)	1 (0.2)	2.0
Abnormal kidney function	14 (2.7)	7 (1.3)	2.1	Vision abnormal	4 (0.8)	2 (0.4)	2.0
Cellulitis	11 (2.1)	9 (1.7)	1.2	Photosensitivity	3 (0.6)	1 (0.2)	3.0
Tachycardia	11 (2.1)	6 (1.1)	1.9	Bone disease	3 (0.6)	1 (0.2)	3.0
Infection, fungal	10 (1.9)	6 (1.1)	1.7	Duodenitis	3 (0.6)	0.0	
Sweat increase	10 (1.9)	5 (0.9)	2.1	Ear disorder	3 (0.6)	0.0	
Fever	9 (1.7)	7 (1.3)	1.3	Gastritis, hemorrhagic	3 (0.6)	1 (0.2)	3.0
Neoplasm	9 (1.7)	4 (0.8)	2.1	Headache, migraine	3 (0.6)	1 (0.2)	3.0
Pain, neck	9 (1.7)	7 (1.3)	1.3	Hypoxia	3 (0.6)	0.0	
Allergy reaction	9 (1.7)	6 (1.1)	1.5	Osteoporosis	3 (0.6)	0.0	
Arthralgia	8 (1.5)	2 (0.4)	3.8	Tenosynovitis	3 (0.6)	1 (0.2)	3.0
Somnolence	8 (1.5)	2 (0.4)	3.8	Vascular disease	3 (0.6)	1 (0.2)	3.0
Alopecia	7 (1.4)	3 (0.6)	2.3	Hepatomegaly	2 (0.4)	0.0	
Coronary artery disease	7 (1.4)	4 (0.8)	1.8	Hydronephrosis	2 (0.4)	0.0	
Cholecystitis	7 (1.4)	0.0		Thrombocytopenia	2 (0.4)	0.0	
Hypercholesterolemia	7 (1.4)	2 (0.4)	3.5	Uremia	2 (0.4)	0.0	

A patient can have more than one event or type of event; each patient is counted only once in each category.

* p < 0.05, BiDil vs. placebo

** p < 0.0001, BiDil vs. placebo

There was one case of lupus-like syndrome reported as joint disorder (narrative 9.5, page 74) which resolved after treatment and without a change to the study medication. Also, there was an excess of arthralgia (almost 4 times as frequent) on BiDil compared to placebo.

As can be seen from the table above, the overall rate of adverse events is not very different between the two treatment arms. Headache and dizziness are statistically significantly different between BiDil and placebo. Differences between BiDil and placebo reached statistical significance with regard to hypotension, nausea and sinusitis. Other adverse events where an increase on BiDil was observed include tachycardia, ventricular tachycardia, palpitations and supraventricular tachycardia; GI disorders and vomiting; paresthesia, sweat increase, and amblyopia and abnormal vision; hyperlipidemia and hypercholesterolemia; abnormal kidney function and uremia; infections (fungal, viral, sepsis and periodontal abscess); allergy reactions,

and angioedema; CVD and cerebral ischemia and/or infarct; arthralgia, malaise, myalgia, tendon disease, and tenosynovitis; hernia; rectal disease and melena; bronchitis, and respiratory disease; cholecystitis and cholelithiasis; somnolence; and neoplasm.

6.1.6.4 Incidence of Common Adverse Events In The V-Heft I And V-Heft II Trials

6.1.6.4.1 Incidence of Adverse Events in Blacks in the V-HeFT Studies

Table 34. Incidence of adverse events in the African-American subpopulation of the V-HeFT trials

Events	BiDil N = 158 n (%)	Placebo N = 79 n (%)	Enalapril N = 106 n (%)
Headache	113 (72%)	43 (54%)	68 (64%)
Dizziness	106 (67%)	42 (53%)	71 (67%)
Arthralgia	103 (65%)	48 (61%)	76 (72%)
Other*	82 (52%)	35 (44%)	63 (59%)
Palpitation	84 (53%)	29 (37%)	52 (49%)
Nausea or Vomiting	75 (47%)	32 (41%)	60 (57%)
Ischemic Chest Pain	58 (37%)	29 (37%)	44 (42%)
Diarrhea	63 (40%)	30 (38%)	46 (43%)
Flushing	50 (32%)	22 (28%)	23 (22%)
Rash	51 (32%)	23 (29%)	37 (35%)
Fever	52 (33%)	17 (22%)	31 (29%)
Syncope	36 (23%)	16 (20%)	16 (15%)

Table from the sponsor's report;

*Was not broken into specific AEs;

6.1.6.4.2 Incidence of Adverse Events in all Patients of the V-HeFT I Study

Six percent (11) and 1% (3) discontinued BiDil and placebo as a result of adverse events.

Table 35. Incidence of adverse events that resulted in dose reduction in V-HeFT I

Adverse Event	HYD/ISDN N = 186 %	Placebo N = 273 %
Any	51.6	22.0
Headache	40.3	5.5
Dizziness	25.8	12.1
Arthralgia	4.8	2.2
Other	11.3	6.6
Palpitations	10.8	2.6
Nausea or vomiting	11.3	5.5
Ischemic chest pain	3.8	2.6
Diarrhea	4.3	1.5
Abdominal pain	7.0	2.9
Flushing	8.6	1.1
Rash	4.3	1.5
Fever	3.8	0.0
Syncope	2.2	4.4

¹ Table from the V-HeFT I Medical/Statistical Review

Table 36. Incidence of adverse events in the V-HeFT I study

Adverse Event	HYD/ISDN	Placebo
	N = 186 %	N = 273 %
Any	94.6	87.2
Headache	74.7	50.9
Dizziness	70.4	59.7
Arthralgia	63.4	57.9
Other	61.3	49.5
Palpitations	55.9	44.0
Nausea or vomiting	52.2	45.1
Ischemic chest pain	48.9	41.4
Diarrhea	46.8	38.8
Abdominal pain	45.2	34.8
Flushing	43.6	30.4
Rash	43.0	38.1
Fever	33.3	26.4
Syncope	26.3	23.8

¹ Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.3 Incidence of Adverse Events in the V-HeFT II Study

Three percent (13) and 2.7% (11) discontinued BiDil and enalapril as a result of adverse events.

Table 37. Adverse events that led to dose reduction in V-HeFT II

Adverse Event	HYD/ISDN	Enalapril
	N = 401 %	N = 403 %
Headache	40.9	11.2
Fatigue/lassitude	28.9	23.6
Dizziness	26.9	19.4
Other	22.4	17.4
Nausea or vomiting	18.0	13.2
Arthralgia	11.0	6.4
Palpitations	10.2	5.0
Hypotension	7.5	9.7
Abnormal lab tests	7.2	11.2

¹ Table from the V-HeFT I Medical/Statistical Review

Table 38. Incidence of adverse events in V-HeFT II

Adverse Event	HYD/ISDN	Enalapril
	N = 401 %	N = 403 %
Any	98	100
Abnormal lab tests	92	97
Fatigue/lassitude	81	82
Headache	77	60
Arthralgia	69	72
Nasal congestion	68	68
Dizziness	67	67
Other	61	65
Palpitations	57	54
Nausea or vomiting	53	59
Chest pain	44	46

Adverse Event	HYD/ISDN N = 401 %	Enalapril N = 403 %
Constipation	42	44

¹ Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.4 Identifying Common and Drug-related Adverse Events

Headache, dizziness, nausea, vomiting, and arthralgia are very likely related to BiDil, and the rationale is that they were observed in excess on BiDil, led to withdrawal and/or dose reduction of BiDil, and were consistently associated with BiDil in the A-HeFT and V-HeFT trials.

Hypotension and postural hypotension are also very likely related to the study drug because of its vasodilating action.

6.1.6.4.5 Additional Analyses and Explorations

Table 39. Common adverse events by age categories

Number (%) of patients with at least one AE	<65 years		RR	≥65 years		RR
	BiDil N = 361 n (%)	Placebo N = 376 n (%)		BiDil N = 156 n (%)	Placebo N = 151 n (%)	
Any AE	342 (94.7)	303 (80.6)	1.2	133 (85.3)	129 (85.4)	1.0
Headache	198 (54.8)	89 (23.7)	2.3	58 (37.2)	22 (14.6)	2.5
Dizziness	115 (31.9)	46 (12.2)	2.6	50 (32.1)	26 (17.2)	1.8
Asthenia	49 (13.6)	45 (12.0)	1.1	21 (13.5)	14 (9.3)	1.5
Nausea	37 (10.2)	19 (5.1)	2.0	13 (8.3)	13 (8.6)	1.0
Bronchitis	30 (8.3)	26 (6.9)	1.2	13 (8.3)	8 (5.3)	1.6
Hypotension	29 (8.0)	18 (4.8)	1.7	12 (7.7)	5 (3.3)	2.3
Peripheral edema	24 (6.6)	25 (6.6)	1.0	1 (0.6)	12 (7.9)	0.1
Ventricular tachycardia	15 (4.2)	12 (3.2)	1.3	6 (3.8)	2 (1.3)	2.9
GI disorder	15 (4.2)	11 (2.9)	2.2	5 (3.2)	3 (2.0)	1.6
Vomiting	15 (4.2)	7 (1.9)	2.2	3 (1.9)	3 (2.0)	1.0
Palpitations	14 (3.9)	12 (3.2)	1.2	6 (3.8)	2 (1.3)	2.9
Paresthesia	14 (3.9)	10 (2.7)	1.4	4 (2.6)	2 (1.3)	2.0
Hyperlipidemia	13 (3.6)	5 (1.3)	2.8	2 (1.3)	5 (3.3)	0.4
Rhinitis	12 (3.5)	11 (2.9)	1.2	7 (4.5)	3 (2.0)	2.3
Amblyopia	10 (2.8)	4 (1.1)	2.5	6 (3.8)	3 (2.0)	1.9
Rash	8 (1.9)	11 (2.9)	0.7	5 (3.2)	3 (2.0)	1.6
Gastritis	7 (1.9)	4 (1.1)	1.7	1 (0.6)	5 (3.3)	0.2
Anorexia	6 (1.7)	4 (1.1)	1.5	2 (1.3)	5 (3.3)	0.4
Anxiety	2 (0.6)	4 (1.1)	0.6	5 (3.2)	2 (1.3)	2.5
Hematuria	5 (1.4)	1 (0.3)	4.7	1 (0.6)	5 (3.3)	0.2

Dizziness, nausea, vomiting and gastritis seem to be more prevalent in younger subjects, while ventricular tachycardia, palpitations, and anxiety were more common in older subjects.

Table 40. Common adverse events by gender

	Male gender		RR	Female gender		RR
	BiDil N = 289 n (%)	Placebo N = 228 n (%)		BiDil N = 337 n (%)	Placebo N = 190 n (%)	
Headache	129 (44.6)	55 (16.3)	2.7	127 (55.7)	56 (29.5)	1.9
Dizziness	83 (28.7)	49 (14.5)	2.0	82 (36.0)	23 (12.1)	3.0
Hypotension	23 (8.0)	12 (3.6)	2.2	18 (7.9)	11 (5.8)	1.4

	Male gender			Female gender		
	BiDil N = 289 n (%)	Placebo N = 228 n (%)	RR	BiDil N = 337 n (%)	Placebo N = 190 n (%)	RR
Bronchitis	18 (6.2)	24 (7.1)	0.9	25 (11.0)	10 (5.3)	2.1
Gout	18 (6.2)	27 (8.0)	0.8	9 (3.9)	5 (2.6)	1.5
Hypertension	15 (5.2)	22 (6.5)	0.8	18 (7.9)	11 (5.8)	1.4
Syncope	12 (4.2)	15 (4.5)	0.9	11 (4.8)	5 (2.6)	1.8
Ventricular tachycardia	11 (3.8)	10 (3.0)	1.3	10 (4.4)	4 (2.1)	2.1
Amblyopia	11 (3.8)	5 (1.5)	2.5	5 (2.2)	2 (1.1)	2.0
Paresthesia	10 (3.5)	9 (2.7)	1.3	8 (3.5)	3 (1.6)	2.2
GI disorder	9 (3.1)	6 (1.8)	1.7	11 (4.8)	8 (4.2)	1.2
Hyperglycemia	9 (3.1)	13 (3.9)	0.8	11 (4.8)	5 (2.6)	1.8
Hyperlipemia	9 (3.1)	4 (1.2)	2.6	6 (2.6)	6 (3.2)	0.8
Insomnia	7 (2.4)	16 (4.8)	0.5	16 (7.0)	8 (4.2)	1.7
Vomiting	7 (2.4)	5 (1.5)	1.6	11 (4.8)	5 (2.6)	1.8
Abnormal kidney function	7 (2.4)	6 (1.8)	1.3	7 (3.1)	1 (0.5)	6.2
Sinusitis	5 (1.7)	1 (0.3)	5.7	17 (7.5)	8 (4.2)	1.8
Palpitations	5 (1.7)	7 (2.1)	0.8	15 (6.6)	7 (3.7)	1.8
Rhinitis	5 (1.7)	7 (2.1)	0.8	14 (6.1)	7 (3.7)	1.6
Nausea vomiting	3 (1.0)	6 (1.8)	0.6	8 (3.5)	5 (2.6)	1.4
Cellulitis	3 (1.0)	8 (2.4)	0.4	8 (3.5)	1 (0.5)	7
Hypoglycemia	3 (1.0)	7 (2.1)	0.48	7 (3.1)	4 (2.1)	1.5
Lung disorder	3 (1.0)	12 (3.6)	0.28	7 (3.1)	3 (1.6)	1.94
Allergic reaction	2 (0.7)	3 (0.9)	0.78	7 (3.1)	3 (1.6)	1.94

Hyperlipidemia, hypotension and sinusitis were observed more frequently in males, while bronchitis, syncope, ventricular tachycardia, palpitations, paresthesia, insomnia, abnormal kidney function, nausea/vomiting, rhinitis, cellulites, lung disorders and allergy reactions were more frequent in women.

6.1.7 Laboratory Findings

6.1.7.1 A-HeFT

Laboratory tests were not conducted routinely to either study the effect of the study drug on laboratory parameter or to monitor safety in the study population, and the reason given by the sponsor was that BiDil has a mature and well-known safety profile. Hematology, chemistry and urinalysis were to be conducted only at baseline for reference.

Laboratory test results were reported only when they were determined to be adverse events, and they were determined as such only if they induced clinical signs or symptoms or required a change in therapy, in which case they were recorded on the AE CRF under the signs, symptoms or diagnosis associated with them.

6.1.7.2 V-HeFT

Changes from baseline in selected laboratory parameters in African Americans who participated in the two V-HeFT studies were summarized and a paired t-test was conducted to test the significance of this change.

Table 41. Change from Baseline in Selected Laboratory Parameters in V-HeFT

Parameters and Statistics	Change in Mean from Baseline on HYD - ISDN	p-value
Alkaline phosphatase U/L N Range Mean SD Median	157 -71.0 - 167.0 6.03 38.6 1.0	0.052
BUN units: ml % N Range Mean SD Median	158 -24.0 - 52.0 1.63 9.18 1.0	0.027
Potassium: mEq/L N Range Mean SD Median	157 -1.6 - 1.5 -0.09 0.44 -0.1	0.007
Magnesium: mEq/L N Range Mean SD Median	108 -13.0 - 87.0 3.24 15.89 0.0	0.036
Sodium: mEq/L N Range Mean SD Median	158 -14.0 - 10.0 -0.59 3.45 0.0	0.032
Hematocrit: % N Range Mean SD Median	155 -31.0 - 10.0 -1.42 5.19 -1.0	<0.001
Segmented neutrophils N Range Mean SD Median	105 -20.0 - 30.0 3.48 10.53 4.0	0.001
Urine proteins N Range Mean SD Median	108 -4 - 8.0 0.3 1.83 0.0	0.095

6.1.8 Vital Signs

6.1.8.1 Overview of Vital Signs Testing in the Development Program

Supine heart rate, SBP and DBP measurements were completed as part of either the complete physical exam that was to be conducted at screening and 6 months, or the brief physical exam that was to be conducted at 3, 6, 9 and 12 months or the final visit.

6.1.8.2 Standard Analyses and Explorations of Vital Signs Data

6.1.8.2.1 Analyses Focused on Measures of Central Tendencies

Table 42. Effect of BiDil on Heart Rate, SBP and DBP, in the A-HeFT Trial

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Baseline												
N	516	526	--	--	517	526	--	--	517	526	--	--
Mean	74.2	73.1	--	--	127.2	125.3	--	--	77.6	75.6	--	--
SD	12.3	11.01	--	--	17.5	18.1	--	--	10.3	10.6	--	--
Median	74	72	--	--	128	125	--	--	80	76	--	--
Range	41 to 10	40 to 108	--	--	80 to 196	82 to 185	--	--	39 to 104	47 to 10	--	--
Month 3												
N	435	469	434	468	436	469	436	468	436	468	436	467
Mean	75.5	74.6	1.3	1.3	123.9	126.2	-3.2*	1.1	74.1	75.7	-3.4*	0.3
SD	11.6	11.8	12.19	11.07	19.6	21.8	17.41	17.6	12.7	13.1	12.6	11.5
Median	76	74	2	0	122	124	-2	0	74	76	-2	0
Range	50 to 116	44 to 131	-40 to 40	-36 to 49	80 to 210	74 to 205	-60 to 70	-45 to 70	42 to 130	48 to 130	-35 to 34	-28 to 46
Month 6												
N	388	376	387	375	389	376	389	375	389	376	389	375
Mean	75.8	73.5	1.3	0.0	125.6	125.5	-1.9*	1.2	75.1	76	-2.4*	0.8
SD	12.2	11.8	13.6	11.9	20.8	19.8	18.9	18.3	12.9	13.1	12.3	11.9
Median	76	73	2	0	121	125	-1	0	73	76	-4	0
Range	47 to 114	43 to 112	-41 to 46	-41 to 32	78 to 200	75 to 187	-82 to 602	-50 to 77	42 to 120	40 to 116	-40 to 36	-36 to 56
Month 9												
N	313	306	312	305	313	305	313	304	313	305	313	304
Mean	76.4	74.6	2.3	1.4	123.6	124.7	-4.7*	0.4	74.2	75.6	-3.3*	0.2
SD	12.4	11.5	13.93	13.2	20.5	20.9	20.3	19.1	13.7	13.2	13.2	12.4
Median	76	74	3	0	122	123	-5	1	72	75	-2	0
Range	45 to 10	48 to 106	-40 to 43	-52 to 43	70 to 192	84 to 190	-60 to 69	-50 to 54	42 to 138	40 to 110	-38 to 34	-32 to 46
Month 12												
N	272	257	271	257	276	258	276	258	276	258	276	258
Mean	75.8	74.3	1.5	0.7	124.8	125.6	-3.1*	2	74.4	75.7	-2.8*	0.9
SD	11.8	12.0	13.4	13.0	20.0	19.6	19.3	17.4	12.1	13.5	13.2	12.0
Median	76	74	2	0	124	125	-2	0	74	74	-2	0
Range	50 to 112	42 to 118	-40 to 47	-44 to 64	78 to 200	82 to 182	-54 to 70	-40 to 62	41 to 116	38 to 120	-40 to 38	-34 to 36
Month 15												
N	222	218	221	217	225	218	225	217	225	218	225	217
Mean	76.2	75.7	1.6	1.7	125.7	124.6	-3.1*	0.9	75.1	75.4	-2.9	0.7
SD	11.9	11.7	13.5	11.9	22.2	20.0	21.2	17.7	13.2	13.0	13.3	12.4
Median	76	76	2	0	122	126	-4	2	76	75	-2	0
Range	40 to 120	48 to 110	-47 to 48	-42 to 28	82 to 210	80 to 188	-92 to 68	-60 to 40	43 to 112	48 to 116	-38 to 30	-24 to 48

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Month 18												
N	197	176	196	175	197	176	197	175	197	176	197	175
Mean	77.3	73.1	3.0	0.4	125.9	125.6	-3.4*	1.2	75.4	74.8	-3.0*	-0.3
SD	11.2	12.0	12.6	13.7	21.2	19.2	20.4	17.5	13.2	14.0	13.4	12.9
Median	78	72	3	0	124	122	-3	0	74	76	-2	0
Range	48 to 113	49 to 116	-34 to 37	-54 to 52	92 to 200	90 to 180	-62 to 89	-56 to 51	44 to 120	40 to 118	-40 to 30	-40 to 41

*p<0.05, two sample t-test

The difference between BiDil and placebo in the mean change from baseline in heart rate ranged between 0 at 3 months and 2.6 bpm at 18 months.

Differences between BiDil and placebo in mean changes from baseline in supine systolic and diastolic blood pressure were sizable, consistent and statistically significant.

6.1.8.2.2 Marked Outliers and Dropouts for Vital Sign Abnormalities

6.1.8.2.2.1 Bradycardia

There were two cases on BiDil and three on placebo that were determined as serious. No cases led to discontinuation of study drug.

6.1.8.2.2.2 Tachycardia

Tachycardia is a known secondary effect of hydralazine and an excess of ventricular tachycardia was observed on BiDil, Table 31 page 46 and Table 33 page 49.

6.1.8.2.2.3 Hypotension

Hypotension was described as serious in 1.5% (8) and 0.6% (3), and led to discontinuation in 1.4% (7) and 0.6% (3) on BiDil and placebo respectively, Table 31 page 46 and Table 32 page 48. Also, a significant number on BiDil (7.9%) compared to placebo (4.4%) experienced hypotension as a common event, Table 33 page 49.

6.1.8.2.2.4 Diastolic Blood Pressure < 60 mmHg

No difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in DBP below 60 (incidence ranged between 7% and 13%).

6.1.8.2.2.5 Systolic Blood Pressure < 90 mmHg

Like DBP, no difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in SBP below 90 (incidence ranged between 1.0% and 3.0%).

6.1.9 The Effect of Concomitant Medication on the Safety Profile

Analyses assessing the effect of concomitant medication on selected adverse events observed in A-HeFT were conducted⁸. The medications considered in these analyses included ACE-I, ARBs, beta-blockers, digitalis glycosides, aldosterone antagonist and other diuretics. The adverse events that were assessed for confounding by concomitant medications included headache, dizziness, pain, chest pain, infection, asthenia, dyspnea, nausea, bronchitis and hypotension.

⁸ Analyses completed by the Sponsor

Adjusting for all concomitant medications in one model and for the medications that seemed to be strong predictors of any adverse event in another model did not explain away the association found between BiDil and headache (OR = 3.7, p-value <0.0001), dizziness (OR = 3.0, p-value <0.0001), nausea (OR = 1.7, p-value = 0.03) and hypotension (OR = 1.9, p-value = 0.02).

6.1.10 Adverse Events Associated with the Components of BiDil

6.1.10.1 Methemoglobinemia associated with ISDN

Methemoglobinemia is an adverse event that is said to occur extremely rarely with ordinary doses of ISDN. No cases were observed in the A-HeFT.

6.1.10.2 SLE-Like Syndrome Associated With Hydralazine

Under PRECAUTIONS, the Hydralazine label says that complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms. None of these were completed in A-HeFT. One case of SLE-like syndrome was reported on BiDil but was coded as joint disorder.

6.1.10.3 Hematologic Adverse Events Associated with Hydralazine

Reduction in hemoglobin and red blood cell count, leucopenia, agranulocytosis, purpura, lymphadenopathy and splenomegaly are listed as adverse events associated with hydralazine.

6.1.11 Immunogenicity

The hydralazine component of BiDil is known to trigger hypersensitive reactions and possibly autoimmune-like reactions especially that of SLE. Whether BiDil triggers the same reactions was not evaluated. In the A-HeFT trial, only one patient was reported to have SLE-like syndrome.

Arthralgia and myalgia 2 of the many symptom that are often associated with many autoimmune reactions, were observed in excess on BiDil 1.5% and 1.4% vs. 0.4% and 0.6% respectively.

6.1.12 Human Carcinogenicity

Four cases of neoplasm/carcinoma were observed on BiDil compared to one on placebo.

6.1.13 Special Safety Studies

None completed.

6.1.14 Human Reproduction and Pregnancy Data

There is no information on drug exposure during pregnancy.

6.1.15 Overdose Experience

No cases of overdose were observed.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

6.2.1.1 Study Type and Design/Patient Enumeration

6.2.1.1.1 A-HeFT

The primary source of the safety data came from the A-HeFT trial (5.1.5.1 page 20).

6.2.1.1.2 V-HeFT

Data from the V-HeFT studies were used as supportive especially V-HeFT I (5.1.5.2 page 22) that compared BiDil to placebo.

6.2.1.2 Demographics

6.2.1.2.1 A-HeFT

Table 10 page 28.

6.2.1.2.2 V-HeFT

Table 11 page 30.

6.2.1.3 Extent of Exposure (dose/duration)

6.2.1.3.1 Extent of Exposure in the A-Heft Study

Table 43. Extent of Exposure in the A-HeFT study as assessed by duration

	BiDil (N = 517)	Placebo (N = 527)
Duration of exposure, days		
Mean (SD)	298.4 (208.3)	313.8 (197.7)
Median	294	301
Range	1 - 594	4 - 624
Patients on study drug at various time points, n (%)		
3 mon	368 (71.2)	417 (79.1)
6 mon	317 (61.3)	333 (63.2)
9 mon	260 (50.3)	269 (51.0)
12 mon	220 (42.6)	228 (43.3)
15 mon	169 (32.7)	186 (35.3)
	139 (26.9)	146 (27.7)

This table excludes 18-month data, dose of study drug not collected consistently at that visit.

Table 44. Extent of Exposure in the A-HeFT study as assessed by total number of tablets taken per day

Total tablets/day	BiDil (N = 517)	Placebo (N = 527)	Total tablets/day	BiDil (N = 517)	Placebo (N = 527)
3 Month			9 Month		
N ²	368	417	n ²	260	269

Total tablets/day ¹	BiDil (N = 517)	Placebo (N = 527)	Total tablets/day	BiDil (N = 517)	Placebo (N = 527)
Mean (SD)	4.4 (2.1)	5.0 (1.9)	Mean (SD)	4.8 (1.9)	5.2 (1.7)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0 - 6	0 - 6
6 Month			12 Month		
N ²	317	333	n ²	220	228
Mean (SD)	4.5 (2.0)	5.1 (1.8)	Mean (SD)	4.8 (1.9)	5.3 (1.6)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0-6	0-6
15 Month					
n ²	169	186	Median	6	6
Mean (SD)	4.9 (1.7)	5.3 (1.7)	Range	0 - 6	0 - 6

This table excludes 18-month data; dose of study drug not collected consistently at that visit;

¹ Total number of tablets recorded on Study Drug Administration CRF if frequency was not t.i.d. or calculated by multiplying "# of tablets" by 3 (if frequency of t.i.d. was recorded);

² Number of patients with dosing information at indicated time point;

As can be seen from the table above, on average, patients took 4 ½ tablets per day at 6 months. Translated to milligrams, patients took on average 169/90 mg of BiDil per day. The average intake increased by close to ½ a tablet from Month 3 visit to 184/98 mg at Month 15. Exposure, whether measured in days or in number of tablets per day, seems to be slightly lower for BiDil compared to placebo.

6.2.1.3.2 Extent of Exposure in the V-HeFT African-American Population

Table 45. Summary of Drug Exposure to HYD – ISDN for African-American Patients in the V-HeFT Trials

Statistics	Values
Time on Study	
N	158
Range	3 – 2009
Mean	994.6
SD	550 – 51
Median	1032
Documented Days on BiDil	
N	158
Range	0 – 2045
Mean	812.3
SD	551.5
Median	727

The sponsor provided extent of exposure only for patients on active treatment.

6.2.1.4 Literature

Information sought by the reviewer included publications about the incidence of SLE on hydralazine and that of methemoglobinemia on organic nitrate therapy..

6.2.2 Adequacy of Overall Clinical Experience

The pivotal trial study design, number of subjects exposed, and duration of exposure to the study drug were adequate.

The A-HeFT assessed the target dose combination of 225/120, and the V-HeFT studies assessed 300/160 mg.

The pivotal study was limited to one ethnic group, and the findings of the BiDil program do not provide evidence to support the use of BiDil in non-African-American subjects.

6.2.3 Adequacy of Special Animal and/or In Vitro Testing

BiDil is a combination of two components already marketed for cardiovascular diseases.

One potential safety issue that was raised in the July-2d-1997 non-approvable letter concerned the potential of carcinogenicity as a result of a possible interaction between the drug substances and the formation of N-nitrosamines. The Sponsor responded to this in an amendment to the NDA in November 2001. For evaluation of the sponsor's response to this concern, refer to the Chemistry review.

6.2.4 Adequacy of Routine Clinical Testing

6.2.4.1 See 6.2.6, page 61

6.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

6.2.5.1 See Drs. Hinderling and Velazquez Reviews

6.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Hydralazine and isosorbide dinitrate are two components that have been marketed in the US. Also the BiDil combination has been reviewed by the Division in an NDA submission in July 1996.

One of the recommendations of the hydralazine label, the completion of blood counts and antinuclear antibody titers before and periodically during prolonged therapy, was not completed.

6.2.7 Assessment of Quality and Completeness of Data

Except for data assessing the effect of the hydralazine component on the immune system, the data available for conducting safety review was relatively complete. These data included adverse events by seriousness and/or whether they led to study drug discontinuation, and by categories of age, gender and treatment. It also included narratives of SAEs and life threatening and fatal events.

V-HeFT safety information summarized in this review is a duplicate of the safety summary in the clinical and statistical reviews completed by the Division in 1997. The latter reviews did not summarize less frequent adverse events because they were merged by the sponsor into the category of "other".

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Systemic lupus erythematosus:

One case of SLE-like syndrome was observed during the trial. Given the known association between hydralazine, a component of BiDil, and this adverse event, it is likely that this case is associated with BiDil. The patient while still taking BiDil was treated

and the symptoms resolved, but there is no data on what happened after the termination of the treatment of SLE.

Arthralgia was observed at an incidence that is almost 4 times as high as that observed on placebo, Table 33 page 49.

Malaise was 6 times as high on BiDil as on placebo, Table 33, page 49.

Myalgia was more than 2 times as high on BiDil as placebo, Table 33 page 49.

Antinuclear antibody titers determination tests should have been conducted in these patient as per the hydralazine label.

Angioedema

A case of angioedema did not resolve completely after discontinuation of benazepril and treatment but did after discontinuation of BiDil. However, the narrative said that study drug was to be restarted 3 days later, but there was no information on what happened after restarting the study drug.

Another case of angioedema that developed 4 days post study drug initiation and resolved after treatment and discontinuation of study drug without discontinuing the patient's ACE inhibitors therapy.

A third case of angioedema that developed 6 days after study drug initiation and resolved with treatment and discontinuation of study drug.

The incidence of angioedema was 6 times higher on BiDil than on placebo, Table 33, page 49.

Clinically significant hypotension

Hypotension that led to a visit to the ER and/or hospitalization was observed in 7 subjects on BiDil. The causal association is very likely given that both component of BiDil could cause and/or predispose to hypotension.

Twice and ½ as many BiDil as placebo subjects developed hypotension as a serious adverse event;

Ventricular tachycardia

An excess was observed on BiDil, Table 33 page 49;

Almost twice as many BiDil as placebo subjects developed serious ventricular tachycardia, Table 31, page 46;

This was more common in older (≥ 65 year) and female subjects;

The association is stronger in the elderly subjects;

Tachycardia

Observed in almost twice as many BiDil as placebo subjects, Table 33 page 49;

It is listed in the hydralazine label as a common adverse event;

Supraventricular tachycardia

Observed in 4 BiDil vs. no placebo subjects;

Headache

The incidence on BiDil was more than twice a high as that on placebo, Table 33, page 49;

Headache is known to be causally related to the ISDN component of BiDil;

Dizziness

The incidence on BiDil was more than twice as high as that on placebo; Table 33, page 49;
This is known to be associated with hydralazine;

Somnolence

It was observed in almost 4 as many BiDil as placebo subjects, Table 33 page 49;

Asthenia

This led to discontinuation in 11 and ½ as many BiDil as placebo patients, Table 32 page 48;

Nausea and Vomiting

Incidence rates on BiDil were each more than 1 ½ as high as those on placebo, Table 33 page 49;

These are known to be associated with hydralazine;

Amblyopia

The incidence on BiDil was more than twice as high as that on placebo, Table 33 page 49;
Abnormal vision was also observed in 4 BiDil vs. 2 placebo subjects;

Hyperlipidemia and hypercholesterolemia

Hyperlipidemia was observed in 50% more on BiDil compared to placebo, Table 33 page 49;

Hypercholesterolemia was observed in 3 ½ as many subjects on BiDil as on placebo, Table 33 page 49;

Abnormal kidney function

This was observed in twice as many BiDil as placebo subjects, Table 33 page 49;

Uremia was observed in 2 additional BiDil subjects;

It could be secondary to hypo-perfusion of the kidney as a result of hypotension;

Cerebral ischemia + infarct

This was observed in 3 as many BiDil as placebo patients;

Could hypoperfusion have triggered or complicated this event?

Coronary artery disease

This was observed in almost twice as many BiDil as placebo subjects, Table 33, page 49;

Cardiovascular disease

Coded as such in 5 BiDil vs. no placebo subjects;

Chest pain

This led to discontinuation in almost 4 as many BiDil as placebo subjects, Table 32 page 48;

Known to be associated with hydralazine, per the label;

Neoplasm

Neoplasm observed in twice as many BiDil as placebo subjects, Table 33 page 49;

Sweat increase, alopecia, cholecystitis

These were also observed at a higher incidence on BiDil than on placebo;

6.4 General Methodology

6.4.1 Pooled Data vs. Individual Study Data

Only one study was prospectively conducted and submitted for review of the proposed indication. Supportive data were submitted in the 1996 NDA, and post hoc analyses by race were conducted and submitted with the current NDA. Data were not pooled because firstly the V-HeFT studies were not designed to assess the effect of BiDil solely in African Americans; secondly the regimen and the schedules of exposure and adverse event assessments used were different; thirdly, the African-American sub-population of the V-HeFT I and the population of A-HeFT seem to be different with regard to background, placebo-associated, rates of common adverse events; and lastly, the medical management of both populations must be different for the medical management of HF has changed since the time V-HeFT I was conducted.

6.4.2 Explorations for Predictive Factors

6.4.2.1 Explorations of Time Dependency for Adverse Findings

Headache and dizziness started within a week, and nausea and hypotension started within a month of BiDil initiation.

6.4.2.2 Explorations for Drug-Demographic Interactions

This has already been completed in section 6.1.6.4.5, page 53 with regard to the common adverse events.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by gender and age, Figure 5 page 39.

BiDil seems to have the same effect on all-cause mortality and hospitalization for HF in both genders and in younger and older subjects.

6.4.2.3 Explorations for Drug-Disease Interactions

This was not conducted as a part of adverse event analyses, but information on the effect of this interaction on mortality and hospitalization can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL in subpopulations with DM, chronic renal insufficiency, ischemic etiology of HF, and history of hypertension, Figure 5 page 39.

As can be see from the figure, the presence of other co-morbidities did not change the effect of BiDil in these subgroups one way or another.

6.4.2.4 Explorations for Drug-Drug Interactions

Confounding of most common AE by concomitant drugs was explored, see 6.1.9 page 57.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by drug categories of ACE-I, ARBs, beta-blockers, CCBs, aldosterone antagonists, non-aldosterone antagonist diuretics and digoxin, Figure 5 page 39.

As can be seen from the figure, BiDil did not interact in a negative way with other drugs.

Interaction with other medications with regard to serious less common AEs was not explored. Therefore, one cannot exclude the potential for a deleterious interaction with any of the concomitant drugs that a HF patient is usually exposed to.

6.4.3 Causality Determination

6.4.3.1 Adverse Events Likely Causally Related to BiDil

Events that are likely causally attributed to BiDil with a certain level of assurance in this study population are headache, dizziness, nausea and vomiting, hypotension, chest pain, asthenia, tachycardia and palpitations, and paresthesia. These events were observed in excess on BiDil, the components of BiDil are labeled for some of these adverse events, and BiDil or any of its components have the mechanistic ability to generate these adverse events.

6.4.3.2 Adverse Events Probably Causally Related to BiDil

Events that are probably causally related to BiDil include arthralgia, myalgia and malaise which were observed in excess on BiDil and could have been symptoms of the SLE-like syndrome attributed to hydralazine; and angioedema because of hydralazine's tendency to affect the immune system.

Somnolence which was observed in excess on BiDil;

6.4.3.3 Adverse Events Possibly Causally Related to BiDil

Events that are possibly causally related to BiDil include abnormal kidney function because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; likewise cerebral ischemia because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; and ventricular tachycardia;

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The A-HeFT trial studied a lower dose and a different regimen than what was previously (V-HeFT I and II) targeted for heart failure, 75/40 mg t.i.d. instead of q.i.d. The lower dose or A-HeFT data were robust and significant in showing the efficacy of BiDil in the AA study population. Data from the higher dose/regimen showed no efficacy on HF in the population studied, but post-hoc analyses showed a trend toward efficacy in the African-American subpopulation, especially in V-HeFT I.

Comparing the most common adverse events (headache and dizziness) in both dosing regimens, both BiDil and placebo subjects in V-HeFT I experienced more of these events than did subjects in A-HeFT, and despite the reduced incidence in A-HeFT, the association between BiDil and these adverse events was stronger than in V-HeFT.

7.2 Interaction with Other Anti-hypertensive Therapies

If approved as a treatment for heart failure, BiDil may be added to other HF treatment regimens which may include other significant antihypertensive medications. Given that BiDil lowers blood pressure and causes hypotension in some patients, it is likely that it could aggravate the risk of hypotension in HF subjects who will not be followed as closely as the A-HeFT subjects were. Therefore, the reviewer recommends initiating BiDil and tapering it slower than it was in A-

HeFT, especially if subjects are receiving the beta-blocking agents that were found to interact with hydralazine (e.g., metoprolol, propanolol).

7.3 Special Populations

The effect of BiDil on heart failure was shown to be positive in African American patients only. BiDil did not seem to have an effect in non-African-American HF patients.

Subgroup analyses by age and gender showed that despite the small number of events in these sub-populations, a trend of effect on the composite endpoint was maintained.

7.4 Pediatrics

A deferral for a pediatric program was granted.

7.5 Advisory Committee Meeting

An advisory committee meeting to discuss the findings of BiDil is scheduled for June 16, 2005.

7.6 Literature Review

The information from literature search provided by the sponsor included the following:

- Publications about the pathophysiology of heart failure;
- Pathophysiological differences that could account for potential race differences in disease outcomes especially those of heart failure;
- Potential mechanism and role played by hydralazine in preventing or deterring tolerance to isosorbide dinitrates;

8 OVERALL ASSESSMENT

8.1 Conclusions

The A-HeFT study has shown that BiDil reduced mortality and the risk of HF hospitalization in African-American heart failure patients. Even though the reduction of mortality was not the primary endpoint, the study was terminated as a result of an effect on mortality that was observed before the study was due to end.

The safety profile of BiDil in A-HeFT was not very different from that of placebo. Given that BiDil had a beneficial effect on all-cause mortality, any adverse event no matter how severe it is, it would be relatively tolerable in this population.

The proposed indication per the label is the treatment of CHF in black patients who are either intolerant or have a contraindication to ACE inhibitors therapy, but the patients studied in the pivotal trial were not enrolled based on their intolerance or the contra-indication to ACE inhibitors. Therefore the reviewer concludes that BiDil should be indicated in the same population in whom it was studied in the A-HeFT study.

8.2 Recommendation on Regulatory Action

Based on the clinical results of A-HeFT, BiDil could be safe and effective in African-American subjects suffering from heart failure.

8.3 Recommendation on the Label

8.3.1 Trial Design

The label should state that A-HeFT was not designed to show that the combination was superior to either of its components. This way it won't indirectly be concluded that either hydralazine or isosorbide dinitrate is inferior to the combination of both.

8.3.2 Intended Population for Indication

If approved, BiDil should be indicated for the treatment of chronic heart failure in all blacks, not only in those who are intolerant or have a contraindication to ACE inhibitors as the proposed label says.

8.3.3 Mechanism of Action

The label should include language regarding the difference in blood pressure control between the treatment groups throughout the trial, and the possibility of this difference accounting, at least partly, for the observed effect.

8.3.4 Medication Regimen

The label should recommend a titration of BiDil over at least a week to prevent discontinuations for headache and dizziness.

Appears This Way
On Original

9 APPENDICES

9.1 A-HeFT Protocol Amendments (Sponsor's Tables)

Table 46. Summary of protocol amendments related to changes in entry and randomization criteria

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Inclusion criterion #3 Have stable, chronic HF, NYHA class III-IV, diagnosed at least 3 months prior to Screening.	3. Have stable, chronic HF diagnosed at least 3 months prior to Screening 4. Have NYHA class III-IV at the time of Screening.	Clarified that NYHA class III-IV requirement applies to assessment at Screening visit. Patient was not required to have NYHA class III-IV HF for at least 3 months prior to Screening.	05 (Dec. 12, 2001)	112 (10.7)
Inclusion criterion #4 (renumbered to #5 with Protocol amendment #5, Dec. 12, 2001) ...Patients receiving beta blockers must have been taking these for at least 6 months...	...Patients receiving beta blockers must have been taking these for at least 3 months.	Decreased requirement for time on beta blocker prior to screening.	02 (Jun. 15, 2001)	2 (0.2)
Inclusion criterion #5 (renumbered to #6 with Protocol amendment #5, Dec. 12, 2001) Have a resting LVEF <35% (by any method) and a resting LVDD >2.9 cm/m ² BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Have a resting LVEF ≤35% (by any method) and a resting LVDD >2.9 cm/m ² BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed LVEF entry criteria from <35% to ≤35%.	03 (Aug. 1, 2001)	10 (1.0)
	Have either a resting LVEF ≤35% (by any method) or a resting LVDD >2.9 cm/m ² BSA (or >6.5 cm) with LVEF < 45% (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed criteria for LV dysfunction to permit abnormal LVEF or abnormal LVDD (as long as LVEF <45%).	04 (Oct. 22, 2001)	55 (5.2)

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
<p>Inclusion criterion #7</p> <p>Have had at least one hospitalization for heart failure during the preceding year, as judged by the investigator."</p>	<p>Criterion deleted.</p>	<p>Eliminated entry criterion in order to enhance recruitment, based on decreasing number of hospitalizations due to change in standard of care to more frequent outpatient management.</p>	<p>08 (Mar. 25, 2003)</p>	<p>544 (51.8)</p>
<p>Criteria for stability</p>				
<p>Procedures to be done at the Baseline Visit: "Confirm that the patient has been stable since the screening visit..."</p>	<p>"Confirm that the patient has been stable for at least 2 weeks since the screening visit..."</p>	<p>Clarified time period for stability of symptoms and HF therapy</p>	<p>02 (Jun. 15, 2001)</p>	<p>2 (0.2)</p>
<p>At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2%."</p>	<p>At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2.5% relative to Screening Visit body weight."</p>	<p>Broadened stability criteria to clarify acceptable weight change limits.</p>	<p>04 (Oct. 22, 2001)</p>	<p>55 (5.2)</p>
<p>Exclusion criterion #4:</p>				
<p>Have coronary artery disease likely to require coronary artery bypass grafting or PTCA during the study period.</p>	<p>Have coronary artery disease likely to require coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during the ensuing year.</p>	<p>Specified a time period for the anticipated clinical event constituting the exclusion.</p>	<p>01 (May 3, 2001)</p>	<p>0 (0)</p>
<p>Exclusion criterion #5:</p>				
<p>Have symptoms of unstable angina or angina precipitated by exercise within 3 months.</p>	<p>Have symptoms of unstable angina within 3 months prior to screening.</p>	<p>Clarified definition of unstable angina (removed "angina precipitated by exercise") and timeframe for exclusion.</p>	<p>01 (May 3, 2001)</p>	<p>0 (0)</p>
<p>Exclusion criterion #6:</p>				
<p>Have had cardiac arrest, ventricular tachycardia or another severe ventricular arrhythmia considered life threatening within 3 months unless treated with an implantable cardiac defibrillator.</p>	<p>Have had cardiac arrest or a sustained ventricular tachycardia considered life threatening and requiring intervention within 3 months, unless treated with an implantable cardiac defibrillator</p>	<p>Clarified definition of arrhythmia considered exclusion.</p>	<p>01 (May 3, 2001)</p>	<p>0 (0)</p>

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Exclusion #9 Have rapidly deteriorating or uncompensated HF such that consideration for cardiac transplantation would be likely over the ensuing year.	Have rapidly deteriorating or uncompensated HF such that cardiac transplantation would be likely over the ensuing 1 year.	Clarified timeframe for the anticipated clinical event constituting the exclusion.	01 (May 3, 2001)	0 (0)
Exclusion #14				
Have received any other investigational drugs within 3 months.	Have received another investigational drug or device within 3 months prior to screening.	Added exclusion of investigational device, clarified timeframe.	01 (May 3, 2001)	0 (0)
Exclusion criterion #15				
Currently require sildenafil (Viagra®).	Currently require... phosphodiesterase-5 inhibitors like sildenafil (Viagra®), vardenafil (Levitra®), or tadalafil (Cialis®)..."	Specify that all available phosphodiesterase-5 inhibitors are excluded.	09 (Aug. 26, 2003)	700 (66.7)

Table 47. Summary of protocol amendments including additions or changes to study assessments

Assessment added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
LV wall thickness assessment added to echocardiographic measurements of LVEF and LVIDD.	Secondary efficacy assessment added.	01 (May 3, 2001)	0 (0)
Echocardiographic measurements to be done at baseline and at six months rather than at every three month visit	Echocardiographic measurements limited to baseline and at 6 months.	01 (May 3, 2001)	0 (0)
Urine pregnancy test added to serum pregnancy test as test permitted to determine pregnancy at baseline	Additional option added for baseline assessment of pregnancy.	01 (May 3, 2001)	0 (0)
Change in echocardiographic assessments from blinded reading by a central laboratory to blinded reading by an external expert. Core Laboratory to inspect echocardiograms for acceptability/readability.	Changed responsibility for secondary efficacy variable assessment.	04 (Oct. 22, 2001)	55 (5.2)

Table 48. Summary of protocol amendments including changes in study procedures

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visit: Timing of visit relative to screening visit changed from two weeks +two days to two weeks +seven days	Allowed additional flexibility in baseline visit scheduling.	01 (May 3, 2001)	0 (0)
Addition of second baseline visit: Patients who were considered not eligible for randomization at baseline could have a second baseline visit scheduled, to occur no more than two weeks after the first baseline visit. Patients who failed to qualify for randomization at the second baseline visit were not to have another baseline visit but could, at the investigator's discretion, begin the screening process over again at a future visit.	Allowed patients who failed to qualify for randomization an additional opportunity to qualify.	01 (May 3, 2001)	0 (0)

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visits: Timing of baseline visit relative to screening visit changed from two weeks +seven days to maximum of 28 days; patients were to be stable in the 14 days prior to the baseline visit.	Allowed additional flexibility in baseline visit scheduling but maintained randomization criteria for stability	02 (Jun. 15, 2001)	2 (0.2)
Timing of baseline visits: Timing of second baseline visit (if patient failed to qualify on first baseline visit) specified as no more than 28 days after screening visit.	Limited maximum duration between screening and randomization to 28 days for patients who required a second baseline visit.	02 (Jun. 15, 2001)	2 (0.2)

9.2 Discrepancies in Adjudication of Cause of Death

Table 49. Investigator-assigned causes of death for patients assessed by ICAC as having deaths due to non-cardiovascular causes

Treatment Patient number	Investigator cause of death
BiDil	
012-014	Cardiopulmonary arrest, hypotension, metabolic acidosis
046-003	Hepatic failure
107-033	Death due to stomach cancer
Placebo	
038-006	Exacerbation of CHF
059-010	Hemoptysis
089-008	Respiratory failure
090-030	Cardiopulmonary arrest
240-001	Cardiac arrest

9.3 Additional Information on V-HeFT I and V-HeFT II

For more information on these two studies, refer to the Division's Reviews.

NDA: 20-727

Reviews: Medical and statistical

Reviewers: James Hung, Ph.D., Shaw Chen, MD., Charles J. Ganley, MD.

Date of completion: 03/04/1997

9.4 Study Committees

9.4.1 ICAC (the Independent Central Adjudication Committee)

An independent review committee referred to as was to adjudicate death, all hospitalizations, unscheduled ER and Office visits, and new heart transplant listing. The committee was composed of 6 cardiologists who are experienced in the diagnosis and treatment of cardiovascular diseases.

The committee was divided into teams of 2 and each team reviewed a number of cases, presented the cases in a meeting where they were discussed and voted on by all committee members.

Death was to be classified as due to HF, other cardiac cause or non-cardiac cause, and as sudden and non-sudden cardiac death.

Hospitalization

9.4.2 DSMB (Data and Safety Monitoring Board)

The Data and Safety Monitoring Board was comprised of for members and these were:

David DeMets, Ph.D. Department of Biostatistics and Medical information, University of Wisconsin, Madison, WI;

Richard Grimm, M.D., Hennepin County Medical Center, Minneapolis, MN;

Pamela Ouyang, M.D., Department of Cardiology, John Hopkins University Medical Center, Baltimore, MD;

Jackson Wright, M.D. Department of Medicine-Hypertension, Case Western Reserve University School of Medicine, Cleveland, OH;

Dr. Ralph D' Agostino was the statistician responsible for the overall data analyses and for preparing the reports that DSMB was to review.

The committee was to be independent and to review data mainly to adjust for the sample size since an accurate estimate of the needed sample size was not possible as a result of the lack of data on the composite primary endpoint.

Interim analyses were to occur periodically and Dr. Ralph was to prepare the data and code it to maintain the blind of the committee as long as possible.

Data to be reviewed include:

Total enrollment at time of review;

Baseline data by treatment groups A and B;

Total number and timing of all SAEs;

Total number and timing of all clinical endpoints;

Listing of all SAEs;

Table summary of all SAEs grouped into treatments of A and B;

Table summary of all investigator-reported clinical endpoints;

Table summary of all investigator-reported clinical endpoints grouped into treatments A and B;

Table summary of all adjudicated clinical endpoint events by treatment groups A and B;

Tables of clinical endpoints and SAEs by protocol specification subgroups;

Other statistical analyses as requested;

9.5 Narratives

Patient 190-003 is a 40 year-old female with HF secondary to “dilated post-partum cardiomyopathy” and hyperlipidemia, cerebrovascular disease, previous myocardial infarction, past history of angina, depression, asthmatic bronchitis, and obesity. Approximately one year after the initiation of treatment the patient developed “lupus-like symptoms”, which were assessed as being of moderate severity. She was treated with hydroxychloroquine (Plaquenil®) for these symptoms, which resolved after approximately seven weeks. There was no change in study drug administration as a result of this adverse event.

Patient 041-002, a 53-year-old female, who 34 days after randomization to BiDil, presented to the ER with swelling of the upper lip. On exam she had an urticarial rash. She was given diphenhydramine and prednisone, had her benazepril discontinued and her swelling improved post discharge. Four days later, she returned to the ER with increased lip swelling that was worse one hour after ingesting the study drug. She was treated with prednisone diphenhydramine and ranitidine, and the study medication was stopped. Another four days later she was seen in follow-up, her swelling had improved, and her study drug was to be restarted in 3 days.

Patient 044-005

This 46-year-old male developed angioedema and was seen in the ER four days after being on study drug. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisone. He was discharged, study drug was discontinued, but his other medications including fosinopril were not modified. The patient recovered completely.

Patient 067-006

This 64-year-old female developed clinically significant hypotension, 77/50, 30 minutes after taking her first pill of the study drug in the study site clinic. The patient was given fluids and monitored for 1 ½ hours before she was discharged into the care of her daughter. The study drug was discontinued and the patient refused to restart it.

Subject 108-027

This 69-year-old male presented to the ER 3 months and 19 days after been randomized to study drug with weakness and diaphoresis and was found to be hypotensive 70/32. Apparently the patient experienced similar episode for which he was hospitalized after being on the drug for 2 months and was instructed to discontinue the study medication, but the patient said that he had continued taking it.

Patient 121-007

This 48-year-old female presented to the ER 4 days after starting the study drug with a complaint of weakness for the last 24 hours. Her BP was found to be 81/43 mmHg. She was treated with IV 1,000 cc of normal saline, her BP rose to 111/63 mmHg, she felt better and was discharged. The patient recovered and no change in medication was made.

Patient 144-013

This 62-year-old female presented to the ER 19 days after starting the study drug. She was found to have hypotension 63/35 mmHg. It was determined that there was a recent doubling of her carvedilol dose and of the study drug as well. The patient was hospitalized, she was treated with IV hydration, and all antihypertensive medications and the study drug were withheld. Home medication regimen was slowly incorporated back to prehospital dosages, except for the

study medication that was held and carvedilol given at ½ the prior dose. Four days after ER visit, her BP was 134/88 mmHg and she was discharged.

Patient 199-008

This 52-year-old female experienced a syncopal episode 1 ½ hours after her first dose, and was reported unconscious for approximately 1 minute and when conscious complained of dizziness. Patient was transported to the ER where her BP was found to be 70/40 mmHg, hydrated and labs done that revealed renal insufficiency. The study drug was discontinued, tosemeide was reduced to 60 mg b.i.d. and she was discharged one day later.

Patient 261-007

This 76-year-old female experienced lightheadedness, nausea, diaphoresis and generalized weakness two days after she had her study drug titrated up to 2 tablets b.i.d. She skipped her midday dose and took her second dose at night. Her symptoms persisted overnight and the following day she called 911 and was transported to the ER. She was diagnosed with a pre-syncopal episode that was felt "almost certainly" related to study medication. The study drug was discontinued and the patient recovered.

Patient 006-001

This 75-year-old male Information with a history of congestive heart failure, adenocarcinoma of the prostate, coronary artery disease, hypertension, hyperlipidemia, aortic insufficiency, mitral regurgitation s/p aortic valve prosthesis, s/p CABG, s/p bi-ventricular pacemaker, s/p AICD and chronic obstructive pulmonary disease. Two months and 15 days later after study drug initiation, he was seen at the emergency room due to firing of the AICD. The patient lost consciousness after the first time the device fired. The AICD was interrogated and found to have ventricular tachycardia at 280 msec with AICD shocks. The study drug was interrupted.

Patient 009-004

This 47-year-old male with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hyperlipidemia, and GERD. On 27-Dec- 2001 the subject was randomized to receive either BiDil or placebo in addition to current therapy.

Nine months after being on the study drug, the patient complained of increasing shortness of breath with exertion and at rest and difficulty sleeping when he presented for a month protocol follow-up visit. The patient was admitted directly from the office for further management. His heart showed an apical systolic murmur and the EKG-poor R wave progression. The patient was treated with dobutamine and intravenous diuretics. 4 days later, the patient experienced an episode of ventricular tachycardia, and he had an AICD placed. There were no complications. The patient was discharged one day later. The subject completely recovered and no action was taken regarding study medication.

Patient 010-012

This 56 year-old male, with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hypertension, COPD, headaches, insomnia, s/p bladder surgery, PVCs, non-sustained ventricular tachycardia, mitral regurgitation, tricuspid regurgitation and seasonal allergies who after one month and 10 days of being on BiDil he was seen in consultation and a holter monitor demonstrated significant ventricular ectopy and short runs of non-sustained ventricular tachycardia. All of these episodes were asymptomatic. The patient was not recommended to have an EP study and not to have an AICD placed at that time. The patient was suggested to start on a beta-blocker and return for follow-up in one month. Twenty six

days later, the patient returned for follow-up and a repeat Holter monitor confirmed that there was no significant change to his ventricular ectopy. The recommendation was to increase the dose of the beta-blocker and repeat the Holter study. Another 26 days later, the patient was seen by his primary physician who noted significant PVCs, bigeminy, trigeminy, and runs of non-sustained ventricular tachycardia on EKG. Because of the PVCs the patient was admitted to the hospital for further evaluation. The patient was originally treated with lidocaine via drip and enoxaparin. The patient was seen in consultation by a cardiologist who suggested increasing the beta-blocker. The enoxaparin and lidocaine were subsequently discontinued and the patient was treated with clopidogrel. His oral digoxin dose was also increased. The patient had a chest CT that demonstrated a right middle lobe infiltrate and also a probable thoracic aneurysm. After discussion, the patient was transferred to another hospital for further evaluation and management, and he was subsequently discharged 4 days later.

Patient 012-017

This 48-year-old male, with a history of CHF, hypertension, atrial fibrillation, hyperlipidemia, COPD, mitral valve disease, s/p CABG, s/p MI, dizziness, nausea, near syncope, headaches, sinusitis, myopia, constipation, lower extremity numbness, s/p URI, obesity, s/p pericardial effusion and tricuspid regurgitation, went to ER 6 days after initiation of BiDil with a complaint of severe dyspnea, fatigue, chest and abdominal pain that lasted for 24 hours. The patient was not able to achieve relief with sublingual nitroglycerin and called the EMT, and he was admitted for evaluation. During the hospital stay, the patient was observed to have numerous episodes of ectopic beats and occasional runs of ventricular ectopy. None of these caused any significant clinical abnormalities. No specific treatment was prescribed for the ectopy. The patient slowly improved and was discharged 7 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 012-018

This 62-year-old female with a history of CHF, cardiomyopathy, hypertension, atrial fibrillation, s/p TIA, mitral and aortic valve disease, s/p mastectomy, elevated liver function tests, glucose intolerance, hypokalemia, pulmonary hypertension, tricuspid regurgitation, anemia, arthritis, indigestion, depression, anxiety, headaches, s/p hysterectomy, hyperopia and constipation, presented to the Emergency Room with a complaint of nausea and being "sick" about 3 months after being on BiDil. The patient had run out of medication 2-3 days prior to presentation. In the ER, the patient was given medicine for BP and sedation and felt better. On examination she was hypertensive. EKG showed sinus rhythm with LVH. Chest X-Ray showed cardiomegaly. Lab data revealed BNP >5000, CK-708, CKMB 20.4, Troponin 0.03 and WBC 9,000. The patient was admitted for further evaluation. The patient was treated with IV diuretics. The patient had an episode of non-sustained ventricular tachycardia. She was started on amiodarone. The patient had a good response to diuretics and lost 12 lbs. BP also improved but was still sub-optimal. The patient slowly improved and was discharged 4 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 032-007

This 72-year-old female with a history congestive heart failure, hypertension, hyperlipidemia, peripheral vascular disease, mitral valvular disease, s/p CABG and s/p MI, presented to the ER 5 months after initiating BiDil with complaints of chest pain radiating to the right arm associated with shortness of breath and nausea. The patient was treated with a nitroglycerin drip and also given enoxaparin and morphine. EKG showed St-T wave depression in the

infero-lateral leads. Two days later, the patient underwent coronary angiography that demonstrated an 80% discrete ostial LAD lesion, a 100% proximal LAD lesion, a 100% ostial left circumflex lesion and a 100% proximal RCA lesion. The SVG to RCA had a 100% proximal lesion. There were no lesions in the SVG to LAD or SVG to Circumflex. It was elected to treat the patient medically. Three days later, the patient had an 18 beat run of non-sustained ventricular tachycardia with a heart rate of 122 beats per minute. There was no evidence to indicate additional treatment was required or that the ventricular tachycardia recurred. The patient was discharged to home the same day, and no change in study drug administration was made.

Patient 037-002

This 52-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, hypertension, atrial fibrillation, s/p CVA, chronic renal insufficiency, gout, hypercholesterolemia and polyarticular arthritis, presented to the hospital after being on BiDil for 4 months and 25 days with a three-day history of dyspnea, PND, orthopnea and weight gain associated with a non-productive cough. The patient also had intermittent chest pain radiating to the back for three days without aggravating factors. Two weeks before admission, patient's digoxin was held due to high levels. The patient also noted decreased urine output with lightheadedness. In the ER, patient was hypotensive and tachycardic. Chest X-Ray showed cardiomegaly with pulmonary vascular congestion. EKG demonstrated atrial fibrillation with rapid ventricular response and old inferior Q waves. Monitor showed sustained ventricular tachycardia. The patient was admitted for further evaluation, went to the ICU and was placed on phenylephrine. Systolic BP increased to 90-100. However, the patient's rhythm degenerated to sustained ventricular tachycardia which was pulseless. The patient was shocked into atrial fibrillation/sinus tachycardia. He was then placed on a lidocaine drip and intubated. He was subsequently placed on dopamine and furosemide. ECHO showed right atrial and ventricular dilation with tricuspid and mitral regurgitation. There was also left atrial enlargement and a suggestion of stagnation of blood in the left ventricle. The patient was anticoagulated and was also treated with amiodarone and digoxin. Eight days later the patient had an AICD placed, but continued to have PVCs on telemetry post AICD placement. He was eventually extubated and made steady improvement. The patient was discharged on the following day. The study medication was held during hospitalization. No information on whether it was reinstated.

Patient 0074-010

This 55-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, diabetes mellitus, CAD, s/p MI, peripheral vascular disease, s/p toe amputation, and s/p left wrist surgery, was admitted for EP evaluation and possible AICD placement after 2 months and 8 days of being on BiDil. The patient has a history of palpitations and non-sustained ventricular tachycardia at home that had not been recorded. Electrophysiologic evaluation demonstrated inducible ventricular flutter associated with hemodynamic collapse. In addition, there were runs of sustained ventricular tachycardia at 250 msec. Cardioversion was required for rescue from the sustained episode. An AICD was placed following the EP study. The subject had a stable post-op course and was discharged 2 days later. The subject completely recovered and study medication was temporarily stopped.

Patient 108-024

This 65-year-old female with a history of congestive heart failure, ischemic cardiomyopathy, hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, s/p CVA, mitral valve disease, aortic valve disease s/p MI, irritable bowel syndrome, GERD, glaucoma, amaurosis fugax and osteoarthritis, was on BiDil when she developed weakness and had an episode of syncope and a Holter monitor was reported to show non-sustained ventricular tachycardia. Five months after being on the study drug, she underwent electrophysiologic evaluation. demonstrated easily inducible, sustained, monomorphic ventricular tachycardia with a left bundle branch block, left axis morphology and a cycle length of 200 msec. This required DC cardioversion to restore to normal sinus rhythm. Following the procedure, the patient was admitted directly to the hospital, and underwent placement of AICD 2 days later. The post procedure course was uneventful. The patient was discharged 1 day later. The subject completely recovered and study medication was temporarily stopped.
Patient 126-001

This 59-year-old male with a history of congestive heart failure, hypertension, diabetes mellitus, ETOH abuse, hyperlipidemia, s/p DVT and chronic renal insufficiency, was on BiDil for 43 days when he was found unconscious in the front of his apartment with a cigarette in his hand. On the ride to the hospital, the patient developed ventricular tachycardia and ventricular fibrillation, and was treated with DC counter-shock two times plus intravenous lidocaine, and was intubated. He responded and upon arrival in the ER, he was placed on dopamine and mechanical ventilation. Heart showed III/VI systolic murmur. EKG showed LBBB. The patient was admitted to the ICU, was treated with intravenous antibiotics and diuretics, and 2 days later, he extubated himself. He was begun on amiodarone therapy. He had reported episodes of non-sustained ventricular tachycardia while on amiodarone. Eight days after the beginning of events, the patient was transferred to the study hospital, and 3 days later he underwent electrophysiologic evaluation which demonstrated inducible monomorphic ventricular tachycardia with a cycle length of 290 msec. Patient experienced syncope during this episode and required 1 DC shock to restore sinus rhythm. The patient subsequently had an AICD placed. He was later discharged, completely recovered and study medication was stopped temporarily.
Patient 228-007

This 55-year-old male with a history of congestive heart failure, hypertension, ventricular tachycardia, s/p AICD implantation, hypothyroidism possibly secondary to amiodarone, and apical thrombus, experienced ventricular tachycardia that triggered the firing of his ICD 6 months after being on BiDil. The patient presented to the hospital due the following day and was admitted for further evaluation. Two days later, the patient was hypotensive with BP 76/63 and had complaints of shortness-of-breath and lightheadedness. The patient was hydrated gently and given oxygen, and afterload reducers, beta-blockers, amiodarone and diuretics were held. His blood pressure increased and was in no acute distress. Other lab studies indicated hypothyroidism felt secondary to amiodarone with TSH of 8.40, and levothyroxine was initiated. Seven days after the beginning of events, the patient was considered stable and was discharged home. The subject completely recovered and study medication administration was temporarily interrupted.
Patient 25-017

This 54-year-old male was on BiDil for 7 months when developed angioedema. Following the morning dose of BiDil, the patient developed shortness of breath, swelling of the tongue and lips and became unresponsive. EMS was called and administered 1 amp D50W with return of

mental status. They also administered diphenhydramine IV. It was noted that the patient was recently switched to a different ACE inhibitor. The patient had not eaten anything that day nor the day before and only consumed alcohol the day before. The patient was brought to the where he was given additional diphenhydramine plus methylprednisolone IV. The swelling of the lips and tongue improved. The patient was recommended to stop ACE inhibitors and refrain from alcohol ingestion.

Patient 032-004

This 63-year-old female was on BiDil for 5 days when she developed angioedema. This was a single episode that was determined to be mild and no action was taken regarding study medication. The subject completely recovered.

Patient 044-005

This 46-year-old male was on BiDil for 6 days when he developed angioedema and light headedness, and was seen at the ER. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisolone. The patient improved, was discharged to home, and his study drug was discontinued.

Patient 074-010

This 55-year-old male who was BiDil for 33 days experienced swelling of the face and "hands breaking out" with itchiness of the hands and visited the ER one day later. He had been placed on lisinopril. On exam there was an erythematous rash on the hands and periorbital edema. He was treated with diphenhydramine and prednisone orally in the ER. The swelling improved and rash improved. The subject was told to stop lisinopril, and was discharged. The subject recovered with sequelae and no action was taken regarding study medication.

Patient 121-011

This 31-year-old female who was on BiDil for a little over 10 months presented to the Emergency Room with a complaint of difficulty swallowing for 1.5 weeks but worse on the day of admission. This was associated with a sore throat, runny nose, chills, hot and cold feeling, and a productive cough with yellow sputum. Patient had vomiting for last 2 days. Also has pain in both ribs with coughing and "body aches". She also notes she is talking in a high-pitched voice for the last 5 days.

On exam, there was a hoarse and squeaky voice with swelling of the uvula. The patient was treated with diphenhydramine and methylprednisolone IV. She subsequently improved and was discharged the same day. She was given a prescription for methylprednisolone orally and was told to discontinue her losartan. She completely recovered and no action was taken regarding study medication.

Patient 174-001

This 53-year-old male who was on BiDil for 6 months experienced angioedema of the lips. It was felt that this was secondary to trimethoprim/sulfamethasoxazole that the patient had been given for an infection. The patient was treated with prednisone. The event ended two days later. The subject completely recovered and no action was taken regarding study medication.

9.6 References

9.6.1 Selected Findings from Literature Referred to in the Review

Figure 6. Mortality from CVD excluding stroke and CHD for 20 mmHg lower BP⁹

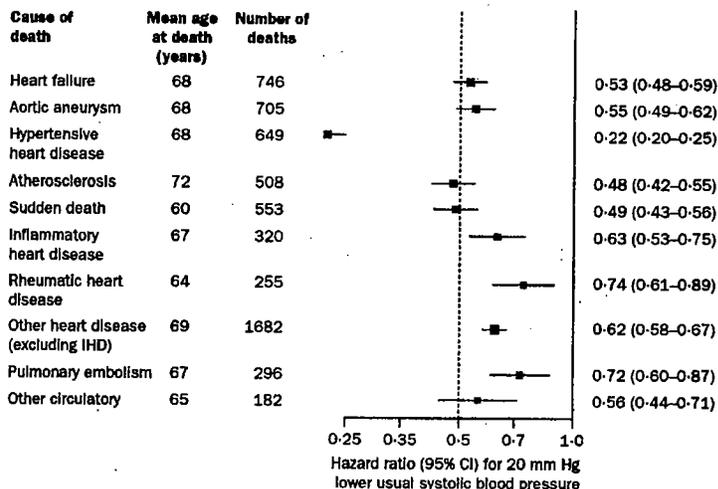


Figure 7: Mortality from other vascular causes (not stroke or ischaemic heart disease): hazard ratios for 20 mm Hg lower usual systolic blood pressure

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⁹ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 7. Effect of hypertension treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs¹⁰

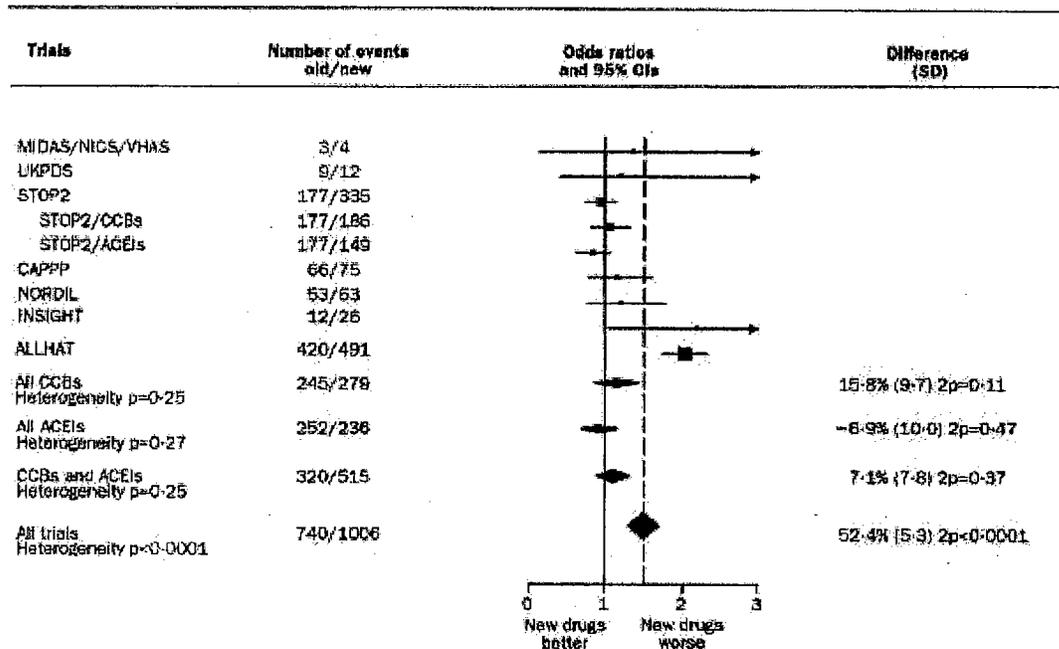


Figure 3: Effects of antihypertensive treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs

¹⁰ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 8. Effect of increased systolic and diastolic blood pressure by decade age increments on CV mortality excluding stroke and IHD¹¹

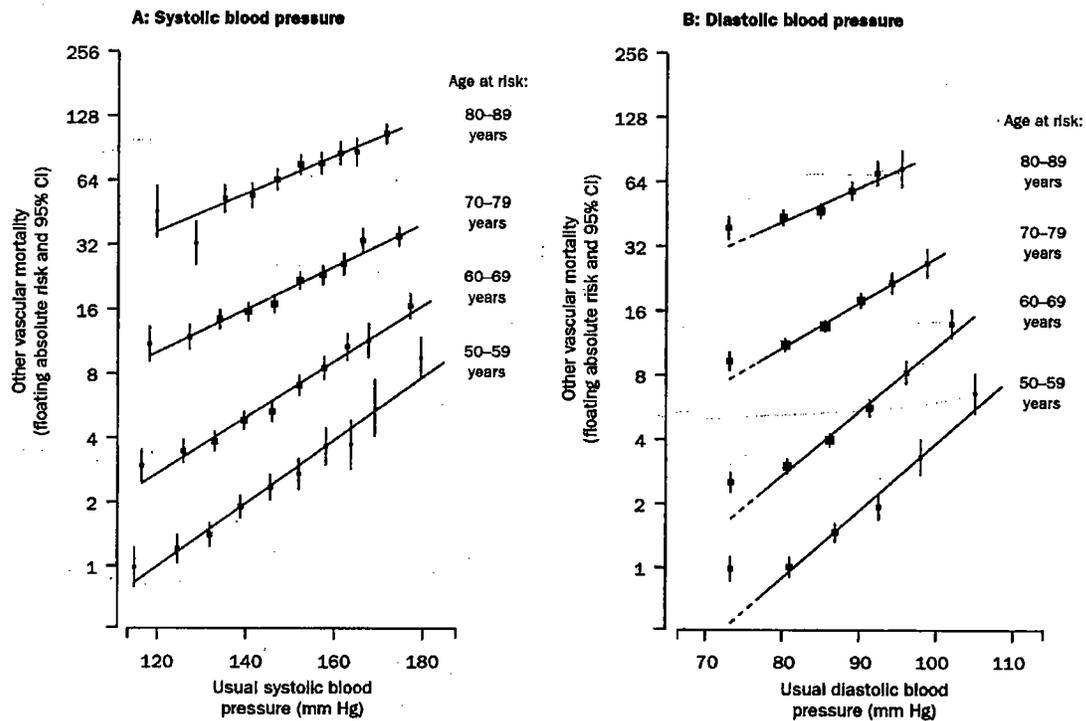


Figure 6: Other vascular (not stroke or ischaemic heart disease) mortality rate in each decade of age versus usual blood pressure at the start of that decade
Conventions as in figure 2.

¹¹ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 9. Relation between systolic blood pressure and cardiovascular mortality and events¹²

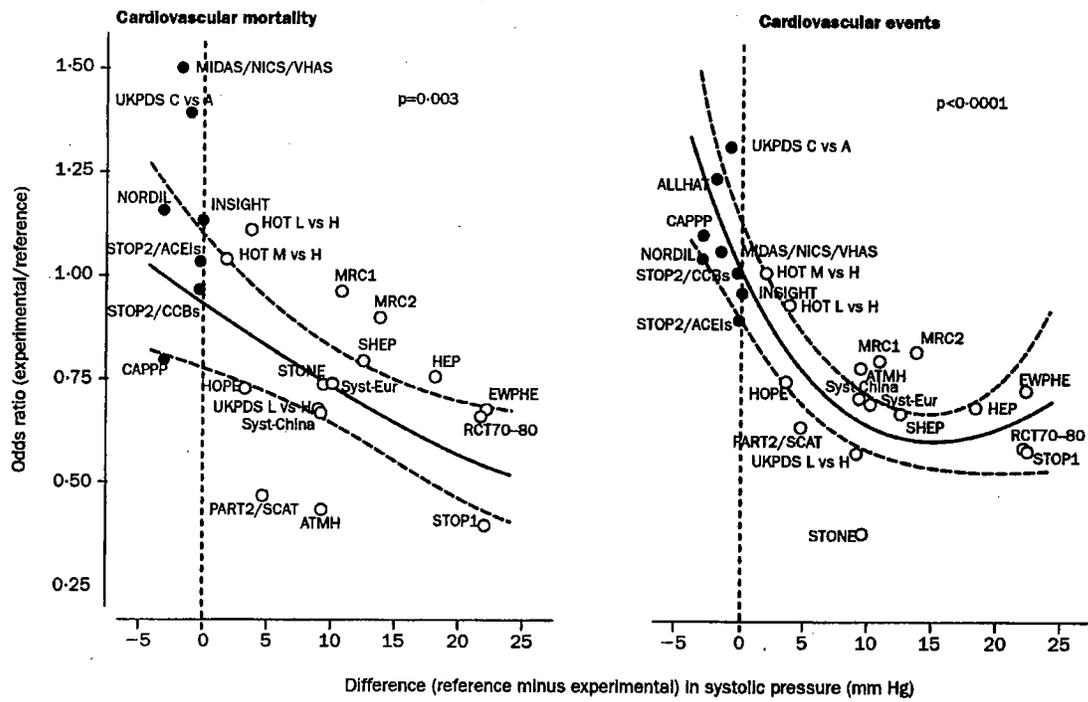


Figure 4: Relation between odds ratios for cardiovascular mortality and all cardiovascular events, and corresponding differences in

¹² Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15

9.7 Line-by-Line Labeling Review

To be completed separately.

See 8.3 Recommendation on the Label, page 67.

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this page is the manifestation of the electronic signature.**

/s/

Salma Lemtouni
5/2/05 05:29:29 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 20-727
Submission Number	20-727
Submission Code	N-000
Letter Date	December 23, 2004
Stamp Date	12/23/04
PDUFA Goal Date	6/23/05
Reviewer Name	Salma Lemtouni
Review Completion Date	4/15/05
Established Name	Hydralazine HCl and Isosorbide dinitrate
(Proposed) Trade Name	BiDil
Applicant	NitroMed, Inc.
Priority Designation	P
Formulation	Hydralazine 75 mg/Isosorbide dinitrate 40 mg
Dosing Regimen	t.i.d.
Indication	Heart Failure
Intended Population	African American

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Appears This Way
On Original

Abbreviations

AA:	African American
ACE-I:	angiotensin converting enzyme inhibitor
AA:	African American
AE:	adverse event
AICD:	automatic implantable cardiac defibrillator
ARB:	angiotensin receptor blocker
BEST:	Beta-blocker Evaluation of Survival Trial
BNP:	brain natriuretic peptides
bpm:	beat per minute
BSA:	body surface area
BSA:	body surface area
CABG:	coronary artery bypass graft
CAD:	coronary artery disease
CCB	calcium channel blockers
CCB:	calcium channel blocker
CHF:	congestive heart failure
CI:	confidence interval
CKMB:	creatinine kinase
CO:	cardiac output
COPD:	chronic obstructive pulmonary disease
COSTART:	coding symbols for thesaurus of adverse reaction terms
CRF:	case report form
CVA:	cerebrovascular accident
CVD:	cardiovascular disease
D50W:	50% dextrose in water
DBP:	diastolic blood pressure
DSMB:	data and safety monitoring board
DVT:	deep venous thrombosis
EF:	ejection fraction
ER:	emergency room
ETOH:	alcohol
GCP:	good clinical practices
GERD:	gastro-esophageal reflux disease
HF:	heart failure

HR:	heart rate
HYD:	hydralazine
ICAC:	Independent Central Adjudication Committee
ICD:	implantable cardiac defibrillator
ISDN:	isosorbide dinitrate
ITT:	intention-to-treat
LBBB:	left bundle branch block
LOCF:	last observation carried forward
LVEF:	left ventricular ejection fraction
LVEF:	left ventricular ejection fraction
LVH:	left ventricular hypertrophy
LVID:	left ventricular internal diameter
LVIDD:	left ventricular internal diameter in diastolic
MLHF	Minnesota living with heart failure
msec:	millisecond
MVO ₂ :	maximum oxygen consumption
NYHA:	New York heart association
MVO ₂ :	maximum oxygen consumption
NO:	nitric oxide
OL:	open label
PCI:	percutaneous coronary intervention
PTCA:	percutaneous transluminal coronary angioplasty
PVC:	premature ventricular contraction
QOL:	quality of life
q.i.d.:	four times daily
SAE:	serious adverse event
SBP:	systolic blood pressure
SD:	standard deviation
SLE:	systemic lupus erythematosus
SOLVD:	Studies of Left Ventricular Dysfunction
TIA:	transient ischemic attack
t.i.d.:	three times daily
UTI:	urinary tract infection
V-HeFT:	Vasodilator-Heart Failure Trial
WBC:	white blood count

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The A-HeFT study was prematurely terminated for a significant reduction of mortality on BiDil. Even though less data than planned was collected as a result of early termination, A-HeFT was able to meet its primary endpoint of a significant favorable change in the mean of the composite score of mortality, first hospitalization for HF and QOL on BiDil compared to placebo.

As to the secondary endpoints, changes in the mean of individual scores of mortality and hospitalization were also significantly different between BiDil and placebo.

The incidence of and the time to death and time to first hospitalization for HF were significantly different between the BiDil and the placebo arms.

Except for headache and dizziness, subjects taking BiDil experienced less adverse events than subjects taking placebo. Headache and dizziness are known to be associated with organic nitrates.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

BiDil is a fixed combination of hydralazine (HYD), a drug approved for essential hypertension, and isosorbide dinitrate (ISDN) approved for the prevention of angina pectoris. BiDil was to be taken orally t.i.d which is the equivalent of 225 mg of HYD and 160 mg of ISDN.

A-HeFT was a randomized, placebo-controlled trial that was designed to enroll 1100 African American subjects with NYHA classes III and IV heart failure, and follow them up to 12 months to evaluate the effect of BiDil on all cause mortality, hospitalization and the quality of life and its safety in this ethnic group.

A total of 1050 patients were randomized to BiDil (49%) and placebo (51%), and 71%, 61%, 50%, 42%, 33% and 30% were exposed to the study drug for 3, 6, 9, 12, 15 and ≥ 15 months respectively.

Findings from two other studies, V-HeFT I and V-HeFT II are used as secondary source of the safety assessment and the effect of BiDil in the African American HF sub-population.

1.2.2 Efficacy

The primary endpoint of the A-HeFT trial was the mean change in the composite score of death (-3 or 0), hospitalization (-1 or 0) and QOL (-2 or +2). Secondary endpoints included the mean change in the individual scores of the components, and the rate of and time to event of death and first hospitalization for HF.

The composite score used in this trial was not studied or validated in any population. It weighed the components based on no data that would enable the translation of the differences in individual and/or population scores into clinically meaningful benefits. For instance a subject who was hospitalized and whose QOL deteriorated by > 10 points would contribute as much to the overall score as a patient who died. There is no data that would tell us

whether these two outcomes, which are known to have different meanings at the individual level, are either equivalent at the population level or perceived in a similar way by the medical community.

However, given that BiDil was shown to have an effect on the rate of the main components of the primary endpoint, the composite score and the weight attributed to its components becomes less critical.

The findings of A-HeFT confirm the trend observed in V-HeFT I of a beneficial effect of BiDil on mortality (see Table 1 below) in African American patients, and support a beneficial effect of BiDil on hospitalization for HF in this population.

Table 1. Mortality and First Hospitalization for HF Experience (Risk Ratio) in AA Patients in the A-HeFT and V-HeFT Trials

Event Risk Ratio	A-HeFT			V-HeFT I			V-HeFT II		
	BiDil	Placebo	p-value	BiDil	Placebo	p-value	BiDil	Enalapril	p-value
Death	0.57	N/A	0.012	0.34	N/A	0.004	0.95	N/A	0.83
First hospitalization	0.61	N/A	<0.001	not evaluated			not evaluated		

1.2.3 Safety

The safety of BiDil in the study population was derived from analyses comparing the effect of exposure to BiDil for an average of 6 months in 519 subjects and to placebo in 532 subjects.

Overall serious adverse events were experienced at a similar rate in both-treatment arms, 35% on BiDil and 34.7% on placebo. The following serious adverse events were observed on BiDil at a slightly higher rate than on placebo: ventricular tachycardia 2.7% (14) vs. 1.5% (8), hypotension 1.5% (8) vs. 0.6% (3), dizziness 1.4% (7) vs. 0.0%, cerebral ischemia 1.0% (5) vs. 0.2% (1), syncope 2.1% (11) vs. 1.5% (8), and cellulites 1.2% (6) vs. 0.4% (2).

There were more discontinuations as a result of adverse events on BiDil compared to placebo 21.1% (109) vs. 12.0% (63). More than half the discontinuations on BiDil were accounted for by headache (7.4%) and dizziness (3.7%). Other adverse events that led to discontinuation at a higher rate on BiDil compared to placebo include asthenia 2.3% (12) vs. 0.2% (1), chest pain 1.5% (8) vs. 0.4% (2), nausea 1.5% (8) vs. 0.4% (2), and hypotension 1.4% (7) vs. 0.4% (3).

1.2.4 Dosing Regimen and Administration

The titration schedule of BiDil in the A-HeFT trial seemed to be brisk and as a result, almost twice as many BiDil as placebo patients discontinued the study drug, and more than half of these were due to headache and dizziness, a good proportion of which could have been avoided had the titration proceeded more cautiously.

1.2.5 Drug-Drug Interactions

No formal assessment of interactions of BiDil with other drugs was undertaken. Of concern are some beta-adrenergic antagonists which were found to interact with hydralazine.

1.2.6 Special Populations

The effect of BiDil in heart failure in this study was assessed solely in African American patients. The results of the A-HeFT study will not be generalizable to other ethnic group. Subgroup analyses showed that BiDil was as efficacious and relatively safe in elderly and in female subjects as it was in younger and in male subjects.

BiDil was not studied in pediatric subjects, and a request for a waiver was submitted with this application. The Division abstained from granting the sponsor a waiver until the application is fully reviewed, and instead granted them a deferral.

2 INTRODUCTION AND BACKGROUND

2.1 Rationale for the A-HeFT Trial

With respect to medical outcomes, African-American patients are diagnosed with HF at a higher rate than whites. Death rate per 100,000 from cardiovascular disease in AA in the 1990s was estimated to be 353 in males and 226 in females, while that of Caucasians was 244 in males and 135 in females.

It is hypothesized that in addition to socioeconomic factors, and differences in access to care and disease management, other factors including response to pharmacological therapies contribute to the observed differences. Some of the factors that were either studied or advanced as potential determinant factors in the differences observed include:

- salt sensitivity and low-renin hypertension;
- left ventricular hypertrophy (LVH) disproportionate to afterload;
- microvascular ischemia in the absence of significant epicardial CAD;
- higher prevalence of hypertension and LVH;
- higher incidence of normal coronary arteries in HF despite a high prevalence of risk factors for coronary atherosclerosis;

Secondary post-hoc analyses of SOLVD, V-HeFT II and BEST data showed differential effect by race in the following:

- enalapril with regard to HF-related hospitalization in SOLVD, Table 2 page 14, and a change in the QOL in V-HeFT II, Table 4 page 14,
- bucindolol with regard to survival in BEST (data not provided).

On the other hand, carvedilol has not been associated with an ethnic effect in HF (data not provided).

The explanation advanced for the difference in response of AA hypertensive subjects to ACE inhibitor therapy, and the observation that AAs fare better with diuretics than with either ACE inhibitors or beta-blockers are suspected to be partially related to nitric oxide (NO) insufficiency in this population. The same explanation is advanced for the apparent reduced responsiveness of AA HF subjects to these medications.

Nitric oxide insufficiency, secondary to either reduced production of NO or its inactivation by overabundant reactive oxygen species as a cause of the reduced responsiveness of AA to the available HF therapies was expected to be addressed by treatment with BiDil which is believed to have both characteristics of an NO donor and an antioxidant.

ISDN/HYD was associated with lower mortality in the study population of the V-HeFT I compared to placebo and prazosin but this did not reach statistical significance. In the V-HeFT II, ISDN/HYD was shown to be statistically significantly inferior to enalapril in reducing mortality at 2 years. Post-hoc analyses have shown that ISDN/HYD was associated with a reduction of mortality in black patients in V-HeFT I, Table 3 page 14, and mortality trends in the V-HeFT II were reversed in blacks toward no difference between BiDil and enalapril while enalapril was superior to BiDil in whites, Table 4 page 14 and Table 29 page 42.

The following tables summarize the findings of the post-hoc analyses of the SOLVD and V-HeFT I and II, and provide the rationale for the conduction of A-HeFT.

Table 2. Ethnic Reanalysis of SOLVD Trial

	Blacks N = 800		Whites N = 1197		Racial Interaction
	Risk Ratio* (CI)	p-Value	Risk Ratio* (CI)	p-Value	p-Value
All-Cause Mortality	0.92 (0.72 - 1.18)	ns	0.95 (0.76 - 1.18)	ns	p=0.7
Cardiovascular Death	0.92 (0.71 - 1.20)	ns	0.96 (0.76 - 1.22)	ns	p=0.6
Hospitalization for CHF	0.95 (0.74 - 1.23)	ns	0.54 (0.41 - 0.71)	p<0.001	p=0.005
Death or Hospitalization for CHF	0.91 (0.75 - 1.12)	ns	0.75 (0.62 - 0.91)	p<0.01	p=0.2

* Enalapril vs. placebo

Table 3. V-HeFT I Data Summary Table¹

	Blacks			Whites			Racial Interaction p-Value
	BiDil N = 49	Placebo N = 79	p-Value	BiDil N = 136	Placebo N = 194	p-Value	
Annual Mortality Rate (%)	9.7	17.3	0.04	16.9	18.8	ns	0.11
Mortality Risk Ratio	0.341	N/A	0.004	0.746	N/A	0.11	0.074
Change in EF at 12 Months vs. Baseline (%)	0.023	0.0136	0.82	0.081	0.012	0.02	0.23
Change in MVO ₂ at 12 M (mL/kg/min)	1.25	-0.394	0.068	0.681	-0.162	0.12	0.69

Table 4. V-HeFT II Data Summary Table¹

	Blacks			Whites			Racial interaction p-value
	BiDil N = 109	Enalapril N = 106	p-value	BiDil N = 282	Enalapril N = 292	p-value	
Annual Mortality Rate (%)	12.9	12.8	ns	14.9	11.0	0.02	0.25

¹ Analyses completed by the sponsor

	Blacks			Whites			Racial interaction p-value
	BiDil N = 109	Enalapril N = 106	p-value	BiDil N = 282	Enalapril N = 292	p-value	
Mortality Risk Ratio	0.95	N/A	0.83	1.48	N/A	0.0087	0.10
Change in EF @ 12 M (%)	2.97	1.32	0.34	3.86	2.48	0.12	0.82
Change in MVO ₂ at 12 M (mL/kg/min)	0.79	0.01	0.15	0.24	-0.42	0.058	0.47
Change in QOL at 12 M	-0.67	1.04	0.04	0.24	0.26	0.97	0.09

2.2 Product Information

BiDil is a fixed combination of hydralazine hydrochloride, a peripheral vasodilator with antihypertensive properties, and diluted isosorbide dinitrate, an organic nitrate with a vasodilating action on both arteries and veins. The proposed name is either BiDil or ZiDil. If approved, per the proposed label, BiDil will be indicated for the treatment of chronic heart failure as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE inhibitors .

2.3 Currently Available Treatment for Indication

Medications that have an indication for heart failure treatments in the US include ACE-I, ARBs and beta-adrenergic antagonists. The effect of these drugs in AA subjects has not been evaluated with adequate power, and therefore not quantified in this subpopulation. It is known that these drugs do not have the same effect in the treatment of hypertension in AA as they do in White subjects.

2.4 Availability of Proposed Active Ingredient in the United States

Isosorbide dinitrate is an organic nitrate available in a generic formulation for the prevention of angina pectoris as sustained release capsules of 40 mg.

Hydralazine hydrochloride is also available in a generic formulation for the treatment of essential hypertension alone or as an adjunct therapy as tablets of 10, 25, 50 and 100 mg.

2.5 Pre-submission Regulatory Activity

The original NDA 20-727 was submitted in July of 1996 for BiDil, and the application initially proposed the use of BiDil for a mortality claim in CHF patients who were intolerant to ACE-I. This was later revised to a claim for symptomatic relief for all CHF patients.

In February of 1997 the BiDil application went before Cardiac and Renal Drugs Advisory Committee who voted 9 to 3 to not approve it because the committee did not believe that the data submitted met the regulatory standard for approval.

A non-approvable letter was sent to the sponsor on July 2, 1997. This letter raised chemistry and pharmacokinetics deficiencies, listed pre-approval requirements and responded to requests by the sponsor, and these included:

- the concern that the sponsor has not adequately addressed the possibility of an interaction between the drug substances to form N-nitrosamines, products that have the potential to be carcinogenic;
- the Division's denial of a bioavailability waiver for the 37.5/20 and 75/20 dose strengths because the 37.5/10 strength showed a slower dissolution performance compared to the former strengths;
- the statement that a proposal for inclusion of information regarding food effect on ISDN/HYD based on published literature could not be acceptable, and that a food effect study, using the to-be marketed formulation of BiDil would be required to support any statement relating to the effect of food on administration of BiDil;

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the sponsor's responses to the pharmacokinetic issues, found the responses acceptable except for the response pertaining to the effect of food on BiDil for which the FDA recommended the inclusion in the label of the following text: "No information is currently available regarding the effect of food on BiDil tablets" which was acceptable to the sponsor.

In the minutes of the end-of-phase-II meeting, the Division expressed the concern that the fixed dose combination would produce tolerance because it would deliver ISDN continuously, a regimen that per the ISDN label is to be avoided. The Agency also stated that animal studies showing that hydralazine protected against tolerance to ISDN were not enough and that human data were needed for support.

2.6 Animal Pharmacology/Toxicology

2.6.1 See Dr. Defelice's Review

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

Data used for the evaluation of efficacy and safety came from one main source, the A-HeFT study. Additional material used for the review of this application included Agency medical and statistical reviews of the V-HeFT I and V-HeFT II trials plus subgroup data of these two studies provided by the sponsor as part of the submission and upon request by the reviewer..

3.2 Tables of Clinical Studies

Table 5. Summary of clinical studies

Study	Design	Type of subjects	Treatment		Duration	Dose	Relevance of Data
			BiDil	Comparator			
A-HeFT	R, DB, PC	AA with HF	518	Placebo 532	6 M	75/40 mg x 3	+++++
V-HeFT I	R, DB, PC	Males with HF	186	Placebo 273	≥ 2 years	75/40 mg x 4	+++

Study	Design	Type of subjects	Treatment		Duration	Dose	Relevance of Data
			BiDil	Comparator			
V-HeFT II	R, DB, AC	Males With HF	401	Enalapril 403	62 M	75/40 mg x 4	++
CB-02	R, OL, CO	Healthy males	149	--	[1]	37.5/40 mg	+
CB-01	R, OL, CO	Healthy	12	--	[1]	75/40 mg	-

3.3 Review Strategy

A paper application was submitted and used for review. A-HeFT was reviewed in greater detail than V-HeFT I and II. For efficacy, A-HeFT was the only source of review, but for safety, additional data from the V-HeFT studies were used.

3.4 Data Quality and Integrity

3.5 Compliance with Good Clinical Practices

The study was conducted in the US and per the study report, the sponsor asserts that they had adhered by the guidelines of GCP in conducting A-HeFT.

The protocol violations that occurred during A-HeFT are summarized in Table 8 page 28.

3.6 Financial Disclosures

The sponsor submitted a list of all investigators and sub-investigators, stated that all these investigators have signed a Form FDA 3454 attesting to the absence of any significant equity interest with the sponsor, and a signed-FDA-3454 Form attesting to such for all investigators and sub-investigators.

4 CLINICAL PHARMACOLOGY

4.1 See Reviews of Drs. Hinderling and Velazquez

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The proposed indication for BiDil is the treatment of CHF as an adjunct to standard therapy in black patients who are intolerant or have a contraindication to ACE-Is.

5.1.1 Purpose and Study Objectives

The trial was intended to provide additional data in support of the findings of V-HeFT subpopulation analyses and to support an NDA.

Three main objectives were specified:

- To demonstrate that BiDil is superior to placebo with regard to a composite score made up of 3 component scores including the QOL, hospitalizations and all-cause mortality;
- to assess the safety and tolerability of BiDil in AA heart failure patients;

--to demonstrate favorable trends in one or more of the individual components of the primary composite endpoint, the total number of hospitalizations, the duration of hospitalizations, unscheduled office and/or emergency room visits, and the echo parameters of cardiac size and function;

5.1.2 Methods

A-HeFT, the placebo-controlled trial of fixed dose of BiDil added to standard therapy in African-American patients with heart failure, was conducted to assess the effect of BiDil mortality, first-time hospitalization rates, and the quality of life.

V-HeFT I and II used two formulations that are different from the fixed dose used in A-HeFT.

A concern regarding the bioequivalence of the formulations used in V-HeFT to the combination formulation used in A-HeFT was raised in the End-of-Phase-II meeting held in November of 1992. Therefore the post-hoc analysis results of efficacy in the two trials will not be used for support of efficacy.

5.1.3 General Discussion of Endpoints

5.1.3.1 A-HeFT Study Endpoints

5.1.3.1.1 Primary Efficacy Endpoint

This is a composite of three scores, death, hospitalization for heart failure (adjudicated), and change in QOL (MLHF questionnaire) at 6 months or last available assessment.

Death = -3 vs. alive at end of trial = 0

Hospitalization for HF = -1 vs. no hospitalization = 0

Change in QOL

Improvement ≥ 10 units = +2

Improvement ≥ 5 and < 10 units = +1

Improvement < 5 units = 0

Worsening ≥ 5 and < 10 units = -1

Worsening ≥ 10 units = -2

The final score ranged between -6 if a patient's QOL worsened by ≥ 10 units, was hospitalized and died; and +2 in a patient was neither hospitalized nor dead and his QOL improved by ≥ 10 units.

In the primary analysis the worst case scenario was to be assumed for missing data and the secondary analysis was to use only available data with no imputed values.

Death: All cause mortality was to be used in the primary efficacy analysis. Death was to be adjudicated by an Independent Central Adjudication Committee (ICAC) and classified by cause including HF and other cardiac or non-cardiac cause, and as sudden or non-sudden death.

Hospitalization: Occurrence of the first hospitalization for HF was to be counted, and like death, the cause was to be adjudicated;

Hospitalization for HF: was defined as such if it lasted more than one calendar day, and the primary reason was worsening of signs or symptoms of HF and the patient required IV medications or other non-parenteral medication given specifically for HF;

QOL: the MLHF questionnaire administered at 6 months or last available measurement if the 6-month one was not;

5.1.3.1.2 Secondary efficacy parameters

They consist of:

- Individual components of the primary composite;
- Death:
 - from any cause;
 - from HF;
 - from cardiac causes other than HF;
 - sudden vs. non-sudden;
- Total number of hospitalizations
 - for HF;
 - for any cause;
- Total days in hospital;
- Overall QOL throughout the trial;
- Number of unscheduled emergency room and/or office/clinic visits (cause adjudicated by ICAC);
- Echocardiogram parameters including LVEF, LVIDD, and LV wall thickness. Echocardiograms were to be inspected for readability by a core laboratory and read by a blinded external expert;
- BNP levels;
- Newly recognized need for cardiac transplantation; this was to be adjudicated by the ICAC and data from patients undergoing transplant during the trial were to be censored;

5.1.3.1.3 Discussion of A-HeFT Endpoints

A-HeFT was the first study to ever use the composite score (discussed in 5.1.3.1.1 page 18), and because of the lack of an estimate of its variability in the intended study or any other population, criteria were built in the design to allow for interim analyses to adjust the sample size.

The primary endpoint would have been difficult to defend had the study not won on the main components of the composite endpoint because it would be difficult to interpret the meaning of a score in terms of a clinical benefit. The other issue would have been whether the components were weighted proportionally to the clinical weight each one has in the study population.

Secondary endpoints included components of the primary composite endpoint, endpoints that revolve around death and hospitalization, unscheduled visits to the ER and/or office/clinic,

echocardiographic parameters and markers of deterioration most of which are clinically relevant to heart failure patients.

The endpoints that were planned to be adjudicated are cause of death, all hospitalizations, unscheduled ER or Office visits and new heart transplant listing.

5.1.3.2 V-HeFT Study Endpoints

See 5.1.5.2 page 22 and 5.1.5.3 page 23;

5.1.4 Study Population

5.1.4.1 A-HeFT Study Population

Eleven hundred patients with NYHA class III-IV and stable chronic heart failure were required to meet the primary objective of A-HeFT.

They were to have a resting LVEF $\leq 35\%$ or LVIDD ≥ 2.9 cm/m² BSA (or > 6.5 cm) plus LVEF $< 45\%$ (by echocardiogram obtained within 6 months), and to be, per the investigator, symptomatically stable for at least 3 months and on a stable treatment regimen for at least 2 weeks (at least 3 months for beta-blockers)

To be excluded were subjects with significant valvular disease, hypertrophic obstructive cardiomyopathy, active myocarditis, uncontrolled hypertension or symptomatic hypotension; subjects who have had unstable angina, MI, cardiac surgery or PTCA, cardiac arrest, life threatening sustained ventricular tachycardia requiring intervention unless treated with an ICD, or stroke within 3 months of screening; subjects who have CAD likely to require CABG or PTCA; subjects who have rapidly deteriorating or uncompensated HF that render cardiac transplantation likely during the ensuing year; subjects who received parenteral inotropic therapy within one month; or subjects who have significant hepatic, renal or other condition that might limit survival over the ensuing one year;

5.1.4.2 V-HeFT Study Populations

See 5.1.5.2 page 22 and 5.1.5.3 page 23;

5.1.5 Study Design

5.1.5.1 Pivotal Trial: “A-HeFT (African-American Heart Failure Trial), a Placebo-Controlled Trial of BiDil Added to Standard Therapy in African-American Patients with Heart Failure”

This is a multicenter, randomized, double-blind, placebo-controlled parallel group study in AA patients in which eligible subjects were to be randomized after a 2-week run-in period to t.i.d. BiDil or identical appearing placebo within strata of beta- or no beta-blocker therapy.

The original protocol of A-HeFT (reviewed under IND 41816) was completed on 3/15/01, and after a little over 3 years and ten amendments, the final A-HeFT protocol was completed (06/08/04, date of the last amendment), just one month before termination of the trial.

Mortality was the main endpoint. Other endpoints were adjudicated by an Independent Central Adjudicated Committee.

The investigational therapy, BiDil was supplied as a fixed-dose combination of ISDN 20 mg plus HYD 37.5 mg (referred to as BiDil 20 Tablets). One tablet of BiDil was to be initiated t.i.d. and if tolerated 3 to 5 days later the dose is to be increased to 2 tablets t.i.d thus delivering an initial dose of 60/112.5 mg/day and maintenance dose of 120/225 mg/day of ISDN/HYD. If not well tolerated, either BiDil or background medication could be adjusted as appropriate. BiDil could be administered as ½ and 1 ½ tablets t.i.d. as well.

BiDil could be titrated down to avert adverse events. For symptomatic hypotension, it was suggested to adjust other anti-hypertensive therapies before altering the dose of BiDil. Following a dose adjustment, another dose titration was to be attempted and if the target dose was not tolerated, the maximally tolerated dose was to be administered.

The plan was to follow patients up to a maximum of 18 months or until the last randomized patient has completed 6 months post-randomization, but because the study was terminated early as a result of a statistically significant difference in mortality between the two treatment arms, 38.7% and 36.8% of the BiDil and placebo groups had less than 6 months exposure. Study design is shown schematically in figure below

Figure 1. Schematic of Study Design (sponsor's schema)

	Screening	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3*	4+ & Final Visit*
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.

* All patients seen every 3 months until either a maximum of 18 months or until the last patient completes visit No. 2.

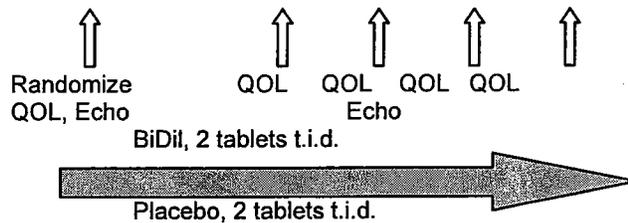


Table 6. Study flow chart (Sponsor's chart)

	Screen	Baseline	Titration	Treatment & Follow-up			
Visit No.	-1	0	0+	1	2	3	4+ & Final Visit
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
Informed consent	X						
Incl./Excl. criteria	X	X					

Visit No.	Screen	Baseline	Titration	Treatment & Follow-up			
	-1	0	0+	1	2	3	4+ & Final Visit
Day/wk/mo. No.	-2 Wk.	0	3-5 Days	3 Mo.	6 Mo.	9 Mo.	12 Mo.
Medical history	X						
Complete physical exam	X				X		
Review qualifying LVEF & LVIDD	X						
Serum or urine pregnancy	X						
NYHA class	X	X		X	X	X	X
Concomitant medications	X	X		X	X	X	X
Adjust background therapy	X		X	X	X	X	X
Interim history		X	X	X	X	X	X
Brief physical exam		X		X	X	X	X
Confirm stability		X					
ECG		X					
Clinical chemistry		X					
Hematology		X					
Urinalysis		X					
Echocardiogram ¹		X			X		
BNP		X			X		
QOL		X		X	X	X	X
Randomize & start study medication		X					
Dispense study medication		X		X	X	X	X
Titrate study medication ²			X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	X
Document Adverse Events		X	X	X	X	X	X

¹ Obtain in all patients for baseline and follow-up LVEF and LVIDD. Baseline results not used for "qualifying".

² May repeat titration visit as needed and may adjust study medication and background therapy anytime as needed.

5.1.5.2 V-HeFT I "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure"

This was a controlled parallel group, placebo, ISDN/HYD and prazosin, multicenter trial that randomized 642 patients with chronic CHF, NYHA class II and III who were on a background therapy of digitalis and diuretics.

The study randomized only male patients who had a history and physical consistent with left ventricular failure and with a limitation of exercise tolerance because of dyspnea and/or fatigue beginning at least 3 months prior to screening. Excluded were patients with

hypertrophic cardiomyopathy, hypertensive patients requiring treatment with drugs other than diuretics, chronic beta blocker therapy, and therapy with vasodilator drugs. The double blind treatment period was to last at least 2 years. Major endpoints included two-year mortality, the number and duration of hospitalization for cardiovascular causes, maximum oxygen consumption during peak exercise, maximum treadmill exercise time on graded test, and duration of exercise on submaximal test.

5.1.5.3 V-HeFT II “A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure”

IND 16-960 submitted on 11/25/85 described the study in a protocol as a multicenter, randomized, double-blind, parallel, active-controlled trial in patients with CHF. Patients were randomized to either ISDN/HYD or enalapril and the duration of the study was projected to be of 62 months with a minimum of 6 months.

Inclusion criteria were similar to those of V-HeFT I with additional specifications including $EF < 0.45$ by radionuclide method, $LVID > 2.7 \text{ cm/m}^2$ at diastole on echocardiography, cardiothoracic ratio ≥ 0.55 , and reduced exercise tolerance. Exclusion criteria were similar to those of V-HeFT I plus diastolic blood pressure $\geq 105 \text{ mmHg}$ or hypertension requiring non-diuretic therapy and dependence on chronic therapy with calcium channel blocker.

Major study endpoints were similar to the V-HeFT I study plus changes in the QOL and oxygen consumption at the anaerobic threshold.

Four hundred and one patients were randomized to ISDN/HYD and 403 to enalapril.

5.1.5.4 Adequacy of Study Design

The design of the pivotal trial was not the required design of a combination product which is usually factorial and compares the combination product to each of the components and placebo. The A-HeFT trial compared BiDil to placebo only. Therefore, we will not be able to know for sure whether the combination is necessary for treatment of the studied condition in the studied population, or either component would have been as effective as and somewhat safer than the combination.

5.1.6 Treatment Plan

In A-HeFT, a target maintenance dose of 120 mg/day of ISDN and 225 mg/day of HYD was to be achieved through 2 BiDil tablets taken t.i.d. If the target maintenance dose was not tolerated, the maximally tolerated dose was to be given by adjusting the number of tablets and/or the portion of a tablet to be taken t.i.d. Background medication was to be adjusted as clinically indicated to increase the likelihood of study drug toleration. Another attempt to titrate the dose to target level in subjects who failed to reach it was to be made within the first month of treatment.

5.1.7 Concomitant Medication

Study subjects were to be symptomatically stable and receiving a stable treatment regimen for at least 2 weeks prior to randomization.

The protocol assumed that study subjects would be on standard HF therapy including ACE-I, beta-blockers and diuretics, and allowed for spironolactone, digitalis or other medications

per the discretion of investigators. Beta blockers were to have been taken for at least 3 months.

Except for patients on phosphodiesterase-5 inhibitors, patients on other medications especially those with potentially significant hemodynamic effects maybe enrolled as long as the regimen of administration was to remain stable for the duration of the trial.

5.1.8 Statistical Methods

The following hypothesis was the basis for the test of superiority of BiDil over placebo:

$$H_0: \mu_B = \mu_P \quad \text{versus} \quad H_a: \mu_B \neq \mu_P$$

μ_B and μ_P are mean composite scores for BiDil and placebo.

5.1.8.1 Primary Efficacy Analyses

The primary analysis was to consist of a comparison of the mean composite score on BiDil to that on placebo using a 2-sample t-test, and constructing a two-sided 95% CI.

ANCOVA was to be used to test for the effect of BiDil controlling for baseline characteristics. The covariates that were to be considered were age (< 65 and \geq 65), sex, and beta-blocker and ACE inhibitor categories (yes/no). Because the centers were numerous and the number of subjects per center was small, only descriptive statistics were to be used to examine the treatment effect across centers.

Summary tables and figures were to include summary statistics of the composite score by treatment groups, and by age, sex, center, and beta-blocker and ACE inhibitors intake.

BiDil was to be considered superior to placebo and to have a treatment effect on the composite score if the null hypothesis above was rejected.

5.1.8.2 Secondary Efficacy Analyses

The consistence and robustness of the treatment effect was to be tested using secondary outcome measures. Two sample t-tests and ANCOVA modeling were to be used for continuous parameters, and Fisher's Exact tests (or Chi-Square tests where appropriate) and logistic regression models were to be used for binary parameters.

5.1.8.3 Analyses Populations

Intent to treat population or full analysis set of patients that consisted of all randomized patients was to be used as the primary efficacy population.

Analyses using the per-Protocol population were to be used for sensitivity analysis. Included were patients who have taken at least one dose of study drug, were still taking at least $\frac{1}{2}$ tablet per day, have completed at least 3 months of treatment, have an QOL assessment without any major deviation from the protocol, and who's compliance \geq 60% (compliance is computed as 100 times the ratio of tablets consumed to the required number prescribed).

For safety, all patients who were randomized and have at least one post baseline safety measure were to be included in the safety analysis.

5.1.8.4 Analysis Time Points

Analysis of the composite score was to use component scores at endpoint, the latter been defined as "death" or "no death" any time after randomization, "first hospitalization" or "no

hospitalization” any time after randomization, and QOL at 6 months (or last measurement available if earlier than 6 months).

5.1.8.5 Handling of Missing Data

For the primary analysis, a worst score was to be assigned to components of the composite endpoint with missing values. Patients who were lost to follow-up were to be assumed to have died with a score of -3, to have been hospitalized (if they have not already being before loss to follow-up) with a score of -1, and their QOL to have worsened by ≥ 10 units and scored as -2 if they had no post randomization QOL measurement.

For secondary analyses, only available data was to be used with no imputation for missing data. Characteristics of drop-outs were to be compared between treatments, and characteristics that significantly differentiate drop-outs from completers were to be controlled in ANCOVA models.

Other analyses deviating from the original worst case scenario assignment to missing data were planned post-hoc and these include three types:

- The first analysis was to use the LOCF for QOL (up to 6 months), HF hospitalization and survival, and the worst score imputation to be used only for QOL, and only when a post-baseline value is unavailable.
- The second analysis is similar to the first except that the LOCF value is not limited by the 6-month QOL.
- The third analysis was to be conducted on a subset of the ITT population, 951 subjects who were randomized on or before April 19, 2004 and who have had the opportunity for a three-month QOL assessment.

5.1.8.6 Background and Demographic Characteristics

They were to be compared between treatment groups. It was stated that in the case an imbalance in baseline characteristics occurred, the treatment effect might be reassessed including the unbalanced characteristics in an ANCOVA model to increase the precision of its estimate.

5.1.8.7 Interim Analyses

No formal analyses were planned, but they were incorporated to determine whether the sample size was adequate. Two interim analyses were to be conducted, the first when 25% (150) and the second when 50% (300) of the patients have completed 6-month follow-up. The generated results were to be reviewed by the DSMB only. The sample size was to be re-estimated, using the Cui, et al. method, to provide an 80% power to detect an effect at a two-sided significance level of 0.02. It was decided that the sample size was to be formally adjusted only after the second interim analysis. The same method used to estimate the standard deviation for sample size calculations (described below) was to be used for sample size re-estimation.

The study was to be treated as a group sequential design (with K=3 Looks total) since the analyses were to be used for sample re-estimation and not to stop early for efficacy. Using the O’Brien-Fleming Boundaries, the two-sided p-values required for statistical significance were 0.00001 at Look 1, 0.0052 at Look 2, and 0.048 at the final Look.

5.1.8.8 Sample Size

For lack of data regarding the variability of the composite score, the estimation of the sample size relied on previous data from studies including V-HeFT II that was designed to detect (with 80% power and a two-sided alpha of 0.05) a difference equivalent to 22.8% of a standard deviation of similar measures with 300 patients in each arm.

Using similar measures, the standard deviation of the proposed composite score was estimated to range between 1 and 2 units, and it was assumed that the study had adequate power to detect a difference of less than ½ a unit.

5.1.9 Protocol Amendments

There were ten amendments to the protocol most of which concerned the inclusion/exclusion criteria, for detail of the amendments, see 9.1. Some of these included a change in the cutoff of the LVEF, in the duration of pre-randomization beta-blocker intake, in the requirement of length of time the patient was in NYHA class III-VI before screening; the addition of a LVEF criteria if LVIDD was to be used as an inclusion criteria; the elimination of the requirement of prior hospitalization; and forbidding current use of phosphodiesterase-5 inhibitors.

LV wall thickness assessment was added to echocardiographic measurements of LVEF and LVIDD; Echocardiographic measurements were to be done only at baseline and at 6- months instead of every three months; and reading of echocardiographic assessments were to be completed by an external expert instead of a core laboratory;

5.1.10 Post Hoc Changes

After the termination of the study the sponsor requested the addition of analyses termed “sensitivity analyses” in which missing data were to be handled differently than originally planned. The worst score was no longer to be imputed for survival and hospitalization and it was to be imputed for the QOL only if a post-baseline value was missing.

5.1.11 Results

5.1.11.1 Study Conduct

5.1.11.1.1 Interim Analyses

There were six DSMB meetings held. The first on March 19, 2002 after 221 subjects have been randomized. During this meeting the DSMB charter was discussed and it was agreed upon that the DSMB was to remain blinded until a decision was imminent. An overview of the sample size reassessment plan was presented, and it was decided that the first DSMB interim analysis was to be conducted when the first 150 patients have completed six-months of follow-up, and that an interim analyses assessing the sample size was to be conducted for the second, August 23, 2002 meeting. The new QOL scoring system was also discussed and it was decided that QOL analyses would be performed first using all participants who had 6-month QOL assessments, and they would be repeated using participants who have at least a 3-month QOL assessment.

At the second, August 23, 2002 DSMB meeting, only 137 participants had 6-month follow-up data. Results of an interim analysis were presented to the DSMB for a first look at the

data. It was decided that next meeting would be scheduled when 300 patients have completed six-month visit.

The third DSMB meeting of March 3, 2003, the committee unexpectedly unblinded itself for a second look at the second interim analysis results, and it was concluded that the treatment difference was small but favorable for BiDil. During this meeting, the committee recommended an increase in the sample size.

The fourth DSMB meeting of March 13, 2004, at this meeting the committee formally unblinded itself, reviewed the third interim analysis results and noted that the mortality trend was getting stronger. The DSMB recommended another safety interim analysis in mid summer of 2004 to review mortality data again, and decided to establish monitoring boundaries for mortality since this was not determined early in the trial. The O'Brien-Fleming type group sequential boundary using the Lan-DeMets alpha spending function was chosen to be constructed for 5 interim analyses including the two that were to take place later on. The spending computation showed that the logrank test comparison of treatment groups fell just below the O'Brien-Fleming boundary value. An estimate of when the logrank z statistic or nominal p-value would cross the boundary values was generated and these were 2.24 for the logrank z statistic and 0.0126 for the p-value. These triggered a discussion by the DSMB about early termination of the trial.

In the meeting of June 9, 2004 with mortality data available on 1014 patients, it was noted that the trend of mortality strongly favoring the active treatment over the placebo group had continued. The boundary for this analysis was crossed with a logrank z statistic of 2.47 and a logrank two-sided p-value of 0.0132 (less than the required nominal p-value for the interim analysis). The committee recommended that the A-HeFT trial be terminated due to a statistically significant favorable mortality benefit on treatment when compared to control.

5.1.11.1.2 Statistical Issues

The statistical analysis plan was modified as a result of early termination of the trial and most of the changes concerned the way missing data were to be handled, see 5.1.8.5 page 25. For detailed description of the statistical method and changes, refer to Dr. Hung's review.

5.1.11.1.3 Protocol Violations

A total of 216 (20.6%) patients had deviations related to inclusion and exclusion criteria, with similar proportions on both BiDil and placebo.

The majority, ten percent and a half in each group, violated the LV dysfunction criteria. More subjects on BiDil had one or more of the conditions that were to be excluded compared to placebo, 2.1% (11) vs. 1.1% (6) respectively. Similar proportions on both treatment arms were exposed to forbidden medications during the trial, see Table 8 page 28.

5.1.11.2 Patient Disposition

5.1.11.2.1 A-HeFT

Table 7. A-HeFT Patient disposition (primary analysis population)

	BiDil (N=518) n (%)	Placebo (N=532) n (%)
Number of patients randomized	518	532
Completers	469 (91%)	457 (86%)
discontinued study drug prematurely	153 (30%)	101 (19%)
Withdrawal for adverse events	109 (21.1)	63 (12.0)
Discontinued from study prematurely	49 (9%)	75 (14%)
Investigator decision	9 (2%)	13 (2%)
Patient withdrew consent	5 (1%)	3 (1%)
Lost to follow-up	2 (0%)	0 (0%)
Cardiac transplantation	3 (1%)	3 (1%)
Death	30 (6%)	54 (10%)
Not reported	0	2 (0%)
Final status for assessment of the composite endpoint		
Vital status known at study completion	518 (100%)	532 (100%)
Hospitalization status known at study completion	505 (98%)	521 (98%)
QOL assessment done at or before six-month visit	472 (91%)	497 (93%)

Source: Sponsor's report;

¹ Two deaths occurred after completion of patient participation in the study and were not captured on the Study Completion CRF and thus are not captured in this table (112-001 and 231-002).

Very few people were lost to follow-up. Nine more percents of the subjects on BiDil discontinued as a result of adverse events, while 5% more of the subjects on placebo withdrew from the study prematurely.

Table 8. Protocol violations

	BiDil (N=518)	Placebo (N=532)
Number took prohibited medication	71 (14%)	90 (17%)
Hydralazine	14 (3%)	15 (3%)
Long-acting nitrate	65 (13%)	78 (15%)
Phosphodiesterase-5 inhibitor	3 (1%)	4 (1%)

5.1.11.2.2 V-HeFT

Table 9. Patient disposition in V-HeFT I (Sponsor's analysis)

	ISDN/HYD	Placebo	All
Randomized	186	273	642
Completed	92	134	
Deaths	72	120	283
Discontinuations	22	19	

Table 10. Patient disposition in V-HeFT II

	ISDN/HYD	Enalapril	All
Randomized	401	403	
Completed	199 (49.6)	233 (57.8)	432
Deaths	153 (38.2)	132 (32.8)	285

	ISDN/HYD	Enalapril	All
Discontinuations	49 (12.2)	38 (9.4)	87

5.1.11.3 Demographics

5.1.11.3.1 A-HeFT

Table 11. Baseline demographic, medical and therapeutic characteristics of the A-HeFT population (Dr. Hung's analysis)

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Gender						
Male	59.2%	66.5%	54.5%	62.9%	56.0%	63.9%
Female	40.8%	33.5%	45.5%	37.1%	44.0%	36.1%
Age (mean ± sd)	56±12	56±14	57±13	57±13	57±13	57±13
< 65	73.2%	74.3%	68.4%	70.3%	69.9%	71.4%
≥ 65	26.8%	25.7%	31.6%	29.7%	30.1%	28.6%
Weight (kg)	91±27	94±25	92±25	94±26	92±26	94±25
Blood pressure						
Systolic	126±20	121±26	128±18	125±22	128±19	124±24
Diastolic	76±19	71±24	77±11	75±14	77±14	74±17
Heart rate	75±12	72±18	74±11	75±11	74±11	74±14
EF (%)	23.6±7.2	23.8±7.3	24.1±7.4	24.3±7.6	23.9±7.3	24.2±7.5
Hypertension	86.0%	86.8%	93.5%	88.4%	91.1%	88.0%
Arrhythmias	33.5%	35.5%	32.2%	34.2%	32.6%	34.6%
Diabetes Mellitus	40.2%	36.2%	46.9%	37.4%	44.8%	37.0%
Hyperlipidemia	45.7%	41.5%	60.5%	52.6%	55.8%	49.4%
Cerebrovascular disease	17.7%	17.1%	14.1%	12.6%	15.3%	13.9%
Peripheral vascular disease	12.8%	13.2%	10.5%	13.4%	11.2%	13.4%
COPD	20.1%	25.7%	16.4%	18.7%	17.6%	20.7%
Chronic renal insufficiency	15.9%	18.4%	16.4%	18.2%	16.2%	18.2%
Valvular disease	29.3%	30.3%	39.0%	39.0%	35.9%	36.5%
Previous implantable pacemaker or ICD	14.6%	14.5%	17.5%	18.4%	16.6%	17.3%
Previous MI	28.7%	25.7%	29.7%	29.7%	29.3%	28.6%
Angina	0.6%	0.0%	0.6%	0.3%	0.6%	0.2%
Unstable angina in the past 3 months	0.0%	0.0%	0.3%	0.0%	0.2%	0.0%
Cigarette smoking during the past year	31.7%	25.7%	25.7%	26.6%	27.6%	26.3%
Previous cigarette smoking	62.8%	66.5%	57.1%	61.8%	58.9%	63.2%
Stroke	11.0%	11.2%	11.3%	10.0%	11.2%	10.3%
Atrial Fibrillation	18.9%	19.7%	13.8%	16.8%	15.4%	17.7%
TIA	6.7%	6.6%	3.4%	3.4%	4.4%	4.3%

Characteristics	Look 2 cohort		Post-look 2 cohort		Entire population	
	BiDil (N=164)	Placebo (N=152)	BiDil (N=354)	Placebo (N=380)	BiDil (N=518)	Placebo (N=532)
Etiology of HF						
Ischemic	22.6%	22.4%	23.7%	22.9%	23.4%	22.7%
Idiopathic	25.0%	29.0%	24.3%	27.1%	24.5%	27.6%
Hypertensive	39.0%	36.2%	40.4%	37.9%	40.0%	37.4%
Valvular	3.7%	4.0%	2.0%	2.9%	2.5%	3.2%
others	9.8%	8.6%	9.6%	9.2%	9.7%	9.0%
Dyspnea						
Mild	25.6%	30.3%	26.8%	30.0%	26.5%	30.1%
Moderate	64.0%	57.2%	62.2%	55.5%	62.7%	56.0%
Severe	7.3%	7.9%	5.4%	8.4%	6.0%	8.3%
None	3.1%	4.6%	5.7%	6.1%	4.8%	5.6%
Orthopnea						
Mild	24.4%	32.9%	32.8%	34.5%	30.1%	34.0%
Moderate	37.2%	38.2%	38.1%	35.8%	37.8%	36.5%
Severe	11.6%	9.2%	7.3%	6.1%	8.7%	7.0%
None	26.8%	19.7%	21.5%	23.7%	23.2%	22.6%
Fatigue						
Mild	26.2%	23.0%	27.4%	29.8%	27.0%	27.8%
Moderate	61.6%	61.2%	57.6%	53.4%	58.9%	55.6%
Severe	8.5%	12.5%	11.0%	11.8%	10.2%	12.0%
None	3.1%	3.3%	4.0%	5.0%	3.7%	4.5%
Hospitalized in the past year for HF	92.7%	96.7%	61.3%	67.6%	71.2%	75.9%
NYHA class						
I	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
II	0.6%	0.0%	0.0%	0.0%	0.2%	0.0%
III	95.7%	92.8%	97.2%	95.5%	96.7%	94.7%
IV	3.7%	7.2%	2.8%	4.5%	3.1%	5.3%
ACE	79.9%	77.0%	72.0%	74.5%	74.5%	75.2%
ARB	14.6%	16.5%	28.3%	22.9%	23.9%	21.1%
ACE or ARB	--	--	--	--	92.3%	93.0%
Beta blockers	76.2%	76.3%	87.3%	84.5%	83.8%	82.1%
Calcium blockers	18.3%	17.1%	22.3%	20.5%	21.0%	19.6%
Non-aldosterone antagonist diuretics	91.5%	95.4%	91.2%	91.8%	91.3%	92.9%
Thiazide diuretic	--	--	--	--	3.5%	3.3%
Aldosterone antagonist	40.2%	33.6%	40.1%	39.5%	40.2%	37.8%
Digitalis glycosides	70.1%	73.7%	53.4%	55.8%	58.7%	60.9%
Insulin	--	--	--	--	97 (18.7)*	67 (12.6)
Oral hypoglycemic drugs	--	--	--	--	156 (30.1)*	119 (22.4)
Potassium supplement	--	--	--	--	256 (49.4)	271 (50.9)

* p < 0.05

As can be seen from the table above, there were more males on placebo.

There were more diabetic patients on BiDil which explains the excess of diabetic drugs in this treatment group.

BiDil subjects had on average higher systolic and diastolic blood pressure;

Subjects on BiDil were more likely to be hypertensive;

Hypertensive as an etiology of HF was more prevalent on BiDil;

5.1.11.3.2 V-HeFT

Table 12. Demographics and other baseline characteristics of the V-HeFT I population

Characteristics	ISDN/HYD	Placebo
Age (yr.)	58.3	58.5
Heart Failure Symptoms (%)		
< 6 mo.	18.9	19.5
6 mo. – 1.5 yr.	23.2	27.2
1.5 – 4.0 yr.	25.4	22.4
> 4 yr.	32.4	30.9
Race (%)		
White	71	70
Black	27	29
Other	2	1
Etiology		
CAD	44.1	44.3
Previous MI	40.3	42.3
Alcohol excess	43.0	38.2
Hypertension	39.7	42.6
Diabetes	17.2	24.5
Previous Surgery		
Coronary Bypass	11.8	13.6
Valve Replacement	4.9	4.0
Previous Therapy*(%)		
Vasodilators	41.9	36.3
Antiarrhythmics	27.4	26.7
Sublingual Nitroglycerin	20.4	19.5
Anticoagulants	17.7	17.6
Clinical data		
Symptom Score	5.6	5.6
Arterial Pressure (mmHg)	119.6/75.0	118.9/76.1
Heart Rate (beats/min.)	83.1	81.5
Cardiothoracic Ratio (%)	52.8	52.9
EF (%)	30.3	30.4
LVIDD (cm/m2)	3.5	3.5
Exercise Duration (min.)	9.7	9.8
Oxygen Consumption (ml/kg/min.)	14.4	15.0

Previous 6 months;

Table 13. Demographics and other baseline characteristics of the V-HeFT II population

Characteristics	ISDN/HYD N = 401	Enalapril N = 403
Age		
Mean (SD)	60.55 (8.52)	60.62 (8.25)
Race		
White	282 (70.32)	292 (72.46)
Black	109 (27.18)	106 (26.30)
Other	10 (2.29)	5 (1.24)
Duration of CHF (months)		
N	387	383
Mean (SD)	40.15 (48.64)	31.20 (37.84)

Characteristics	ISDN/HYD N = 401	Enalapril N = 403
NYHA class		
I	22 (5.49)	24 (5.96)
II	210 (52.37)	200 (49.63)
III	167 (41.65)	178 (44.17)
IV	2 (0.50)	1 (0.25)
CAD	213 (53.25)	220 (54.59)
Previous MI	189 (47.13)	197 (48.88)
CVA (n, %)	38 (9.48)	46 (11.41)
Coronary Bypass Surgery	87 (21.70)	85 (21.09)
Hypertension (n, %)	182 (45.39)	199 (49.62)
Diabetes	80 (19.95)	84 (20.84)
Excessive use of alcohol	147 (36.65)	135 (33.50)
Tobacco Use (n, %)	132 (32.92)	135 (33.50)
Previous Therapy*(%)		
Vasodilators	247 (61.60)	250 (62.03)
Antiarrhythmics	106 (26.43)	100 (24.81)
Sublingual Nitroglycerin	67 (16.71)	64 (15.88)
Anticoagulants	88 (21.95)	84 (20.84)
Clinical Assessment		
Arterial Pressure (mmHg)		
Mean systolic/diastolic	126.98/78.44	125.53/77.97
EF (%)		
Mean (SD)	29.42 (11.53)	28.61 (10.87)
Oxygen consumption (ml/kg/min)		
Mean (SD)	13.54 (3.52)	13.84 (3.46)
Heart Rate (beats/min.)		
Mean (SD)	77.25 (11.93)	78.35 (12.06)
Cardiothoracic Ratio (%)		
Mean (SD)	53.0 (6.2)	53.7 (6.0)
LVIDD (cm/m ²)		
Mean (SD)	3.23 (1.22)	3.58 (1.42)
Plasma Norepinephrine (pg/ml)		
Mean (SD)	543.79 (226.78)	592.59 (388.12)
Plasma rennin activity (ng/ml/hr)		
Mean (SD)	15.65 (28.09)	19.86 (52.64)
Atrial fibrillation (n, %)	63 (15.71)	46 (11.41)
S, Gallop (n, %)	69 (17.21)	89 (17.21)

5.1.11.4 Efficacy Findings

5.1.11.4.1 A-HeFT

5.1.11.4.1.1 Primary Efficacy Endpoint

5.1.11.4.1.1.1 Composite Score of All-Cause Mortality, First Hospitalization for HF and QOL

Table 14. Scoring of the components of the primary endpoint (from Sponsor's Report)

Component	Score	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)
Death			
Yes	-3	32 (6.2)	54 (10.2)
No	0	486 (93.8)	478 (89.8)
Missing	-3	0 (0.0)	0 (0.0)
First hospitalization for heart failure			
Yes	-1	85 (16.4)	130 (24.4)
No	0	420 (81.1)	391 (73.5)
Missing	-1	13 (2.5)	11 (2.1)
Change from baseline in QOL at 6 months			
Improvement ≥ 10 units	2	180 (38.1)	166 (33.4)
Improvement ≥ 5 and < 10 units	1	49 (10.4)	56 (11.3)
Change < 5 units	0	117 (22.6)	126 (23.7)
Worsening ≥ 5 and < 10 units	-1	46 (8.9)	32 (6.4)
Worsening ≥ 10 units	-2	80 (16.9)	117 (23.5)
Missing	-2	46 (8.9)	35 (6.6)

Table 15. Mean change in composite score of Mortality, Hospitalization for HF, and QOL

Composite score	BiDil (N = 518)	Placebo (N = 532)	p-value
Mean change	-0.16	-0.47	0.011 ¹ 0.016 ² 0.021 ³
Median	0	0	
Range	-6 to 2	-6 to 2	

¹ unadjusted two-sample t test² sponsor's calculation using adaptive two-sample t test of Cui, Hung and Wang incorrectly³ Dr. Hung's calculation using adaptive two-sample t test of Cui, Hung and Wang**Table 16. Mean change in composite score before and after sample size re-estimation at the 2d interim analysis (analyses completed by Dr. Hung)**

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	Difference (B - P)	BiDil (N=354)	Placebo (N=380)	Difference (B - P)
Composite score	-0.23	-0.47	0.24	-0.07	-0.38	0.31

5.1.11.4.1.2 Secondary Efficacy Endpoints

5.1.11.4.1.2.1 Individual Scores of the Components of the Primary Composite

Table 17. Change in the mean of individual scores of the components of the composite endpoint (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	p-value ¹
Death	-0.19	-0.30	0.019

	BiDil (N=518)	Placebo (N=432)	p-value ¹
First hospitalization for heart failure	-0.19	-0.27	0.003
Change from baseline in QOL at 6 months	0.21	0.10	0.24

¹ two-sample analysis

As can be seen from the table above, the significant change in the composite score was driven by mortality and hospitalization. The QOL score changed in the right direction but not significantly.

Table 18. Event rate and time to event analysis for deaths and first hospitalization for heart failure (Sponsor's and Dr. Hung's analyses)

	BiDil (N=518)	Placebo (N=432)	Hazard ratio (95% CI)	p-value ¹
Death	32 (6.2%)	54 (10.2%)	0.57 (0.37, 0.89)	0.012
First hospitalization for heart failure	85 (16.4%)	130 (24.4%)	0.61 (0.46, 0.80)	< 0.001

¹ Cox regression analysis

Table 19. Mean change in the composite score at the 2d interim analysis or Look 2 (analyses completed by Dr. Hung)

	Look-2 cohort			post Look-2 cohort		
	BiDil (N=164)	Placebo (N=152)	HR (95% CI)	BiDil (N=354)	Placebo (N=380)	HR (95% CI)
Death	18 (11.0%)	18 (11.8%)	0.93 (0.49, 1.79)	14 (4.0%)	36 (9.5%)	0.38 (0.21, 0.71)
First HF hospitalization	35 (21.3%)	48 (31.6%)	0.66 (0.42, 1.01)	50 (14.1%)	82 (21.6%)	0.58 (0.41, 0.82)

5.1.11.4.1.2.2 Death from Any Cause

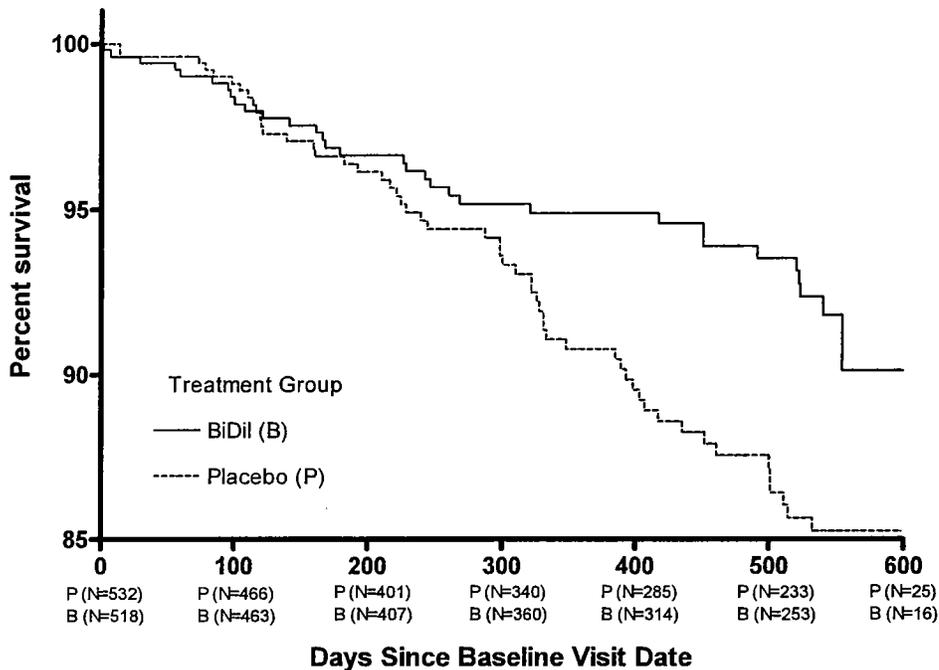
Table 20. Tabulation of causes of death as adjudicated by ICAC (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)
All-cause mortality	32 (6.2%)	54 (10.2%)	0.57 (0.37, 0.89)
Heart failure deaths	21 (4.1%)	42 (7.9%)	0.61 (0.46, 0.80)
Sudden cardiac death	17 (3.3%)	24 (4.5%)	
Pump failure death	4 (0.8%)	16 (3.0%)	
MI-related death	0 (0.0%)	2 (0.4%)	
Cardiac procedure-related death	0 (0.0%)	0 (0.0%)	
Other cardiac cause-related death	0 (0.0%)	0 (0.0%)	
Non-heart failure (vascular death)	5 (1.0%)	3 (0.6%)	
Cerebrovascular accident death	4 (0.8%)	3 (0.6%)	
Vascular-related death	1 (0.2%)	0 (0.0%)	
Pulmonary embolism-related death	0 (0.0%)	0 (0.0%)	
Other vascular cause-related death	0 (0.0%)	0 (0.0%)	
Non-cardiovascular death	6 (1.2%)	9 (1.7%)	
Non-cardiovascular cause death	3 (0.6%)	5 (0.9%)	
Unknown cause death	3 (0.6%)	4 (0.8%)	

The reduction in all cause mortality was mainly due the reduction in cardiac failure deaths. The risk of sudden death is slightly higher on placebo, but not significantly different.

One case on BiDil and three cases on placebo were classified by the investigator as due to cardiovascular causes, but due to non-cardiovascular causes by the ICAC, Table 50 page 75.

Figure 2. Kaplan-Meier estimates for all-cause mortality by treatment (Sponsor's analysis)



5.1.11.4.1.2.3 Number of Hospitalizations and Total Days in Hospital

Table 21. Hospitalization event rate and total days in hospital (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value
Event rate for hospitalization			
HF hospitalization	85 (16.4%)	130 (24.4%)	< 0.001 [#]
All cause hospitalization	202 (39.0%)	221 (41.5%)	0.41 ^{\$}
Other cardiac cause hospitalization	80 (15.4%)	90 (16.9%)	0.56 ^{\$}
Non-cardiac cause hospitalization	109 (21.0%)	117 (22.0%)	0.76 ^{\$}
Days in hospital (days/patient)			
HF hospitalization			
Mean (SD)	13.7 (16.6)	15.3 (20.2)	0.54 [*]
Range	2 - 122	2 - 164	
All cause hospitalization			
Mean (SD)	13.0 (15.6)	17.7 (21.6)	0.012 [*]
Range	2 - 135	2 - 196	
Other cardiac cause hospitalization			
Mean (SD)	7.2 (10.0)	7.4 (5.7)	0.90 [*]
Range	2 - 84	2 - 26	
Non-cardiac cause hospitalization			
Mean (SD)	8.1 (6.8)	10.6 (11.8)	0.051 [*]
Range	2 - 34	2 - 65	

Table compiled by Dr. Hung

log-rank test \$ Fisher's exact test * two-sample t test

Hospitalization for all causes, for other cardiac causes and for non-cardiac causes was not different between the treatment arms.

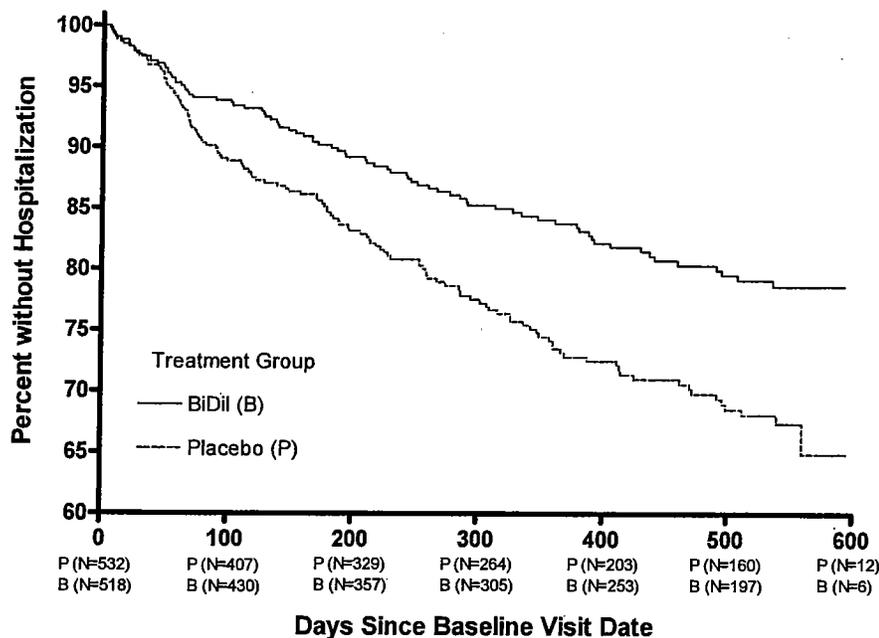
Days in hospital for HF were slightly different between BiDil and placebo, but not statistically significant. This is in contrast of a significant reduction in the rate of first HF hospitalization on BiDil. The lack of a significant difference in days spent in the hospital in the face of a significant difference in the rate of hospitalization for HF could be explained by a competing increased mortality on placebo.

Days in hospital for all causes were significantly reduced on BiDil and days in hospital for non-cardiac causes were of borderline significance.

Table 22. Event rate and time to event analysis for all-cause deaths and hospitalization (post hoc added secondary efficacy analysis)

	BiDil (N=518)	Placebo (N=532)	Hazard ratio (95% CI)	p-value ^[1]
First hospitalization for heart failure or all-cause mortality	108 (20.8%)	158 (29.7%)	0.63 (0.49, 0.81)	< 0.001
All-cause hospitalization or all-cause mortality	215 (41.5%)	237 (44.5%)	0.86 (0.72, 1.04)	0.12

Figure 3. Kaplan-Meier estimate for first heart failure hospitalization by treatment as adjudicated by the ICAC (Sponsor's analyses)

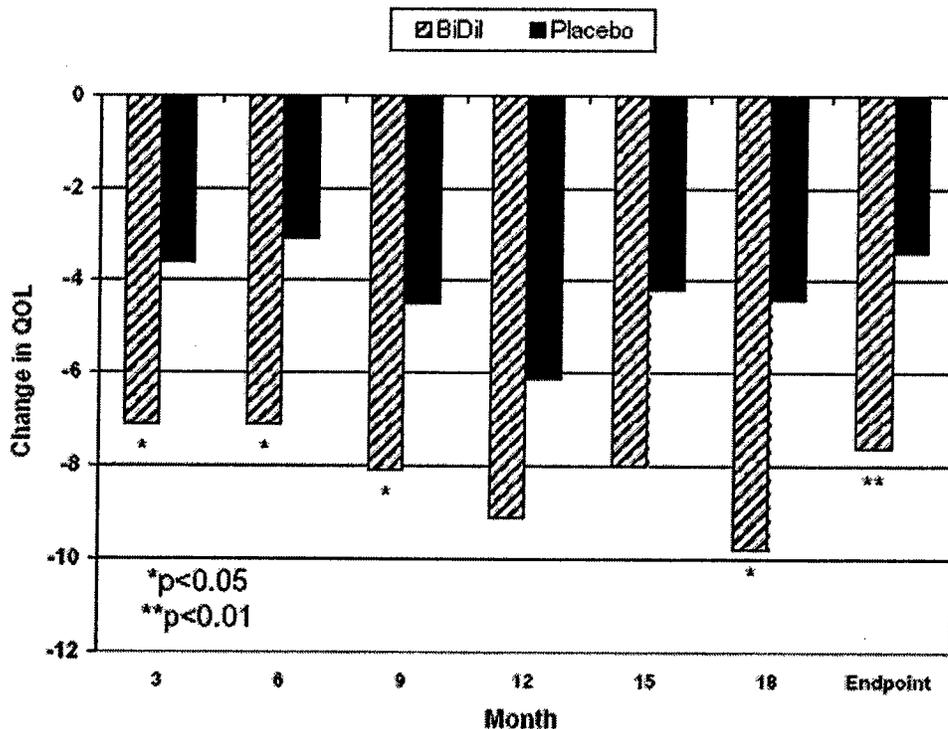


5.1.11.4.1.2.4 Overall Quality Of Life throughout the Trial

Table 23. Quality of Life scores by treatment (Sponsor's analysis)

	BiDil (N=518)	Placebo (N=532)	p-value[1]
Overall score			
Mean baseline	50.9	50.8	
Mean change (SD)	-7.6 (22.6)	-3.4 (22.7)	0.003
Range of change	-91 – 68	-105 – 70	
Physical score			
Mean baseline	22.1	22.0	
Mean change (SD)	-3.5 (10.5)	-1.4 (10.6)	0.002
Range of change	-40 – 29	-401 – 30	
Emotional score			
Mean baseline	10.4	10.4	
Mean change (SD)	-1.3 (6.8)	-0.7 (6.5)	0.13
Range of change	-25 – 22	-25 – 17	

Figure 4. Mean change from baseline in MLHF overall score throughout the trial (Sponsor's analysis)



N	BiDil	423	369	307	269	226	198	512
	Placebo	441	371	305	250	218	184	528

5.1.11.4.1.2.5 Number of Unscheduled Emergency Room and Office/Clinic Visits

Table 24. Number (%) of patients with unscheduled emergency room or office/clinic visits by cause (Sponsor's analysis)

	BiDil (N = 518) n (%)	Placebo (N = 532) n (%)	p-value ¹
Unscheduled ER visits for any reason			
0	379 (73.2)	385 (72.4)	0.782
1	88 (17.0)	87 (16.4)	
2	27 (5.2)	29 (5.5)	
3	10 (1.9)	17 (3.2)	
≥4	14 (2.7)	14 (2.3)	
Unscheduled ER visits for HF			
0	500 (96.5)	502 (94.4)	0.105
1	14 (2.7)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	1 (0.2)	4 (0.8)	
Unscheduled ER visits for other cardiac cause			
0	486 (93.8)	505 (94.9)	0.503
1	27 (5.2)	24 (4.5)	
2	3 (0.6)	2 (0.4)	
3	2 (0.4)	1 (0.2)	
Unscheduled ER visits for non-cardiac cause			
0	401 (77.4)	416 (78.2)	0.767
1	80 (15.4)	77 (14.5)	
2	23 (4.4)	21 (3.9)	
3	7 (1.4)	6 (1.1)	
≥4	7 (1.4)	12 (2.3)	
Unscheduled office/clinic visits for HF			
0	511 (98.6)	528 (99.2)	0.379
1	6 (1.2)	4 (0.8)	
2	0 (0.0)	0 (0.0)	
3	1 (0.2)	0 (0.0)	

¹Fisher's exact test

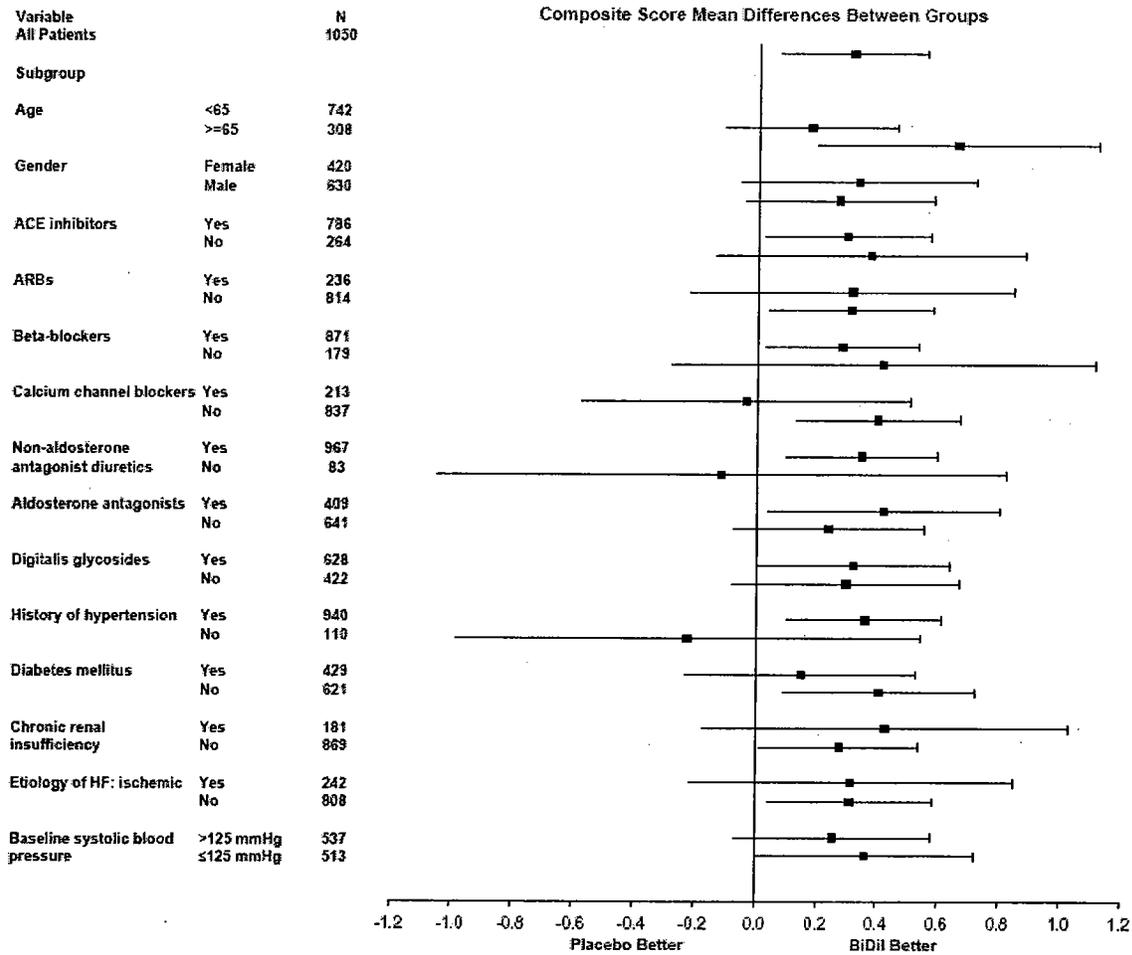
There were no differences between the two treatment groups with regard unscheduled visits for any cause. This may be due to the competing cause of mortality with subjects that would likely have had an unscheduled visit having died.

5.1.11.4.1.2.6 LVEF, LVIDD And LV Wall Thickness

Request to omit these findings from the submission were granted by the Division.

5.1.11.4.1.2.7 Composite Score Mean Differences by Baseline Demographic, Clinical and Therapeutic Characteristics

Figure 5. Composite score mean change by baseline characteristics (Sponsor's analysis)



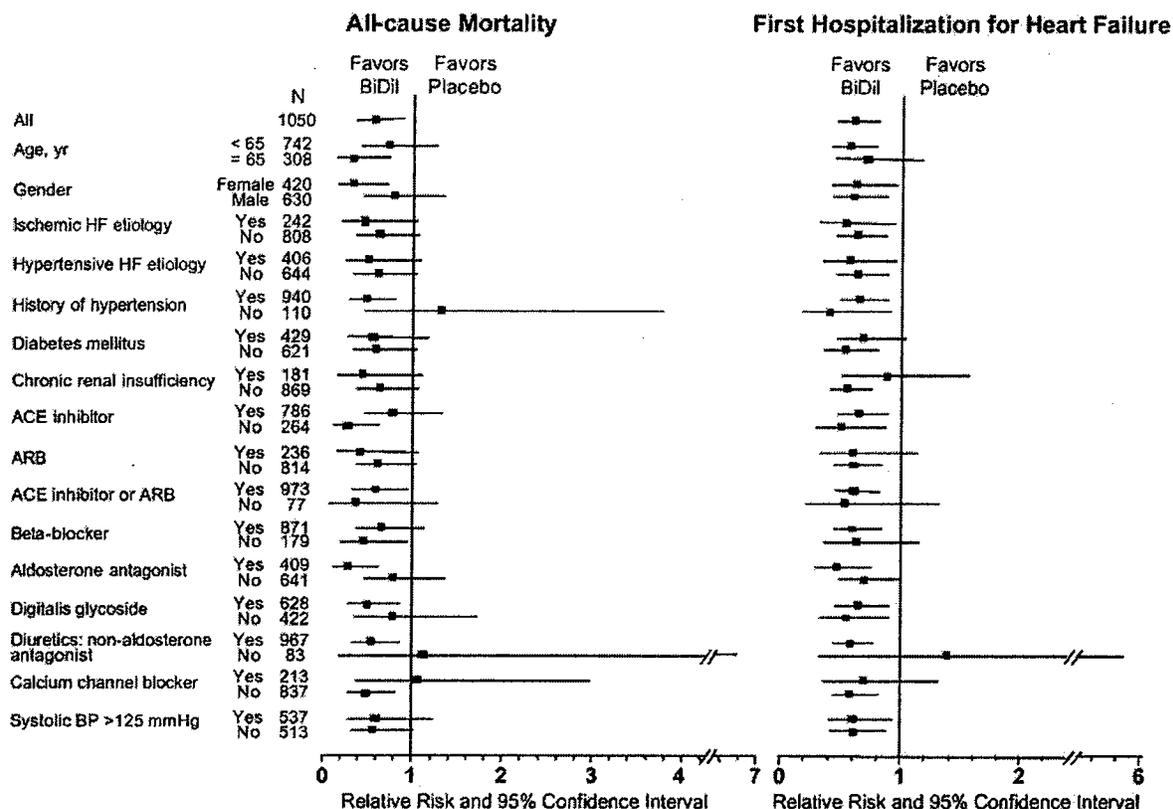
"History of hypertension" means whether the patient had been diagnosed as hypertensive at some point in time;

"Non-aldosterone antagonist diuretics" includes about 3.5% on a thiazide diuretic.

All subgroup categories seem to have benefited in their score, except for three categories and these are subjects on calcium channel blockers, patients not receiving non-aldosterone antagonist diuretics, and patients with no history of hypertensive with the point estimates of the latter two categories trending toward a worse score than placebo.

The association between BiDil and the composite score mean is more robust in subjects 65 years or older, subjects on aldosterone antagonists and subjects whose baseline SBP ≤ 125 mmHg.

Figure 6. All-cause mortality and hospitalization for HF by baseline characteristics (Sponsor's analysis)



All categories seem to have benefited from the effect of BiDil on all-cause mortality except for the category of patients with a history of hypertension, that of patients not taking non-aldosterone-antagonist diuretics, and that of patients taking calcium channel blockers.

The effect of BiDil on hospitalization for HF was observed in all categories except for that of patients not taking non-aldosterone antagonist diuretics.

The effect of BiDil on mortality and hospitalization in subjects receiving aldosterone antagonists was more pronounced than in subjects not receiving them.

It seems that patients not on diuretics, especially non-aldosterone antagonist diuretics, are at a disadvantage with regard to death or hospitalization for HF as an outcome.

Although BiDil seems to have no apparent effect on mortality in subjects on CCBs, it seems to have reduced their risk of hospitalization for HF.

5.1.11.4.1.3 Potential Confounding Factors Of Efficacy

Gender -A predominance of males in the placebo group with a difference of 8% between the two groups was observed. Gender being a significant risk factor of cardiovascular disease and death could have put the placebo group at a disadvantage with regard to HF outcomes.

Blood pressure -the BiDil group had higher systolic (+4 mmHg) and diastolic (+3 mmHg) blood pressure readings at baseline. If this difference stemmed from a high

prevalence of hypotension in the placebo group this could have put this group at a disadvantage given that hypotension is not a desirable risk factor for HF.

Diabetes mellitus –almost 8% more of the BiDil group had DM at baseline. DM is a significant factor of cardiovascular disease progression and mortality, and it could have put the BiDil group at a disadvantage.

Hyperlipidemia –a little over 5% more of the BiDil group had hyperlipidemia at baseline. Hyperlipidemia a significant risk factor of cardiovascular diseases, and apart from its indirect prediction of the incidence of HF and its progression, it is not known what direct effect this has on the outcome of HF.

Etiology of HF -2.5% more of the placebo group had a non-hypertensive etiology, and 3% more has an idiopathic etiology of HF. The findings of A-HeFT show that BiDil was more effective in the subgroup with a history of hypertension.

COPD –a predominance (+3%) of COPD was observed in the placebo group. Given pulmonary edema is a complication of CHF, COPD could have played a role in the deterioration and possibly fatal outcomes of CHF and put the placebo group at a disadvantage.

Other baseline imbalances include 4% more of the placebo patients had a history of previous smoking, 2% more had peripheral vascular disease even if there were less diabetics on placebo, 2% more had arrhythmia, and 2% less each were on concomitant ARBs and aldosterone antagonists known to be beneficial in HF disease.

5.1.11.4.2 V-HeFT

5.1.11.4.2.1 V-HeFT I Efficacy Findings

Table 25. Crude mortality rate and cause of death in the V-HeFT I trial²

	BiDil (N = 186)	Placebo (N = 273)	Prazosin (N = 183)
# of deaths	72	120	91
Crude mortality rate	38.7%	44.0 %	49.7%
Cause of death	n (%)	n (%)	n (%)
Pump failure	22 (31)	38 (32)	33 (36)
Primary arrhythmia	27 (37)	45 (38)	32 (35)
Other	6 (8)	4 (3)	6 (7)
Unknown	5 (7)	4 (3)	3 (3)
Cardiac	1 (1)	-	-
Suspected cardiac	10 (14)	20 (17)	-
Not specified	1 (1)	9 (7)	17 (19)

Table 26. Crude mortality and 95% CI for population subgroups²

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
CAD						
Yes	82	41.5	121	50.4	-8.9	-22.8, 5.0
No	84	36.5	152	38.8	-2.3	-14.4, 9.8
Race						
Black	49	30.6	79	44.3	-13.7	-30.6, 3.2

² Dr. Hung's review of V-HeFT I

Baseline	BiDil		Placebo		BiDil - Placebo	95% CI
	N	Rate (%)	N	Rate (%)		
Non-black	136	41.9	194	43.8	-1.9	-12.7, 8.9
Baseline EF						
> median	88	29.5	123	33.3	-3.8	-16.5, 8.9
< median	88	48.9	131	51.9	-3.0	-16.5, 10.5
Baseline Max O ₂						
> median	93	33.3	139	32.4	-1.0	-11.3, 13.3
< median	92	44.6	133	55.6	-11.1	-24.3, 2.1

5.1.11.4.2.2 V-HeFT II Efficacy Findings

Table 27. Crude mortality rate in the V-HeFT II Trial³

Crude mortality	BiDil N = 401 n (%)	Enalapril N = 403 n (%)
2-year mortality	95 (23.7)	68 (16.9)
5-year mortality	153 (38.2)	132 (32.8)

Table 28. Cumulative mortality from Life Table Analysis³

Year	Number alive at start		Cumulative mortality (%)	
	BiDil	Enalapril	BiDil	Enalapril
1	401	4.3	13.0	09.0
2	329	344	25.0	18.0
3	239	262	36.0	31.0
4	152	165	47.0	42.0
5	84	85	54.0	48.0

p (logrank for survival) 0.019 (2 years), 0.083 (overall)

Table 29. Crude mortality rates based on race and alcohol use³

	N	BiDil: Enalapril	BiDil - Enalapril	95% CI	95% CI Hazard Ratio
Black	109	0.36 : 0.37	-0.010	-0.14, 0.12	0.65, 1.58
Non-black	292	0.39 : 0.31	0.077	0.00, 0.15	1.01, 1.74
Alcohol use	147	0.37 : 0.39	-0.011	-0.12, 0.10	0.78, 1.66
No alcohol use	254	0.39 : 0.30	0.087	0.01, 0.17	0.97, 1.75

5.1.11.4.2.3 V-HeFT Trial Analyses Findings by Race

Post-hoc analyses of the V-HeFT I and V-HeFT II study data were used to promote the benefit of BiDil in African-American CHF patients. See Table 3 and Table 4 in 2.1, page 13.

5.1.11.4.3 Efficacy Conclusions

In the pivotal trial, the primary composite endpoint score was shown to be statistically significantly different between the BiDil and placebo treatment arms. The effect on all-cause mortality and first hospitalization for heart failure, two components of the composite endpoint, was shown to be substantial and statistically significant. The score of the third component of this

³ Dr. Hung's review of V-HeFT II

composite, the QOL was shown not to be statistically significantly different between the treatment arms, but a trend of an effect was observed. This does not carry as much weight because it is not as robust in predicting the progression of HF as the other two components of the primary endpoint.

From the supportive trials in the overall study populations, the difference in mortality rates was either not statistically significant when BiDil was compared to placebo (V-HeFT I), Table 25, page 41, or it was higher on BiDil compared to enalapril (V-HeFT II), Table 27, page 42 and Table 28, page 42. Subgroup analyses have shown that crude mortality rates in Blacks on BiDil were either substantially reduced compared to placebo (V-HeFT I), Table 26 page 41, or not different from enalapril, Table 29 page 42.

5.1.11.4.3.1 Could Lowering Blood Pressure Have Accounted for the Difference Observed in Effect?

Blood pressure on BiDil was consistently and statistically significantly reduced at all visits including the 6-month time point; Table 43, page 59.

Additionally, subgroup analysis showed that BiDil had more effect in subjects with a history of hypertension than those without, Figure 5 page 39.

In the V-HeFT II trial, systolic and diastolic blood pressure on enalapril decreased to a greater degree compared to BiDil (-3-4 mmHg vs. -1-1.5 mmHg) at 12 months.

A meta-analysis investigating whether pharmacological properties of antihypertensive drugs or reduction of systolic pressure accounted for cardiovascular outcome in hypertensive or high-risk patients was conducted⁴. The authors' conclusion was that the effect of anti-hypertensive drugs, ACE inhibitors and betablockers had an effect on the prognosis of cardiovascular diseases through their anti-hypertensive effects.⁵

5.1.11.4.3.2 The Effect Of Other Covariates

Analyses conducted by Dr. Hung adjusting for baseline characteristics (discussed in 5.1.11.4.3.2 page 43) that are believed to be associated with HF outcomes, did not change the magnitude or the significance of the effect of BiDil on the primary endpoint.

5.1.11.4.3.3 Is It a Difference of Race?

To think in terms of a difference in effect of a biopharmaceutical substance one can't help thinking in terms of a difference in the pathophysiology of the condition intended for treatment. This was the hypothesis that the Sponsor put forward to explain the failure of the V-HeFT trials in demonstrating the effect of BiDil in a population that was predominantly Caucasian, the V-HeFT post-hoc analysis findings by race, and the success of A-HeFT in preventing undesirable HF outcomes in an African-American population.

What is problematic in relating the effect observed in A-HeFT to race and interpreting it at the pathophysiological or molecular level is the definition used, an old-fashioned way of determining race which relies one's perception of one's race.

⁴ Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; 358: 1305-15

⁵ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903-13

The difference by race in the response of hypertension to ACE inhibitors was determined as a result of consistent findings from many ACE inhibitor hypertension trials even though a difference in response at the physiological level was demonstrated only in small numbers of patients and using only surrogate markers.

Given that Caucasians respond favorably to ACE inhibitors for the treatment of both hypertension and heart failure and that AA do not respond well to ACE inhibitors for the treatment of hypertension, one would expect that AA would not respond well to ACE inhibitors for the treatment of heart failure either.

Hypertension is a well-established determinant of incident heart failure and of its prognosis. Racial differences in patients with heart failure were reported to be in the mean age, prevalence of hypertension, left ventricular hypertrophy and ejection fraction. It is also reported that hypertension is more prevalent as an etiologic factor of HF in African Americans than in Caucasians. The characteristics (cited above) of the average African American failing heart are telling of a prevalent pathophysiology of systemic resistance as a cause of and/or a precipitating factor of HF. Common sense dictates that the reduction of this resistance would not only prevent HF, but its deleterious outcomes as well.

The reviewer's argument is that finally a drug is probably able to efficiently control blood pressure in AAs and prevent the consequences of both hypertension and HF. Facts that support and those that do not support the reviewer's argument follow:

--Facts NOT supporting:

- Lack of data that the ISDN/HYD combination is effective in the treatment of hypertension in AAs;
- Lack of data that the combination is superior to ACE-Is, ARBs and/or beta-blockers in the treatment of hypertension in AAs;
- Lack of data from well-conducted clinical trials that lowering BP is the mechanism by which the above therapies reduce and/or delay the outcomes of HF;

--Facts supporting:

- Anti-hypertensive therapies are well documented therapies for HF;
- Most medications that were shown to be effective in HF including ACE-Is, beta-blockers, ARBs, aldosterone antagonists and now BiDil have a strong feature in common, lowering blood pressure;
- Findings of the V-HeFT trials: in the V-HeFT I, BiDil seems⁶ to be superior to placebo in AAs, and in the V-HeFT II, BiDil seems to be "non-inferior"⁷ to enalapril in AA patients, especially that enalapril was shown to be clearly superior to BiDil in the overall population;
- In A-HeFT:
 - the group of patients on BiDil had a higher prevalence of hypertension at baseline and a higher prevalence of history of hypertension factor of HF;

⁶ the term "seem" is used because the analyses were not pre-specified, and the findings are result of post-hoc analysis

⁷ the design was not a non-inferiority design, but the trend was shifted toward no difference between AA on BiDil and AA on enalapril

- the mean BP at baseline of the subjects on BiDil was higher than that of subjects on placebo;
- the mean change from baseline in blood was significantly greater on BiDil compared to placebo;
- Keeping in mind that ACE-I + diuretic work better than ACE-I alone in control of BP in African Americans, subgroup analysis in A-HeFT showed that BiDil + ACE-I + diuretic was not statistically significantly different from ACE-I + diuretic with regard to mortality.
- In V-HeFT II enalapril lowered BP to a greater extent than BiDil;
- Data from two meta-analyses concluding that lowering blood pressure in HF wards off its undesirable outcomes (see selected figures from these publications: Figure 7 page, Figure 8 page 86, Figure 9 page 87 and Figure 10 page 88):
 - Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15.
 - Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

In the pivotal trial, assessment of safety was to consist of monitoring and recording all adverse events, SAEs, measurements of vital signs, and findings of physical examinations.

It was assumed that the safety profile of BiDil was known, therefore, there was to be no routine laboratory monitoring. Abnormal laboratory values or test results were considered as adverse events only if they induced clinical signs or symptoms or required change in therapy.

Hospitalization for HF, worsening of HF, and unscheduled office or emergency room visits for HF were not to be reported as adverse events because they were to be assessed as efficacy endpoints.

An independent Data and Safety Monitoring Board was to monitor the conduct of the study, review periodic reports of safety data by blinded treatment group, and make recommendations to the Steering Committee.

In addition, data from the V-HeFT I and V-HeFT II studies and from the CB-01 and CB-02 were reviewed for safety.

CB-01 "The 36-Hour Relative Bioavailability of BiDil, a Fixed Combination of Hydralazine/Isosorbide dinitrate, compared to Equivalent Doses of Reference Products (Pilot Study)". In this study 12 subjects received one dose of BiDil.

CB-02 "The Relative Bioavailability of Low and High dose BiDil, a fixed combination of Hydralazine HCl and isosorbide dinitrate, compared to an Oral Solution, Tablet, and Capsule of Hydralazine HCl and ISDN (Pivotal Bioequivalence Study)"

6.1.1 Overview of Adverse Events

Table 30. Summary of overall adverse events (Sponsor's summary)

	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Patients with at least one adverse event	475 (91.9)	432 (82.0)
Patients with at least one drug-related adverse event ¹	350 (67.7)	167 (31.7)
Patients with at least one serious adverse event ²	181 (35.0)	183 (34.7)
Patients with at least one drug-related serious adverse event ^{1, 2}	13 (2.5)	15 (2.8)
Patients who died ³	32 (6.2)	54 (10.2)
Patients who permanently discontinued study drug due to adverse events ⁴	109 (21.1)	63 (12.0)

¹ Assessed by the investigator as being possibly, probably, or definitely related to study drug.

² Serious adverse events exclude clinical endpoint HF hospitalization and adverse event death.

³ Adjudicated by the ICAC includes two patients (112-001 and 231-002) who died post-study.

⁴ As recorded on the adverse event CRF, includes patients who completed the study and those who did not complete the study, may include patients who temporarily stopped study drug as well as permanent discontinuations.

6.1.2 Deaths

Deaths are summarized under the efficacy section because all cause mortality is a component of the primary endpoint and stands on its own as a secondary endpoint.

6.1.3 Other Serious Adverse Events

6.1.3.1 Serious Adverse Events that led to Discontinuation

Table 31. Serious adverse events that led to discontinuation, overall incidence

AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)	AE leading to discontinuation[1]	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Any AE N (%)	29 (5.6)	32 (6.1)			
Chest pain	3 (0.6)	1 (0.2)	CVA	1 (0.2)	3 (0.6)
Heart arrest	3 (0.6)	3 (0.6)	Syncope	1 (0.2)	0.0
Heart failure	3 (0.6)	4 (0.8)	Gastroenteritis	1 (0.2)	1 (0.2)
Hypotension	3 (0.6)	1 (0.2)	Myasthenia	1 (0.2)	0.0
Kidney failure	3 (0.6)	1 (0.2)	Dyspnea	1 (0.2)	2 (0.4)
Infection	2 (0.4)	0.0	Edema of the lung	1 (0.2)	0.0
Ventricular fibrillation	2 (0.4)	0.0	Angioedema	1 (0.2)	0.0
Dizziness	2 (0.4)	0.0	Carcinoma of the breast	1 (0.2)	0.0
Arrhythmia	1 (0.2)	0.0	Uremia	1 (0.2)	0.0

As can be seen from the table above, the numbers are very small but more events, the ones expected to be observed, on BiDil were serious and led to discontinuation including hypotension, dizziness and chest pain. Of note are 3 cases of kidney failure vs. 1, and 2 cases of ventricular fibrillation vs. none on BiDil and placebo respectively.

6.1.3.2 Serious Adverse Events

Table 32. Serious adverse events, overall incidence

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Number (%) of patients with at least one SAE	181 (35.0)	183 (34.7)
Chest pain	33 (6.4)	29 (5.5)
Heart failure	16 (3.1)	41 (7.8)
Ventricular tachycardia	14 (2.7)	8 (1.5)
Pneumonia	12 (2.3)	8 (1.5)
Syncope	11 (2.1)	8 (1.5)
Dyspnea	10 (1.9)	12 (2.3)
Arrhythmia	9 (1.7)	7 (1.3)
Hypotension	8 (1.5)	3 (0.6)
Heart arrest	7 (1.4)	9 (1.7)
CVA	7 (1.4)	13 (2.5)
Dizziness	7 (1.4)	0.0
Cellulites	6 (1.2)	2 (0.4)
DM	6 (1.2)	5 (0.9)
Cerebral ischemia	5 (1.0)	1 (0.2)
Coronary artery disease	5 (1.0)	2 (0.4)
Anemia	5 (1.0)	3 (0.6)
Bronchitis	5 (1.0)	3 (0.6)
Dehydration	5 (1.0)	4 (0.8)
Angina pectoris	5 (1.0)	5 (0.9)
Hyperglycemia	5 (1.0)	5 (0.9)
Hypoglycemia	5 (1.0)	5 (0.9)
Infection	5 (1.0)	5 (0.9)
Acute kidney failure	5 (1.0)	8 (1.5)
Neoplasm/carcinoma	4 (0.8)	1 (0.2)
Gout	4 (0.8)	3 (0.6)
Atrial fibrillation	4 (0.8)	3 (0.6)
GI hemorrhage	4 (0.8)	5 (0.9)
Kidney failure	4 (0.8)	5 (0.9)
Myocardial infarct	4 (0.8)	9 (1.7)
Sepsis	3 (0.6)	1 (0.2)
Asthma	3 (0.6)	2 (0.4)
Injury, accidental	3 (0.6)	8 (1.5)
Cholecystitis	3 (0.6)	0.0
Cholelithiasis	3 (0.6)	0.0
Supraventricular tachycardia	3 (0.6)	0.0
Esophagitis	2 (0.4)	1 (0.2)
Edema of the lung	2 (0.4)	1 (0.2)
Headache	2 (0.4)	2 (0.4)
Osteomyelitis	2 (0.4)	2 (0.4)
Peripheral vascular disease	2 (0.4)	2 (0.4)
Bradycardia	2 (0.4)	3 (0.6)
Digitalis intoxication	2 (0.4)	4 (0.8)
Gastroenteritis	2 (0.4)	4 (0.8)
Hyperkalemia	2 (0.4)	5 (0.9)
Hemorrhage, cerebral+	2 (0.4)	0.0

SAEs	BiDil N = 517 n (%)	Placebo N = 527 n (%)
subarachnoid		
Thrombophlebitis, deep	2 (0.4)	0.0
Angioedema	2 (0.4)	0.0
Ascites	2 (0.4)	0.0
Infection viral/fungal	2 (0.4)	0.0
Fibrillation, ventricular	2 (0.4)	0.0
Anomaly Vascular	1 (0.2)	1 (0.2)
Coagulation disorder	1 (0.2)	1 (0.2)
Creatinine increased	1 (0.2)	1 (0.2)
Hyponatremia	1 (0.2)	1 (0.2)
Diarrhea	1 (0.2)	1 (0.2)
Liver failure	1 (0.2)	1 (0.2)
Neoplasm of the prostate	1 (0.2)	1 (0.2)
Myasthenia	1 (0.2)	1 (0.2)
Palpitations	1 (0.2)	1 (0.2)
UTI	1 (0.2)	1 (0.2)
Dyspepsia	1 (0.2)	2 (0.4)
Kidney function abnormal	1 (0.2)	4 (0.8)
Anemia, iron deficiency	1 (0.2)	0.0
Alkalosis	1 (0.2)	0.0
Arrhythmia NOD	1 (0.2)	0.0
Arthralgia	1 (0.2)	0.0
Carcinoma of the breast	1 (0.2)	0.0
Hypokalemia	1 (0.2)	0.0
Ketosis	1 (0.2)	0.0
Cerebral infarct	1 (0.2)	0.0
Emotional lability	1 (0.2)	0.0
Edema of the face	1 (0.2)	0.0
Gastritis, hemorrhagic	1 (0.2)	0.0
Gait abnormal	1 (0.2)	0.0
Hematemesis	1 (0.2)	0.0
Herpes Zoster	1 (0.2)	0.0
Uremia	1 (0.2)	0.0
Leucopenia	1 (0.2)	0.0
Thrombocytopenia	1 (0.2)	0.0
Necrosis	1 (0.2)	0.0
Ophthalmitis	1 (0.2)	0.0
Parathyroid disease	1 (0.2)	0.0
Respiratory distress	1 (0.2)	0.0
Skin ulcer	1 (0.2)	0.0
Thinking abnormal	1 (0.2)	0.0
Vascular disease	1 (0.2)	0.0
Wrist drop	1 (0.2)	0.0
Gastritis	1 (0.2)	2 (0.4)

As can be seen from the table above, some of the adverse events that were expected to be observed were reported as serious in excess on BiDil including hypotension, dizziness and syncope. Other serious adverse events were also reported in excess on BiDil compared to placebo and these are ventricular tachycardia, pneumonia, cellulites, cerebral ischemia, CAD, anemia and bronchitis.

6.1.4 Other Significant Adverse Events

6.1.4.1 Overall Profile of Dropouts

Forty nine (9.5%) of the subjects on BiDil and 75 (14%) of the subjects on placebo discontinued the study prematurely. One hundred and nine (21%) of the subjects on BiDil and 63 (12%) of the placebo patients discontinued the study medication as a result of adverse events. Five BiDil and 3 placebo subjects withdrew consent, 2 BiDil subjects were lost to follow-up, 9 (1.7%) BiDil and 13 (2.4%) placebo patients discontinued per investigator decision, 3 in each study group discontinued for cardiac transplant and 32 BiDil and 54 placebo patients died.

6.1.4.2 Adverse Events Associated with Permanent Discontinuation

Twenty one percent (109) on BiDil and 12% (63) on placebo permanently discontinued the study drug as a result of adverse events. Using the number of events, 5.9% (170 of all events) compared to placebo 3.3% (91 of all events) led to permanent discontinuation.

Table 33. Adverse events leading to treatment discontinuation (number and % of subjects)

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Any AE N (%)	109 (21.1)	63 (12.0)			
Asthenia	12 (2.3)	1 (0.2)	Ventricular fibrillation	2 (0.4)	0.0
Headache	38 (7.4)	4 (0.8)	Angioedema	1 (0.2)	0.0
Dizziness	19 (3.7)	4 (0.8)	Amblyopia	1 (0.2)	0.0
Pain	4 (0.8)	1 (0.2)	Anorexia	1 (0.2)	0.0
Chest pain	8 (1.5)	2 (0.4)	Neck pain	1 (0.2)	0.0
Nausea	8 (1.5)	2 (0.4)	Carcinoma	1 (0.2)	0.0
Hypotension	7 (1.4)	3 (0.6)	Carcinoma of the breast	1 (0.2)	0.0
Abdominal pain	2 (0.4)	1 (0.2)	Dehydration	1 (0.2)	0.0
Chills	2 (0.4)	1 (0.2)	Edema of the face	1 (0.2)	0.0
Kidney failure	2 (0.4)	1 (0.2)	Edema peripheral	1 (0.2)	0.0
Malaise	2 (0.4)	1 (0.2)	Edema of the lung	1 (0.2)	0.0
Heart arrest	3 (0.6)	3 (0.6)	Fever	1 (0.2)	0.0
Confusion	2 (0.4)	2 (0.4)	Hyperglycemia	1 (0.2)	0.0
Diarrhea	2 (0.4)	2 (0.4)	Hypertension	1 (0.2)	0.0
Gastroenteritis	1 (0.2)	1 (0.2)	Infection	1 (0.2)	0.0
Back pain	1 (0.2)	1 (0.2)	Infection fungal	1 (0.2)	0.0
Acute kidney failure	1 (0.2)	1 (0.2)	Impotence	1 (0.2)	0.0
Myasthenia	1 (0.2)	1 (0.2)	Ketosis	1 (0.2)	0.0
Nervousness	1 (0.2)	1 (0.2)	Breast neoplasm	1 (0.2)	0.0
Pruritus	1 (0.2)	1 (0.2)	Lab tests abnormal	1 (0.2)	0.0
Heart failure	3 (0.6)	4 (0.8)	Myalgia	1 (0.2)	0.0
Dyspepsia	1 (0.2)	2 (0.4)	Photophobia	1 (0.2)	0.0
Cerebrovascular accident	1 (0.2)	3 (0.6)	Pleural effusion	1 (0.2)	0.0
Constipation	1 (0.2)	3 (0.6)	Somnolence	1 (0.2)	0.0
CVA	1 (0.2)	3 (0.6)	Sweat	1 (0.2)	0.0
Dyspnea	1 (0.2)	4 (0.8)	Vasodilatation	1 (0.2)	0.0
Nausea vomiting	3 (0.6)	0.0	Weight decrease	1 (0.2)	0.0
Paresthesia	3 (0.6)	0.0	Uremia	1 (0.2)	0.0
Abnormal kidney function	2 (0.4)	0.0	Hypoglycemia	0.0	2 (0.4)
Kidney function	2 (0.4)	0.0	Myocardial infarction	0.0	4 (0.8)

AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)	AE leading to discontinuation	BiDil N = 517 n (%)	Placebo N = 527 n (%)
abnormal					
Palpitations	2 (0.4)	0.0	Rash	0.0	3 (0.6)
Syncope	2 (0.4)	0.0	Rectal hemorrhage	0.0	2 (0.4)

Table excludes hospitalization for HF and death. A patient can have more than one event or type of event; each patient is counted only once in each category.

Discontinuation of study drug due to adverse events was observed in excess (80% excess in risk) on BiDil, and headache alone accounted for a third of these. Headache, dizziness, asthenia, chest pain, nausea, and hypotension accounted for 84% of the discontinuations on BiDil and only 25% of the discontinuations on placebo.

Of note are two cases of ventricular fibrillation, and two cases of syncope on BiDil vs. none on placebo.

6.1.4.3 Adverse Events Associated with Temporary Discontinuation or Dose Adjustment

Dose adjustment or temporary study drug discontinuation occurred at a higher incidence in patients on BiDil 42.2% (218) compared to those on placebo 25.2% (133), and of these 19.3% (42) and 26.3% (35) returned to pre-event dose level.

Twenty percent (570) and 13% (341) of the events led to temporary discontinuation or dose level adjustment in BiDil and placebo respectively.

6.1.5 Other Search Strategies

The clinical and statistical results of the V-HeFT studies reported here are those summarized by the Division's review of the original NDA (Doctors Hung, Chen and Ganley, 1997).

6.1.6 Common Adverse Events

6.1.6.1 Eliciting Adverse Events Data in The Development Program

Investigators were instructed to report all adverse events that occur before, during or within 14 days following the cessation of treatment whether or not believed to be related to the study drug. Patients were assessed every three months when they returned for a study visit.

There were no plans to assess of the effect of BiDil on laboratory parameters, QT interval and the immune system because it was assumed that its safety profile was known.

6.1.6.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse events were summarized by body system and using the COSTART preferred term. This categorization and the preferred term used were used in other trials and deemed acceptable.

6.1.6.3 Incidence of Common Adverse Events in the A-Heft Trial

Table 34. Common adverse events, overall incidence by treatment ($\geq 0.8\%$)

Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)	Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)
N (%) with at least one AE	475 (91.9)	432 (82.0)			
Headache	256 (49.5)	111 (21.1)	Hypercholesterolemia	7 (1.4)	2 (0.4)

Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)	Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Dizziness	165 (31.9)	72 (13.7)	Infection, viral	7 (1.4)	3 (0.6)
Pain	84 (16.2)	85 (16.1)	Myalgia	7 (1.4)	3 (0.6)
Pain, chest	81 (15.7)	80 (15.2)	Rectal disorder	7 (1.4)	4 (0.8)
Infection	70 (13.5)	67 (12.7)	Abscess peridontal	6 (1.2)	4 (0.8)
Asthenia	70 (13.5)	59 (11.2)	Epistaxis	6 (1.2)	11 (2.1)
Dyspnea	65 (12.6)	92 (17.5)	Hematuria	6 (1.2)	6 (1.1)
Nausea	50 (9.7)	32 (6.1)	Hyponatremia	6 (1.2)	5 (0.9)
Heart failure	49 (9.5)	80 (15.2)	Joint disorder	6 (1.2)	7 (1.3)
Bronchitis	43 (8.3)	34 (6.5)	Sputum increased	6 (1.2)	11 (2.1)
Hypotension	41 (7.9)	23 (4.4)	Vascular disease, peripheral	6 (1.2)	9 (1.7)
Hypertension	33 (6.4)	33 (6.3)	Periph vascular disease	6 (1.2)	9 (1.7)
Injury, accidental	29 (5.6)	36 (6.8)	Abscess peridontal	6 (1.2)	4 (0.8)
Cough increased	27 (5.2)	41 (7.8)	Angioedema	6 (1.2)	1 (0.2)
Diarrhea	27 (5.2)	30 (5.7)	Cerebral ischemia + infarct	6 (1.2)	2 (0.4)
Gout	27 (5.2)	32 (6.1)	Infection, sepsis	6 (1.2)	1 (0.2)
Edema peripheral	25 (4.8)	37 (7.0)	Malaise	6 (1.2)	1 (0.2)
Pain, abdominal	25 (4.8)	35 (6.6)	Hypomagnesemia	5 (1.0)	8 (1.5)
Pain, back	24 (4.6)	28 (5.3)	Melena	5 (1.0)	3 (0.6)
Syncope	23 (4.4)	20 (3.8)	Pleural effusion	5 (1.0)	5 (0.9)
Sinusitis	22 (4.3)	9 (1.7)	Abscess	5 (1.0)	4 (0.8)
Anemia	21 (4.1)	26 (4.9)	Hernia	5 (1.0)	0.0
Ventricular tachycardia	21 (4.1)	14 (2.7)	MI	5 (1.0)	9 (1.7)
Hyperglycemia	20 (3.9)	18 (3.4)	Melena	5 (1.0)	3 (0.6)
GI disorder	20 (3.9)	14 (2.7)	Cardiovascular disease	5 (1.0)	0.0
Palpitations	20 (3.9)	14 (2.7)	Hernia	5 (1.0)	0.0
UTI	19 (3.7)	26 (4.9)	Melena	5 (1.0)	3 (0.6)
Pneumonia	19 (3.7)	21 (4.0)	Tendon disease	5 (1.0)	2 (0.4)
Rhinitis	19 (3.7)	14 (2.7)	Colitis	4 (0.8)	5 (0.9)
Constipation	18 (3.5)	28 (5.3)	Ecchymosis	4 (0.8)	7 (1.3)
Paresthesia	18 (3.5)	12 (2.3)	GI hemorrhage	4 (0.8)	6 (1.1)
Vomiting	18 (3.5)	10 (1.9)	Hemoptysis	4 (0.8)	5 (0.9)
Pharyngitis	17 (3.3)	24 (4.6)	Leucocytosis	4 (0.8)	3 (0.6)
Dyspepsia	16 (3.1)	24 (4.6)	Chills	4 (0.8)	4 (0.8)
Amblyopia	16 (3.1)	7 (1.3)	Cyst	4 (0.8)	4 (0.8)
Hypokalemia	15 (2.9)	18 (3.4)	Lab test abnormal	4 (0.8)	4 (0.8)
Hyperlipidemia	15 (2.9)	10 (1.9)	Vascular anomaly	4 (0.8)	1 (0.2)
Arrhythmia	14 (2.7)	20 (3.8)	Postural hypotension	4 (0.8)	2 (0.4)
Abnormal kidney function	14 (2.7)	7 (1.3)	Cholelithiasis	4 (0.8)	1 (0.2)
Pruritus	13 (2.5)	13 (2.5)	Hypotension, postural	4 (0.8)	2 (0.4)
Asthma	12 (2.3)	15 (2.8)	Respiratory disease	4 (0.8)	2 (0.4)
Edema	12 (2.3)	14 (2.7)	Tachycardia, supraventricular	4 (0.8)	0.0
hyperkalemia	12 (2.3)	20 (3.8)	Vascular, anomaly	4 (0.8)	1 (0.2)
Rash	12 (2.3)	14 (2.7)	Vision abnormal	4 (0.8)	2 (0.4)
Influenza syndrome	12 (2.3)	18 (3.4)	Impotence	3 (0.6)	6 (1.1)
Dehydration	11 (2.1)	11 (2.1)	Neuropathy	3 (0.6)	4 (0.8)
Nausea & vomiting	11 (2.1)	11 (2.1)	Vasodilation	3 (0.6)	4 (0.8)
Cellulitis	11 (2.1)	9 (1.7)	Digitalis intoxication	3 (0.6)	7 (1.3)
Tachycardia	11 (2.1)	6 (1.1)	Ventricular extra-systoles	3 (0.6)	4 (0.8)
DM	10 (1.9)	15 (2.8)	Hemorrhage	3 (0.6)	7 (1.3)
Hypoglycemia	10 (1.9)	11 (2.1)	Vasodilation	3 (0.6)	4 (0.8)

Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)	Adverse events	BiDil N = 517 n (%)	Placebo N = 527 n (%)
Leg cramps	10 (1.9)	12 (2.3)	Bone disease	3 (0.6)	1 (0.2)
Lung disorder	10 (1.9)	15 (2.8)	Duodenitis	3 (0.6)	0.0
Infection, fungal	10 (1.9)	6 (1.1)	Ear disorder	3 (0.6)	0.0
Sweat increase	10 (1.9)	5 (0.9)	Headache, migraine	3 (0.6)	1 (0.2)
Arthritis	8 (.5)	7 (1.3)	Hypoxia	3 (0.6)	0.0
Gastroenteritis	9 (1.7)	9 (1.7)	Osteoporosis	3 (0.6)	0.0
Liver function abnormal	9 (1.7)	11 (2.1)	Photosensitivity	3 (0.6)	1 (0.2)
Angina pectoris	9 (1.7)	9 (1.7)	Tenosynovitis	3 (0.6)	1 (0.2)
Allergy reaction	9 (1.7)	6 (1.1)	Vascular disease	3 (0.6)	1 (0.2)
Fever	9 (1.7)	7 (1.3)	Conjunctivitis	2 (0.4)	6 (1.1)
Neoplasm	9 (1.7)	4 (0.8)	Dysphagia	2 (0.4)	6 (1.1)
Pain, neck	9 (1.7)	7 (1.3)	NPN increased	2 (0.4)	4 (0.8)
Anorexia	8 (1.5)	9 (1.7)	Rectal hemorrhage	2 (0.4)	5 (0.9)
Kidney failure, acute	8 (1.5)	15 (2.8)	Skin ulcer	2 (0.4)	7 (1.3)
Weight increased	8 (1.5)	13 (2.5)	Vertigo	2 (0.4)	5 (0.9)
Atrial fibrillation	8 (1.5)	8 (1.5)	Bradycardia	2 (0.4)	8 (1.5)
Arthralgia	8 (1.5)	2 (0.4)	Hepatomegaly	2 (0.4)	0.0
Gastritis	8 (1.5)	9 (1.7)	Hydronephrosis	2 (0.4)	0.0
Somnolence	8 (1.5)	2 (0.4)	Thrombocytopenia	2 (0.4)	0.0
Flatulence	7 (1.4)	8 (1.5)	Uremia	2 (0.4)	0.0
Hypervolemia	7 (1.4)	8 (1.5)	Breast pain	1 (0.2)	5 (0.9)
Kidney failure	7 (1.4)	6 (1.1)	Lymphadenopathy	1 (0.2)	5 (0.9)
Myasthenia	7 (1.4)	6 (1.1)	Prothrombin increased	1 (0.2)	6 (1.1)
CVA	7 (1.4)	13 (2.5)	Hypothyroidy	0.0	5 (0.9)
Heart arrest	7 (1.4)	9 (1.7)	Neuralgia	0.0	4 (0.8)
Alopecia	7 (1.4)	3 (0.6)	pancreatitis	0.0	4 (0.8)
Cholecystitis	7 (1.4)	0.0	Urinary retention	0.0	4 (0.8)
Coronary artery disease	7 (1.4)	4 (0.8)	Pancreatitis	0.0	4 (0.8)

A patient can have more than one event or type of event; each patient is counted only once in each category.

There was one case of lupus-like syndrome reported as joint disorder (narrative 9.5, page 77) which resolved after treatment and without a change to the study medication. Also, there was an excess of arthralgia (almost 4 times as frequent) on BiDil compared to placebo.

As can be seen from the table above, the overall rate of adverse events is not very different between the two treatment arms. Headache and dizziness are statistically significantly different between BiDil and placebo. Differences between BiDil and placebo reached statistical significance with regard to hypotension, nausea and sinusitis. Other adverse events where an increase on BiDil was observed include tachycardia, ventricular tachycardia, palpitations and supraventricular tachycardia; GI disorders and vomiting; paresthesia, sweat increase, and amblyopia and abnormal vision; hyperlipidemia and hypercholesterolemia; abnormal kidney function and uremia; infections (fungal, viral, sepsis and periodontal abscess); allergy reactions, and angioedema; CVD and cerebral ischemia and/or infarct; arthralgia, malaise, myalgia, tendon disease, and tenosynovitis; hernia; rectal disease and melena; bronchitis, and respiratory disease; cholecystitis and cholelithiasis; somnolence; and neoplasm.

6.1.6.4 Incidence of Common Adverse Events In The V-Heft I And V-Heft II Trials

6.1.6.4.1 Incidence of Adverse Events in Blacks in the V-HeFT Studies

Table 35. Incidence of adverse events in the African-American subpopulation of the V-HeFT trials

Events	BiDil N = 158 n (%)	Placebo N = 79 n (%)	Enalapril N = 106 n (%)
Headache	113 (72%)	43 (54%)	68 (64%)
Dizziness	106 (67%)	42 (53%)	71 (67%)
Arthralgia	103 (65%)	48 (61%)	76 (72%)
Other*	82 (52%)	35 (44%)	63 (59%)
Palpitation	84 (53%)	29 (37%)	52 (49%)
Nausea or Vomiting	75 (47%)	32 (41%)	60 (57%)
Ischemic Chest Pain	58 (37%)	29 (37%)	44 (42%)
Diarrhea	63 (40%)	30 (38%)	46 (43%)
Flushing	50 (32%)	22 (28%)	23 (22%)
Rash	51 (32%)	23 (29%)	37 (35%)
Fever	52 (33%)	17 (22%)	31 (29%)
Syncope	36 (23%)	16 (20%)	16 (15%)

Table from the sponsor's report;

*Was not broken into specific AEs;

6.1.6.4.2 Incidence of Adverse Events in all Patients of the V-HeFT I Study

Six percent (11) and 1% (3) discontinued BiDil and placebo as a result of adverse events.

Table 36. Incidence of adverse events that resulted in dose reduction in V-HeFT I

Adverse Event	ISDN/HYD N = 186 %	Placebo N = 273 %
Any	51.6	22.0
Headache	40.3	5.5
Dizziness	25.8	12.1
Arthralgia	4.8	2.2
Other	11.3	6.6
Palpitations	10.8	2.6
Nausea or vomiting	11.3	5.5
Ischemic chest pain	3.8	2.6
Diarrhea	4.3	1.5
Abdominal pain	7.0	2.9
Flushing	8.6	1.1
Rash	4.3	1.5
Fever	3.8	0.0
Syncope	2.2	4.4

Table from the V-HeFT I Medical/Statistical Review

Table 37. Incidence of adverse events in the V-HeFT I study

Adverse Event	ISDN/HYD N = 186 %	Placebo N = 273 %
Any	94.6	87.2
Headache	74.7	50.9
Dizziness	70.4	59.7

Adverse Event	ISDN/HYD	Placebo
	N = 186 %	N = 273 %
Arthralgia	63.4	57.9
Other	61.3	49.5
Palpitations	55.9	44.0
Nausea or vomiting	52.2	45.1
Ischemic chest pain	48.9	41.4
Diarrhea	46.8	38.8
Abdominal pain	45.2	34.8
Flushing	43.6	30.4
Rash	43.0	38.1
Fever	33.3	26.4
Syncope	26.3	23.8

Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.3 Incidence of Adverse Events in the V-HeFT II Study

Three percent (13) and 2.7% (11) discontinued BiDil and enalapril as a result of adverse events.

Table 38. Adverse events that led to dose reduction in V-HeFT II

Adverse Event	ISDN/HYD	Enalapril
	N = 401 %	N = 403 %
Headache	40.9	11.2
Fatigue/lassitude	28.9	23.6
Dizziness	26.9	19.4
Other	22.4	17.4
Nausea or vomiting	18.0	13.2
Arthralgia	11.0	6.4
Palpitations	10.2	5.0
Hypotension	7.5	9.7
Abnormal lab tests	7.2	11.2

Table from the V-HeFT I Medical/Statistical Review

Table 39. Incidence of adverse events in V-HeFT II

Adverse Event	ISDN/HYD	Enalapril
	N = 401 %	N = 403 %
Any	98	100
Abnormal lab tests	92	97
Fatigue/lassitude	81	82
Headache	77	60
Arthralgia	69	72
Nasal congestion	68	68
Dizziness	67	67
Other	61	65
Palpitations	57	54
Nausea or vomiting	53	59
Chest pain	44	46
Constipation	42	44

Table from the V-HeFT I Medical/Statistical Review

6.1.6.4.4 X-A-HeFT Four-Month Safety Update

6.1.6.4.4.1 Background

As of April 8 2005, 187 subjects have continued onto X-A-HeFT, an open-label, non-controlled extension trial, and generated the safety data discussed below. The extent of exposure was not provided and only a listing of patients with serious AEs was.

6.1.6.4.4.2 Adverse Events

--two deaths, one cardiac arrest and the other unspecified;

--hospitalization for:

-CHF exacerbation in 2;

-exacerbation of cardiomyopathy in 2;

-pneumonia in 4;

-worsening of COPD in 2;

-other respiratory in 4;

-acute renal failure in 1;

-other: chest pain in 1, TIA in 1, mental in 2, DVT in 1, bone fracture in 1 and acute gastroenteritis in 1;

6.1.6.4.5 Safety Data from Other Studies

6.1.6.4.5.1 Findings from Clinical Pharmacology Studies (Summarized from Dr. Hinderling' review)

CB-01

A single dose of BiDil given as a fixed combination of 37.5 mg/ 20 mg b.i.d. was compared to the same dose given, in two formulations, as HYD tablet and ISDN tablet, and as HYD capsule and ISDN tablet. Twelve healthy subjects were randomized into the three formulation groups in a three-period crossover design with a 7 day wash out period.

There were two cases of serious postural hypotension, and 9 out of 12 subjects refused to progress to the next treatment period as a result of adverse events. Headache was reported by 10 subjects. The study was terminated early.

CB-02

The bioavailability of low and high doses (37.5/10 mg and 75/40 mg tablets) of a fixed combination of HYD and ISDN were compared to HYD 37.5 mg tablet plus ISDN 10 mg tablet and HYD 37.5 mg capsule plus ISDN 10 mg tablet in 149 healthy males and females who have been initiated on a single dose of HYD HCl 37.5 mg/ISDN 10 mg solution. Of the 88 subjects who were identified as slow acetylators, 75 were randomized to participate in Phase B. In Phase B subjects were randomized into groups A (low fixed dose), B (tablet/tablet formulation), C (capsule/tablet formulation) and D (high fixed dose) with 19 subjects in each group, and with the exception of one, all subjects completed Phase B.

In Phase A, a total of 211 AEs were reported in 110 subjects including one orthostatic hypotension that led to hospitalization. Two subjects experienced severe AEs including hypotension and syncope in one, and dizziness and syncope in the other. Four subjects had a syncopal episode. The most frequent AEs included headache in 62%, dizziness in 17% and nausea in 13% of the subjects.

In Phase B, a total of 96 AEs were reported in 46 subjects. The incidence of any AE was highest in the highest dose (75/40 mg) group of BiDiL. In all treatment groups the most common AEs were headache and dizziness.

Severe AEs included severe headache in a subject in the highest dose group. Eleven subjects had hypotensive episodes, but none had a syncope episode.

6.1.6.4.6 Identifying Common and Drug-related Adverse Events

Headache, dizziness, nausea, vomiting, and arthralgia are very likely related to BiDil, and the rationale is that they were observed in excess on BiDil, led to withdrawal and/or dose reduction of BiDil, and were consistently associated with BiDil in the A-HeFT and V-HeFT trials.

Hypotension and postural hypotension are also very likely related to the study drug because of its vasodilating action.

6.1.6.4.7 Additional Analyses and Explorations

Table 40. Common adverse events by age categories

Number (%) of patients with at least one AE	<65 years		≥65 years	
	BiDil N = 361 n (%)	Placebo N = 376 n (%)	BiDil N = 156 n (%)	Placebo N = 151 n (%)
Any AE	342 (94.7)	303 (80.6)	133 (85.3)	129 (85.4)
Headache	198 (54.8)	89 (23.7)	58 (37.2)	22 (14.6)
Dizziness	115 (31.9)	46 (12.2)	50 (32.1)	26 (17.2)
Asthenia	49 (13.6)	45 (12.0)	21 (13.5)	14 (9.3)
Nausea	37 (10.2)	19 (5.1)	13 (8.3)	13 (8.6)
Bronchitis	30 (8.3)	26 (6.9)	13 (8.3)	8 (5.3)
Hypotension	29 (8.0)	18 (4.8)	12 (7.7)	5 (3.3)
Peripheral edema	24 (6.6)	25 (6.6)	1 (0.6)	12 (7.9)
Ventricular tachycardia	15 (4.2)	12 (3.2)	6 (3.8)	2 (1.3)
GI disorder	15 (4.2)	11 (2.9)	5 (3.2)	3 (2.0)
Vomiting	15 (4.2)	7 (1.9)	3 (1.9)	3 (2.0)
Palpitations	14 (3.9)	12 (3.2)	6 (3.8)	2 (1.3)
Paresthesia	14 (3.9)	10 (2.7)	4 (2.6)	2 (1.3)
Hyperlipidemia	13 (3.6)	5 (1.3)	2 (1.3)	5 (3.3)
Rhinitis	12 (3.5)	11 (2.9)	7 (4.5)	3 (2.0)
Amblyopia	10 (2.8)	4 (1.1)	6 (3.8)	3 (2.0)
Rash	8 (1.9)	11 (2.9)	5 (3.2)	3 (2.0)
Gastritis	7 (1.9)	4 (1.1)	1 (0.6)	5 (3.3)
Anorexia	6 (1.7)	4 (1.1)	2 (1.3)	5 (3.3)
Anxiety	2 (0.6)	4 (1.1)	5 (3.2)	2 (1.3)
Hematuria	5 (1.4)	1 (0.3)	1 (0.6)	5 (3.3)

Dizziness, nausea, vomiting and gastritis seem to be more prevalent in younger subjects, while ventricular tachycardia, palpitations, and anxiety were more common in older subjects.

Table 41. Common adverse events by gender

	Male gender		Female gender	
	BiDil N = 289 n (%)	Placebo N = 228 n (%)	BiDil N = 337 n (%)	Placebo N = 190 n (%)
Headache	129 (44.6)	55 (16.3)	127 (55.7)	56 (29.5)
Dizziness	83 (28.7)	49 (14.5)	82 (36.0)	23 (12.1)
Hypotension	23 (8.0)	12 (3.6)	18 (7.9)	11 (5.8)

	Male gender		Female gender	
	BiDil N = 289 n (%)	Placebo N = 228 n (%)	BiDil N = 337 n (%)	Placebo N = 190 n (%)
Bronchitis	18 (6.2)	24 (7.1)	25 (11.0)	10 (5.3)
Gout	18 (6.2)	27 (8.0)	9 (3.9)	5 (2.6)
Hypertension	15 (5.2)	22 (6.5)	18 (7.9)	11 (5.8)
Syncope	12 (4.2)	15 (4.5)	11 (4.8)	5 (2.6)
Ventricular tachycardia	11 (3.8)	10 (3.0)	10 (4.4)	4 (2.1)
Amblyopia	11 (3.8)	5 (1.5)	5 (2.2)	2 (1.1)
Paresthesia	10 (3.5)	9 (2.7)	8 (3.5)	3 (1.6)
GI disorder	9 (3.1)	6 (1.8)	11 (4.8)	8 (4.2)
Hyperglycemia	9 (3.1)	13 (3.9)	11 (4.8)	5 (2.6)
Hyperlipemia	9 (3.1)	4 (1.2)	6 (2.6)	6 (3.2)
Insomnia	7 (2.4)	16 (4.8)	16 (7.0)	8 (4.2)
Vomiting	7 (2.4)	5 (1.5)	11 (4.8)	5 (2.6)
Abnormal kidney function	7 (2.4)	6 (1.8)	7 (3.1)	1 (0.5)
Sinusitis	5 (1.7)	1 (0.3)	17 (7.5)	8 (4.2)
Palpitations	5 (1.7)	7 (2.1)	15 (6.6)	7 (3.7)
Rhinitis	5 (1.7)	7 (2.1)	14 (6.1)	7 (3.7)
Nausea vomiting	3 (1.0)	6 (1.8)	8 (3.5)	5 (2.6)
Cellulitis	3 (1.0)	8 (2.4)	8 (3.5)	1 (0.5)
Hypoglycemia	3 (1.0)	7 (2.1)	7 (3.1)	4 (2.1)
Lung disorder	3 (1.0)	12 (3.6)	7 (3.1)	3 (1.6)
Allergic reaction	2 (0.7)	3 (0.9)	7 (3.1)	3 (1.6)

Hyperlipidemia, hypotension and sinusitis were observed more frequently in males, while bronchitis, syncope, ventricular tachycardia, palpitations, paresthesia, insomnia, abnormal kidney function, nausea/vomiting, rhinitis, cellulites, lung disorders and allergy reactions were more frequent in women.

6.1.7 Laboratory Findings

6.1.7.1 A-HeFT

Laboratory tests were not conducted routinely to either study the effect of the study drug on laboratory parameter or to monitor safety in the study population, and the reason given by the sponsor was that BiDil has a mature and well-known safety profile. Hematology, chemistry and urinalysis were to be conducted only at baseline for reference.

Laboratory test results were reported only when they were determined to be adverse events, and they were determined as such only if they induced clinical signs or symptoms or required a change in therapy, in which case they were recorded on the AE CRF under the signs, symptoms or diagnosis associated with them.

6.1.7.2 V-HeFT

Changes from baseline in selected laboratory parameters in African Americans who participated in the two V-HeFT studies were summarized and a paired t-test was conducted to test the significance of this change.

Table 42. Change from Baseline in Selected Laboratory Parameters in V-HeFT

Parameters and Statistics	Change in Mean from Baseline on HYD - ISDN	p-value
Alkaline phosphatase U/L N Range Mean SD Median	157 -71.0 - 167.0 6.03 38.6 1.0	0.052
BUN units: ml % N Range Mean SD Median	158 -24.0 - 52.0 1.63 9.18 1.0	0.027
Potassium: mEq/L N Range Mean SD Median	157 -1.6 - 1.5 -0.09 0.44 -0.1	0.007
Magnesium: mEq/L N Range Mean SD Median	108 -13.0 - 87.0 3.24 15.89 0.0	0.036
Sodium: mEq/L N Range Mean SD Median	158 -14.0 - 10.0 -0.59 3.45 0.0	0.032
Hematocrit: % N Range Mean SD Median	155 -31.0 - 10.0 -1.42 5.19 -1.0	<0.001
Segmented neutrophils N Range Mean SD Median	105 -20.0 - 30.0 3.48 10.53 4.0	0.001
Urine proteins N Range Mean SD Median	108 -4 - 8.0 0.3 1.83 0.0	0.095

6.1.8 Vital Signs

6.1.8.1 Overview of Vital Signs Testing in the Development Program

Supine heart rate, SBP and DBP measurements were completed as part of either the complete physical exam that was to be conducted at screening and 6 months, or the brief physical exam that was to be conducted at 3, 6, 9 and 12 months or the final visit.

Blood pressure was measured at each patient visit; patient study visits were scheduled to occur at times convenient for the patient and clinical site personnel, and did not take into account how recently the patient had taken his/her prior study medication dose.

6.1.8.2 Standard Analyses and Explorations of Vital Signs Data

6.1.8.2.1 Analyses Focused on Measures of Central Tendencies

Table 43. Effect of BiDil on Heart Rate, SBP and DBP, in the A-HeFT Trial

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Baseline												
N	516	526	--	--	517	526	--	--	517	526	--	--
Mean	74.2	73.1	--	--	127.2	125.3	--	--	77.6	75.6	--	--
SD	12.3	11.01	--	--	17.5	18.1	--	--	10.3	10.6	--	--
Median	74	72	--	--	128	125	--	--	80	76	--	--
Range	41 to 10	40 to 108	--	--	80 to 196	82 to 185	--	--	39 to 104	47 to 10	--	--
Month 3												
N	435	469	434	468	436	469	436	468	436	468	436	467
Mean	75.5	74.6	1.3	1.3	123.9	126.2	-3.2*	1.1	74.1	75.7	-3.4*	0.3
SD	11.6	11.8	12.19	11.07	19.6	21.8	17.41	17.6	12.7	13.1	12.6	11.5
Median	76	74	2	0	122	124	-2	0	74	76	-2	0
Range	50 to 116	44 to 131	-40 to 40	-36 to 49	80 to 210	74 to 205	-60 to 70	-45 to 70	42 to 130	48 to 130	-35 to 34	-28 to 46
Month 6												
N	388	376	387	375	389	376	389	375	389	376	389	375
Mean	75.8	73.5	1.3	0.0	125.6	125.5	-1.9*	1.2	75.1	76	-2.4*	0.8
SD	12.2	11.8	13.6	11.9	20.8	19.8	18.9	18.3	12.9	13.1	12.3	11.9
Median	76	73	2	0	121	125	-1	0	73	76	-4	0
Range	47 to 114	43 to 112	-41 to 46	-41 to 32	78 to 200	75 to 187	-82 to 602	-50 to 77	42 to 120	40 to 116	-40 to 36	-36 to 56
Month 9												
N	313	306	312	305	313	305	313	304	313	305	313	304
Mean	76.4	74.6	2.3	1.4	123.6	124.7	-4.7*	0.4	74.2	75.6	-3.3*	0.2
SD	12.4	11.5	13.93	13.2	20.5	20.9	20.3	19.1	13.7	13.2	13.2	12.4
Median	76	74	3	0	122	123	-5	1	72	75	-2	0
Range	45 to 10	48 to 106	-40 to 43	-52 to 43	70 to 192	84 to 190	-60 to 69	-50 to 54	42 to 138	40 to 110	-38 to 34	-32 to 46
Month 12												
N	272	257	271	257	276	258	276	258	276	258	276	258
Mean	75.8	74.3	1.5	0.7	124.8	125.6	-3.1*	2	74.4	75.7	-2.8*	0.9
SD	11.8	12.0	13.4	13.0	20.0	19.6	19.3	17.4	12.1	13.5	13.2	12.0
Median	76	74	2	0	124	125	-2	0	74	74	-2	0
Range	50 to 112	42 to 118	-40 to 47	-44 to 64	78 to 200	82 to 182	-54 to 70	-40 to 62	41 to 116	38 to 120	-40 to 38	-34 to 36

	Heart Rate				Supine SBP				Supine DBP			
	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff	BiDil Mean	P Mean	BiDil Mean Diff	P Mean Diff
Month 15												
N	222	218	221	217	225	218	225	217	225	218	225	217
Mean	76.2	75.7	1.6	1.7	125.7	124.6	-3.1*	0.9	75.1	75.4	-2.9	0.7
SD	11.9	11.7	13.5	11.9	22.2	20.0	21.2	17.7	13.2	13.0	13.3	12.4
Median	76	76	2	0	122	126	-4	2	76	75	-2	0
Range	40 to 120	48 to 110	-47 to 48	-42 to 28	82 to 210	80 to 188	-92 to 68	-60 to 40	43 to 112	48 to 116	-38 to 30	-24 to 48
Month 18												
N	197	176	196	175	197	176	197	175	197	176	197	175
Mean	77.3	73.1	3.0	0.4	125.9	125.6	-3.4*	1.2	75.4	74.8	-3.0*	-0.3
SD	11.2	12.0	12.6	13.7	21.2	19.2	20.4	17.5	13.2	14.0	13.4	12.9
Median	78	72	3	0	124	122	-3	0	74	76	-2	0
Range	48 to 113	49 to 116	-34 to 37	-54 to 52	92 to 200	90 to 180	-62 to 89	-56 to 51	44 to 120	40 to 118	-40 to 30	-40 to 41

*p<0.05, two sample t-test

The difference between BiDil and placebo in the mean change from baseline in heart rate ranged between 0 at 3 months and 2.6 bpm at 18 months.

Differences between BiDil and placebo in mean changes from baseline in supine systolic and diastolic blood pressure were sizable, consistent and statistically significant.

6.1.8.2.2 Marked Outliers and Dropouts for Vital Sign Abnormalities

6.1.8.2.2.1 Bradycardia

There were two cases on BiDil and three on placebo that were determined as serious. No cases led to discontinuation of study drug.

6.1.8.2.2.2 Tachycardia

Tachycardia is a known secondary effect of hydralazine and an excess of ventricular tachycardia was observed on BiDil, Table 32 page 47 and Table 34 page 50.

6.1.8.2.2.3 Hypotension

Hypotension was described as serious in 1.5% (8) and 0.6% (3), and led to discontinuation in 1.4% (7) and 0.6% (3) on BiDil and placebo respectively, Table 32 page 47 and Table 33 page 49. Also, a significant number on BiDil (7.9%) compared to placebo (4.4%) experienced hypotension as a common event, Table 34 page 50.

6.1.8.2.2.4 Diastolic Blood Pressure < 60 mmHg

No difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in DBP below 60 (incidence ranged between 7% and 13%).

6.1.8.2.2.5 Systolic Blood Pressure < 90 mmHg

Like DBP, no difference between the two treatment groups was observed at any follow-up visit in the incidence of a drop in SBP below 90 (incidence ranged between 1.0% and 3.0%).

6.1.9 The Effect of Concomitant Medication on the Safety Profile

Analyses assessing the effect of concomitant medication on selected adverse events observed in A-HeFT were conducted⁸. The medications considered in these analyses included ACE-I, ARBs, beta-blockers, digitalis glycosides, aldosterone antagonist and other diuretics. The adverse events that were assessed for confounding by concomitant medications included headache, dizziness, pain, chest pain, infection, asthenia, dyspnea, nausea, bronchitis and hypotension.

Adjusting for all concomitant medications in one model and for the medications that seemed to be strong predictors of any adverse event in another model did not explain away the association found between BiDil and headache (OR = 3.7, p-value <0.0001), dizziness (OR = 3.0, p-value <0.0001), nausea (OR = 1.7, p-value = 0.03) and hypotension (OR = 1.9, p-value = 0.02).

6.1.10 Adverse Events Associated with the Components of BiDil

6.1.10.1 Methemoglobinemia associated with ISDN

Methemoglobinemia is an adverse event that is said to occur extremely rarely with ordinary doses of ISDN. No cases were observed in the A-HeFT.

6.1.10.2 SLE-Like Syndrome Associated With Hydralazine

Under PRECAUTIONS, the Hydralazine label says that complete blood counts and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise, or other unexplained signs or symptoms. None of these were completed in A-HeFT. One case of SLE-like syndrome was reported on BiDil but was coded as joint disorder.

6.1.10.3 Hematologic Adverse Events Associated with Hydralazine

Reduction in hemoglobin and red blood cell count, leucopenia, agranulocytosis, purpura, lymphadenopathy and splenomegaly are listed as adverse events associated with hydralazine.

6.1.11 Immunogenicity

The hydralazine component of BiDil is known to trigger hypersensitive reactions and possibly autoimmune-like reactions especially that of SLE. Whether BiDil triggers the same reactions was not evaluated. In the A-HeFT trial, only one patient was reported to have SLE-like syndrome.

Arthralgia and myalgia 2 of the many symptom that are often associated with many autoimmune reactions, were observed in excess on BiDil 1.5% and 1.4% vs. 0.4% and 0.6% respectively.

6.1.12 Human Carcinogenicity

Four cases of neoplasm/carcinoma were observed on BiDil compared to one on placebo.

6.1.13 Special Safety Studies

None completed.

⁸ Analyses completed by the Sponsor

6.1.14 Human Reproduction and Pregnancy Data

There is no information on drug exposure during pregnancy.

6.1.15 Overdose Experience

No cases of overdose were observed.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

6.2.1.1 Study Type and Design/Patient Enumeration

6.2.1.1.1 A-HeFT

The primary source of the safety data came from the A-HeFT trial (5.1.5.1 page 20).

6.2.1.1.2 V-HeFT

Data from the V-HeFT studies were used as supportive especially V-HeFT I (5.1.5.2 page 22) that compared BiDil to placebo.

6.2.1.2 Demographics

6.2.1.2.1 A-HeFT

Table 11 page 29.

6.2.1.2.2 V-HeFT

Table 12 page 31.

6.2.1.3 Extent of Exposure (dose/duration)

6.2.1.3.1 Extent of Exposure in the A-Heft Study (from Sponsor's Report)

Table 44. Extent of Exposure in the A-HeFT study as assessed by duration

	BiDil (N = 517)	Placebo (N = 527)
Duration of exposure, days		
Mean (SD)	298.4 (208.3)	313.8 (197.7)
Median	294	301
Range	1 - 594	4 - 624
Patients on study drug at various time points, n (%)		
3 mon	368 (71.2)	417 (79.1)
6 mon	317 (61.3)	333 (63.2)
9 mon	260 (50.3)	269 (51.0)
12 mon	220 (42.6)	228 (43.3)
15 mon	169 (32.7)	186 (35.3)
	139 (26.9)	146 (27.7)

This table excludes 18-month data, dose of study drug not collected consistently at that visit.

Table 45. Extent of Exposure in the A-HeFT study as assessed by total number of tablets taken per day

Total tablets/day ¹	BiDil (N = 517)	Placebo (N = 527)	Total tablets/day ¹	BiDil (N = 517)	Placebo (N = 527)
3 Month			9 Month		
N	368	417	N	260	269
Mean (SD)	4.4 (2.1)	5.0 (1.9)	Mean (SD)	4.8 (1.9)	5.2 (1.7)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0 - 6	0 - 6
6 Month			12 Month		
N	317	333	N	220	228
Mean (SD)	4.5 (2.0)	5.1 (1.8)	Mean (SD)	4.8 (1.9)	5.3 (1.6)
Median	6	6	Median	6	6
Range	0 - 6	0 - 6	Range	0-6	0-6
15 Month					
N	169	186	Median	6	6
Mean (SD)	4.9 (1.7)	5.3 (1.7)	Range	0 - 6	0 - 6

This table excludes 18-month data; dose of study drug not collected consistently at that visit;

¹ Total number of tablets recorded on Study Drug Administration CRF if frequency was not t.i.d. or calculated by multiplying "# of tablets" by 3 (if frequency of t.i.d. was recorded);

As can be seen from the table above, on average, patients took 4 ½ tablets per day at 6 months. Translated to milligrams, patients took on average 169/90 mg of BiDil per day. The average intake increased by close to ½ a tablet from Month 3 visit to 184/98 mg at Month 15. Exposure, whether measured in days or in number of tablets per day, seems to be slightly lower for BiDil compared to placebo.

6.2.1.3.2 Extent of Exposure in the V-HeFT African-American Population

Table 46. Summary of Drug Exposure to HYD – ISDN for African-American Patients in the V-HeFT Trials

Statistics	Values
Time on Study	
N	158
Range	3 – 2009
Mean	994.6
SD	550 – 51
Median	1032
Documented Days on BiDil	
N	158
Range	0 – 2045
Mean	812.3
SD	551.5
Median	727

The sponsor provided extent of exposure only for patients on active treatment.

6.2.1.4 Literature

Information sought by the reviewer included publications about the incidence of SLE on hydralazine and that of methemoglobinemia on organic nitrate therapy.

6.2.1.4.1 Hydralazine-induced SLE-like Syndrome

Hydralazine-induced SLE-like syndrome occurs following prolonged use of hydralazine, and it is believed that it may be dose related and limiting the daily dose to 200 mg is to be recommended.

SLE induced by drugs, primarily hydralazine and procainamide was compared to idiopathic SLE⁹. The average age of drug-induced SLE was reported to be nearly twice that of patients with idiopathic SLE, and the gender distribution to be equal compared to the 92%-female predominance of idiopathic SLE. Musculo-skeletal symptoms are reported to be the most clinically predominant manifestation of drug-induced SLE.

In a study of that compared 26 hydralazine-induced lupus cases to three groups (healthy subjects; slow-acetylating hypertensive patients treated with hydralazine for one year without having developed lupus; and patients with idiopathic SLE), hydralazine-induced lupus was more common in women (4 to 1), and 25 out of the 26 patients were slow acetylators¹⁰.

6.2.2 Adequacy of Overall Clinical Experience

The pivotal trial study design, number of subjects exposed, and duration of exposure to the study drug were adequate.

The A-HeFT assessed the target dose combination of 120/225, and the V-HeFT studies assessed 160/300mg.

The pivotal study was limited to one ethnic group, and the findings of the BiDil program do not provide evidence to support the use of BiDil in non-African-American subjects.

6.2.3 Adequacy of Special Animal and/or In Vitro Testing

BiDil is a combination of two components already marketed for cardiovascular diseases.

One potential safety issue that was raised in the July-2d-1997 non-approvable letter concerned the potential of carcinogenicity as a result of a possible interaction between the drug substances and the formation of N-nitrosamines. The Sponsor responded to this in an amendment to the NDA in November 2001. For evaluation of the sponsor's response to this concern, refer to the Chemistry review.

6.2.4 Adequacy of Routine Clinical Testing

6.2.4.1 See Error! Reference source not found., page 64

6.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

6.2.5.1 See Drs. Hinderling and Velazquez Reviews

6.2.6 Assessment of Quality and Completeness of Data

Except for data assessing the effect of the hydralazine component on the immune system, the data available for conducting safety review was relatively complete. These data included adverse events by seriousness and/or whether they led to study drug discontinuation, and by categories of age, gender and treatment. It also included narratives of SAEs and life threatening and fatal events.

V-HeFT safety information summarized in this review is a duplicate of the safety summary in the clinical and statistical reviews completed by the Division in 1997. The latter reviews did not

⁹ Stratton MA: Drug-induced systemic lupus erythematosus. Clin Pharma. 1985; 4(6):657-63

¹⁰ Spears CJ, Batchelor JR: Drug-Induced Autoimmune Disease. Adv Nephrol 1987; 16:219-229

summarize less frequent adverse events because they were merged by the sponsor into the category of "other".

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Systemic lupus erythematosus:

One case of SLE-like syndrome was observed during the trial. Given the known association between hydralazine, a component of BiDil, and this adverse event, it is likely that this case is associated with BiDil. The patient while still taking BiDil was treated and the symptoms resolved, but there is no data on what happened after the termination of the treatment of SLE.

Arthralgia was observed at an incidence that is almost 4 times as high as that observed on placebo, Table 34 page 50.

Malaise was 6 times as high on BiDil as on placebo, Table 34, page 50.

Myalgia was more than 2 times as high on BiDil as placebo, Table 34 page 50.

It is not known whether these symptoms represent manifestations of SLE. Antinuclear antibody titers determination tests should have been conducted in these patient as per the hydralazine label.

Angioedema

A case of angioedema did not resolve completely after discontinuation of benazepril and treatment but did after discontinuation of BiDil. However, the narrative said that study drug was to be restarted 3 days later, but there was no information on what happened after restarting the study drug.

Another case of angioedema that developed 4 days post study drug initiation and resolved after treatment and discontinuation of study drug without discontinuing the patient's ACE inhibitors therapy.

A third case of angioedema that developed 6 days after study drug initiation and resolved with treatment and discontinuation of study drug.

The incidence of angioedema was 6 times higher on BiDil than on placebo, Table 34, page 50.

Clinically significant hypotension

Hypotension that led to a visit to the ER and/or hospitalization was observed in 7 subjects on BiDil. The causal association is very likely given that both component of BiDil could cause and/or predispose to hypotension.

Twice and ½ as many BiDil as placebo subjects developed hypotension as a serious adverse event;

Ventricular tachycardia

An excess was observed on BiDil, Table 34 page 50;

Almost twice as many BiDil as placebo subjects developed serious ventricular tachycardia, Table 32, page 47;

This was more common in older (≥ 65 year) and female subjects;

The association is stronger in the elderly subjects;

Tachycardia

Observed in almost twice as many BiDil as placebo subjects, Table 34 page 50;

It is listed in the hydralazine label as a common adverse event;

Supraventricular tachycardia

Observed in 4 BiDil vs. no placebo subjects;

Headache

The incidence on BiDil was more than twice as high as that on placebo, Table 34, page 50;

Headache is known to be causally related to the ISDN component of BiDil;

Dizziness

The incidence on BiDil was more than twice as high as that on placebo; Table 34, page 50;

This is known to be associated with hydralazine;

Somnolence

It was observed in almost 4 as many BiDil as placebo subjects, Table 34 page 50;

Asthenia

This led to discontinuation in 11 and $\frac{1}{2}$ as many BiDil as placebo patients, Table 33 page 49;

Nausea and Vomiting

Incidence rates on BiDil were each more than $1 \frac{1}{2}$ as high as those on placebo, Table 34 page 50;

These are known to be associated with hydralazine;

Amblyopia

The incidence on BiDil was more than twice as high as that on placebo, Table 34 page 50;

Abnormal vision was also observed in 4 BiDil vs. 2 placebo subjects;

Hyperlipidemia and hypercholesterolemia

Hyperlipidemia was observed in 50% more on BiDil compared to placebo, Table 34 page 50;

Hypercholesterolemia was observed in $3 \frac{1}{2}$ as many subjects on BiDil as on placebo, Table 34 page 50;

Abnormal kidney function

This was observed in twice as many BiDil as placebo subjects, Table 34 page 50;

Uremia was observed in 2 additional BiDil subjects;

It could be secondary to hypo-perfusion of the kidney as a result of hypotension;

Cerebral ischemia + infarct

This was observed in 3 as many BiDil as placebo patients;

Could hypoperfusion have triggered or complicated this event?

Coronary artery disease

This was observed in almost twice as many BiDil as placebo subjects, Table 34,

page 50;

Cardiovascular disease

Coded as such in 5 BiDil vs. no placebo subjects;

Chest pain

This led to discontinuation in almost 4 as many BiDil as placebo subjects, Table 33 page 49;

Known to be associated with hydralazine, per the label;

Neoplasm

Neoplasm observed in twice as many BiDil as placebo subjects, Table 34 page 50;

Sweat increase, alopecia, cholecystitis

These were also observed at a higher incidence on BiDil than on placebo;

6.4 General Methodology

6.4.1 Pooled Data vs. Individual Study Data

Only one study was prospectively conducted and submitted for review of the proposed indication. Supportive data were submitted in the 1996 NDA, and post hoc safety analyses by race were conducted and submitted with the current NDA. Data were not pooled because firstly the V-HeFT studies were not designed to assess the effect of BiDil solely in African Americans; secondly the regimen and the schedules of exposure and adverse event assessments used were different; thirdly, the African-American sub-population of the V-HeFT I and the population of A-HeFT seem to be different with regard to background, placebo-associated, rates of common adverse events; and lastly, the medical management of both populations must be different for the medical management of HF has changed since the time V-HeFT I was conducted.

6.4.2 Explorations for Predictive Factors

6.4.2.1 Explorations of Time Dependency for Adverse Findings

Headache and dizziness started within a week, and nausea and hypotension started within a month of BiDil initiation.

6.4.2.2 Explorations for Drug-Demographic Interactions

This has already been completed in section 6.1.6.4.7, page 56 with regard to the common adverse events.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by gender and age, Figure 5 page 39.

BiDil seems to have the same effect on all-cause mortality and hospitalization for HF in both genders and in younger and older subjects.

6.4.2.3 Explorations for Drug-Disease Interactions

This was not conducted as a part of adverse event analyses, but information on the effect of this interaction on mortality and hospitalization can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first

hospitalization for HF + change in QOL in subpopulations with DM, chronic renal insufficiency, ischemic etiology of HF, and history of hypertension, Figure 5 page 39.

As can be see from the figure, the presence of other co-morbidities did not change the effect of BiDil in these subgroups one way or another.

6.4.2.4 Explorations for Drug-Drug Interactions

Confounding of most common AE by concomitant drugs was explored, see 6.1.9 page 61.

Additional information can be deduced from analyses completed as part of the exploration of the effect of BiDil on the composite score of all cause mortality + first hospitalization for HF + change in QOL by drug categories of ACE-I, ARBs, beta-blockers, CCBs, aldosterone antagonists, non-aldosterone antagonist diuretics and digoxin, Figure 5 page 39.

As can be seen from the figure, BiDil did not interact in a negative way with other drugs.

Interaction with other medications with regard to serious less common AEs was not explored.

Therefore, one cannot exclude the potential for a deleterious interaction with any of the concomitant drugs that a HF patient is usually exposed to.

6.4.3 Causality Determination

6.4.3.1 Adverse Events Likely Causally Related to BiDil

Events that are likely causally attributed to BiDil with a certain level of assurance in this study population are headache, dizziness, nausea and vomiting, hypotension, chest pain, asthenia, tachycardia and palpitations, and paresthesia. These events were observed in excess on BiDil, the components of BiDil are labeled for some of these adverse events, and BiDil or any of its components have the mechanistic ability to generate these adverse events.

6.4.3.2 Adverse Events Probably Causally Related to BiDil

Events that are probably causally related to BiDil include arthralgia, myalgia and malaise which were observed in excess on BiDil and could have been symptoms of the SLE-like syndrome attributed to hydralazine; and angioedema because of hydralazine's tendency to affect the immune system.

Somnolence which was observed in excess on BiDil;

6.4.3.3 Adverse Events Possibly Causally Related to BiDil

Events that are possibly causally related to BiDil include abnormal kidney function because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; likewise cerebral ischemia because of its excess on BiDil and the possibility of hypoperfusion as a triggering factor; and ventricular tachycardia;

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The A-HeFT trial studied a lower dose and a different regimen than what was previously (V-HeFT I and II) targeted for heart failure, 75/40 mg t.i.d. instead of q.i.d. The lower dose or A-HeFT data were robust and significant in showing the efficacy of BiDil in the AA study population. Data from the higher dose/regimen showed no efficacy on HF in the population

studied, but post-hoc analyses showed a trend toward efficacy in the African-American subpopulation, especially in V-HeFT I.

Comparing the most common adverse events (headache and dizziness) in both dosing regimens, both BiDil and placebo subjects in V-HeFT I experienced more of these events than did subjects in A-HeFT, and despite the reduced incidence in A-HeFT, the association between BiDil and these adverse events was stronger than in V-HeFT.

7.2 Interaction with Other Anti-hypertensive Therapies

If approved as a treatment for heart failure, BiDil may be added to other HF treatment regimens which may include other significant antihypertensive medications. Given that BiDil lowers blood pressure and causes hypotension in some patients, it is likely that it could aggravate the risk of hypotension in HF subjects who will not be followed as closely as the A-HeFT subjects were. Therefore, the reviewer recommends initiating BiDil and tapering it slower than it was in A-HeFT, especially if subjects are receiving the beta-blocking agents that were found to interact with hydralazine (e.g., metoprolol, propranolol).

7.3 Special Populations

The effect of BiDil on heart failure was shown to be positive in African American patients only. BiDil did not seem to have an effect in non-African-American HF patients.

Subgroup analyses by age and gender showed that despite the small number of events in these sub-populations, a trend of effect on the composite endpoint was maintained.

7.4 Pediatrics

A deferral for a pediatric program was granted.

7.5 Advisory Committee Meeting

An advisory committee meeting to discuss the findings of BiDil is scheduled for June 16, 2005.

7.6 Literature Review

The information from literature search provided by the sponsor included the following:

- Publications about the pathophysiology of heart failure;
- Pathophysiological differences that could account for potential race differences in disease outcomes especially those of heart failure;
- Potential mechanism and role played by hydralazine in preventing or deterring tolerance to isosorbide dinitrates;

8 OVERALL ASSESSMENT

8.1 Conclusions

The A-HeFT study has shown that BiDil reduced mortality and the risk of HF hospitalization in African-American heart failure patients. Even though the reduction of mortality was not the primary endpoint, the study was terminated as a result of an effect on mortality that was observed before the study was due to end.

Except for headache, dizziness and hypotension, the safety profile of BiDil in A-HeFT was not very different from that of placebo. Given that BiDil had a beneficial effect on all-cause mortality, any adverse event, no matter how severe it was, would be relatively tolerable in this population.

The proposed indication per the label is the treatment of CHF in black patients who are either intolerant or have a contraindication to ACE-I therapy, but the patients studied in the pivotal trial were not enrolled based on their intolerance or the contra-indication to ACE inhibitors, and as a matter of fact, $\frac{3}{4}$ of all subjects were ACE-I therapy at baseline. Therefore the reviewer concludes that BiDil should be indicated in the same population in whom it was studied in the A-HeFT study.

8.2 Recommendation on Regulatory Action

Based on the clinical results of A-HeFT, BiDil seems to be safe and effective in African-American subjects suffering from heart failure.

8.3 Recommendation on the Label

8.3.1 Trial Design

The label should state that A-HeFT was not designed to show that the combination was superior to either of its components. This way it won't indirectly be concluded that either hydralazine or isosorbide dinitrate is inferior to the combination of both.

8.3.2 Intended Population for Indication

If approved, BiDil should be indicated for the treatment of chronic heart failure in all blacks, not only in those who are intolerant or have a contraindication to ACE inhibitors as the proposed label says.

8.3.3 Mechanism of Action

The label should include language regarding the difference in blood pressure control between the treatment groups throughout the trial, and the possibility of this difference accounting, at least partly, for the observed effect.

8.3.4 Medication Regimen

The label should recommend a titration of BiDil over at least a week to prevent discontinuations for headache and dizziness.

9 APPENDICES

9.1 A-HeFT Protocol Amendments (Sponsor's Tables)

Table 47. Summary of protocol amendments related to changes in entry and randomization criteria

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Inclusion criterion #3				
Have stable, chronic HF, NYHA class III-IV, diagnosed at least 3 months prior to Screening.	3. Have stable, chronic HF diagnosed at least 3 months prior to Screening 4. Have NYHA class III-IV at the time of Screening.	Clarified that NYHA class III-IV requirement applies to assessment at Screening visit. Patient was not required to have NYHA class III-IV HF for at least 3 months prior to Screening.	05 (Dec. 12, 2001)	112 (10.7)
Inclusion criterion #4 (renumbered to #5 with Protocol amendment #5, Dec. 12, 2001)				
...Patients receiving beta blockers must have been taking these for at least 6 months...	...Patients receiving beta blockers must have been taking these for at least 3 months.	Decreased requirement for time on beta blocker prior to screening.	02 (Jun. 15, 2001)	2 (0.2)
Inclusion criterion #5 (renumbered to #6 with Protocol amendment #5, Dec. 12, 2001)				
Have a resting LVEF <35% (by any method) and a resting LVIDD >2.9 cm/m ² BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Have a resting LVEF ≤35% (by any method) and a resting LVIDD >2.9 cm/m ² BSA or >6.5 cm (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed LVEF entry criteria from <35% to ≤35%.	03 (Aug. 1, 2001)	10 (1.0)
	Have either a resting LVEF ≤35% (by any method) or a resting LVIDD >2.9 cm/m ² BSA (or >6.5 cm) with LVEF <45% (by echocardiogram) obtained anytime within the prior 6 months using the most recent values available.	Changed criteria for LV dysfunction to permit abnormal LVEF or abnormal LVIDD (as long as LVEF <45%).	04 (Oct. 22, 2001)	55 (5.2)

NDa 207-27
A-HeFT: BiDiI for the treatment of HF

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Inclusion criterion #7				
Have had at least one hospitalization for heart failure during the preceding year, as judged by the investigator.	Criterion deleted.	Eliminated entry criterion in order to enhance recruitment, based on decreasing number of hospitalizations due to change in standard of care to more frequent outpatient management.	08 (Mar. 25, 2003)	544 (51.8)
Criteria for stability				
Procedures to be done at the Baseline Visit: "Confirm that the patient has been stable since the screening visit..."	"Confirm that the patient has been stable for at least 2 weeks since the screening visit..."	Clarified time period for stability of symptoms and HF therapy	02 (Jun. 15, 2001)	2 (0.2)
At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2%."	At Baseline visit, patients are eligible for randomization if: "Body weight has not changed by more than 2.5% relative to Screening Visit body weight."	Broadened stability criteria to clarify acceptable weight change limits.	04 (Oct. 22, 2001)	55 (5.2)
Exclusion criterion #4:				
Have coronary artery disease likely to require coronary artery bypass grafting or PTCA during the study period.	Have coronary artery disease likely to require coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during the ensuing year.	Specified a time period for the anticipated clinical event constituting the exclusion.	01 (May 3, 2001)	0 (0)
Exclusion criterion #5:				
Have symptoms of unstable angina or angina precipitated by exercise within 3 months.	Have symptoms of unstable angina within 3 months prior to screening.	Clarified definition of unstable angina (removed "angina precipitated by exercise") and timeframe for exclusion.	01 (May 3, 2001)	0 (0)
Exclusion criterion #6:				
Have had cardiac arrest, ventricular tachycardia or another severe ventricular arrhythmia considered life threatening within 3 months unless treated with an implantable cardiac defibrillator.	Have had cardiac arrest or a sustained ventricular tachycardia considered life threatening and requiring intervention within 3 months, unless treated with an implantable cardiac defibrillator	Clarified definition of arrhythmia considered exclusion.	01 (May 3, 2001)	0 (0)

A-HeFT: BiDil for the treatment of HF

Original entry criterion	Modification	Reason for change	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Exclusion #9				
Have rapidly deteriorating or uncompensated HF such that consideration for cardiac transplantation would be likely over the ensuing year.	Have rapidly deteriorating or uncompensated HF such that cardiac transplantation would be likely over the ensuing 1 year.	Clarified timeframe for the anticipated clinical event constituting the exclusion.	01 (May 3, 2001)	0 (0)
Exclusion #14				
Have received any other investigational drugs within 3 months.	Have received another investigational drug or device within 3 months prior to screening.	Added exclusion of investigational device, clarified timeframe.	01 (May 3, 2001)	0 (0)
Exclusion criterion #15				
Currently require sildenafil (Viagra®).	Currently require... phosphodiesterase-5 inhibitors like sildenafil (Viagra®), vardenafil (Levitra®), or tadalafil (Cialis®)...	Specify that all available phosphodiesterase-5 inhibitors are excluded.	09 (Aug. 26, 2003)	700 (66.7)

Table 48. Summary of protocol amendments including additions or changes to study assessments

Assessment added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
LV wall thickness assessment added to echocardiographic measurements of LVEF and LVIDD.	Secondary efficacy assessment added.	01 (May 3, 2001)	0 (0)
Echocardiographic measurements to be done at baseline and at six months rather than at every three month visit	Echocardiographic measurements limited to baseline and at 6 months.	01 (May 3, 2001)	0 (0)
Urine pregnancy test added to serum pregnancy test as test permitted to determine pregnancy at baseline	Additional option added for baseline assessment of pregnancy.	01 (May 3, 2001)	0 (0)
Change in echocardiographic assessments from blinded reading by a central laboratory to blinded reading by an external expert. Core Laboratory to inspect echocardiograms for acceptability/readability.	Changed responsibility for secondary efficacy variable assessment.	04 (Oct. 22, 2001)	55 (5.2)

Table 49. Summary of protocol amendments including changes in study procedures

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visit: Timing of visit relative to screening visit changed from two weeks +two days to two weeks +seven days	Allowed additional flexibility in baseline visit scheduling.	01 (May 3, 2001)	0 (0)
Addition of second baseline visit: Patients who were considered not eligible for randomization at baseline could have a second baseline visit scheduled, to occur no more than two weeks after the first baseline visit. Patients who failed to qualify for randomization at the second baseline visit were not to have another baseline visit but could, at the investigator's discretion, begin the screening process over again at a future visit.	Allowed patients who failed to qualify for randomization an additional opportunity to qualify.	01 (May 3, 2001)	0 (0)

Procedure added or changed	Comment	Protocol amendment (date)	No. (%) of patients enrolled when change implemented
Scheduling of baseline visits: Timing of baseline visit relative to screening visit changed from two weeks +seven days to maximum of 28 days; patients were to be stable in the 14 days prior to the baseline visit.	Allowed additional flexibility in baseline visit scheduling but maintained randomization criteria for stability	02 (Jun. 15, 2001)	2 (0.2)
Timing of baseline visits: Timing of second baseline visit (if patient failed to qualify on first baseline visit) specified as no more than 28 days after screening visit.	Limited maximum duration between screening and randomization to 28 days for patients who required a second baseline visit.	02 (Jun. 15, 2001)	2 (0.2)

9.2 Discrepancies in Adjudication of Cause of Death

Table 50. Investigator-assigned causes of death for patients assessed by ICAC as having deaths due to non-cardiovascular causes

Treatment Patient number	Investigator cause of death
BiDil	
012-014	Cardiopulmonary arrest, hypotension, metabolic acidosis
046-003	Hepatic failure
107-033	Death due to stomach cancer
Placebo	
038-006	Exacerbation of CHF
059-010	Hemoptysis
089-008	Respiratory failure
090-030	Cardiopulmonary arrest
240-001	Cardiac arrest

9.3 Additional Information on V-HeFT I and V-HeFT II

For more information on these two studies, refer to the Division's Reviews.

NDA: 20-727

Reviews: Medical and statistical

Reviewers: James Hung, Ph.D., Shaw Chen, MD., Charles J. Ganley, MD.

Date of completion: 03/04/1997

9.4 Study Committees

9.4.1 ICAC (the Independent Central Adjudication Committee)

An independent review committee referred to as was to adjudicate death, all hospitalizations, unscheduled ER and Office visits, and new heart transplant listing. The committee was composed of 6 cardiologists who are experienced in the diagnosis and treatment of cardiovascular diseases.

The committee was divided into teams of 2 and each team reviewed a number of cases, presented the cases in a meeting where they were discussed and voted on by all committee members.

Death was to be classified as due to HF, other cardiac cause or non-cardiac cause, and as sudden and non-sudden cardiac death.

Hospitalization

9.4.2 DSMB (Data and Safety Monitoring Board)

The Data and Safety Monitoring Board was comprised of for members and these were:

David DeMets, Ph.D. Department of Biostatistics and Medical information, University of Wisconsin, Madison, WI;

Richard Grimm, M.D., Hennepin County Medical Center, Minneapolis, MN;

Pamela Ouyang, M.D., Department of Cardiology, John Hopkins University Medical Center, Baltimore, MD;

Jackson Wright, M.D. Department of Medicine-Hypertension, Case Western Reserve University School of Medicine, Cleveland, OH;

Dr. Ralph D' Agostino was the statistician responsible for the overall data analyses and for preparing the reports that DSMB was to review.

The committee was to be independent and to review data mainly to adjust for the sample size since an accurate estimate of the needed sample size was not possible as a result of the lack of data on the composite primary endpoint.

Interim analyses were to occur periodically and Dr. Ralph was to prepare the data and code it to maintain the blind of the committee as long as possible.

Data to be reviewed include:

Total enrollment at time of review;

Baseline data by treatment groups A and B;

Total number and timing of all SAEs;

Total number and timing of all clinical endpoints;

Listing of all SAEs;

Table summary of all SAEs grouped into treatments of A and B;

Table summary of all investigator-reported clinical endpoints;

Table summary of all investigator-reported clinical endpoints grouped into treatments A and B;

Table summary of all adjudicated clinical endpoint events by treatment groups A and B;

Tables of clinical endpoints and SAEs by protocol specification subgroups;

Other statistical analyses as requested;

9.5 Narratives

Patient 190-003 is a 40 year-old female with HF secondary to “dilated post-partum cardiomyopathy” and hyperlipidemia, cerebrovascular disease, previous myocardial infarction, past history of angina, depression, asthmatic bronchitis, and obesity. Approximately one year after the initiation of treatment the patient developed “lupus-like symptoms”, which were assessed as being of moderate severity. She was treated with hydroxychloroquine (Plaquenil®) for these symptoms, which resolved after approximately seven weeks. There was no change in study drug administration as a result of this adverse event.

Patient 041-002, a 53-year-old female, who 34 days after randomization to BiDil, presented to the ER with swelling of the upper lip. On exam she had an urticarial rash. She was given diphenhydramine and prednisone, had her benazepril discontinued and her swelling improved post discharge. Four days later, she returned to the ER with increased lip swelling that was worse one hour after ingesting the study drug. She was treated with prednisone diphenhydramine and ranitidine, and the study medication was stopped. Another four days later she was seen in follow-up, her swelling had improved, and her study drug was to be restarted in 3 days.

Patient 044-005

This 46-year-old male developed angioedema and was seen in the ER four days after being on study drug. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisone. He was discharged, study drug was discontinued, but his other medications including fosinopril were not modified. The patient recovered completely.

Patient 067-006

This 64-year-old female developed clinically significant hypotension, 77/50, 30 minutes after taking her first pill of the study drug in the study site clinic. The patient was given fluids and monitored for 1 ½ hours before she was discharged into the care of her daughter. The study drug was discontinued and the patient refused to restart it.

Subject 108-027

This 69-year-old male presented to the ER 3 months and 19 days after been randomized to study drug with weakness and diaphoresis and was found to be hypotensive 70/32. Apparently the patient experienced similar episode for which he was hospitalized after being on the drug for 2 months and was instructed to discontinue the study medication, but the patient said that he had continued taking it.

Patient 121-007

This 48-year-old female presented to the ER 4 days after starting the study drug with a complaint of weakness for the last 24 hours. Her BP was found to be 81/43 mmHg. She was treated with IV 1,000 cc of normal saline, her BP rose to 111/63 mmHg, she felt better and was discharged. The patient recovered and no change in medication was made.

Patient 144-013

This 62-year-old female presented to the ER 19 days after starting the study drug. She was found to have hypotension 63/35 mmHg. It was determined that there was a recent doubling of her carvedilol dose and of the study drug as well. The patient was hospitalized, she was treated with IV hydration, and all antihypertensive medications and the study drug were withheld.

Home medication regimen was slowly incorporated back to prehospital dosages, except for the study medication that was held and carvedilol given at ½ the prior dose. Four days after ER visit, her BP was 134/88 mmHg and she was discharged.

Patient 199-008

This 52-year-old female experienced a syncopal episode 1 ½ hours after her first dose, and was reported unconscious for approximately 1 minute and when conscious complained of dizziness. Patient was transported to the ER where her BP was found to be 70/40 mmHg, hydrated and labs done that revealed renal insufficiency. The study drug was discontinued, tosemeide was reduced to 60 mg b.i.d. and she was discharged one day later.

Patient 261-007

This 76-year-old female experienced lightheadedness, nausea, diaphoresis and generalized weakness two days after she had her study drug titrated up to 2 tablets b.i.d. She skipped her midday dose and took her second dose at night. Her symptoms persisted overnight and the following day she called 911 and was transported to the ER. She was diagnosed with a pre-syncopal episode that was felt "almost certainly" related to study medication. The study drug was discontinued and the patient recovered.

Patient 006-001

This 75-year-old male Information with a history of congestive heart failure, adenocarcinoma of the prostate, coronary artery disease, hypertension, hyperlipidemia, aortic insufficiency, mitral regurgitation s/p aortic valve prosthesis, s/p CABG, s/p bi-ventricular pacemaker, s/p AICD and chronic obstructive pulmonary disease. Two months and 15 days later after study drug initiation, he was seen at the emergency room due to firing of the AICD. The patient lost consciousness after the first time the device fired. The AICD was interrogated and found to have ventricular tachycardia at 280 msec with AICD shocks. The study drug was interrupted.

Patient 009-004

This 47-year-old male with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hyperlipidemia, and GERD. On 27-Dec- 2001 the subject was randomized to receive either BiDil or placebo in addition to current therapy.

Nine months after being on the study drug, the patient complained of increasing shortness of breath with exertion and at rest and difficulty sleeping when he presented for a month protocol follow-up visit. The patient was admitted directly from the office for further management. His heart showed an apical systolic murmur and the EKG-poor R wave progression. The patient was treated with dobutamine and intravenous diuretics. 4 days later, the patient experienced an episode of ventricular tachycardia, and he had an AICD placed. There were no complications. The patient was discharged one day later. The subject completely recovered and no action was taken regarding study medication.

Patient 010-012

This 56 year-old male, with a history of congestive heart failure, idiopathic dilated cardiomyopathy, hypertension, COPD, headaches, insomnia, s/p bladder surgery, PVCs, non-sustained ventricular tachycardia, mitral regurgitation, tricuspid regurgitation and seasonal allergies who after one month and 10 days of being on BiDil he was seen in consultation and a holter monitor demonstrated significant ventricular ectopy and short runs of non-sustained ventricular tachycardia. All of these episodes were asymptomatic. The patient was not

recommended to have an EP study and not to have an AICD placed at that time. The patient was suggested to start on a beta-blocker and return for follow-up in one month. Twenty six days later, the patient returned for follow-up and a repeat Holter monitor confirmed that there was no significant change to his ventricular ectopy. The recommendation was to increase the dose of the beta-blocker and repeat the Holter study. Another 26 days later, the patient was seen by his primary physician who noted significant PVCs, bigeminy, trigeminy, and runs of non-sustained ventricular tachycardia on EKG. Because of the PVCs the patient was admitted to the hospital for further evaluation. The patient was originally treated with lidocaine via drip and enoxaparin. The patient was seen in consultation by a cardiologist who suggested increasing the beta-blocker. The enoxaparin and lidocaine were subsequently discontinued and the patient was treated with clopidogrel. His oral digoxin dose was also increased. The patient had a chest CT that demonstrated a right middle lobe infiltrate and also a probable thoracic aneurysm. After discussion, the patient was transferred to another hospital for further evaluation and management, and he was subsequently discharged 4 days later.

Patient 012-017

This 48-year-old male, with a history of CHF, hypertension, atrial fibrillation, hyperlipidemia, COPD, mitral valve disease, s/p CABG, s/p MI, dizziness, nausea, near syncope, headaches, sinusitis, myopia, constipation, lower extremity numbness, s/p URI, obesity, s/p pericardial effusion and tricuspid regurgitation, went to ER 6 days after initiation of BiDil with a complaint of severe dyspnea, fatigue, chest and abdominal pain that lasted for 24 hours. The patient was not able to achieve relief with sublingual nitroglycerin and called the EMT, and he was admitted for evaluation. During the hospital stay, the patient was observed to have numerous episodes of ectopic beats and occasional runs of ventricular ectopy. None of these caused any significant clinical abnormalities. No specific treatment was prescribed for the ectopy. The patient slowly improved and was discharged 7 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 012-018

This 62-year-old female with a history of CHF, cardiomyopathy, hypertension, atrial fibrillation, s/p TIA, mitral and aortic valve disease, s/p mastectomy, elevated liver function tests, glucose intolerance, hypokalemia, pulmonary hypertension, tricuspid regurgitation, anemia, arthritis, indigestion, depression, anxiety, headaches, s/p hysterectomy, hyperopia and constipation, presented to the Emergency Room with a complaint of nausea and being "sick" about 3 months after being on BiDil. The patient had run out of medication 2-3 days prior to presentation. In the ER, the patient was given medicine for BP and sedation and felt better. On examination she was hypertensive. EKG showed sinus rhythm with LVH. Chest X-Ray showed cardiomegaly. Lab data revealed BNP >5000, CK-708, CKMB 20.4, Troponin 0.03 and WBC 9,000. The patient was admitted for further evaluation. The patient was treated with IV diuretics. The patient had an episode of non-sustained ventricular tachycardia. She was started on amiodarone. The patient had a good response to diuretics and lost 12 lbs. BP also improved but was still sub-optimal. The patient slowly improved and was discharged 4 days later. The subject completely recovered and no action was taken regarding study medication.

Patient 032-007

This 72-year-old female with a history congestive heart failure, hypertension, hyperlipidemia, peripheral vascular disease, mitral valvular disease, s/p CABG and s/p MI, presented to the ER

5 months after initiating BiDil with complaints of chest pain radiating to the right arm associated with shortness of breath and nausea. The patient was treated with a nitroglycerin drip and also given enoxaparin and morphine. EKG showed ST-T wave depression in the infero-lateral leads. Two days later, the patient underwent coronary angiography that demonstrated an 80% discrete ostial LAD lesion, a 100% proximal LAD lesion, a 100% ostial left circumflex lesion and a 100% proximal RCA lesion. The SVG to RCA had a 100% proximal lesion. There were no lesions in the SVG to LAD or SVG to Circumflex. It was elected to treat the patient medically. Three days later, the patient had an 18 beat run of non-sustained ventricular tachycardia with a heart rate of 122 beats per minute. There was no evidence to indicate additional treatment was required or that the ventricular tachycardia recurred. The patient was discharged to home the same day, and no change in study drug administration was made.

Patient 037-002

This 52-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, hypertension, atrial fibrillation, s/p CVA, chronic renal insufficiency, gout, hypercholesterolemia and polyarticular arthritis, presented to the hospital after being on BiDil for 4 months and 25 days with a three-day history of dyspnea, PND, orthopnea and weight gain associated with a non-productive cough. The patient also had intermittent chest pain radiating to the back for three days without aggravating factors. Two weeks before admission, patient's digoxin was held due to high levels. The patient also noted decreased urine output with lightheadedness. In the ER, patient was hypotensive and tachycardic. Chest X-Ray showed cardiomegaly with pulmonary vascular congestion. EKG demonstrated atrial fibrillation with rapid ventricular response and old inferior Q waves. Monitor showed sustained ventricular tachycardia. The patient was admitted for further evaluation, went to the ICU and was placed on phenylephrine. Systolic BP increased to 90-100. However, the patient's rhythm degenerated to sustained ventricular tachycardia which was pulseless. The patient was shocked into atrial fibrillation/sinus tachycardia. He was then placed on a lidocaine drip and intubated. He was subsequently placed on dopamine and furosemide. ECHO showed right atrial and ventricular dilation with tricuspid and mitral regurgitation. There was also left atrial enlargement and a suggestion of stagnation of blood in the left ventricle. The patient was anticoagulated and was also treated with amiodarone and digoxin. Eight days later the patient had an AICD placed, but continued to have PVCs on telemetry post AICD placement. He was eventually extubated and made steady improvement. The patient was discharged on the following day. The study medication was held during hospitalization. No information on whether it was reinstated.

Patient 0074-010

This 55-year-old male with a history of congestive heart failure, idiopathic cardiomyopathy, diabetes mellitus, CAD, s/p MI, peripheral vascular disease, s/p toe amputation, and s/p left wrist surgery, was admitted for EP evaluation and possible AICD placement after 2 months and 8 days of being on BiDil. The patient has a history of palpitations and non-sustained ventricular tachycardia at home that had not been recorded. Electrophysiologic evaluation demonstrated inducible ventricular flutter associated with hemodynamic collapse. In addition, there were runs of sustained ventricular tachycardia at 250 msec. Cardioversion was required for rescue from the sustained episode. An AICD was placed following the EP study. The

subject had a stable post-op course and was discharged 2 days later. The subject completely recovered and study medication was temporarily stopped.

Patient 108-024

This 65-year-old female with a history of congestive heart failure, ischemic cardiomyopathy, hypertension, atrial fibrillation, diabetes mellitus, hyperlipidemia, s/p CVA, mitral valve disease, aortic valve disease s/p MI, irritable bowel syndrome, GERD, glaucoma, amaurosis fugax and osteoarthritis, was on BiDil when she developed weakness and had an episode of syncope and a Holter monitor was reported to show non-sustained ventricular tachycardia. Five months after being on the study drug, she underwent electrophysiologic evaluation. demonstrated easily inducible, sustained, monomorphic ventricular tachycardia with a left bundle branch block, left axis morphology and a cycle length of 200 msec. This required DC cardioversion to restore to normal sinus rhythm. Following the procedure, the patient was admitted directly to the hospital, and underwent placement of AICD 2 days later. The post procedure course was uneventful. The patient was discharged 1 day later. The subject completely recovered and study medication was temporarily stopped.

Patient 126-001

This 59-year-old male with a history of congestive heart failure, hypertension, diabetes mellitus, ETOH abuse, hyperlipidemia, s/p DVT and chronic renal insufficiency, was on BiDil for 43 days when he was found unconscious in the front of his apartment with a cigarette in his hand. On the ride to the hospital, the patient developed ventricular tachycardia and ventricular fibrillation, and was treated with DC counter-shock two times plus intravenous lidocaine, and was intubated. He responded and upon arrival in the ER, he was placed on dopamine and mechanical ventilation. Heart showed III/VI systolic murmur. EKG showed LBBB. The patient was admitted to the ICU, was treated with intravenous antibiotics and diuretics, and 2 days later, he extubated himself. He was begun on amiodarone therapy. He had reported episodes of non-sustained ventricular tachycardia while on amiodarone. Eight days after the beginning of events, the patient was transferred to the study hospital, and 3 days later he underwent electrophysiologic evaluation which demonstrated inducible monomorphic ventricular tachycardia with a cycle length of 290 msec. Patient experienced syncope during this episode and required 1 DC shock to restore sinus rhythm. The patient subsequently had an AICD placed. He was later discharged, completely recovered and study medication was stopped temporarily.

Patient 228-007

This 55-year-old male with a history of congestive heart failure, hypertension, ventricular tachycardia, s/p AICD implantation, hypothyroidism possibly secondary to amiodarone, and apical thrombus, experienced ventricular tachycardia that triggered the firing of his ICD 6 months after being on BiDil. The patient presented to the hospital due the following day and was admitted for further evaluation. Two days later, the patient was hypotensive with BP 76/63 and had complaints of shortness-of-breath and lightheadedness. The patient was hydrated gently and given oxygen, and afterload reducers, beta-blockers, amiodarone and diuretics were held. His blood pressure increased and was in no acute distress. Other lab studies indicated hypothyroidism felt secondary to amiodarone with TSH of 8.40, and levothyroxine was initiated. Seven days after the beginning of events, the patient was considered stable and was

discharged home. The subject completely recovered and study medication administration was temporarily interrupted.

Patient 25-017

This 54-year-old male was on BiDil for 7 months when developed angioedema. Following the morning dose of BiDil, the patient developed shortness of breath, swelling of the tongue and lips and became unresponsive. EMS was called and administered 1 amp D50W with return of mental status. They also administered diphenhydramine IV. It was noted that the patient was recently switched to a different ACE inhibitor. The patient had not eaten anything that day nor the day before and only consumed alcohol the day before. The patient was brought to the where he was given additional diphenhydramine plus methylprednisolone IV. The swelling of the lips and tongue improved. The patient was recommended to stop ACE inhibitors and refrain from alcohol ingestion.

Patient 032-004

This 63-year-old female was on BiDil for 5 days when she developed angioedema. This was a single episode that was determined to be mild and no action was taken regarding study medication. The subject completely recovered.

Patient 044-005

This 46-year-old male was on BiDil for 6 days when he developed angioedema and light headedness, and was seen at the ER. He was treated with diphenhydramine, dexamethasone, ranitidine and methylprednisolone. The patient improved, was discharged to home, and his study drug was discontinued.

Patient 074-010

This 55-year-old male who was BiDil for 33 days experienced swelling of the face and "hands breaking out" with itchiness of the hands and visited the ER one day later. He had been placed on lisinopril. On exam there was an erythematous rash on the hands and periorbital edema. He was treated with diphenhydramine and prednisone orally in the ER. The swelling improved and rash improved. The subject was told to stop lisinopril, and was discharged. The subject recovered with sequelae and no action was taken regarding study medication.

Patient 121-011

This 31-year-old female who was on BiDil for a little over 10 months presented to the Emergency Room with a complaint of difficulty swallowing for 1.5 weeks but worse on the day of admission. This was associated with a sore throat, runny nose, chills, hot and cold feeling, and a productive cough with yellow sputum. Patient had vomiting for last 2 days. Also has pain in both ribs with coughing and "body aches". She also notes she is talking in a high-pitched voice for the last 5 days.

On exam, there was a hoarse and squeaky voice with swelling of the uvula. The patient was treated with diphenhydramine and methylprednisolone IV. She subsequently improved and was discharged the same day. She was given a prescription for methylprednisolone orally and was told to discontinue her losartan. She completely recovered and no action was taken regarding study medication.

Patient 174-001

This 53-year-old male who was on BiDil for 6 months experienced angioedema of the lips. It was felt that this was secondary to trimethoprim/sulfamethasoxazole that the patient had been

given for an infection. The patient was treated with prednisone. The event ended two days later. The subject completely recovered and no action was taken regarding study medication.

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9.6 Other Trials

An Open label, non-controlled extension trial of BiDil (X-A-HeFT) is in progress. All 1050 patients who have participated in A-HeFT were to be offered the option to enroll in X-A-HeFT. The overall objective was to demonstrate continued safety and tolerability, and to assess compliance with treatment for the duration of 12 months. BiDil was to be given to a target dose of 225/120 mg of HYD/ISDN.

9.7 Minnesota Living with Heart Failure Questionnaire

Table 51. The Minnesota Living with Heart Failure (MLWHF) Questionnaire

Did your heart failure prevent you from living as you wanted during the last month by:							
		No	Very little				Very much
		0	1	2	3	4	5
1	Causing swelling in your ankles, legs etc.?	0	1	2	3	4	5
2P	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3P	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4P	Making your Working Around the house or yard difficult?	0	1	2	3	4	5
5P	Making your going places away from home difficult?	0	1	2	3	4	5
6P	Making your sleeping well at night difficult	0	1	2	3	4	5
7P	Making your sleeping to or doing things with your friend s or family difficult?	0	1	2	3	4	5
8	Making your working to earn a living difficult?	0	1	2	3	4	5
9	Making your recreational pastimes, sports or hobbies difficult	0	1	2	3	4	5
10	Making you sexual activities more difficult?	0	1	2	3	4	5
11	Making you eat less of the foods you like?	0	1	2	3	4	5
12P	Making you short of breath?	0	1	2	3	4	5
13P	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14	Making you stay in a hospital?	0	1	2	3	4	5
15	Costing you money for medical care?	0	1	2	3	4	5
16	Giving you side effects from medications?	0	1	2	3	4	5
17E	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18E	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19E	Making you worry?	0	1	2	3	4	5
20E	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21E	Making you feel depressed?	0	1	2	3	4	5

The QOL questionnaire, per publication consists of four dimensions:

- 1 global score (all questions);
- 2 physical dimension score (questions # 2-7 and 12 and 13);
3. emotional dimension (Questions 17-21) and
4. economic dimension;

Copyright University of Minnesota 1986:

Rector, TS; Kubo, SH and Cohn, JN; " Content, Reliability and Validity of a New Measure, The Minnesota Living with Heart Failure Questionnaire; Heart Failure, 1987; 198-209.

E-Emotional component

P-Physical Dimension

9.8 References

9.8.1 Selected Findings from Literature Referred to in the Review

Figure 7. Mortality from CVD excluding stroke and CHD for 20 mmHg lower BP¹¹

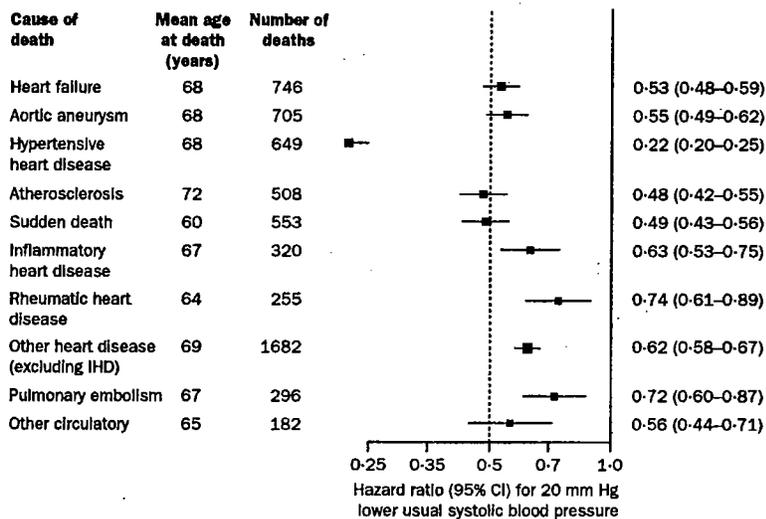


Figure 7: Mortality from other vascular causes (not stroke or Ischaemic heart disease): hazard ratios for 20 mm Hg lower usual systolic blood pressure

¹¹ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903-13

Figure 8. Effect of hypertension treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs¹²

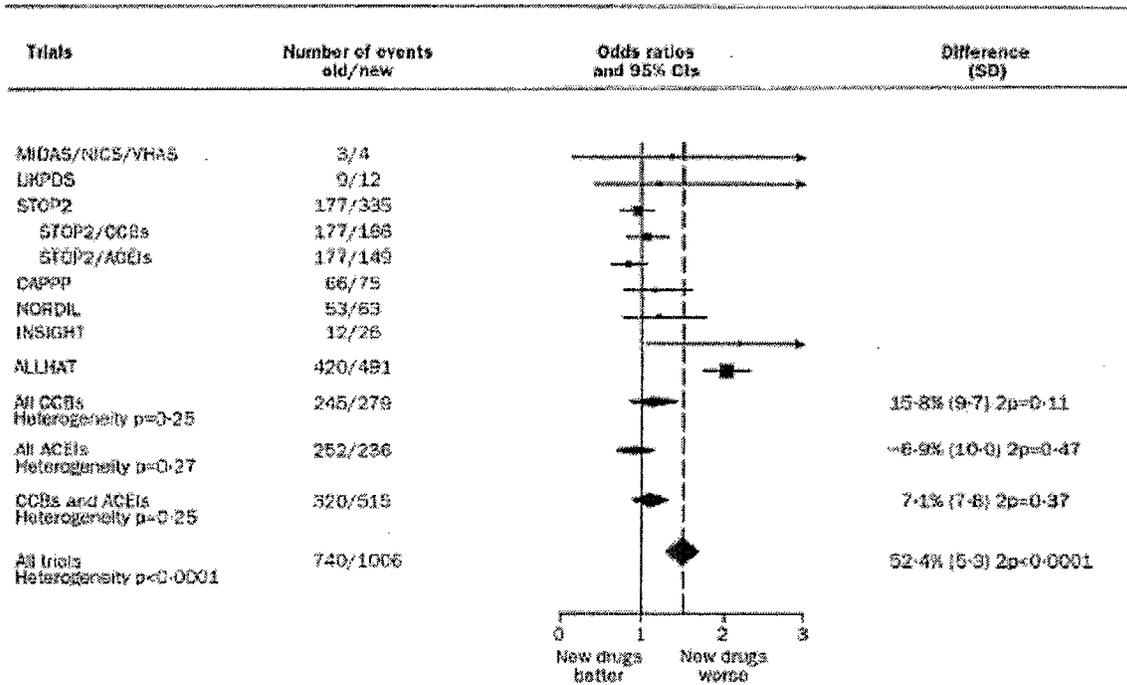


Figure 3: Effects of antihypertensive treatment on fatal and non-fatal congestive heart failure in trials comparing old with new drugs

¹² Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13

Figure 9. Effect of increased systolic and diastolic blood pressure by decade age increments on CV mortality excluding stroke and IHD¹³

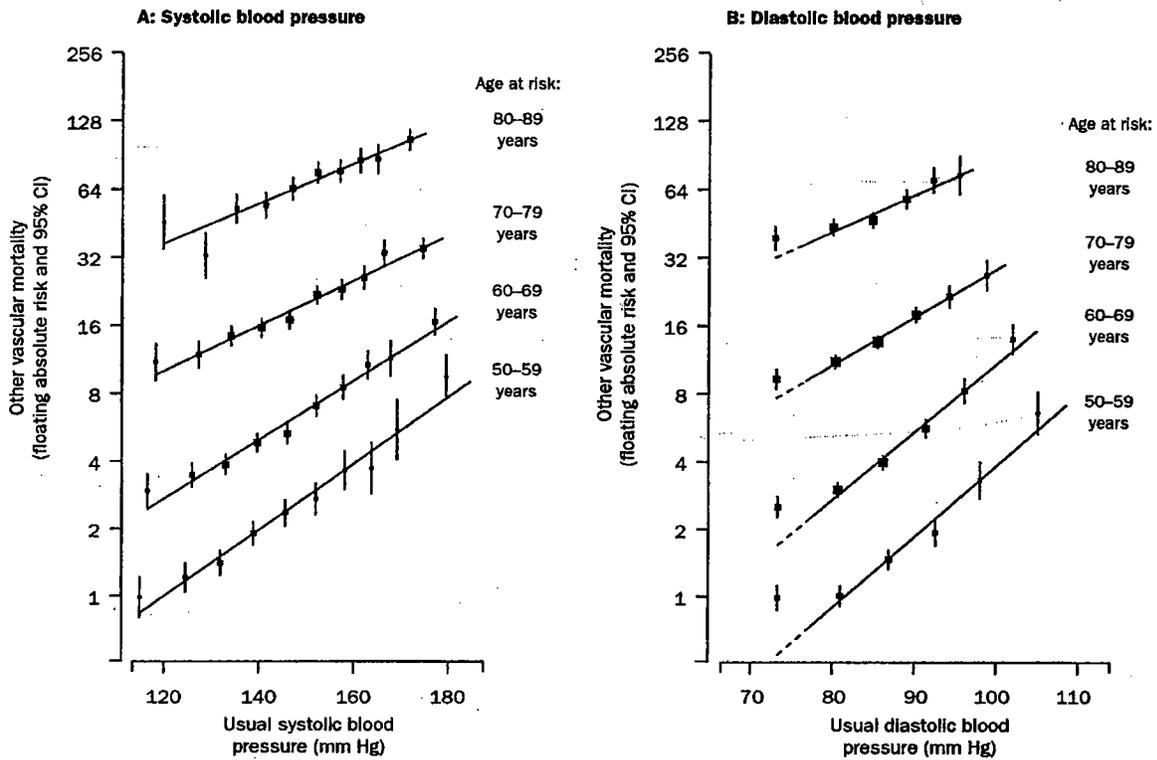


Figure 6: Other vascular (not stroke or ischaemic heart disease) mortality rate in each decade of age versus usual blood pressure at the start of that decade
 Conventions as in figure 2.

¹³ Prospective Studies Collaboration, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360: 1903-13

Figure 10. Relation between systolic blood pressure and cardiovascular mortality and events¹⁴

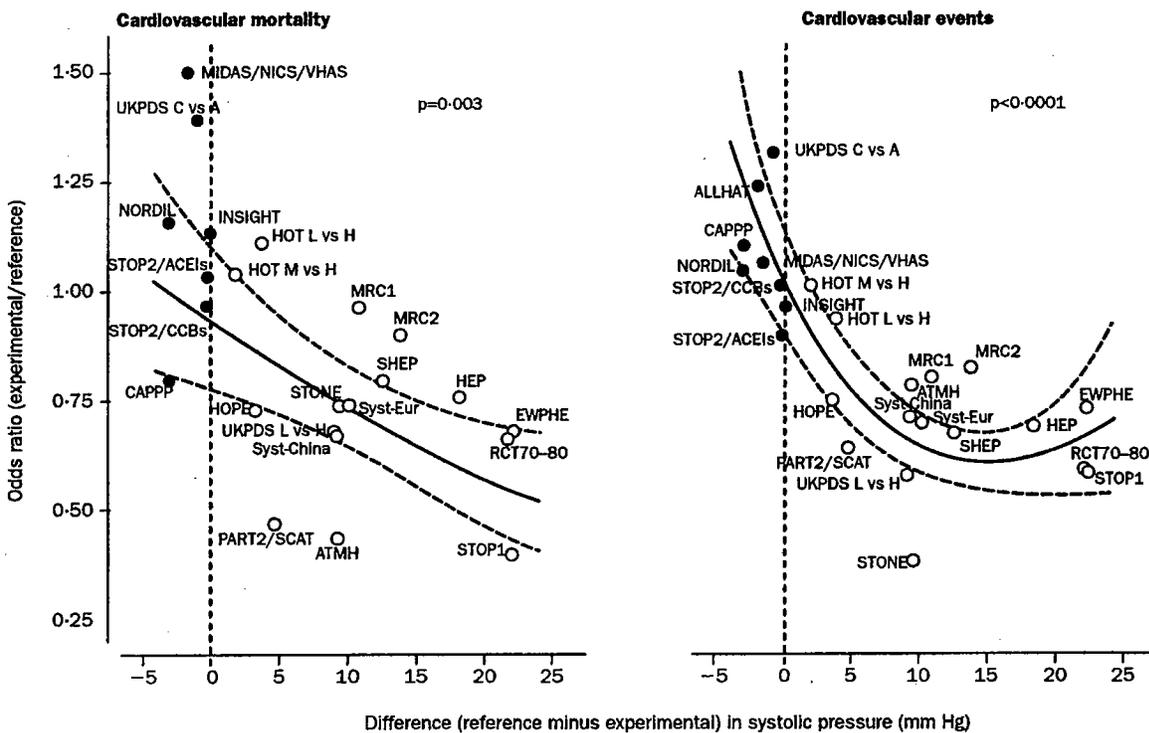


Figure 4: Relation between odds ratios for cardiovascular mortality and all cardiovascular events, and corresponding differences in

¹⁴ Staessen, JA, Wang JG, Thijs L, Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001; 358: 1305-15

9.9 Labeling Review

To be completed separately.

See 8.3 Recommendation on the Label, page 70.

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Salma Lemtouni
6/23/05 10:26:30 AM
MEDICAL OFFICER
To replace original medical review

JUL 3 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
Division of Cardio-Renal Drug Products

Public Health Service

Memorandum

DATE : APR 18 1997

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 *Lipishy*

SUBJECT: Non-Approval of NDA 20-727, isosorbide dinitrate/hydralazine fixed-dose combination product (BiDil) for the treatment of congestive heart failure. Medco Research, Inc.

TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

The Cardiovascular and Renal Drugs Advisory Committee met on February 27, 1997 and recommended not-approval of BiDil for the treatment of congestive failure. The Division and its reviewers concur with that recommendation. The attached reviews offer the documentation. A not-approvable letter is also attached, for your signature.

There could have been a list of potential issues to resolve (e.g., tolerance to isosorbide, bioequivalence of the to-be-marketed formulation to any of the formulations that were used in any of the trials, the importance of Cox regression analyses for baseline co-variables, how to explicitly analyze a "positive control trial", VO₂ vs exercise duration and how to analyze an exercise tolerance endpoint, ejection fraction as a surrogate, etc., nitrosoamines in the product, an unknown "impurity" in the product). None of those need extensive discussion in this memorandum.

There were essentially 3 major features within this NDA:

- 1) The results of two, multicenter, controlled clinical trials that had prospectively declared mortality as a major endpoint. VHEFT I, a placebo controlled trial, and VHEFT II, controlled with enalapril (which at the time of the trial had not yet been approved).
- 2) The bioavailability results of the to-be-marketed formulation to the formulations used in the two major trials.
- 3) The well known issues of tolerance associated with isosorbide dinitrate when used in a qid dosing regimen for the treatment of angina pectoris.

Unresolved Manufacturing and Controls observations:

- 1) Control of N-Nitrosoamines to only []
- 2) During routine methods validation, the Cincinnati Laboratory (the only one from which results have been received to date), detected a large peak (not identified by the sponsor nor reported by the sponsor), and additionally (even ignoring the "new peak") found the product to exceed the impurities testing limits of NMT [] So the methods are either not suitable or the product has unknown impurities.

These are part of the not-approval letter. Although potentially resolvable, at present they are not resolved and are therefore incorporated as part of the basis of not-approval.

BiDil is a fixed-dose, combination drug product. The to-be-marketed formulations consist of 4 unit doses of 37.5/10, 37.5/20, 75/20 and 75/40 mg for the combination of hydralazine/isosorbide dinitrate, respectively. This formulation would be taken 4 times daily.

The Major Clinical Trials

VHEFT I

This was a controlled parallel group, (placebo, isosorbide dinitrate/hydralazine, prazosin), multicenter trial that randomized 642 patients with chronic (of at least 3 months duration) congestive heart failure, NYHA class II and III who were on a background therapy of digitalis and diuretics. It was a Veterans Administration Hospital study and randomized only male patients. The study was projected to be 5 years in duration, with enrollment taking 3 of those 5 years, so the shortest duration of follow-up was to be 2 years. It planned to enroll 308 patients to placebo, and 206 patients to each active arm, for a total of 720 patients (to have 84% power for an alpha equal to 0.025 (one-sided) for a comparison of each treatment group to placebo provided there was a 33% treatment effect and the 2 year placebo mortality rate was 30%). Enrollment was stopped prematurely because of a lack of funding, but at the 5 year duration of the trial, investigators were contacted to determine the status of each patient randomized (no case report forms).

The first patient was randomized May, 1980 (almost 2 decades ago), the protocol was written prior to that. It had 6 major endpoints. Mortality at 2 years or mortality over the entire study period was clearly of major interest, since the study size was estimated regarding those endpoints. The prospectively stated analysis was to be a single log-rank statistic with 2 degrees of freedom, or each treatment arm could be compared to placebo (again log-rank), or if the active treatment arms were similar, the combined vasodilator arms could be compared (again log-rank) to placebo. So there were three variations. A Cox regression analysis was specified in the protocol, not as a definitive test of the null hypothesis but simply to explore the role of baseline covariates. There were 4 formal interim analyses planned.

There were 120 deaths in the placebo group (number at risk = 273), 91 deaths in the prazosin group (number at risk = 183), and 72 deaths in the combination group (number at risk = 186). Crude mortality rates were 44, 49.7 and 38.7% for placebo, prazosin and the combination, respectively. The log-rank for the combination vs placebo gave a p value of 0.093 and 0.056 for overall survival and 2-year survival, respectively. Bunches of other approaches were also taken, see review by Drs. Hung, Chen and Ganley for elegant discussion of each analysis. Regardless of how one approaches the problem, survival is suggestive but a survival benefit of treatment with isosorbide dinitrate/hydralazine is not established to the degree of certainty that would be necessary to reach an approval decision on the basis of a single trial.

The easiest way to describe the other variables prospectively identified (except for ejection fraction, which was unquestionably favorably affected by combination treatment), is unadjusted, nominal p values sometimes approaching a value of 0.5 (not 0.05 as most would think appropriate).

VHEFT II

This was a parallel group, multicenter, controlled trial that randomized 804 (403 to enalapril and 401 to isosorbide dinitrate/hydralazine) patients with chronic congestive heart failure, NYHA class II and III who were on a background therapy of digitalis and diuretics. The study was projected to be of 5 years duration. It too was a Veterans Administration Hospital study and randomized only male patients. The study was powered to detect a 30% difference in mortality between the two groups (based on an annual mortality of 13% based on VHEFT I) with a 2-sided p of 0.05. The protocol estimated that a 10% difference in exercise tolerance, based on oxygen consumption, could be detected with a 2-sided p of 0.01.

The first patient was randomized in March, 1986 and the last patient was randomized in September, 1990; the study was terminated in February, 1991. Of the 804 randomized patients, 121 had participated in VHEFT I.

Both 2 year mortality and 5 year mortality were prospectively indicated as major endpoints (2 out of the 6 major endpoints listed in the protocol. Two year mortality clearly favored enalapril ($p = 0.019$ by log-rank and 0.024 by Cox regression) as well as at 5 years ($p 0.083$ by log-rank. The isosorbide dinitrate/hydralazine group survival curves were superimposable upon that of the same group in VHEFT I, which might allow one to conclude that the isosorbide dinitrate/hydralazine group in VHEFT II may have been better than that of placebo (but not with any more assurance than can be derived from VHEFT I). A comparison to the results of the SOLVD treatment trial did not help conclude that the isosorbide dinitrate/hydralazine group mortality results in VHEFT II would have been better than placebo, had placebo been present in the VHEFT II trial.

There were 276 and 264 total, all-cause hospitalizations in the enalapril and isosorbide dinitrate/hydralazine groups, respectively. Hospitalizations for congestive heart failure were 112 and 110 for the enalapril and isosorbide dinitrate/hydralazine groups, respectively. Not a hint of anything there.

Consequently, there are no data that can be regarded as confirming the VHEFT I mortality result.

Exercise tolerance in VHEFT II is claimed (NEJM 325: 303-310, 1991) to have been statistically significantly superior in the isosorbide dinitrate/hydralazine group, compared to the enalapril group. Our analyses do not confirm that reported difference (which was based upon an analysis that excluded patients that did not stop exercise testing because of shortness of breath, post randomization).

Ejection fraction may have been increased by 0.012 ($p = 0.026$) in the isosorbide dinitrate/hydralazine group, compared to the enalapril group at 3 months, but otherwise the groups were not differentiable on the basis of ejection fraction (4 other measurements through 48 months).

Other Clinical Trials

There are no other clinical trials related to the effects of isosorbide dinitrate/hydralazine on morbidity/mortality in patients with congestive heart failure. One literature report (JACC 26: 1575-1580, 1995) of a hemodynamic investigation in 28 patients with congestive heart failure coupled with several literature reports of in vitro and whole animal studies (reviewed by Dr. DeFelice) strongly suggest that hydralazine prevents the development of tolerance to nitrates. The animal and in-vitro studies are compelling and the single clinical trial is consistent with (but I do not think prove) that the in-vitro and whole animal studies have clinical predictive value. At one point in the recent past, I was extremely reluctant to accept that there could be a clinically meaningful effect of isosorbide dinitrate when administered in regularly spaced, qid fashion (as was the case in both VHEFT I and VHEFT II). Had the results of VHEFT I and VHEFT II been more convincing, I would have abandoned the notion that tolerance to nitrates was a very important variable with respect to the use of the combination product in the treatment of congestive heart failure. As it stands now, I am only hesitant.

Chemistry

The LNC Committee decided that the name "BiDil" can be construed as "twice-a-day" (bid) and that since BiDil should be taken four-times-a-day (qid), that the name was unacceptable. The Division disagrees with this decision and recommends that the name BiDil be approved. I doubt that any written or verbal order can be construed to require the administration "ii" (or II, or iL, or iL) twice-a-day. The name suitably states the formulation is composed of 2 (Bi) vasodilators (dil) and seems totally acceptable to the Division.

N-Nitrosoamines are known to be carcinogenic; the ingredients of the tablet (upon storage) could form N-nitrosoamines. Consequently, methods should be sensitive enough to detect less than [] N-nitrosoamines as tablets are followed for stability. The sponsor should commit to monitor for that, and have not.

Based on one field laboratory methods validation, the formulation cannot be manufactured within specifications (to have impurities at less than []) but the lab found impurities in four lots to be [], [], [], []. The one field laboratory also found an unidentifiable peak. The conclusion of the field laboratory was that the methods were unsatisfactory. That may be, but I do not know how the differentiation between methodology failure and manufacture failure was able to be made.

I suspect that these manufacturing and controls problems can be resolved (another method, better write-up of the existing method, another lab, more communication, etc.). As it now stands, the manufacturing and controls section of this NDA is not acceptable.

Biopharmaceutics

VHEFT I and VHEFT II did not utilize a fixed-dose, combination product. Each ingredient of BiDil was administered in the commercially available dosage forms available at the time of trials (but, enclosed in a capsule, with an identical placebo for VHEFT I). There are many uncertainties, among them being that the actual formulation of hydralazine used in VHEFT I is no longer commercially available (the trial having been conducted almost 2 decades ago). Some were found in somebody's stock somewhere. Other uncertainties come from the fact that both drugs have first-pass metabolism and only normal volunteers were studied. No multiple dose "bioavailability studies" have been conducted, only single dose. There is a discrepancy between the data reported on paper and the equivalent numbers when calculated from an electronic submission (not resolved).

As it now stands (post-1997-advisory committee), the to-be-marketed formulation of isosorbide dinitrate/hydralazine (BiDil) has not been administered to patients with congestive heart failure; at any dose. The formulations used in VHEFT I and VHEFT II have been compared, in a single dose study utilizing normal volunteers (Study CB-02), to BiDil. BiDil is not bioequivalent to either of the formulations used in the morbidity/mortality trials. The mean values are shown in the following table (numbers are from the sponsors paper submission).

Dose & weight-normalized values, Phase B of study CB-02 (Table 4, page 23 of Dr. Marroum's review).

Low BiDil = 37.5 mg hydralazine/10 mg ISDN, to be marketed BiDil Tablets

VHEFT I = capsule used in VHEFT I = 37.5 mg hydralazine + 10 mg tablet ISDN

VHEFT II = tablet used in VHEFT II = 37.5 mg hydralazine + 10 mg tablet ISDN

Hi BiDil = 75 mg hydralazine/40 mg ISDN, to be marketed BiDil Tablets

	Low BiDil	VHEFT I	VHEFT II	Hi BiDil
Hydralazine				
AUC	35.11	32.99	24.40	40.90
C _{max}	56.3	77.3	29.6	44.0
T _{max}	0.96	0.74	1.03	1.02
T _{1/2}	2.31	2.38	2.05	3.52
ISDN				
AUC	26.0	26.7	26.1	30.9
C _{max}	30.0	26.5	22.8	19.0
T _{max}	0.64	0.65	0.75	1.05
T _{1/2}				
IS-2MN				
AUC	97.6	103.8	108.6	116.3
C _{max}	29.5	30.7	28.7	24.4
T _{max}	0.89	0.80	0.76	1.61
T _{1/2}				
IS-5-MN				
AUC	881.0	861.1	932.3	843.4
C _{max}	110.2	118.0	112.7	126.4
T _{max}	1.63	1.24	0.93	2.20
T _{1/2}	5.40	5.45	5.82	5.45

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Simple perusal of the table above is entirely consistent with the conclusions drawn from more detailed analysis. The to-be-marketed formulation of BiDil is not bioequivalent to either of the formulations that were studied in the clinical trials. The differences are not overwhelming but do approach mean differences of 50%, in some cases.

Instructions for use would recommend titrating to maximum tolerated dose, so there would be a clinical guide that would probably make the observed non-equivalence not dispositive with respect to approval or non-approval. The fact that the to-be-marketed formulation has not been administered to patients with heart failure (the liver can be involved in the disease and both drugs have first-pass metabolism) makes the apparent formulation differences harder to evaluate (they could conceivably be much greater in the face of hepatic metabolism deficits).

The sponsor has agreed to a multiple-dose, high- and low-dose, steady-state comparison in patients with congestive heart failure. Should the application be resubmitted (following not-approval), the results of that study would be a condition for filing.

The results of dissolution tests do not allow waiver of the requirement of bioavailability testing for the intermediate strengths of BiDil (namely the 37.5/20 and 75/20 tablets). However, in the proposed bioavailability study in patients with congestive heart failure, this problem will be obviated (but this will be a data-dependent resolution) and cannot be guaranteed.

Since bioavailability of both components appear to be formulation dependent, the absence of a study of the effects of food on the bioavailability of BiDil is a problem. I do not see how we can rely on literature that deals with individual entities and formulations other than BiDil.

Summary

I have added nothing to the well done Medical/Statistical reviews performed by Drs. Chen and Ganley (medical) and Dr. Hung (statistical). Although the two Veterans Administration trials were outstanding with respect to foresight and establishing guideposts for those interested in evaluating the treatment of congestive heart failure, they are insufficiently convincing to warrant approval of the combination product. The combination may be a useful therapy, certainly it does no harm (compared to placebo), the question is how sure can one be that it does better than placebo. The answer is, not sure enough.

In that regard, were I a practicing physician and were I faced with a patient who was progressively deteriorating and could not take an ACE inhibitor, I would probably try hydralazine/ISDN. But in so doing, I would make it clear that I had no expectation and that if the patient felt worse, or didn't like the fuss, etc. that it would be stopped. There is indeed a difference between what practicing physicians might do and approval. Especially, I think, when instructions for use require that the maximum tolerated dose be employed. Approval would be promulgating the notion that, provided the combination is used as directed, there would be a mortality benefit. I see no viable way to support that notion.

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cc:

Orig.

HFD-110

HFD-110/GBuehler

HFD-110/RLipicky

sb/4/16/97;4/18/97

R/D: JAdvani/4/4/97

JShort for RWolters/4/4/97

PMarroum/4/4/97

CGanley/4/11/97

SChen/4/8/97

JHung/4/11/97

NMorgenstern/4/11/97;4/17/97

C. Buchler
MAR 14 1997

Medical/Statistical Review

NDA #: 20-727
DRUG NAME: BiDil®
SPONSOR: Medco
TYPE OF DOCUMENT: Original NDA
CORRESPONDENCE DATE: 7/3/96
DATE RECEIVED: 7/3/96
DATE REVIEW COMPLETED: 3/4/97
REVIEWERS: James Hung, Ph.D., Shaw Chen, MD., Charles J. Ganley, MD.

The NDA included an archival copy (paper) and SAS data sets that included data from the case report forms. Information from the following submissions are included in this review. Dr. Ganley reviewed V-HeFT I. Dr. Chen reviewed V-HeFT II. Dr. Hung provided the statistical analyses and the interpretation of results for both V-HeFT I and V-HeFT II.

- Original NDA Submission
- Document 20-727/BM (correspondence date 11/20/96)
- Document 20-727/BM (correspondence date 12/11/96)
- Document 20-727/BZ (correspondence date 12/13/96)
- Document 20-727/BM (correspondence date 1/2/96)
- Document 20-727/BZ (correspondence date 1/2/96)
- Document 20-727/BZ (correspondence date 1/9/96)

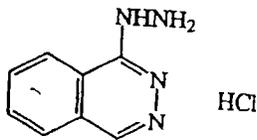
GENERAL INFORMATION

Name of Drug

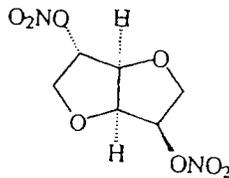
Generic: hydralazine HCl and isosorbide dinitrate (H-ISDN)

Proposed Trade: BiDil®

Chemical: 1-hydrazinophthalazine monohydrate and 1,4,3,6-dianhydro-D-glucitol-2,5- dinitrate



hydralazine HCl



isosorbide dinitrate

Pharmacologic Category

Proposed Indication: Congestive Heart Failure

Dosage Form and Route of Administration: oral tablets in hydralazine /isosorbide dinitrate strengths of 37.5/10, 37.5/20, 75/20, 75/40 mgs.

RESUME

The submission includes the results of two randomized, double-blind survival trials. V-HeFT I randomized patients with CHF to placebo (N = 273), H-ISDN (N = 186) or prazosin (N = 183). V-HeFT II randomized patients with CHF to enalapril (N = 403) or H-ISDN (N = 401). The major endpoints in both studies included overall mortality, 2-year mortality and maximum oxygen consumption. The determination of a significant difference between treatments for mortality in V-HeFT I is dependent on the analysis used and the adjustment made for interim analyses and multiple endpoints. Other endpoints in V-HeFT I, except for ejection fraction, showed no significant difference between treatments. Ejection fraction significantly increased (by approximately 4%) in H-ISDN patients compared to placebo. In V-HeFT II, there is a significant difference between treatments in favor of enalapril for 2-year mortality.

Introduction

NDA 20-727 includes the data and results from two mortality studies and two pharmacokinetic studies. The mortality studies, V-HeFT I and V-HeFT II, compared the long term survival of CHF patients on H-ISDN to placebo (V-HeFT I) and enalapril (V-HeFT II). The results of these studies are summarized in this review. The pharmacokinetic studies, CB-01 and CB-02, were single dose, open label, multi-formulation, multi-period crossover trials. CB-02 compared BiDil® to the formulations of hydralazine and ISDN utilized in the V-HeFT I and V-HeFT II studies. The pharmacokinetic studies were reviewed by Dr. Patrick Marroum.

The sponsor has included numerous peer reviewed articles from the medical literature that do not include source data. These can be found in volumes 1.17, 1.18, 1.20 and 1.46. These will not be reviewed in detail. Some of these articles are referenced in the discussion of several issues associated with this drug product.

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V-HeFT I

[Cohn JN, Archibald DG, Ziesche S, et al. Effect of Vasodilator therapy on mortality in chronic congestive heart failure. NEJM 1986;314:1547 - 1552.]

Protocol (Based on a review of the original protocol)

The objective of this study was to determine whether the addition of vasodilator therapy to standard medical therapy improves the mortality and morbidity of patients with congestive heart failure. This was a randomized, double-blind, placebo controlled, parallel dose trial. The trial consisted of a four week placebo stabilization period followed by a double-blind treatment period of at least 2 years duration. Patients were randomized to placebo, hydralazine/isosorbide dinitrate (H-ISDN) or prazosin. Patients started therapy with 1 capsule (hydralazine 37.5 mg or prazosin 2.5 mg or placebo) and 1 tablet (placebo or ISDN 20 mg) four times daily. The dose was titrated to 2 capsules and 2 tablets four times daily as tolerated by the patients. During the double-blind treatment period, patients were evaluated every 2 weeks for 8 weeks and then every 4 weeks for the remainder of the first year of therapy. After one year, visits occurred at 3 month intervals.

Table P.1 outlines the visit schedule and the procedures performed during the study.

Table P.1. Flowchart

Visit	1	2	3	4	5	6	7	8-11	12	13-17	18	19	20	21	22	23	24	25+	
Week	-4	2	0	2	4	6	8	12-24	28	32-48	52	65	78	91	104	117	130		
Therapy	placebo		double-blind treatment																
History	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PE	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood Test			*				*		*		*		*		*		*		
CXR			*				*		*		*		*		*		*		
ECG			*				*		*		*		*		*		*		
Echo			*				*		*		*		*		*		*		
STI			*				*		*		*		*		*		*		
Ral Imaging ³			*				*		*		*		*		*		*		
Exercise Test		* ²	*				*		*		*		*		*		*		
Holter			*				*		*		*		*		*		*		
Dig level	*	* ¹	* ¹																
Optional tests ⁴			*																

¹ If dose of dig changed at previous visit.

² Performed if compliant with therapy.

³ To measure ejection fraction

⁴ invasive PAP and CO, non-invasive CO by CO₂ rebreathing, radionuclide imaging for EF, stress Echo.

STI = systolic time interval

Subjects undergoing screening at visit 1 (week -4) had to fulfill the inclusion and exclusion criteria listed in table P.2 in order to be enrolled into the placebo stabilization period. Additionally, an assessment of the adequacy of digitalis and diuretic therapy was made¹. If the dose of digitalis or diuretic was perceived to be inadequate, dose adjustments were made at visit 1.

Table P.2. Inclusion and Exclusion Criteria

Screening Inclusion Criteria	Screening Exclusion Criteria
<ul style="list-style-type: none"> • Male subjects between 18 and 75^A years of age • history and physical consistent with left ventricular failure • limitation of exercise tolerance because of dyspnea and / or fatigue beginning at least 3 months prior to screening 	<ul style="list-style-type: none"> • MI or cardiac surgery within 3 months • hypertrophic cardiomyopathy • significant LV outflow obstruction • significant mitral valve stenosis • severe aortic or mitral valve insufficiency • hypertensive patients requiring treatment with anti-

¹ Adequacy of digitalis therapy was based on the following criteria: 1) digitalis was taken on a regular basis; 2) there were measurable blood levels of digitalis; 3) either digitalis toxicity occurred at a higher dose or the investigator did not feel a higher dose would benefit the patient.

Adequacy of diuretic therapy was demonstrated by; 1) diuretics were taken on a regular basis or attempts to initiate therapy did not result in improvement; 2) previous attempts to increase diuretic dose did not result in improvement.

Table P.2. Inclusion and Exclusion Criteria

Screening Inclusion Criteria	Screening Exclusion Criteria
	hypertensive drugs other than diuretics <ul style="list-style-type: none"> • hemodynamically significant pericardial disease • SLE • allergy or intolerance to hydralazine, prazosin or nitrates • chronic bronchopulmonary disease • anemia (hematocrit < 30%) • severe intrinsic renal or hepatic disease • angina pectoris requiring long acting nitrates • chronic beta blocker therapy • inability to perform a bicycle exercise tolerance test for non-cardiac reasons • therapy with vasodilator drugs • disease process that may limit 2 year survival • participation in another simultaneous trial or history of non-compliance

^A increased from 70 years to 75 years on 10/23/81

At visit 2 (week -2), an exercise treadmill test was performed if the patients ingested at least 70% of the prescribed medication between visit 1 and 2. If the maximal oxygen consumption at peak exercise was > 20 ml oxygen/kg/min., the patient was dropped from the trial. Patients who stopped the exercise test due to fatigue or shortness of breath with maximal oxygen consumption less than 20 ml oxygen/kg/min were continued on and returned at visit 3 (week 0). If angina or arrhythmia stopped the exercise test or the patient was not compliant with therapy, the patient returned for visit 2A and underwent repeat testing.

At visit 3, the patients repeated the exercise testing. In order to be randomized, the following criteria had to be met:

- Cardiothoracic ratio > .55 or Cardiothoracic ratio < .55 and echo left ventricular internal dimension at end diastole > 2.7 cm/m² or Cardiothoracic ratio < .55 and a resting ejection fraction < .45 by radionuclide multiple gated acquisition scan or left ventriculogram performed with contrast medium;
- Medications have not changed in the previous 2 weeks;
- Body weight is within 3% of previous visit;
- Pill count shows that ≥ 70% of the prescribed dose was ingested;
- Oxygen consumption at maximum exercise is within ± 4 ml/kg/min of the previous test or maximal exercise duration is within ± 2 minutes of the previous test.

If these criteria were not met, patients returned for additional visits (3A, 3B, 3C and 3D) at 2 week intervals until 2 successive visits fulfilled the criteria.

Patients fulfilling the randomization criteria were randomized in a ratio of 3:2:2 to placebo, hydralazine 37.5 mg/isorbide dinitrate 20 mg or prazosin 2.5 mg administered four times daily. The randomization code for each patient was assigned by the Study Coordinating Center in response to a phone call. Patients were originally stratified based on etiology (CAD vs. Non-CAD) and average maximal oxygen consumption² (> 12 ml/kg/min vs. ≤ 12 ml/kg/min). On 10/23/81, stratification based on oxygen consumption was discontinued.

During subsequent visits, the dose of medication was increased or decreased based on tolerability of the therapy. The maximum achievable dose of active therapy was hydralazine 75 mg/isorbide dinitrate 40 mg or prazosin 5 mg four times per day. The minimum dose of active therapy was hydralazine 37.5 mg/isorbide dinitrate 20 mg or prazosin 2.5 mg two times per day. The goal of therapy was to treat the patients with the highest tolerable dose.

² If oxygen consumption was not measured, stratification was based on exercise duration (> 9 minutes vs. ≤ 9 minutes).

Endpoints

There are six major endpoints listed in the protocol. The sample size was based on the mortality endpoints. The major and minor endpoints are listed in table P.3.

Table P.3. Major and Minor Endpoints

Major Endpoints	Minor Endpoints
<ul style="list-style-type: none"> • mortality during the entire study period • two year mortality • the number and duration of hospitalizations for cardiovascular causes • maximum oxygen consumption during the peak exercise • maximum treadmill exercise time on graded test • duration of exercise on submaximal tests 	<ul style="list-style-type: none"> • heart size by echo • heart size by chest x-ray • ejection fraction by radionuclide studies • left ventricular function by echocardiography • left ventricular function by systolic time intervals (PEP/LVET) • arrhythmias detected by holter monitoring • quality of life

Sample Size and Study Duration

The primary objective of the study was to determine if survival time is increased on vasodilator therapy as compared to the survival time in the placebo group. The study duration was projected to be 5 years with enrollment occurring for three years. The last patient enrolled was to be followed for 2 years unless the trial was stopped at an interim analysis. Total sample size was projected to be 720 with 308 randomized to placebo and 206 randomized to each active treatment group. This sample size gives a power of 84% for an alpha equal to .025 (one sided) for the comparison of each treatment group to placebo based on a 2 year placebo mortality rate of 30%³ and a reduction in mortality of 33%. The protocol also projected the sample size to detect a difference of 5 ml/kg/min. in maximal O₂ consumption between treatment groups. For a 99% probability of detecting a 5 ml/kg/min. difference (with alpha = .01, two-sided), 49 patients in each treatment group would be required.

Statistical Analysis

The protocol specified analysis for survival is a Logrank test. Two alternatives are described in the protocol. The first tests the hypothesis of no difference between the three survival curves with a single Logrank test with 2 degrees of freedom. The second compares each drug regimen to placebo using a one sided test at the .025 level⁴. The protocol also states that if the survival curves of the two vasodilator regimens are similar, the survival curve of the combined vasodilator regimens can be compared to placebo by use of the Logrank test.

The life table regression procedures of Cox was to be used to identify variables which are prognostically important and to obtain estimates of treatment effects adjusted for any inequality in their distribution between the treatments.

The change from baseline in oxygen consumption was to be calculated for the maximum exercise tests at 8 weeks, 6 months, 1 year, 18 months, 2 years etc. Repeated measures techniques were to be used and at each interval the difference among treatment groups was to be tested by an F test.

Analysis for other variables were not specified.

Committees

Three committees were responsible for overseeing the conduct of the study. Table P.4 lists the committees and their function.

³ This assumes a yearly dropout rate of 6% and no adjustment for multiple comparisons. A conservative adjustment for multiple comparisons with alpha equal to .0125 (one sided) yields a power of 77% to 90% depending on the projected treatment effect (see volume 1.20, p. 36)

⁴ The protocol states that this controls for the effects of multiple comparisons (volume 1.20, page 39). This is not the case since a one-sided p of .0125 (volume 1.20, p. p. 36-37) would conservatively account for the multiple comparison if prazosin and H-ISDN are compared to placebo separately.

Table P.4. Committees and Their Function as Outlined in the Protocol

Committee	Function
Operations	The committee meets twice a year to review the progress of the trial and make recommendations to the Chief Cooperative Studies Program as to whether the study should be continued or terminated. Patient acquisition and data summaries will be presented at each meeting.
Human Rights	The committee meets in conjunction with the Operations Committee to ensure that patients rights and safety have been properly protected.
Executive	The committee meets at 6 month intervals. The committee is the management and decision-making body for the operational aspects of the trial. It also monitors the performance of the hospitals.

Coordinating Center

The Cooperative Studies Program Coordination Center (CSPCC) provided the randomization number to the investigator. Case report forms were sent to the chairman where they were reviewed for completeness and then forward to the CSPCC where they were keypunched. The chairman was blinded to the study results.

Interim Analysis

The protocol states that two approaches to sequential analysis of the survival curves will be discussed at the first meeting of the Operations Committee. These include: 1) the computer simulated boundaries as presented by Canner⁵; 2) procedures presented by Armitage⁶ which calculate the Logrank statistic at the time of each death.

Results

Twelve VA hospitals participated in the trial but only eleven recruited patients. Table R.1 lists the number of patients randomized by each center. The first patient was randomized on 5/7/80 and the last patient was randomized on 6/15/85. The trial was terminated on 12/15/85. The protocol specified that 720 patients would be randomized into the trial with a minimum follow-up of 2 years if the study was not stopped prematurely at an interim analysis. The study randomized only 642 patients and the minimum follow-up was 6 months. During the course of the study, recruitment was slower than expected. The Operations Committee extended the recruitment period but attempted to keep the overall trial duration the same as proposed in the original protocol. As a consequence, there were fewer patients randomized and the minimum follow-up was less than originally projected. Limited funding prevented an extension of the trial duration.

Table R.1. Centers and Number of Patients Randomized at Each Center [vol. 1.19, p.79]

#	Location	Investigators	Placebo	HEISDN	Prazosin	Total
1	Washington, DC	Saunders Wish	14	10	9	33
2	Milwaukee, WI	Tristani Hughes	31	21	21	73
3	Los Angeles, CA	Shah Wong	22	14	16	52
4	Minneapolis, MN	Francis	21	15	14	50
5	Durham, NC	Cobb Higgenbotham	21	16	13	50
6	Hines, IL	Jacobs Loeb	27	18	19	64
7	Tucson, AZ	Goldman Hager	26	16	17	59
8	Cincinnati, OH	Flohr	25	17	16	58
10	Philadelphia, PA	Dunkman Ledy	33	23	23	79

⁵ Canner PL. Monitoring Treatment Differences in Long-Term Clinical Trials. *Biometrics* (1977) 33:603

⁶ Armitage P. *Sequential Medical Trials*. John Wiley & Sons, Inc., New York, 1975

Table R.1. Centers and Number of Patients Randomized at Each Center [vol. 1.19, p.79]

#	Location	Investigators	Placebo	H-ISDN	Prazosin	Total
11	Nashville, TN	Harston	34	23	23	80
12	Little Rock, AR	Franciosa Baker	19	13	12	44

Six major and seven minor endpoints are specified in the protocol. This review will describe the results of all of the major endpoints and two minor endpoints, ejection fraction and quality of life.

Disposition

Eleven centers screened 3425 patients and randomized 642 patients. Table R.2 lists the number of patients randomized to each treatment group and the disposition of those patients. Randomization was carried out at each center in each stratification group in blocks of seven. A query of the final clinic visit form for each survivor was performed to determine the date of the final visit. Of the 359 patients who were reportedly alive on the trial termination date of 12/15/85, only nine had a clinic visit on or after 12/15/85. The sponsor was asked to provide documentation of patient follow-up for the 350 patients without a clinic visit on or after 12/15/85. The sponsor responded that a separate discontinuation form for each patient was not completed. Rather, in December of 1985, a computer list was sent to each investigator. The list included information on death, date of death and randomization date. Each center was to review this patient list and determine whether the survival status for each patient was correct. Any corrections were written directly on the computer list and returned to the study biostatistician. For the majority of survivors, it is not documented how the survivor status was ascertained by the centers in December 1985. A listing of the dates of the last clinic visit for placebo and H-ISDN survivors is provided in the appendix (appendix pages 2 - 8).⁷

Table R.2. Patient Disposition Based on Sponsor's Analysis [vol. 1.21, p. 62; vol. 1.23, p. 3]

	Placebo	Prazosin	H-ISDN	Total
Screened				3425
Randomized	273	183	186	642
Completed	134		92 ²	
Deaths	120	91	72	283
Discontinuations ¹	19		22	

¹ Includes only survivors who discontinued all randomized therapy based on the sponsor's analysis. Six H-ISDN patients and fourteen placebo patients who died had prematurely discontinued both therapies prior to death. [listing 8, volume 1.25]

² Of the 91 who completed, 5 discontinued hydralazine only and 11 discontinued ISDN only.

Twenty-two H-ISDN survivors and nineteen placebo survivors discontinued all randomized therapy (both medications) prior to study completion. Table R.3 list the reasons survivors discontinued prematurely. A complete listing of the survivors discontinued from therapy prematurely is listed in the appendix (appendix page 9). Table R.3a lists the number of patients who discontinued therapy prematurely then subsequently died while off of therapy.

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⁷ The sponsor searched the VA BIRLS database using patient social security numbers. Of the 267 placebo and H-ISDN patients reported as alive on 12/15/85, 149 were confirmed by BIRLS were alive on 12/15/85 and died thereafter. Forty-seven patients did not have social security numbers on the case report form and could not be checked through the BIRLS system. Seventy-one patients had no record in the BIRLS which means they did not apply for VA death benefits.

Table R.3. Reasons Surviving Patients Permanently Discontinued Both Medications Prematurely [Sponsor's Analysis]

Survivors [volume 1.25, Listing 23]		
	Placebo	H-ISDN
# Discontinued	19	22*
Adverse Event	3	11
New or Worsened Heart Failure	2	2
Increased CHF	3	3
Patient's Decision	6	10

Patient can have more than one reason for discontinuation. Reasons are not mutually exclusive.

* Excludes patient 12010 (H-ISDN) who was found to have completed the study (see vol. 1.19, p. 182) on therapy but is included in listing 23.

Table R.3a. The Number of Patients Who Permanently Discontinued Medications Prematurely and Subsequently Died [Sponsor's Analysis]

Non-Survivors *		
Medication Discontinued	Placebo	H-ISDN
Both Medications	12	2
hydralazine or ISDN	0	5

* included in sponsor's submission of 12/11/96; Note - this is different from listing 8, volume 1.25.

The FDA analysis for discontinuations was performed by examining the number of capsules and pills prescribed in the final study medication case report form (form F) completed for each patient. Those patients who had zero capsules or pills prescribed were considered to have discontinued prematurely unless other information suggested otherwise. In addition, there were some patients who had greater than zero capsules and pills prescribed on their final form F but who had a discontinuation form (form P) completed at a later date indicating discontinuation of therapy. Table R.3b lists the patients thought to have permanently discontinued both or one of the medications prematurely. The difference between the sponsor's analysis and FDA's analysis does not need to be rectified at this time since the primary analysis for mortality is an intent to treat analysis. All of the patients included in the sponsor's analysis are included in the FDA analysis except for 3 patients (2 placebo: 22025, 44013; 1 H-ISDN: 31001). It should be noted that the sponsor's analysis deviates from the analysis published in the literature (NEJM 1986;314:1547 - 1552). A complete list of patients discontinued prematurely are included in the appendix (appendix page 10 - 12).

Table R.3b. The Number of Patients Who Permanently Discontinued Medications Prematurely [FDA Analysis]

Medication Discontinued	Placebo	H-ISDN
Both Medications	40	30
Hydralazine only	3	13
ISDN only	6	19

The mean follow-up was 2.3 years and ranged from 6 months to 5.7 years (sponsor's analysis).

Demographics (sponsor's analysis)

The study enrolled all males. The average age of patients was 58 years in each treatment group. Table R.4 lists the demographics of patients randomized to each treatment group. There are no significant differences in demographic variables between the placebo and H-ISDN treatment groups.

Table R.4. Demographics (from volume 1.19, p. 56 and NEJM 1986;314:1547 - 1552)

	Placebo (N = 273)	Prazosin (N = 183)	H-ISDN (N = 186)
Age (yr.)	58.5	58.3	58.3
Heart Failure Symptoms (%)			
< 6 mo.	19.5	14.8	18.9
6 mo. - 1.5 yr.	27.2	27.5	23.2
1.5 - 4.0 yr.	22.4	27.5	25.4
> 4 yr.	30.9	30.2	32.4
Race (%)			
White	70		71
Black	29		27
Other	1		2
Etiology			
Coronary Artery Disease	44.3	44.3	44.1
Previous MI	42.3	41.2	40.3
Alcohol Excess	38.2	40.3	43.0
Hypertension	42.6	39.8	39.7
Diabetes	24.5	18.7	17.2
Previous Surgery			
Coronary Bypass	13.6	12.6	11.8
Valve Replacement	4.0	6.6	4.9
Previous Drug Therapy* (%)			
Vasodilators	36.3	36.8	41.9
Antiarrhythmics	26.7	26.9	27.4
Sublingual Nitroglycerin	19.5	15.4	20.4
Anticoagulants	17.6	23.6	17.7
Clinical Data			
Symptom Score	5.6	5.7	5.6
Arterial Pressure (mmHg)	118.9/76.1	119.2/75.7	119.6/75.0
Heart Rate (beats/min.)	81.5	82.3	83.1
Cardiothoracic Ratio (%)	52.9 ^d	54.3	52.8 ^e
Ejection Fraction (%)	30.4 ^a	29.0	30.3 ^b
LVIDD (cm/m ²) ^c	3.5	3.5	3.5
Exercise Duration (min.)	9.8	9.1	9.7
Oxygen Consumption (ml/kg/min)	15.0 ^c	14.4	14.4

* previous 6 months; ^c Left Ventricular Internal Diastolic Diameter

a N = 264 ; b N = 181; c N = 270; d N = 265; e N = 183

Treatment Exposure and Compliance (volume 1.19, p. 80)

Approximately 92% of placebo patients achieved full dose of both medications at some time during the trial. Seventy-one percent of the H-ISDN patients achieved full dose at some time during the trial. After 6 months of therapy, 91% of placebo patients and 59% of H-ISDN patients were receiving full doses of both medications. There was no difference in the incidence of patients on full doses of capsules and tablets. In the H-ISDN group, the percentage of patients ever tolerating maximum doses of capsules (H) was greater than the percent tolerating maximum dose of ISDN (88% vs. 72%).

The average patient compliance in the placebo and H-ISDN treatment groups was determined by dividing the number of pills used divided by the number of pills prescribed. The average compliance for each patient was calculated and then from this the average of the treatment group was calculated. Table R.5 lists the average compliance for the placebo and H-ISDN groups. The compliance ranged from 73 to 82%. Compliance with ISDN was lower compared with hydralazine and placebo.

Table R.5. Average Compliance * for Each Treatment Group

	Placebo Treatment		H-ISDN Treatment	
	Hydralazine	Placebo	ISDN	Placebo
Average Compliance	82.4%	80.2%	82.1%	73.5%

* (# pills used) / (# pills prescribed) for each patient (average of all visits). Take average of all patients within a treatment group.

Concomitant medication (volume 1.19, p. 81 - 82)

In the placebo and H-ISDN treatment groups, > 98% of patients received digoxin and ≥ 85% of patients received furosemide at some time during the trial⁸. There were slight differences between treatments in the use of quinidine (26% placebo vs. 30% H-ISDN), aspirin (25% placebo vs. 35% H-ISDN), vasodilators (30% placebo vs. 37% H-ISDN) and beta blockers (5% placebo vs. 3% H-ISDN).

Interim Analysis

Four interim analysis for possible early stopping were performed using the O'Brien /Fleming methodology⁹. The study was stopped prior to the time (i.e. 720 patients randomized and minimum follow-up of 2 years) specified by the original protocol. The decision to stop was not based on the stopping rules. Recruitment was slower than anticipated so the Operations Committee in 1982 extended the recruitment period without extending the total duration of the trial.¹⁰ This resulted in a shorter minimum follow-up and enrollment of fewer patients than originally anticipated.

Major Endpoint - Survival

Mortality during the entire study period and two year mortality are major endpoints. The study was powered based on the treatment effect on mortality. The protocol states that the null hypothesis of no difference between the three survival curves can be tested by a single Logrank statistic with 2 degrees of freedom. Alternatively, each treatment group can be compared to placebo or if the survival curves of the vasodilator regimens are similar, the survival curve of the combined vasodilator regimens can be compared to placebo by use of the Logrank test. Thus, there are three variations (depending on which treatment groups are compared) of the Logrank specified in the protocol. An analysis utilizing the Cox regression was also specified in the protocol¹¹.

Table R.6 lists the crude mortality rates and the cause of death specified on the case report form by the investigator. The distribution of the causes of death are similar in the two treatment groups.

Table R.6. Crude Mortality Rate and Cause of Death

	Placebo (N = 275)	H-ISDN (N = 186)	Prazosin (N = 183)
# of deaths	120	72	91
Crude Mortality Rate	44%	38.7%	49.7%
Cause of Death	N (%) ¹	N (%) ¹	N (%) ¹
Pump Failure	38 (32%)	22 (31%)	33 (36%)
Primary Arrhythmia	45 (38%)	27 (37%)	32 (35%)
Other	4 (3%)	6 (8%)	6 (7%)
unknown	4 (3%)	5 (7%)	3 (3%)
Cardiac	-	1 (1%)	-
Suspected Cardiac	20 (17%)	10 (14%)	-
Not specified	9 (7%)	1 (1%)	17 (19%)

¹ as % of deaths

Table R.6a lists the crude mortality rates for each treatment group by center.

⁸ many patients may have received a concomitant medication for only one day

⁹ Biometrics 1979;35:549-556. The O'Brien Fleming rule was not stated in the protocol. The statistician associated with the study used the O'Brien Fleming rule for the analysis presented to the committee in September 1983.

¹⁰ from fax communication from Medco on 1/16/97; the decision regarding the time to stop the trial was made by the Operations Committee in September of 1982

¹¹ Cox regression was to be used to identify variables which are prognostically important and to obtain estimates of treatment effects adjusted for any inequality in their distribution between the treatments.

Table R.6a. Crude Mortality Rate by Center in V-HeFT I.

#	Location	Placebo		H-ISDN	
		N	Crude Mortality	N	Crude Mortality
1	Washington, DC	14	57%	10	30%
2	Milwaukee, WI	31	55%	21	29%
3	Los Angeles, CA	22	50%	14	36%
4	Minneapolis, MN	21	52%	15	27%
5	Durham, NC	21	29%	16	31%
6	Hines, IL	27	52%	18	61%
7	Tucson, AZ	26	42%	16	50%
8	Cincinnati, OH	25	35%	17	47%
10	Philadelphia, PA	33	33%	23	22%
11	Nashville, TN	34	44%	23	52%
12	Little Rock, AR	19	47%	13	38%

Table R.7 lists the results of the various analysis for survival reported in the published literature. Unadjusted p values range from .028 to .093 for the two endpoints depending on which analysis is performed.

Table R.7. Results of Survival Analysis Reported in the Literature [placebo vs. H-ISDN].

Source	Endpoint	Analysis	Comparison	Risk Reduction	P-value
NEJM 1986; 314:1547 - 1552	Overall Survival	log-rank	placebo vs. H-ISDN		.093
	Overall Survival	Generalized Wilcoxon	placebo vs. H-ISDN		.046
	2 year Survival	log-rank	placebo vs. H-ISDN		.053
	2 year Survival	Cox Regression ²	placebo vs. H-ISDN	34% (95% C.I.: 4 - 54)	.028
	3 year Survival	log-rank	placebo vs. H-ISDN		.36
	3 year Survival	?	placebo vs. H-ISDN	36% (95% C.I.: 11 - 54)	
Circulation 1987;75(suppl. IV):IV49 - IV54	Overall Survival	Cox Regression ³	placebo vs. H-ISDN	28% (95% C.I.: 3 - 46)	

¹ No adjustment for interim analysis and multiple major endpoints

² Adjusted for baseline variables: ejection fraction, cardiothoracic ratio, history of CAD, presence of diabetes, heart rate, peak oxygen consumption during maximum exercise and previous use of anti-arrhythmics, anti-coagulants or vasodilators

³ Adjusted for baseline variables: ejection fraction, cardiothoracic ratio, peak oxygen consumption during maximum exercise and previous use of anti-arrhythmics.

Figure R.1. plots the cumulative mortality (life table) for the three treatment groups.

Figure R.1. Cumulative Mortality from Randomization (NEJM 1986;314:1547 - 1552)

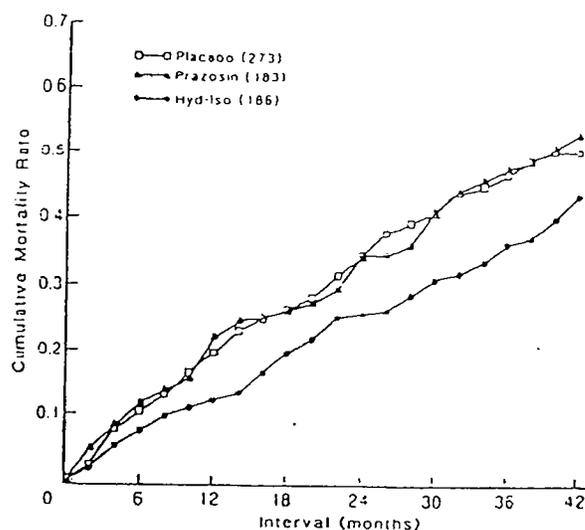


Figure 1. Cumulative Mortality from the Time of Randomization in the Three Treatment Groups.

Table R.7a lists the crude mortality rates for various subsets of patients. The study was underpowered to detect treatment differences within subgroups.

Table R.7a. Crude Mortality and 95% Confidence Intervals for Various Subsets (Sponsor's Analysis)

Baseline		H-ISDN		Placebo		Difference*	95% C.I.
		N	Rate (%)	N	Rate (%)		
CAD	yes	82	41.5	121	50.4	-8.9	-22.8 to 5.0
	no	104	36.5	152	38.8	-2.3	-14.4 to 9.8
Race	Black	49	30.6	79	44.3	-13.7	-30.6 to 3.2
	non-black	136	41.9	194	43.8	-1.9	-12.7 to 8.9
Baseline EF	> median	88	29.5	123	33.3	-3.8	-16.5 to 8.9
	< median	88	48.9	131	51.9	-3.0	-16.5 to 10.5
Baseline Max O ₂	> median	93	33.3	139	32.4	-1.0	-11.3 to 13.3
	< median	92	44.6	133	55.6	-11.1	-24.3 to 2.1

* H-ISDN minus placebo

On behalf of the sponsor, Dr. Lloyd Fisher, Ph.D. performed a Cox Regression analysis of the survival data (placebo vs. H-ISDN). Covariates used in the analysis were suggested by Dr. Milton Packer, MD,¹² with concurrence from the Division of Cardio-Renal Drug Products. Dr. Fisher's analysis yielded a p value from the Cox proportional hazards model Wald statistic. Patients were re-randomized using the pseudorandom numbers generated by the S-plus for Windows software. These assignments were then used to obtain coefficients from the Cox model using the BMDP software system. This re-randomization was

¹² It was pointed out in an FDA statistical review of the V-HeFT I trial dated February 21, 1990 that the Cox model used in the NEJM article might have a lack of fit in the sense that the baseline covariates used appeared to violate the proportional hazards assumption or linearity assumption, based on graphical examination. In the meeting of February 12, 1991 between Dr. Jay Cohn and Wyeth-Ayerst and the Agency, it was proposed that Dr. Milton Packer (Cardio-Renal Advisory Committee member at the time) could pick up to 10 covariates that could be used in the statistical re-analysis. In a letter dated March 10, 1992 to Dr. Cohn, Dr. Packer selected cause of heart failure, left ventricular ejection fraction and maximal oxygen consumption that were measured in V-HeFT I. In an FDA meeting of November 20, 1992 with the sponsor (Medco Research), Dr. Lloyd Fisher proposed using randomization distribution for inference with Cox proportional hazards model.

performed 10,000 times (Monte Carlo Method). The p-values were obtained as the number of the 10,001 test (10,000 re-randomizations and 1 actual trial result) statistics that exceeded or equaled the observed value of the test statistic for the trial.

The baseline covariates recommended by Dr. Packer included left ventricular ejection fraction, maximum oxygen consumption and etiology of congestive heart failure¹³. As there are some missing values for each of these variables in some patients, two analysis were performed by Dr. Fisher. One analysis included only patients with all variables identified and another that included all patients by imputing values for missing data. Table R.8 lists the results from Dr. Fisher's analysis.

Table R8. Dr. Fisher's Analysis Overall Survival (volume 1.21, p. 40)

	Instantaneous Relative Risk	95% Confidence Interval of Relative Risk		P-value
		Lower Limit	Upper Limit	
Cox Proportional Hazards Model				
Analysis of Patients with All Baseline Variables (N=404) ¹	.63	.46	.87	.0053
Analysis of All Patients (N=459)	.73	.54	.98	.035
Monte Carlo Randomization				
Analysis of Patients with All Baseline Variables (N=404) ¹				.0053
Analysis of All Patients (N=459)				.0323

¹ Patients with Missing Baseline values for ejection fraction or maximum oxygen consumption at peak exercise or etiology are not included. This analysis excludes all data on 55 patients.

Fifty-five patients, 35 placebo and 20 H-ISDN, were missing at least one value of the covariates used in the Cox regression. Table R.9 lists the number of patients in each treatment group that had missing covariate values.

Table R.9. Number of patients having missing covariate values

Covariate	Placebo (N= 273)		H-ISDN (N= 186)	
	Dead	Alive	Dead	Alive
Ejection Fraction	12	9	3	7
Max. O2 Consumption	4	10	8	2
CAD	0	0	0	0
Valvular Disease	0	2	0	0
Hypertension	0	0	0	0
Alcohol	0	0	0	0
Other	0	1	0	0
Total	14	21	11	9

The H-ISDN group had 11 (5.9%=11/186) patients who died and had missing values on the selected covariates. The placebo group had 14 (5.1%=14/273). A covariate analysis that excludes patients who have missing values is subject to bias. The bias tends to favor H-ISDN as shown in table R.10. More deaths are excluded from the H-ISDN group compared to the placebo group.

Table R.10. Mortality Rate Before And After Deletion Of Patients With No Covariate Value

	All Patient	Patients with Selected Covariates
Placebo	120/273 (44.0%)	106/238 (44.5%)
H-ISDN	72/186 (38.7%)	61/166 (36.7%)
% Difference	5.3%	7.8%
% Ratio [H-ISDN/Placebo]	.88	.82

¹³ Etiology of heart Failure variable included yes or no answers for hypertension, excessive alcohol use, coronary artery disease, valvular heart disease and an other category.

The exclusion of 12% of the patient data does not increase the accuracy of the prediction of the treatment effect in the Cox Regression but does raise questions regarding bias. For this reason, the FDA does not endorse an analysis that excluded patients with missing covariate values.

The FDA analysis of the survival data attempted to answer two questions. First, what effect did the imputation of values for missing baseline covariate variables have on the p values using the Cox model? Second, what effect did performing the Logrank first, finding it not significant and then performing the Cox analysis have on the p value?

In response to the first question, missing values were imputed by three different methods to give a range of p-values and to assess the impact of imputation on statistical significance. The strategies included: 1) imputing the mean value of those patients with non-missing baseline covariate data for those missing values; 2) imputing the maximum value of those patients with non-missing baseline covariate values for death and the minimum value for those who survived; and 3) imputing the minimum value of those patients with non-missing baseline covariate values for death and the maximum value for those who survived. Only three patients had missing values for Etiology of Heart Failure. In all three strategies, patients with missing Etiology of Heart Failure values were assumed to not have the disease. The first strategy is similar to that performed by the sponsor¹⁴. If one believes that ejection fraction and maximum O₂ consumption are positively correlated with the survival, then strategy #2 gives the worst case scenario while strategy #3 gives the best scenario.

Table R.11 lists the results of the FDA analysis utilizing the three strategies (the simulation is explained in detail in the appendix pages 15 - 16). Since the Logrank does not involve covariates, the Logrank result is unchanged. The Logrank test yields a two sided p value of .093 for overall survival and .056 for 2 year survival. The p-value of any test related to Cox regression was estimated on the basis of randomization (or permutation) distribution of the test. This is the same procedure utilized by Dr. Fisher. Each simulation run consists of 10,000 replications. Each replication involved treatment re-assignment for all patients which is the basis for generating a randomization distribution.¹⁵ The p-values were obtained as the number of the 10,001 test (10,000 re-randomizations and 1 actual trial result) statistics that exceeded or equaled the observed value of the test statistic for the trial. The Cox regression analysis yields two sided unadjusted¹⁶ p values that range from .019 to .11 for overall survival and .022 to .063 for 2 year survival depending on the values imputed for the missing covariates. The results of Cox regression analysis using the sample mean to impute ejection fraction and max O₂ consumption are similar to the results of Dr. Fisher's analysis.

The second question attempts to address the fact that the Logrank was the protocol specified primary analysis and was not significant for 2 year or overall survival. A significant Logrank test for 2 year or overall survival would not have prompted extensive subsequent analysis to detect a statistically significant treatment effect. As a consequence, the test criterion is equivalent to the larger of the Logrank and Cox test. A simulation similar to that performed for the Cox analysis was performed. In this simulation, each replication calculated a test statistic of the Logrank and Cox analysis on the re-randomized patients. The larger test statistic of the Logrank and the Cox analysis for each replication was included in the simulation distribution. From this distribution, the p value was determined by counting the number of replications with a test statistic greater than or equal to the Cox test statistic¹⁷ from the actual V-HeFT I data. This type of analysis yielded unadjusted p values that were slightly greater than the p values obtained for the Cox analysis alone. The p values ranged from .027 to .11 for overall survival and .029 to .065 for 2 year survival. The results of this analysis are listed in table R.11 under Logrank/Cox.

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¹⁴ Submission correspondence date 12/13/96: the average value of all non-missing baseline data was used as an estimate for missing values of ejection fraction and maximum oxygen consumption

¹⁵ Only one random number seed is used throughout.

¹⁶ not adjusted for interim analysis and multiple major endpoints

¹⁷ The observed value of the Cox test is larger than the observed value of the Logrank in this trial.

Table R.11. Two-sided unadjusted p value ^A Calculated for Overall survival and 2-year survival [FDA Analysis Based on Simulation Using 10,000 Replications]

Imputation strategy for missing baseline EF and max O ₂ ^B	Overall Survival			2-year Survival		
	Logrank	Cox	Logrank/Cox ^C	Logrank	Cox	Logrank/Cox ^C
max for death min for survivor ^D	.093	.11	.11	.056	.063	.065
mean for death and survivor ^E	.093	.038 ^E	.051	.056	.033 ^E	.04
min for death max for survivor ^F	.093	.019	.027	.056	.022	.029

^A not adjusted for interim analysis or multiple major endpoints

^B For the etiology of heart failure covariates, it was assumed that a missing answer was a no answer.

^C Logrank/Cox: Using maximum test statistic of Logrank or Cox Regression for each replication in the simulation distribution

^D Worst case: high EF and max O₂ associated with decreased survival

^E Analysis similar to that performed by Dr. Fisher

^F Best case: high EF and max O₂ associated with increased survival

Table R.11a lists the one-sided p values utilizing the same strategy used to calculate the two-sided p values.

Table R.11a. One-sided unadjusted p value ^A Calculated for Overall survival and 2-year survival [FDA Analysis Based on Simulation Using 10,000 Replications]

Imputation strategy for missing baseline EF and max O ₂ ^B	Overall Survival			2-year Survival		
	Logrank	Cox	Logrank/Cox ^C	Logrank	Cox	Logrank/Cox ^C
max for death min for survivor ^D	.047	.054	.053	.033	.029	.030
mean for death and survivor ^E	.047	.016 ^E	.023	.033	.013 ^E	.017
min for death max for survivor ^F	.047	.007	.011	.033	.010	.013

^A not adjusted for interim analysis or multiple major endpoints

^B For the etiology of heart failure covariates, it was assumed that a missing answer was a no answer.

^C Logrank/Cox: Using maximum test statistic of Logrank or Cox Regression for each replication in the simulation distribution

^D Worst case: high EF and max O₂ associated with decreased survival

^E Analysis similar to that performed by Dr. Fisher

^F Best case: high EF and max O₂ associated with increased survival

The p values determined from the simulations are not adjusted for the four interim analysis and the multiple major endpoints. If the O'Brien-Fleming stopping rule was used with four interim analyses and the overall survival is the only major efficacy endpoint, the unadjusted two sided p-value for an overall survival endpoint needs to be smaller than 0.042 to be considered significant. If the only major efficacy endpoints are the 2-year survival and the overall survival, then the unadjusted two sided p-value for the overall or 2-year survival needs to be smaller than some level between 0.021 and 0.042 to be statistically significant. The analysis that incorporates the results of the Logrank and Cox analysis test statistics probably provides the best estimate of a p value as it reflects what has actually transpired with regard to the choice of the appropriate analysis (i.e. the Logrank was not significant so the Cox Regression is performed to detect a statistically significant treatment effect). The p values (table R.11 Logrank/Cox analysis) from the Logrank/Cox analysis ranged from .027 to .11 for overall survival and from .029 to .065 for 2 year survival depending on which imputation strategy is used. If the mean value of the baseline variable is imputed for missing values (this is the approach taken by the sponsor), the p values are .051 for overall survival and .04 for 2-year survival. The p values are close but do not achieve statistical significance.

If the only major efficacy endpoints are the 2-year survival and the overall survival, then the unadjusted one sided p-value for the overall or 2-year survival needs to be smaller than some level between 0.01 and 0.021 to be statistically significant. The analysis that incorporates the results of the Logrank and Cox analysis test statistics yield p values of .023 and .017 for all cause and 2-year survival respectively.

Based on all the data summaries and reports presented to the VHeFT Operations Committee (Data Monitoring Board), the survival endpoint was tested in Sept.-81, Aug.-82, Feb.-83, May-83, Sept.-83, Dec-83, Aug.-84, May-85 and Sept.-85 (see the table on page 007, NDA amendment BZ, submitted 01/13/97, received 01/15/97 by CDER)¹⁸. From the reports, there appeared to be only four formal interim analyses plus the final analysis for survival. The reports also indicated that prazosin was also compared with placebo for survival in all the formal or informal analyses. Thus, had the prazosin group been distinguishable from the placebo group with respect to survival, the study would have reported it as a significant finding. Thus, in our view, statistical significance on the findings need be assessed under the condition that the overall type I error rate involved in the comparisons of the three treatment groups does not exceed the nominal level of significance (usually set at 5%).

Major Endpoints - Maximum Oxygen Consumption at Peak Exercise and Exercise Time

Maximum oxygen consumption during the peak exercise, maximum treadmill exercise time on graded test and duration of exercise on submaximal tests are major endpoints. Maximal¹⁹ and submaximal²⁰ exercise testing was performed at baseline (visits 1, 2 and 3), at week 8 and then at 6 month intervals for the remainder of the trial. If a scheduled exercise test was not performed, the reason for not performing the test should have been included on a CRF (Form I) for that visit. Reasons for not performing a test on the CRF included limiting symptoms due to CHF, limiting symptoms due to angina and other.

Two types of analysis for the maximum oxygen consumption are specified in the protocol, a repeated measures analysis and, at each interval, the difference between treatments analyzed by the F test. There are no analysis specified for the exercise duration endpoints but it is not unreasonable to analyze them in a manner similar to peak oxygen consumption.

Table R.12 lists the mean change in maximum O₂ consumption over time. Five percent of the patients in each treatment group did not have a baseline maximum O₂ consumption. Although the mean change from baseline is numerically greater at all visits in the H-ISDN treatment group, none of the treatment differences are significantly different (F test). These results deviate slightly from the results reported in Circulation 1993;87 (suppl. VI):VI56 - VI64. In figure R.2 (figure 1 from Circulation 1993;87 (suppl. VI):VI56 - VI64), the change in peak oxygen consumption over time is plotted. In the published analysis, there is a significant difference between treatment groups at week 52 (p = .04). Note, there is a slight difference in the number of patients at each visit for the two analysis.

Table R.12. Mean Change In Maximum O₂ Consumption At Each Visit.
(vol. 1.19, p. 61; vol. 1.21, p. 46; Sponsor's Analysis)

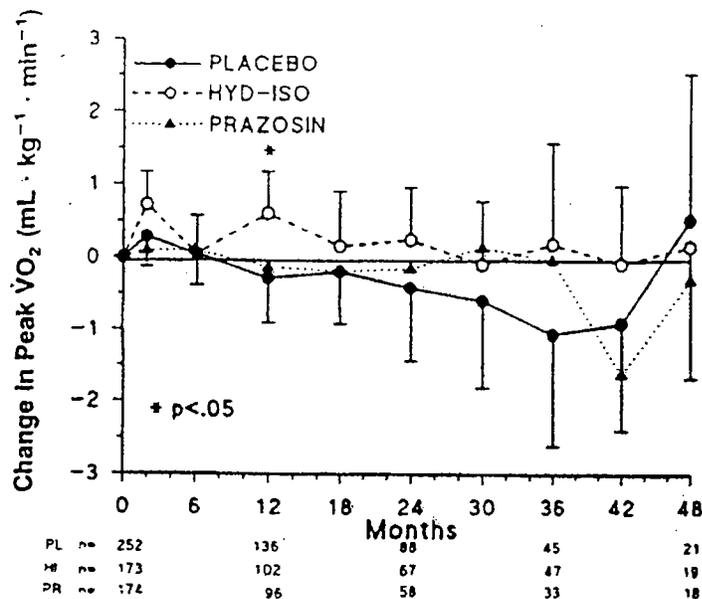
	Placebo			H-ISDN			t-test p values
	N	Mean (SD) ml/kg/min	Mean Change from Baseline	N	Mean (SD) ml/kg/min	Mean Change from Baseline	
Baseline	259	14.94 (3.85)		176	14.69 (3.93)		
Week 8	221	15.35 (4.38)	.183 (2.96)	151	15.46 (4.32)	.662 (2.81)	.125
Week 28	193	15.37 (4.00)	.099 (2.89)	136	15.33 (4.83)	.371 (3.81)	.4717
Week 52	155	15.02 (4.63)	-.181 (3.72)	113	15.41 (4.08)	.649 (2.98)	.056
Week 78	111	15.08 (4.19)	-.229 (3.27)	95	15.34 (4.42)	.252 (3.83)	.341
Week 104	99	15.32 (4.27)	-.352 (3.51)	73	15.34 (3.35)	.228 (3.11)	.27

¹⁸ The Logrank test was used to compare the treatment groups throughout the study except for the first two analyses which used the Wilcoxon test.

¹⁹ Maximum exercise was performed on an upright exercise bicycle with expired air collected and analyzed for volume, oxygen and carbon dioxide. Patients began pedaling at 50 - 60 rpm at an initial work rate of 25 W. The work rate was increased progressively every 4 minutes by 25 W. Patients were instructed to exercise maximally to exhaustion. Peak oxygen consumption was calculated from the final 60 seconds of exercise.

²⁰ Submaximal exercise was performed 1 - 4 hours after maximal exercise. The submaximal work rate was constant and was arbitrarily chosen as 25 W below the highest work rate achieved in the maximal exercise test at baseline. Patients pedaled at 50 - 60 rpm until exhaustion or for a maximum of 20 minutes.

Figure R.2. Change in peak oxygen consumption from baseline. [figure 1 from Circulation 1993;87 (suppl. VI):VI56 - VI64]



The FDA analysis reproduced the results of the sponsor's analysis. Multivariate repeated measures analyses with various models suggest a trend toward possible improved maximum O₂ consumption in the H-ISDN group (unadjusted p-value ranging from 0.05 to 0.12).

There was no significant difference between treatment groups in the mean exercise duration with maximal exercise testing. At each visit, the mean change in maximal exercise testing was greater in the H-ISDN treatment group compared to placebo. Table R.13 lists the mean changes in maximal exercise testing at each visit. Multivariate repeated measures analyses with various models suggest a trend toward possible improved exercise duration in the H-ISDN group compared with the placebo group (unadjusted p-value ranging from 0.073 to 0.089). An analysis that imputed zero for patients with missing exercise duration values²¹ because of worsening heart failure do not yield a significant p-value (unadjusted p-value = 0.14).

Table R.13. Mean Change In Maximum Exercise Test Duration At Each Visit. (vol. 1.21, p. 47; Sponsor's Analysis)

	Placebo			H-ISDN			Diff. (Sec)	Test p values
	N	Mean (SD) (min)	Mean Change from Baseline	N	Mean (SD) (min)	Mean Change from Baseline		
Baseline	273	9.83 (4.07)		186	9.71 (4.33)			
Week 8	232	10.0 (4.25)	-.004 (2.08)	157	10.4 (4.51)	.382 (2.14)	22.8	.077
Week 28	198	9.95 (4.46)	-.206 (2.67)	141	10.1 (4.44)	.065 (2.85)	16.2	.37
Week 52	163	9.84 (4.66)	-.287 (2.95)	117	10.4 (4.54)	.308 (2.75)	36	.089
Week 78	114	9.83 (4.40)	-.476 (2.9)	97	9.94 (4.56)	-.128 (3.26)	21	.41
Week 104	100	10.1 (4.56)	-.714 (3.62)	77	10.1 (4.26)	.011 (3.12)	43.4	.16

* [(H-ISDN mean change from baseline) - (placebo mean change from baseline)]

Any conclusions to be drawn from the submaximal exercise duration data is limited because only 60% or less of the patients in each treatment group had baseline values and less than 50% had post-randomization testing. Table R.14 lists the mean change in submaximal exercise duration at each visit.

²¹ they were unable to perform the test

Table R.14. Mean Change (minutes) in Submaximal Exercise Duration from Baseline [Table 3 in Circulation 1993;87 (suppl. VI):VI56 - VI64]

	Placebo (N = 273)		H-ISDN (N = 186)	
	N	Mean Change from Baseline (SD)	N	Mean Change from Baseline (SD)
Baseline Mean	162	9.63 (4.32)	100	9.31 (4.16)
8 weeks	131	1.50 (5.17)	74	1.66 (5.14)
26 weeks	113	1.32 (6.09)	71	1.08 (5.67)
1 year	90	.50 (6.68)	56	2.78 (5.34)
1.5 years	59	.35 (6.95)	42	1.13 (6.38)
2 years	46	-.021 (7.24)	31	3.11 (7.7)

Major Endpoints - Number and Duration of Hospitalizations for Cardiac Causes

The clinic visit case report form collected information on the type and duration of hospital admissions. The hospitalizations were classified as either for CHF, other cardiac cause or as other. In some instances, investigators listed more than one reason for the same hospital admission in an individual patient. The number of hospitalizations may be underestimated because the final clinical form available for most of the survivors was completed prior to the trial end date. Mortality information was the only information on the computerized list completed by each center at the trial end date.

The number and duration of hospitalizations for cardiovascular causes was one of the pre-specified major endpoints. Table R.15 lists the number of patients hospitalized for CHF subdivided by the reasons hospitalized. There was no significant difference between treatments in the total number of patients hospitalized ($p = .56$; Chi Square) and in the number hospitalized for any cardiac cause ($p = .68$; Chi-Square).

Table R.15. Hospitalizations

	Hydralazine/ ISDN	Placebo	Prazosin
# randomized	186	273	183
# patients hospitalized at least once (as a percent of # randomized)	127 (68.3%)	199 (72.9%)	137 (74.9%)
total # hospitalizations (any cause)	333	506	433
# hospitalizations / # randomized	1.79	1.85	2.36
# hospitalizations for heart failure ^A	137	194	178
# patients hospitalized at least once for CHF (as a percent of # randomized)	77 (41.4%)	115 (42.1%)	86 (47.0%)
# hospitalizations for heart failure / # patients hospitalized at least once for CHF	1.78	1.69	2.06
duration of hospitalization for CHF (median)	8	9	10
duration of hospitalization for CHF (mean)	8.96 (\pm 6.35)	12.8 (\pm 13.8)	12.8 (\pm 14.2)
# hospitalizations for other cardiac cause ^A	67	129	103
# patients hospitalized at least once for other cardiac cause (as a percent of # randomized)	44 (23.7%)	87 (31.9%)	58 (31.7%)
# hospitalizations for CHF or other cardiac cause ^{A,*}	190	310	262
# patients hospitalized at least once for CHF or other cardiac cause (as a percent of # randomized)	98 (52.7%)	155 (56.8%)	105 (57.4%)
# hospitalizations / # randomized	1.02	1.14	1.43
# hospitalizations for other cause ^A	163	220	197
# patients hospitalized at least once for other cause (as a percent of # randomized)	85 (46%)	113 (41.4%)	95 (51.9%)

^A Each hospital admission may have more than one reason for hospitalization. Thus, the sum of the hospitalization for CHF, cardiac cause and other cause will be greater than the total # of hospitalizations.

* Major Endpoint

There was no significant difference in the number of hospitalizations for cardiac causes and the duration of hospitalization (sponsor's analysis). Analysis of time to first hospitalization, time to first hospitalization for CHF and duration of hospitalization is listed in the appendix (appendix pages 13 - 14).

Minor Endpoint - Ejection Fraction

The mean changes in ejection fraction from baseline are listed in table R.16. The results of the sponsor's univariate and multivariate analyses were confirmed by the reviewers. There was a trend toward improvement of ejection fraction with H-ISDN compared to placebo (unadjusted p-values from GEE analyses with various models are less than 0.0006). The H-ISDN group consistently had a 2% to 4% greater improvement in ejection fraction than the placebo group in the first 2 years of treatment (unadjusted p-value < 0.03 at every visit).

Table R.16. Mean Change in Ejection Fraction [EF] From Baseline (%) [volume 1.21, p. 42]

	Placebo		H-ISDN		t-test*
	N	Mean EF	N	Mean EF	
Baseline	252	.30 (.14)	176	.30 (.13)	
		Mean Change in EF		Mean Change in EF	
8 weeks	230	.004 (.062)	143	.029 (.073)	.0004
28 weeks	199	.001 (.074)	141	.037 (.092)	.0001
1 year	166	.003 (.092)	124	.046 (.10)	.0002
1.5 years	128	-.013 (.087)	101	.020 (.10)	.0093
2 years	107	-.012 (.085)	85	.020 (.10)	.0261
2.5 years	89	-.016 (.097)	75	.008 (.10)	.1277

* treatment difference in change from baseline

Minor Endpoint - Quality of Life

Quality of Life was assessed by noting on the CRF whether there was a change in the ability to perform activities compared to baseline at 8 weeks and every 6 months after randomization as assessed by the physician and the patient. There was a categorical scale of 1 to 5 with 1 equal to marked improvement and 5 equal to marked decrease. Table R.17 lists the physician's responses for each visit. There were no significant differences between treatments

Table R.17. Quality of Life - Physician Response

Week	N	Treatment	Scale					P value*
			1	2	3	4	5	
8	235	Placebo	8.5%	28.9%	54.9%	5.1%	1.3%	.43
	158	H-ISDN	5.1%	34.8%	56.3%	3.2%	0.6%	
28	207	Placebo	7.7%	27.1%	57.0%	6.8%	0.5%	.76
	153	H-ISDN	6.5%	32.0%	53.6%	6.5%	0.0%	
52	166	Placebo	9.6%	28.9%	50.0%	9.0%	1.2%	.27
	129	H-ISDN	8.5%	40.3%	39.5%	8.5%	2.3%	
78	140	Placebo	10.0%	30.7%	42.9%	12.9%	2.9%	.6
	107	H-ISDN	8.4%	29.9%	50.5%	7.5%	3.7%	
104	114	Placebo	7.0%	29.8%	48.2%	13.2%	1.8%	.95
	92	H-ISDN	5.4%	28.3%	48.9%	13.0%	3.3%	
130	94	Placebo	10.6%	25.5%	44.7%	16.0%	2.1%	.28
	81	H-ISDN	3.7%	35.8%	40.7%	13.6%	3.7%	

^A Scale: 1 = Markedly Improved, 2 = Moderately Improved, 3 = Unchanged, 4 = Moderately Decreased, 5 = Markedly Decreased.; * Chi-Square

Note: The total for each visit does not equal 100%. Some patients had missing data or were coded 6 or 999.

Table R.18 lists the patient's responses for each visit.

Table R.18. Quality of Life - Patient's Response

Week	N	Treatment	Scale ^A					P value *
			1	2	3	4	5	
8	235	Placebo	12.8%	35.3%	44.7%	6.4%	0.9%	0.54
	158	H-ISDN	10.1%	35.4%	50.0%	3.2%	0.6%	
28	207	Placebo	16.4%	31.9%	42.5%	8.7%	0.5%	0.75
	153	H-ISDN	15.7%	34.6%	43.8%	5.9%	0.0%	
52	166	Placebo	19.3%	31.3%	40.4%	6.6%	1.8%	0.32
	129	H-ISDN	15.5%	41.9%	31.8%	8.5%	1.6%	
78	140	Placebo	16.4%	32.9%	34.3%	14.3%	2.1%	0.24
	107	H-ISDN	12.1%	31.8%	44.9%	7.5%	3.7%	
104	114	Placebo	14.0%	31.6%	39.5%	13.2%	1.8%	0.72
	92	H-ISDN	14.1%	25.0%	40.2%	15.2%	4.3%	
130	94	Placebo	20.2%	27.7%	31.9%	14.9%	4.3%	0.59
	81	H-ISDN	12.3%	29.6%	39.5%	16.0%	2.5%	

^A Scale: 1 = Markedly Improved, 2 = Moderately Improved, 3 = Unchanged, 4 = Moderately Decreased, 5 = Markedly Decreased. ; * Chi-Square

Note: The total for each visit does not equal 100%. Some patients had missing data or were coded 6 or 999.

Change in Blood Pressure

There was no significant difference in the change in systolic blood pressure from baseline between placebo and H-ISDN. Surprisingly, the change in diastolic blood pressure did not differ between treatments when analyzed at each visit. A multivariate analysis was significantly different ($p = .0056$). Table R.19 lists the mean change in systolic and diastolic blood pressure at each visit.

Table R.19. Mean Change in Systolic and Diastolic Blood Pressure (mm Hg) [volume 1.21, p. 50]

	Placebo			H-ISDN		
	N	Diastolic BP (mm Hg)	Systolic BP (mm Hg)	N	Diastolic BP (mm Hg)	Systolic BP (mm Hg)
8 weeks	253	.488 (10.1)	-.044 (15.2)	170	-1.52 (10.5)	.559 (17.2)
28 weeks	221	-.742 (11.0)	.181 (16.5)	161	-1.93 (10.0)	-.820 (15.5)
1 year	180	-.383 (11.5)	.96 (19.1)	136	-.89 (11.2)	1.0 (16.9)
1.5 years	146	.116 (11.0)	-.014 (17.6)	114	-1.13 (10.5)	1.53 (15.5)
2 years	122	.156 (12.7)	.73 (18.3)	95	-2.11 (10.8)	.547 (19.4)
2.5 years	100	-.30 (13.4)	2.42 (19.0)	81	-3.32 (11.9)	-.877 (17.0)

Safety

Adverse Events

The case report form (form F) included questions regarding the occurrence of specific adverse events. A listing of the specific adverse events are included in tables S.1 through S.4. The number of patients with at least one adverse event was 87% and 95% in the placebo and H-ISDN groups respectively. The tables include the overall incidence of adverse events (table S.1), adverse events resulting in dose reduction (table S.2), adverse events based on causality assessment (table S.3) and adverse event incidence based on severity (table S.4). For most of the individual adverse events, there is a higher incidence, a higher percent requiring dose reduction, a higher incidence listed as probable and a higher incidence of severe adverse events in the H-ISDN group compared to the placebo group.

Table S.1. Adverse Event * Incidence (%)

Adverse Event	Percent of Patient with Adverse Event	
	Placebo N = 273	HEISDN N = 186
Any Adverse Event	87.2	94.6
Headache	50.9	74.7
Dizziness	59.7	70.4
Arthralgias	57.9	63.4
Other	49.5	61.3
Palpitation	44.0	55.9
Nausea Or Vomiting	45.1	52.2
Ischemic Chest Pain	41.4	48.9
Diarrhea	38.8	46.8
Abdominal Pain	34.8	45.2
Flushing	30.4	43.6
Rash	38.1	43.0
Fever	26.4	33.3
Syncope	23.8	26.3

* Includes adverse events listed in the case report form (form F). Patients with multiple events of the same symptom are only counted once.

Table S.2. Incidence of Adverse Events Resulting In Dose Reduction

Adverse Event	Percent of Patients with Adverse Event That Resulted in Dose Reduction	
	Placebo N = 273	HEISDN N = 186
Any Adverse Event	22.0	51.6
Headache	5.5	40.3
Dizziness	12.1	25.8
Arthralgias	2.2	4.8
Other	6.6	11.3
Palpitation	2.6	10.8
Nausea Or Vomiting	5.5	11.3
Ischemic Chest Pain	2.6	3.8
Diarrhea	1.5	4.3
Abdominal Pain	2.9	7.0
Flushing	1.1	8.6
Rash	1.5	4.3
Fever	0	3.8
Syncope	4.4	2.2

Table S.3. Incidence of Adverse Events Based on Causality Assessment by the Investigator

Adverse Event	Placebo N = 273			H-ISDN N = 186		
	Not Related	Possibly	Probably	Not Related	Possibly	Probably
Any Adverse Event	32.6	39.6	15.0	15.6	33.3	45.2
Headache	28.2	16.1	6.2	12.3	26.9	35.0
Dizziness	24.9	27.1	7.7	25.3	22.0	22.0
Arthralgias	44.7	11.7	.7	48.4	11.8	3.2
Other	35.9	10.6	1.1	39.8	15.1	3.2
Palpitation	32.2	10.6	.4	31.7	18.3	5.4
Nausea Or Vomiting	29.3	13.1	1.8	31.7	12.4	8.1
Ischemic Chest Pain	31.9	8.1	1.1	40.9	7.0	.5
Diarrhea	32.6	4.8	1.1	35.0	11.3	.5
Abdominal Pain	25.3	8.4	.7	33.3	8.01	2.2
Flushing	19.8	8.4	2.2	24.2	12.4	7.0
Rash	32.2	4.4	1.1	35.5	5.4	1.6
Fever	25.6	.7	0	30.1	2.2	1.1
Syncope	19.4	4.0	.4	19.4	4.3	1.1

Table S.4. Incidence of Adverse Events Based on Severity

Adverse Event	Placebo N = 273			H-ISDN N = 186		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Any Adverse Event	41.8	24.2	20.5	26.9	25.8	41.4
Headache	33.0	11.8	3.3	27.4	16.7	27.4
Dizziness	39.6	11.0	7.3	35.0	17.7	12.9
Arthralgias	37.0	14.3	3.3	37.6	15.1	5.4
Other	34.4	5.1	5.9	43.6	8.1	6.5
Palpitation	34.1	6.7	1.1	34.4	11.3	4.3
Nausea Or Vomiting	27.5	10.3	2.6	25.8	14.0	5.4
Ischemic Chest Pain	27.5	6.6	4.0	33.3	7.0	2.2
Diarrhea	23.8	5.1	3.3	26.3	8.1	4.3
Abdominal Pain	22.3	5.9	2.9	26.9	5.9	4.3
Flushing	19.4	4.8	.4	28.5	4.8	2.2
Rash	25.3	4.8	1.1	23.1	8.1	1.6
Fever	16.5	1.5	.4	17.2	4.3	1.6
Syncope	10.6	1.1	3.7	10.8	1.1	1.6

Table S.5 lists the number of patients in each treatment group with adverse event information at each visit. The percentage of these patients who experienced headache at each visit is plotted in figure S.1. After the initial increase in the incidence of headache at the early visits in the H-ISDN patients, the percentage of patients with headaches in the H-ISDN treatment group was similar to the placebo treatment group.

Table S.5. Number of Patients with Adverse Event Form Completed at Each Visit

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
# placebo patients	270	264	262	257	243	228	210	190	171	153	143	123	114	101	85	80	64
# H-ISDN patients	186	181	177	173	168	163	148	138	133	116	105	98	89	83	76	69	58

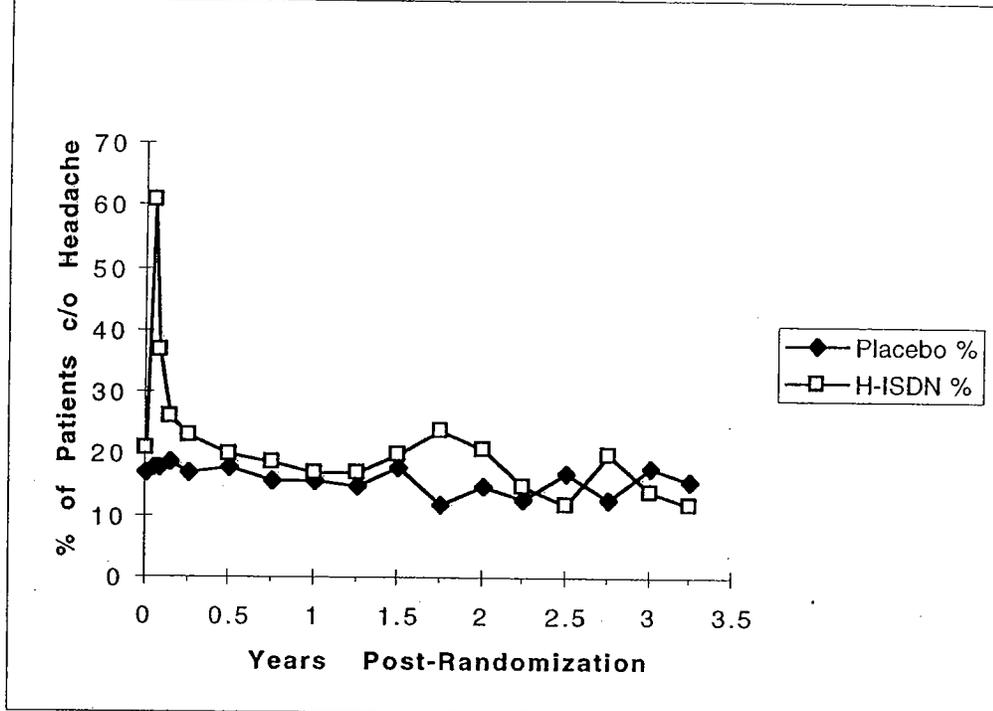
Figure S.1. Incidence of Headache by Time Post-Randomization*Discontinuations Due to Adverse Events*

Table S.5 lists the patients discontinued permanently from both medications due to adverse events. This list is probably incomplete based on the discrepancy between the number of discontinuations in the sponsor's analysis and the FDA analysis (see tables R.3, R.3a and R.3b.).

Table S.5. Patients Discontinued From Both Treatments due to Adverse Events [vol. 1.25, Listing 23]

Center	Patient #	Treatment	Day	Adverse Event
1	2010	H-ISDN	545	headache, dizziness
3	1001	H-ISDN	683	dizziness or syncope, disorientation
3	2017	H-ISDN	30	headache, dizziness or syncope, disorientation
4	2002	H-ISDN	586	arthralgias
4	2008	H-ISDN	926	not specified
4	2029	H-ISDN	206	headache
4	4004	H-ISDN	1354	dizziness or syncope
7	1014	H-ISDN	24	headache, dizziness or syncope
7	3017	H-ISDN	484	not specified
7	4001	H-ISDN	315	headache, dizziness or syncope, nausea
7	4007	H-ISDN	13	headache, dizziness or syncope
7	1006	placebo	565	dizziness or syncope
7	1009	placebo	724	not specified
7	3012	placebo	23	dizziness or syncope
10	1007	placebo	1416	embolism

*. day discontinued

V-HeFT II

[Cohn JN, Johnson G, Ziesche S et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *NEJM* 1991;325(5):303-310.]

Protocol

The following description of the study plan is based on a review of the protocol submitted to IND 16,960 on 11/25/85 (attached to the study report as Appendix B NDA Vol. 1.29). This was compared to the description provided in the primary publication for V-HeFT II. The protocol was not amended, and all revisions were made prior to randomization of the first patient (see Appendix B of Sponsor's Study Report).

In the design of V-HeFT II, H-ISDN was used as the active control.

Objectives

The objectives of the study were:

- to compare the effects of H-ISDN and enalapril in heart failure patients.
- to explore the mechanism of heart failure and various factors affecting response to therapies and to measure physiological parameters or hemodynamic effects

Design

This is a multi-center, randomized, double blind, parallel active-controlled (no placebo) in patients with congestive heart failure. Eligible patients were randomized to either H-ISDN or enalapril. The duration of the study was projected to be 62 months with the minimal duration of treatment being six months. The study was to be performed at 13 VA hospital Centers. Patients treated with placebo or prazosin in V-HeFT I were eligible for enrollment in V-HeFT II²².

Inclusion Criteria

The patient selection criteria were almost identical to those of V-HeFT I. Male patients between the ages of 18 and 75 years were screened if "they have a history and physical findings compatible with left ventricular failure and are symptomatic in spite of traditional therapy with digitalis and diuretics". The diagnosis of heart failure would be based on "a history which includes limitation of exercise tolerance because of dyspnea and/or fatigue beginning at least 3 months prior to screening".

Within 30 days of screening, patients had further evaluation. To be eligible for randomization, one of the following criteria²³ were met:

- cardiothoracic ratio ≥ 0.55 on chest radiography;
- left ventricular internal diameter $>2.7 \text{ cm/M}^2$ at diastole on echocardiography;
- ejection fraction <0.45 by radionuclide method;
- Reduced exercise tolerance defined as (see study plan in Section V) baseline exercise test²⁴ terminated by dyspnea or fatigue at peak oxygen consumption of $<25 \text{ ml/kg/min}$, or in the absence of metabolic data, exercise duration <17 minutes.

During the 4-week baseline stabilization period (may be extended to 14 weeks), patients were required to be stable with regard to cardiovascular medications, reasons for stopping exercise tests (dyspnea or fatigue), body weights (variation within 3%), peak oxygen consumption ($\pm <4 \text{ ml/kg/min}$, average $<25 \text{ ml/kg/min}$) and exercise duration ($\pm <2 \text{ min}$, average $<17 \text{ min}$).

Exclusion Criteria

In addition to the more generic exclusion criteria²⁵, patients with the following cardiovascular conditions were excluded from V-HeFT II:

- Myocardial infarction or cardiac surgery within 3 months of screening.
- Hypertrophic cardiomyopathy with echocardiographic evidence.

²² According to the protocol, approximately 12 % of all planned enrollment would be patients who participated, but were not randomized to H-ISDN, in V-HeFT I.

²³ Patients who participated in V-HeFT I must have one of the above conditions at the last visit of the main study.

²⁴ Pre-treatment exercise tests were performed at least twice prior to randomization at Visit 3.

²⁵ hypersensitivity to study drugs, serious systemic disease [e.g. lupus, anemia, renal/hepatic impairment], reduced survival of non-cardiac reasons, non-compliance and participation in other trials

- Significant aortic/mitral stenosis/insufficiency (functioning prosthesis acceptable).
- Diastolic blood pressure ≥ 105 mmHg on diuretics or hypertension requiring non-diuretic therapy.
- Hemodynamically significant pericardial disease.
- Chronic bronchopulmonary disease which may be a limiting factor in exercise testing.
- Exercise test stopped by angina, or angina pectoris requiring long-acting nitrate or > 4 tabs of sublingual nitroglycerin.
- Dependent on chronic therapy with beta blockers or calcium channel blockers.
- Inability to perform bicycle exercise tests due to non-cardiac reasons.

Except for a less detailed protocol in the published report, there is no evidence that these admission criteria were changed during the trial.

Randomization

Randomization was stratified by hospitals and participation in V-HeFT I, with a 6-subject permuted block design. Randomization codes were assigned centrally.

Dosage/Administration

Hydralazine/Isosorbide dinitrate: Patients randomized to this group would start with a tablet containing 37.5 mg hydralazine and a 1/2 tablet containing 20 mg isosorbide dinitrate 4 times daily, plus an enalapril-matching placebo tablet twice a day.

Enalapril: Patients assigned to this regimen would take 5 mg enalapril twice a day plus one and a half placebo tablets 4 times daily to match the hydralazine/isosorbide.

If tolerated, the dosages in both groups would double at the 2 week follow-up and maintained thereafter, with provision for downward adjustment if attributable adverse effects occurred and restoration of full dose if again tolerated.

Withdrawal Criteria

Patients were withdrawn from the study if they developed:

- Lupus like syndrome
- absolute neutrophils $< 1,000/\text{mm}^3$
- creatinine > 3.0 mg% and 50% over baseline

In addition, study drug may be discontinued temporarily (or permanently), for patients who:

- developed progressive worsening of heart failure which may require acute treatment of vasodilators or inotropic agents;
- underwent cardiac (e.g., coronary bypass, valve replacement) or non-cardiac surgery;
- had new or unstable angina which required long-acting nitrate or discontinuation of hydralazine;
- developed acute myocardial infarction;
- had other acute medical illnesses.

Study Plan

Eligible patients at screening entered a Stabilization Period. During the Stabilization Period, patients were evaluated every 2 weeks on at least 3 occasions. The objective during this period was to achieve stable measurements of parameters relevant to the patient's heart failure status (i.e. body weights, background therapies, exercise testing with oxygen consumption). If the patients' status vary greater than that outlined in the protocol, this period could be extended by up to 5 additional biweekly visits in order to stabilize the patients prior to randomization. All previous vasodilator therapies were discontinued and dosages of digitalis and diuretics adjusted.

When stability was achieved, each patient was evaluated with pre-treatment studies as listed below in the Schedule and Methods of Assessment. Provided there were no significant changes in their status, patients were randomized and treatment with study drugs was initiated within 4 days. The dosage of therapy was adjusted as outlined previously.

After randomization, patients were followed at Week 2, 4, 13 and every 3 months thereafter for 5 years. In addition to laboratory tests (hematology, chemistry and urinalysis), exercise tolerance and quality of life was evaluated every 6 months and other pre-treatment studies repeated once a year.

All patients were followed until the end of the study, regardless of their dates of randomization.

Schedule and Methods of Assessment

Stabilization..... (Visits 1 & 2)	History and Physical examination. Adjustment of diuretics/digitalis. Exercise test, oxygen consumption every 2 weeks until stabilized (see entry criteria) or up to 12 weeks.
Pre-Treatment, Week 0..... (Visit 3)	Clinical assessment and blood tests Review and adjustment of medications Exercise tests, Quality of life Chest X-ray 12-lead ECG Echocardiograph Left ventricular ejection fraction by radionuclide Holter monitoring Plasma norepinephrine (other optional invasive/non-invasive tests, see Section VIII)
At Week 2, 4..... (Visits 4 & 5)	Clinical assessment and blood tests Review and adjustment of medications
At Week 13 (Visit 6) and..... at the end of every year	Clinical assessment and blood tests Review and adjustment of medications Exercise tests, Quality of life Chest X-ray Left ventricular ejection fraction by radionuclide Holter monitoring Plasma norepinephrine
At 6 months (Visit 7)..... and every 6 months	Clinical assessment and blood tests Review and adjustment of medications Exercise tests, Quality of life Echocardiograph (Visit 7 only)
At 9 months (Visit 8)..... and every 3 months	Clinical assessment Review and adjustment of medications

Details of exercise tests and other procedures were provided as Appendix to the study report and protocol. Questionnaires for assessing "quality of life" were included in the patient case report forms.

Definitions of Diagnoses

Except for a definition of coronary artery disease (see Section VII of the protocol), diagnoses of various cardiovascular conditions were not defined in detail in the protocol, but instead were made clinically by the investigators.

Definitions of Efficacy Endpoints

There were six major and four minor endpoints listed in the protocol. Table IIP.1 lists the major and minor endpoints.

Table IIP.1. Major and Minor Endpoints

Major Endpoints	Minor Endpoints
<ul style="list-style-type: none"> • Mortality during the entire study period. • Mortality in 2 years • Maximum oxygen consumption during peak exercise. • Oxygen consumption at the anaerobic threshold. • Frequency and duration of hospitalizations for cardiovascular causes. • Changes in quality of life. 	<ul style="list-style-type: none"> • Heart size by chest X-ray. • Ejection fraction by radionuclide studies. • Arrhythmias by Holter monitoring. • Plasma norepinephrine levels.

The protocol did not pay too much attention to the statistical aspects of specifying primary/secondary endpoints. These study outcomes were probably considered as "major" or "minor" according to their clinical significance by the investigators, not intended to be the "primary" or "secondary" endpoints for hypothesis testing.

Case Report Forms

The blank Case Report Forms, as provided in Appendix I of the protocol (Item 8, Pages 71-101), are, in general, adequately designed for collection of pertinent clinical data.

Sample Size Calculation

The study protocol proposed to randomize 952 patients (476 per group). Using an exponential model for survival, a sample size of 952 (835 new patients plus 117 from V-HeFT I) would have a power of 87% to detect a 30% difference in mortality between H-ISDN (annual mortality rate of 13% based on V-HeFT I) and enalapril (estimated annual mortality rate 9%), on a two-sided test at 0.05 level. For the strata of 835 new patients, the power would be 79%. (see Plan for Biostatistics and Research Data Processing, or BRDP, in CSPCC Supplement of the protocol.)

The investigators also estimated that for oxygen consumption, the sample size of 835 new patients would have a power of 99% to detect a 10% difference between H-ISDN and enalapril, with a two-sided significance at 0.01.

Plan of Data Analysis

The primary analysis was defined as a comparison of the survival curves of the two treatment groups, using Logrank statistic to test the difference. Subgroup analyses were proposed using the following baseline variables: presence of coronary artery disease, oxygen consumption at maximal exercise ($>$ or $<$ 12 ml/kg/ml), and prior use of vasodilators. The Cox life-table regression model would identify factors which are prognostically important and to obtain estimates of treatment effects adjusted for any imbalance in the distributions of these factors between the treatments. Analyses similar to those used in V-HeFT I were also planned for other endpoints (e.g. oxygen consumption, etc.)

The protocol proposed that sequential analyses using techniques of O'Brien and Fleming were to be performed to provide guidelines for early stopping based on the survival endpoint. Five interim analyses separated by equal numbers of events (deaths) were planned.

The protocol did not specify how patients who were withdrawn or those with missing data would be handled in efficacy analyses.

Organization and Monitoring of the Study

The study was not monitored by the sponsor (Medco), but instead was supported by VA's Cooperative Studies Program Coordinating Center (CSPCC) and managed by the V-HeFT Investigators through the following committees (membership lists on Appendix G of the protocol):

- Planning Committee
- Executive Committee
- Operations Committee (Data Monitoring Board)
- Coordinating Centers
- Human Right Committee

The Operations Committee would have access to outcome data, review interim analyses and make recommendation to the chief of CSPCC regarding continuation of the trial. The protocol stated that "frequent tabulation of mortality/morbidity data would be provided and presented at each Operations Committee meeting". Study investigators would not serve as members of the Operation Committee.

The Human Right Committee would meet once a year with the Operations Committee to ensure that the patients' rights and safety were properly protected. It is not clear how much premature exposure to study outcome the former group would have. If patient recruitment was far behind schedule at an individual center, participation of the medical center could be terminated (Item D, Section XXI of protocol).

Results

Analysis of the efficacy results of V-HeFT II for the major endpoints (i.e., overall and two year mortality, exercise tolerance, maximum oxygen consumption) and ejection fraction were performed using the original data set and are included in this review. Analyses performed by the sponsor and its consultant,

Dr. Fisher, are not presented in this review, but will be commented upon when appropriate. Other secondary variables were of minor importance for regulatory purposes and will be described only briefly, based on the information provided by the sponsor.

Patient Disposition

Recruitment for V-HeFT II started in March 1986. The V-HeFT II Study was completed in about five years, with the last patient randomized on 9/4/90 and the study stopped on 2/28/91. A total of 804 patients were randomized to enalapril (403 patients) or H-ISDN (401 patients). The numbers of patients enrolled in the 13 centers²⁶ ranged from 22 to 119, with almost equal distribution of treatment groups at each center (stratified by center, see above in protocol). A query of the final clinic visit form for each survivor was performed to determine the date of the final visit. All of the survivors except for patient # 6732004 (enalapril) had a clinic visit form completed after the study stop date (2/28/91). Table IIR.1. lists the patient disposition.

Table IIR.1. Patient Disposition (Text Table 8 of Study Report)

	Enalapril	H-ISDN
Randomized	403	401
Died*	132 (32.8%)	153 (38.2%)
Completed	233 (57.8%)	199 (49.6%)
Discontinued	38 (9.4%)	49 (12.2%)

* including those who completed or discontinued from the study

Compared with the enalapril group, fewer patients who were treated with H-ISDN completed the study and more died or discontinued (see Efficacy below). Of those 87 discontinued (from patient listing of Appendix E2), more H-ISDN patients refused to continue or withdrew for unspecified reasons. But for adverse events or treatment failure as reasons for drop-out, the two groups were similar.

Table IIR.2. Reasons Patients Permanently Discontinued Therapy Prematurely *

	Enalapril	H-ISDN
Refuse to take meds, other or unknown reasons ^A	11	20
Adverse events ^B	14	13
Treatment failure ^C	13	16

* Lists the primary reason patient discontinued based on analysis by the medical reviewer.

^A mutually exclusive from groups with adverse events or treatment failure.

^B including cardiac surgery, new/worsening angina, acute MI and non-cardiac surgery.

^C including vasodilators administration and worsening CHF.

Demographics and Baseline Characteristics

As summarized in Table IIR.3. (Text Table 9 of the Study Report), the two treatment groups were well-matched in their demographic and baseline characteristics. Because it was a VA study, patients were all male. The mean age of subjects was 61 years. Approximately 70% of the patients were white and 27% black. The H-ISDN treated patients had a slightly longer mean duration of heart failure (40 vs 31 months in enalapril group), but the severity of heart failure (mostly NYHA classes II-III, > 93%), underlying cardiovascular disorders (coronary artery disease, > 50%) and risk factors were similar.

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²⁶ includes the eleven VA centers from V-HeFT I plus Tampa, FL and San Diego, CA

Table IIR.3. Demographics (Sponsor's Analysis - No Analysis Performed by FDA)

**Summary of Baseline Characteristics
All Patients Treated**

Variable	Enalapril N=403	H/ISDN N=401
Historical Data		
Age (years)		
Mean (SD)	60.62 (8.25)	60.55 (8.52)
Race (n, %)		
White	292 (72.46)	282 (70.32)
Black	106 (26.30)	109 (27.18)
Other	5 (1.24)	10 (2.29)
Duration of CHF (months)		
N	383	387
Mean (SD)	31.20 (37.84)	40.15 (48.64)
New York Heart Association Class (n, %)		
I	24 (5.96)	22 (5.49)
II	200 (49.63)	210 (52.37)
III	178 (44.17)	167 (41.65)
IV	1 (0.25)	2 (0.50)
Coronary Artery Disease (n, %)	220 (54.59)	213 (53.25)
Previous Myocardial Infarction (n, %)	197 (48.88)	189 (47.13)
Cerebrovascular Accident (n, %)	46 (11.41)	38 (9.48)
Coronary Bypass Surgery (n, %)	85 (21.09)	87 (21.70)
Hypertension (n, %)	199 (49.62)	182 (45.39)
Diabetes (n, %)	84 (20.84)	80 (19.95)
Excessive Use of Alcohol (n, %)	135 (33.50)	147 (36.66)
Tobacco Use (n, %)	135 (33.50)	132 (32.92)
Drug Therapy Prior 6 mo. (n, %)		
Vasodilators	250 (62.03)	247 (61.60)
Antiarrhythmics	100 (24.81)	106 (26.43)
Sublingual Nitroglycerin	64 (15.88)	67 (16.71)
Anticoagulants	84 (20.84)	88 (21.95)
Clinical Assessment		
Arterial Pressure (mm/Hg)		
Mean systolic/diastolic	125.53/77.97	126.98/78.44
Ejection Fraction (%)		
N	388	384
Mean (SD)	28.61 (10.87)	29.42 (11.53)
O ₂ Consumption (ml/kg/min)		
N	398	400
Mean (SD)	13.84 (3.46)	13.54 (3.52)
Heart Rate (beats/min)		
Mean (SD)	78.35 (12.06)	77.25 (11.93)
Cardiothoracic Ratio (%)		
N	392	392
Mean (SD)	53.7 (6.0)	53.0 (6.2)
LVIDD (cm/m ²)		
N	170	159
Mean (SD)	3.58 (1.42)	3.23 (1.22)
Plasma Norepinephrine (pg/ml)		
N	372	371
Mean (SD)	592.59 (388.12)	543.79 (296.78)
Plasma renin activity (ng/ml/hr)		
N	371	366
Mean (SD)	19.86 (52.64)	15.65 (28.09)
Atrial Fibrillation (n, %)	46 (11.41)	63 (15.71)
S ₃ Gallop (n, %)	89 (22.08)	69 (17.21)

NOTE: Ns are provided only where they were not equal to 403 for enalapril and 401 for H/ISDN. Data for this table were derived from Tables 28A and 28B (Appendix E1).

Of the total of 804 patients, 121 patients were rolled over from V-HeFT I. They were equally randomized to the treatments (60 to enalapril and 61 to H-ISDN). Analyses excluding these "old" patients were performed by the sponsor, but this historical information was not provided in the data set (submitted in Supplemental Statistical Report of 12/13/96) and the results were not verified by us.

Protocol Violations/Deviations

Other than discontinuation and compliance data, information related to protocol violations or deviations was not presented in the study report. The number of treated patients who did not satisfy the entry criteria and of those who did not comply with the protocol after randomization were not presented. It is not likely that these protocol violations/deviations, if any, would have had significant impact on the final conclusion.

Compliance, Dosages and Treatment Duration

Compliance, mean actual dosages of the study drugs and the percentages of patients on the full dose are summarized in table IIR.4. (from Table 2, Section 10 of Study Report).

Table IIR.4. Compliance, Average Dose and Number of Patients on Full Dose

	Enalapril	H-ISDN
Compliance		
Enalapril	93.1%	92.8% (placebo)
Hydralazine	90.2% (placebo)	85.6%
ISDN	91.1% (placebo)	85.5%
Average dose		
Enalapril	15.3 mg (1.53 tabs)	1.57 tabs (placebo)
Hydralazine	6.17 tabs (placebo)	201.8 mg (5.38 tabs)
ISDN	3.18 tabs (placebo)	101.2 mg (2.53 tabs)
% of patients on full dose* by 6 months**		
Enalapril	92.8%	93.7% (placebo)
Hydralazine	89.1% (placebo)	81.3%
ISDN	91.6% (placebo)	72.1%
All Study Meds	85.9%	67.3%

* Full dose for enalapril: 20 mg (2 tabs), hydralazine: 300 mg (8 tabs), ISDN: 160 mg (4 tabs).

** Slightly higher percentages for *any time* at full dose (see Table 2 of Study Report).

Overall, compliance with randomized treatments was greater than 85% and slightly better for the enalapril group (93% vs 86% for H-ISDN). It is interesting to note that even within the group randomized to receive H-ISDN, compliance with the enalapril-matching placebo (93%) was better than that of taking the assigned study drug, H-ISDN (86%). On the other hand, the H-ISDN matching placebo was apparently more tolerable than the real drug (90-91% compliance in the enalapril group). Patients in the H-ISDN group also reached full doses of study drug much later than those randomized to enalapril (only 67% at the end of 6 months).

Eligible patients were randomized more or less evenly over time during the 54 month patient intake period, with slightly longer treatment duration for the enalapril group. Table IIR.4a lists the treatment duration for each group.

Table IIR.4a. Treatment Duration

	Enalapril	H-ISDN
Means	31 months	29 months
Ranges	13-1818 days	2-1833 days
Medians	934 days	874 days

Approximately 75% of patients assigned to H-ISDN were treated with both study drugs for at least 6 months, compared to 87% for patients receiving enalapril (see Table 4, Section 10 of Study Report). As was also suggested by the rates of discontinuation, compliance and dosage information indicate that enalapril was better tolerated than H-ISDN in this study.

Concomitant Therapies

The two groups were well-matched with respect to the number of patients receiving concomitant treatments for heart failure (Table 3, Part A of Study Report) and medications for other common medical conditions (Table 3, Part B).

For digoxin (98% of patients) and furosemide (all patients), the mean and maximum dosages were also comparable. Patients in the H-ISDN group were on a higher average dose of hydrochlorothiazide (48 vs 37 mg, 20% of randomized patients), but the maximum dose was lower. Most frequently used concomitant medications not directly related to heart failure were potassium supplement (80%), antiplatelet drugs (50%), anticoagulants (25%) and potassium sparing diuretics (20%). Unspecified "other drugs" were also equally common in both groups (87%).

Major Endpoint - Survival

Crude mortality rates at end of 2 years and overall (5 year) are shown in table IIR.5. Table IIR.6 lists the cumulative mortality calculated from the life table analysis. The life-table estimate of 2-year survival was 82% for enalapril and 75% for H-ISDN. The mortality risk for H-ISDN was about 39% greater than that for enalapril.

Table IIR.5. Crude Mortality Rate

Crude Mortality	5-year mortality	2-year mortality
Enalapril (E)	132/403 (32.8%)	68/403 (16.9%)
H-ISDN (HI)	153/401 (38.2%)	95/401 (23.7%)
HI minus E	5.40%	6.80%
HI/E	1.16	1.40

Table IIR.6. Cumulative Mortality From Life Table Analysis

Year	# Alive at Start		Cumulative Mortality (%)	
	Enalapril	H-ISDN	Enalapril	H-ISDN
1	403	401	09.0	13.0
2	344	329	18.0	25.0
3	262	239	31.0	36.0
4	165	152	42.0	47.0
5	85	84	48.0	54.0
p (logrank for survival) 0.019 (2 yrs.), 0.083 (overall)				

(From Listing 7, Appendix E2 and Appendix E3.)

As specified in the original protocol, five-year and two-year survival data are to be analyzed using the Logrank test (equivalently, Cox regression analysis containing treatment indicator only). This test gives a p-value of 0.083 for 5 year mortality, suggesting that there is a trend in favor of overall survival in the enalapril group. The 2-year survival also favors enalapril (Logrank p-value = 0.019). Significance of treatment differences by Cox regression²⁷ (with the same selected covariates used in V-HeFT I) was similar to that by Logrank test (p-value by Cox analysis is 0.11 for 5-year and 0.024 for 2-year). For all subgroups²⁸, the trend in mortality favors enalapril. The only notable exceptions involve the analyses based on race and alcohol use where the trend is reversed. Table IIR.7 lists the crude mortality for each treatment group as a function of race and alcohol use.

²⁷ According to the protocol, factors which are prognostically important and may require adjustment for imbalance in estimates of treatment effect would be identified by the Cox life-table regression model. Covariates included maximum O₂ consumption and etiology of heart failure.

²⁸ demographic variables, underlying cardiovascular disorders or participation in V-HeFT I (see V-HeFT II subset analyses in the sponsor's Supplemental Statistical Report of 12/13/96)

Table IIR.7. Crude Mortality Rates Based on Race and Alcohol Use.

	N	H-ISDN: Enal	H-ISDN-Enal	95% CI	95% CI Hazard Ratio
Black	109	0.36 : 0.37	-0.010	-0.14-0.12	0.65-1.58
Non-blacks	292	0.39 : 0.31	0.077	0.00-0.15	1.01-1.74
Alcohol abuse	147	0.37 : 0.39	-0.011	-0.12-0.10	0.78-1.66
No Alcohol abuse	254	0.39 : 0.30	0.087	0.01-0.17	0.97-1.75

Major Endpoint - Maximum Oxygen Consumption at Peak Exercise and Exercise Time

The results of the reviewer's analyses on exercise duration are similar to that presented in the Study Report (Tables 29-32, pages 259-263, Volume 1.68). The only hint of treatment difference was from comparison at the 3 month visits, which had an unadjusted p of 0.02 (see Table IIR.8). Based on multivariate repeated measures analyses, unadjusted p-values for between group comparison of changes from baseline were < 0.05 for only 2 of the 9 models tested (p range: 0.015 to 0.68). The model that best describes the data based on the maximum likelihood principle gave a p-value of 0.68.

Table IIR.8. Maximum Exercise Duration

Visit	Treatment	N	Mean	SD	Change from baseline		
					Mean	SD	P-value
RAND	Enalapril	403	7.45	2.23			
	H-ISDN	401	7.26	2.26			
3 months	Enalapril	340	7.41	2.34	-0.14	1.41	
	H-ISDN	335	7.41	2.26	0.10	1.22	0.016
6 months	Enalapril	309	7.62	2.34	-0.06	1.45	
	H-ISDN	301	7.55	2.35	0.14	1.51	0.10
1 year	Enalapril	287	7.28	2.43	-0.35	1.64	
	H-ISDN	251	7.34	2.44	-0.17	1.64	0.20
1.5 year	Enalapril	228	7.32	2.24	-0.48	1.83	
	H-ISDN	190	7.25	2.37	-0.32	2.04	0.40
2 years	Enalapril	193	7.32	2.42	-0.76	2.07	
	H-ISDN	165	7.27	2.42	-0.39	2.16	0.10
2.5 years	Enalapril	141	7.00	2.33	-0.96	1.96	
	H-ISDN	138	7.02	2.25	-0.66	2.03	0.20
3 years	Enalapril	109	7.34	2.11	-0.97	1.67	
	H-ISDN	106	6.97	2.00	-0.70	1.69	0.25
3.5 years	Enalapril	79	7.20	2.37	-1.22	1.87	
	H-ISDN	78	7.05	2.25	-0.86	1.73	0.22
4 years	Enalapril	53	7.53	2.55	-1.37	1.87	
	H-ISDN	51	7.10	2.26	-0.89	1.71	0.18
4.5 years	Enalapril	39	7.46	1.93	-1.40	1.62	
	H-ISDN	31	7.04	2.40	-1.04	1.61	0.36

Thus, over the five years or in the first three years, there was no convincing, statistically significant treatment effect in exercise duration other than the 3 month visit comparison.

The results of the reviewer's analyses on maximum oxygen consumption, using the sponsor's database, are similar to that presented in the Study Report (Tables 29-32, pages 259-263, Volume 1.68). Compared with exercise duration, changes in maximum oxygen consumption favored H-ISDN at more time points over the course of the study (with an unadjusted p-value < 0.05, i.e., 0.02 at 3 months, 0.017 at 1 year, 0.0035 at 2 years, and 0.037 at 4 years, see table IIR.9.). However, at 6 months, 1.5 years, and 2.5 years, 3 years, 3.5 years and 4.5 years, the differences are inconclusive (unadjusted p-value > 0.10). In addition, by multivariate repeated measures analyses, none of the models tested gave a p of < 0.05 for between group comparison in changes from baseline (unadjusted p-value ranging from 0.08 to 0.62, depending on the models). Therefore, similar to that concluded for exercise duration, there was no consistent, statistically significant treatment effect in oxygen consumption over the five years or in the first three years.

Table IIR.9. Maximum Oxygen Consumption (FDA Analysis)

Maximum Oxygen Consumption			Change from baseline				
Visit	Treatment	N	Mean	SD	Mean	SD	p-value
RAND	Enalapril	398	13.84	3.46			
	H-ISDN	400	13.54	3.52			
3 months	Enalapril	333	13.9	3.72	-0.048	2.43	
	H-ISDN	326	14.06	3.85	0.39	2.39	0.020
6 months	Enalapril	302	14.42	3.56	0.25	2.53	
	H-ISDN	289	14.37	4.2	0.6	2.74	0.11
1 year	Enalapril	273	13.76	3.7	-0.32	2.67	
	H-ISDN	247	14.18	3.85	0.24	2.68	0.017
1.5 year	Enalapril	223	14.03	3.38	-0.24	2.82	
	H-ISDN	187	14.32	4.04	0.19	3.17	0.16
2 years	Enalapril	187	13.94	3.69	-0.67	2.71	
	H-ISDN	160	14.38	3.66	0.16	2.55	0.0035
2.5 years	Enalapril	133	13.67	3.48	-0.58	2.70	
	H-ISDN	135	13.87	3.64	-0.26	2.90	0.35
3 years	Enalapril	104	14.1	3.69	-0.46	3.01	
	H-ISDN	102	13.65	3.15	-0.64	2.77	0.67
3.5 years	Enalapril	74	14.48	4.01	-0.72	2.97	
	H-ISDN	76	13.87	3.69	-0.61	3.03	0.82
4 years	Enalapril	50	14.02	3.68	-1.24	2.49	
	H-ISDN	50	14.5	3.6	-0.15	2.65	0.037
4.5 years	Enalapril	39	14.7	3.25	-0.97	2.61	
	H-ISDN	30	14.46	3.63	-0.19	2.75	0.23

Major Endpoint - Frequency and Duration of Hospitalizations for Cardiac Causes

Frequency and duration of hospitalizations for cardiovascular causes was a major endpoint. There was no significant difference between treatment groups in the number or duration of hospitalizations for cardiac causes. A listing of the frequency and duration of hospitalizations can be found on page 41 of the appendix.

Minor Endpoint - Ejection Fraction

Treatment effects on ejection fraction were at best marginally in favor of H-ISDN in V-HeFT II. Compared to enalapril, there was a trend toward greater improvement of ejection fraction with H-ISDN over three years (unadjusted p-values from generalized estimating equation analyses were 0.027-0.028 by two models and ranged from 0.044 to 0.054 by the other 7 models, Table 30 of NDA). Of the comparisons at different time points (see Table IIR.10), only the p value at 3 months was < 0.05. At that visit, the mean ejection fraction increased from 29.4% at baseline to 32.3% for H-ISDN and 28.6% to 31.0% for enalapril. The averages of individual patient's absolute increases were 3.3% for H-ISDN and 2.1% for enalapril. The treatment difference in ejection fraction, while numerically favoring H-ISDN most of the time, decreased during the study thereafter (p ranged 0.12-0.68 afterwards) and reversed its direction at the 48 month visit. The results (Tables 30 and 31, page 261-262, Vol. 1.68) of the sponsor's univariate and multivariate analyses on ejection fraction have been verified by the reviewers.

Table IIR.10. Ejection Fraction

Visit	Treatment	N	Mean	SD	Change from baseline		
					Mean	SD	P-value
RAND*	Enalapril	388	0.286	0.109			
	H-ISDN	384	0.294	0.115			
3 months	Enalapril	359	0.310	0.114	0.021	0.067	
	H-ISDN	335	0.323	0.127	0.033	0.071	0.026
12 months	Enalapril	308	0.312	0.124	0.025	0.084	
	H-ISDN	275	0.326	0.137	0.036	0.087	0.120
24 months	Enalapril	229	0.316	0.124	0.025	0.085	
	H-ISDN	209	0.331	0.131	0.031	0.099	0.531
36 months	Enalapril	141	0.335	0.137	0.033	0.103	
	H-ISDN	137	0.329	0.128	0.037	0.109	0.679
48 months	Enalapril	73	0.324	0.124	0.040	0.105	
	H-ISDN	73	0.333	0.137	0.027	0.107	0.197

* Tests for difference between groups at randomization gave a p of 0.315 by t-test and 0.336 by Wilcoxon.

Other Minor Endpoints

Results of other secondary endpoints are summarized in table IIR.11 (blood pressures and heart rates are probably more of safety than efficacy concern). As the findings are of no regulatory consequences, the analyses were not verified by the reviewers.

Table IIR.11.

Variables	Results
Cardiothoracic ratio	No treatment difference
Blood pressures	Both systolic and diastolic blood pressures were decreased to a greater degree in the enalapril group (-3-4 mmHg vs -1-1.5 mmHg for H-ISDN at 12 months, Table 29, Appendix E1).
Heart rates	Heart rates were decreased in the enalapril group but increased in the H-ISDN group. The differences were statistically significant by multivariate analyses and over the first year.

Safety

The extent of drug exposure was described briefly in the section on Compliance, Dosages and Treatment Duration. Regardless of dosage, the numbers of patients in each group treated for various length of time are summarized in the table IIS.1.

Table IIS.1. Duration of Treatment

Duration	Enalapril	Hydralazine	ISDN
randomized	403	401	401
6 month	351	314	298
1 year	297	267	250
2 years	225	181	174
3 years	133	112	105
4 years	67	60	56

As noted above, approximately 75% and 87% of patients received H-ISDN and enalapril, respectively, for 6 months. Slightly fewer patients were treated with the study drugs for at least one year (62-66% for H-ISDN and 74% for enalapril).

There were few surprises in the adverse experiences of V-HeFT II, almost all of which have been described in the package inserts of the approved individual component and related to vasodilatation.

Adverse Events

It was not surprising in a long-term study that almost all patients reported at least one adverse event (see Table below). Nearly all adverse events were considered drug-related. Of the adverse experiences, about half were severe or required dose-reduction. Unusual, drug-related reactions and discontinuation due to adverse events were rare (using more inclusive definition of the latter would increase the frequency slightly, see above in Patient Disposition). There were no significant differences between groups in these incidences.

Table IIS.2. Incidence of All Adverse Events.

Adverse Experiences *	Enalapril (N=403)	H-ISDN (N=401)
Any AE	401 (99.5%)	394 (98.2%)
Drug-related AE	370 (91.8%)	373 (93.0%)
AE required dose reduction	168 (41.7%)	237 (59.1%)
Any severe AE	190 (47.2%)	214 (53.4%)
Severe or unusual, drug related	5 (1.2%)	7 (1.7%)
Discontinuation due to AE**	8 (2.0%)	10 (2.5%)

* see Mortality in Efficacy for distribution of deaths.

** not including certain cardiac events, see patients disposition.

(from Text Table 14 of Study Report)

The patterns of most common complaints in the two treatment groups are surprisingly similar (except for headache and cough, see table IIS.3 and discussion below). However, adverse experiences in V-HeFT II were solicited with a "pre-printed list of terms". Events that were not listed were recorded under "other". Since the terms included in "other" were not available, between group imbalance of other adverse events remains possible.

Table IIS.3. Incidence of Individual Adverse Events

Adverse Experiences	Enalapril (N=403)	H-ISDN (N=401)
Abn lab tests *	390 (97%)	367 (92%)
Fatigue/lassitude	330 (82%)	326 (81%)
Headache	242 (60%)	307 (77%)
Arthralgias	288 (72%)	276 (69%)
Nasal congestion	272 (68%)	271 (68%)
Dizziness	269 (67%)	268 (67%)
Other	262 (65%)	246 (61%)
Palpitation	217 (54%)	227 (57%)
Nausea/Vomiting	237 (59%)	213 (53%)
Chest pain	187 (46%)	178 (44%)
Constipation	176 (44%)	169 (42%)

(from Text Table 16 of Study Report)

* see discussion below.

While headache was more frequent in the H-ISDN patients (77% vs 60% for enalapril), cough appeared to be less common in the same group (34.2% vs 44.2% for enalapril, not listed above). Both findings are well-known phenomena for the drugs. In general, almost all of the adverse experiences listed in the table were non-specific, not serious and not unexpected in the study population, especially in a long-term trial.

Serious Events, Deaths and Hospitalizations

It was not very clear how "serious" adverse events were defined in the protocol and there was no discussion of such events in the study report. Instead, there were description of "severe" events in the study report, but the number of patients with such events was variable and the criteria for "severity" confusing. For instance, while about half of all patients had "severe AEs" and there were 12 patients with "severe or unusual" events (see Table above), the sponsor described only 7 patients whose adverse events met the criteria for submission of FDA Forms 1639 to the study chairman. In another placé, "nasal congestion" was also considered a "severe" event in 8-9% of patients (see Section 6.6.3.3 of Study Report). Review of the 7 cases of FDA Forms 1639 (2 in H-ISDN with lupus-like syndrome, and 5 in enalapril

group with elevation of BUN/creatinine, arthralgia and hypotension) did not reveal any significant safety problem which may affect approvability or require labeling attention.

While overall incidences of arthralgia were similar in the two treatment groups (see Table above), slightly more in the H-ISDN group required dose reduction for that reason (6.4% enalapril vs 11% in H-ISDN, see below). In 27 (10 enalapril, 17 H-ISDN) patients, arthralgia was associated with a newly developed and mostly sustained elevation of ANA titer (Section 6.6.3.4 of Study Report). Another 15 patients (8 enalapril, 7 H-ISDN) had study drugs interrupted or discontinued for suspected lupus-like syndrome. Positive ANA was pre-existing in about one third of the patients in the H-ISDN group.

Since mortality is an efficacy endpoint, the number of deaths will not be discussed further in this section. Most of the causes for death were related to underlying cardiac dysfunctions (85% [enalapril] and 90% [H-ISDN] of deaths). More enalapril patients died from pump failure, but there were more sudden deaths in the H-ISDN group. Table IIS.4 lists the causes of death in the study.

Table IIS.4. Cause of Death as Determined by the Investigators

Causes of Deaths	Enalapril (N=132)	H-ISDN (N=153)
pump failure	50 (44.6%)	40 (29.2%)
sudden death, no warning	41 (36.6%)	63 (46.0%)
sudden death, w/ warning	16 (14.3%)	29 (21.2%)

In patients who died, there was no clear trend or between group difference in daily dosage of study drugs or ranges of treatment durations (Listing 8, Appendix E2, Vol 1.36).

Approximately 67% of patients were hospitalized during V-HeFT II study. There were no significant differences between treatment groups, either in total numbers, or in reasons of hospitalizations. Specifically, 27.8% of enalapril and 27.4% of H-ISDN patients were admitted to the hospitals for CHF (see Table IIS.5.).

Table IIS.5. Incidence and Reason for Hospitalization

Hospitalizations	Enalapril (N=403)	H-ISDN (N=401)
for Adverse events	8 (2.0%)	4 (1.0%)
for CHF	112 (27.8%)	110 (27.4%)
for other Cardiac causes	126 (31.3%)	133 (33.2%)
for Other causes	200 (49.6%)	162 (40.4%)
TOTAL	276 (68.5%)	264 (65.8%)

(from Table 5, Section 10 of Study Report)

Events Leading to Withdrawal or Dose Reduction

According to the Study Report, premature withdrawals were defined as patients who were discontinued from *both* study medications. As noted in Patient Disposition, approximately 10% of all patients were discontinued. Excluding certain cardiac events (cardiac surgery, new/worsening angina, acute MI) and non-cardiac surgery (see table IIS.6.), withdrawals due to adverse effects accounted for 2.0% of enalapril and 2.5% of H-ISDN patients. The most common reasons were headache, nausea, dizziness/syncope, hypotension and unspecified "other" causes. There were no significant treatment differences in these adverse experiences leading to withdrawals.

Cardiac and surgical events were also rare and well-matched between treatment groups.

Table IIS.6. Reason for Premature Discontinuation of Both Medications for Cardiac Events and Non-Cardiac Surgery

Withdrawals for:	Enalapril (N=403)	H-ISDN (N=401)
vasodilator administration	11 (2.7%)	10 (2.5%)
worsening CHF	2 (0.5%)	6 (1.5%)
cardiac surgery	2 (0.5%)	2 (0.5%)
new/worsening angina	1 (0.2%)	1 (0.2%)
acute MI	3 (0.7%)	0 (0.0%)
non-cardiac surgery	1 (0.2%)	0 (0.0%)

(from Text Table 8, Section 6.1 of Study Report)

Again, H-ISDN appeared to be less tolerable than enalapril (see also above in Patient Disposition). While the adverse experiences infrequently led to withdrawals, reduction of dosages for H-ISDN were often required. As shown in table IIS.7, headache, fatigue, dizziness and palpitation were cited as reasons in substantially more patients in the H-ISDN group (>5% in difference).

Table IIS.7. Adverse Events That Lead to Dose Reduction or Permanent Discontinuation of Therapy

Dose Reduction for:	Enalapril (N=403)	H-ISDN (N=401)
Headache	11.2%	40.9%
Fatigue/lassitude	23.6%	28.9%
Dizziness	19.4%	26.9%
Others	17.4%	22.4%
Nausea/Vomiting	13.2%	18.0%
arthralgia	6.4%	11.0%
Palpitation	5.0%	10.2%
Hypotension	9.7%	7.5%
Abn lab tests	11.2%	7.2%

(Section 6.6.3.1 of Study Report)

Clinical Laboratory Events

There was no clinically relevant mean changes in hematology or blood chemistry (Table 6 of Section 10, Study Report). Not surprisingly, enalapril patients had a slightly greater mean increase in creatinine (0.16 vs 0.04 mg/dl for H-ISDN) and BUN (6.6 vs 2.5 mg/dl for H-ISDN). Mean increases in ANA titer were observed in both groups, but the between group difference was small and not meaningful.

For maximum changes from baseline, the two treatment groups were similar for most of the laboratory parameters, except for creatine (increase of 5.4 mg/dl for enalapril vs 2.2 mg/dl for H-ISDN) and BUN (increase of 162 mg/dl for enalapril vs 56 mg/dl for H-ISDN). See again Table 6 of Section 10, Study Report.

Clinical Pharmacology

Hemodynamics

The sponsor did not perform any hemodynamic studies that evaluated the intracardiac effect of BiDil®. Instead, they have provided numerous references²⁹ from the medical literature that describe hemodynamic studies with hydralazine, nitrates and the combination. None of the source data from these reports is provided. The majority of these studies are self-controlled trials with fewer than 30 patients. In two studies³⁰, oral hydralazine alone was associated with acute decreases in systemic vascular resistance and increases in stroke volume index and cardiac index. These effects persisted with long term therapy (3 - 16 months). Pulmonary artery pressure decreased significantly in one trial but not the other.

Nitrate therapy (transdermal or oral) was associated with decreases in LVFP, systemic vascular resistance and mean arterial pressure³¹.

²⁹ (volume 1.17, p. 51 through volume 1.18); summary of references in volume 1.17, p. 22 - 32

³⁰ Am J Card 1979;44:303-309. Ann Int Med 1980;92:600-604.

³¹ Am J Med 1978;64:207-213.

The combination of H-ISDN has been reported to decrease pulmonary capillary wedge pressure, systemic vascular resistance and right atrial pressure and increase cardiac output and stroke volume index at rest and with maximum exercise.³²

Nitrate Tolerance

The sponsor has provided four publications from the medical literature to support the view that nitrate tolerance is attenuated by the addition of hydralazine. An extensive review of these studies will not be performed because the primary data is not available. Each reference is included in the appendix. Table CP.1 briefly summarizes the results of the studies.

Table CP.1. Summary of Studies of Nitrate Tolerance

Reference	Model	Results
JACC 1995; 26(7):1575-1580	Human	Randomized, unblinded trial in 28 CHF patients who demonstrated a hemodynamic response to IV NTG infusion. Subjects were randomized to IV NTG (N = 14) or IV NTG plus hydralazine for 24 hours. Right heart cath was performed and hemodynamic parameters measured. Initial reductions in mean blood pressure (BP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) in the NTG only group was attenuated at 24 hours. In the NTG plus hydralazine group, the attenuation of effect on BP, PAP and PCWP was not evident.
J. Cardiovascular Pharm. 1993;21:478-483.	Rat Aortic Segments ^A	Segment tension was measured isometrically with a force transducer. The concentration response (% relaxation) to NTG on phenylephrine pre-contracted rings was measured in a control and hydralazine incubated preparation. Hydralazine incubation potentiated the response to NTG in rings from animals exposed to nitrates (figure 3 in reference).
J. Clin. Invest. 1996;98(6):1465-1470.	Rabbit Aortic Segments ^B	The concentration response (% relaxation) to NTG on phenylephrine pre-contracted rings was measured. NTG pre-treatment attenuated the relaxation response to NTG. NTG plus hydralazine pre-treatment exhibited a response similar to the control group (table 1 in reference).
Circulation 1991;84:(1)35-39.	CHF rat	Continuous infusion of NTG alone (N=7) or in combination with hydralazine bolus (N=8) with measurement of left ventricular end diastolic pressure (LVEDP) and left ventricular peak systolic pressure (LVPSP). Initial reduction in LVEDP with NTG infusion returns to baseline measure at hour 10 of infusion. Attenuation of effect did not occur when concomitant hydralazine administered (figure 2 in reference).

* Authors interpretation of the results.

^A from nitrate exposed and untreated animals

^B from animals exposed to NTG, hydralazine, the combination or untreated

The study in JACC suggests that the attenuation of the reductions in blood pressure, pulmonary artery pressure and pulmonary capillary wedge pressure observed in CHF patients with continued nitroglycerin infusion for 24 hours does not occur when concomitant hydralazine was administered. The study does not appear to be blinded so the results should be viewed with some caution. The study also does not address the chronic use of nitrates.

Pharmacokinetics

The pharmacokinetics of hydralazine, ISDN and the combination are described in the Biopharm review. In summary, the BiDil formulation is not bioequivalent³³ to the hydralazine and ISDN formulations used in V-HeFT I and V-HeFT II based on the equivalence limits of 80 - 125%. It should be noted that the hydralazine and ISDN formulations used in V-HeFT I are not bioequivalent to the

³² Br Heart J 1981;45:376 - 84.

³³ C_{max} and AUC

formulations used in V-HeFT II. The clinical significance of the differences between the formulations is unknown. Fulfillment of the FDA bioequivalence limits was not a prerequisite for approval.

Summary

Efficacy

V-HeFT I

V-HeFT I is a double-blind, placebo controlled trial that randomized 642 male patients with congestive heart failure to placebo (N = 272), H-ISDN (N = 186) and prazosin (N = 183) at eleven VA Centers. Six major and six minor endpoints were specified in the protocol. The major endpoints included overall mortality, 2-year mortality, the number and duration of cardiovascular hospitalizations, the maximum oxygen consumption during peak exercise, maximum treadmill exercise time on graded test and duration of exercise on submaximal tests. The sample size calculation was based on the mortality endpoints.

The primary analysis for survival was a Logrank test. The protocol proposed that the three survival curves be tested by a single Logrank test or by comparing each treatment to placebo or to combine the two vasodilator therapies and compare them to placebo.

The trial was conducted from 5/7/80 until 12/15/85. The mean follow-up was 2.3 years and ranged from 6 months to 5.7 years. Four interim analyses were performed during the course of the study but none achieved a significance level that warranted premature stopping of the trial. Table S.1 lists the crude mortality rates and cumulative mortality rates from the life table analysis for overall and 2-year mortality.

Table S.1. Crude Mortality and Cumulative Mortality Rates

	Placebo	H-ISDN	Risk Reduction
Overall Mortality			
Crude	44%	38.7%	12%
Cumulative ^A	63.8%	55.6%	13%
2-Year Mortality			
Crude	34.3%	25.6%	25%
Cumulative ^A	31.5%	22.6%	28%

^A Derived from the Life Table Analysis [vol. 1.68, p.26].

The Logrank test comparing placebo and H-ISDN yielded unadjusted 2-sided p values of .093 and .056 for overall mortality and 2-year mortality respectively. The sponsor performed a Cox Regression analysis with ejection fraction, maximum oxygen consumption and etiology of heart failure as the covariates. The Cox analysis yielded unadjusted³⁴ 2-sided p values of .035 and .034 for overall and 2-year mortality respectively. The Cox analysis does not take into account that the Logrank analysis was the specified primary analysis and was not significant. The FDA analysis incorporates this fact into a Logrank/Cox analysis which yields unadjusted 2 sided p values of .051 and .04 for overall and 2-year mortality respectively. The 2-sided p values are not statistically significant when adjustments for four interim analyses and multiple major endpoints are factored into the calculation. The 2-sided p value limit for declaring significance lies somewhere between .021 and .042 (i.e. accounting for four interim analyses using the O'Brien Fleming rule and only two major endpoints). The 2 sided p values are close but do not achieve statistical significance. The one-sided unadjusted p values from the Logrank/Cox analysis are .023 and .017 for overall and 2-year mortality respectively. . The one-sided p value limit for declaring significance lies somewhere between .01 and .021 (i.e. accounting for four interim analyses using the O'Brien Fleming rule and only two major endpoints). The one-sided p value for overall mortality is not significant. The one-sided p value for 2-year survival may be significant. The power calculation in the protocol uses one-sided p values but the publication of the study states that "all statistical tests were two-tailed"³⁵.

None of the other major endpoints in the study showed a statistically significant difference between treatments.

³⁴ unadjusted for interim analysis and multiple major endpoints; Not using Monte Carlo simulation

³⁵ NEJM 1986;314:1547 - 1552. (page 1548)

- There was no significant difference in maximum oxygen consumption between treatments (multivariate analysis yielded unadjusted p values of .05 - .12). The numerical difference between treatments favors H-ISDN.
- There was no significant difference in maximum exercise duration between treatments (multivariate analysis yielded unadjusted p values of .073 - .089). The numerical difference between treatments favors H-ISDN.
- The number of hospitalizations for heart failure and other cardiac causes may be under reported for all treatments because a clinic visit form was not completed for most patients at the time of trial completion (12/15/85). The only information collected on patients from the time of their last clinic visit to the trial end date was mortality data. There was no significant difference in the number and duration of cardiovascular hospitalizations.

Among the minor endpoints, the only endpoints analyzed for this review included ejection fraction (EF) and quality of life. The data strongly suggest an improvement in ejection fraction in the H-ISDN group compared to placebo (unadjusted p values from various models are less than .0006). The maximum mean change in EF was approximately 4%. There is no significant difference in quality of life as assessed by the physician or the patient.

V-HeFT II

V-HeFT II is a double-blind, placebo controlled trial that randomized 804 male patients with congestive heart failure to enalapril (N = 403) and H-ISDN (N = 401) at thirteen VA Centers. Six major and four minor endpoints were specified in the protocol. The major endpoints included overall mortality, 2-year mortality, the number and duration of cardiovascular hospitalizations, the maximum oxygen consumption during peak exercise, oxygen consumption at anaerobic threshold and changes in quality of life. The sample size calculation was based on the mortality endpoints.

There was a significant difference in 2-year mortality in favor of enalapril (logrank p of 0.019). Overall mortality was not significantly different between treatments (logrank p of 0.083). Crude mortality analysis was also consistent with the life-table findings, showing a 39% increase (vs enalapril) in mortality risk for patients received H-ISDN. The conclusion was not affected by other analyses or subgroup comparisons.

For exercise tolerance and other endpoints related to cardiac function, H-ISDN has very little advantage over enalapril. For maximum oxygen consumption, multivariate analysis showed no significant difference between treatments. Analyses of treatment differences at each individual visit yielded p values ranging from .0035 - .82 (see table IIR.9 on page 33). Unadjusted³⁶ p values were less than .05 for the 3 month test (p = .02) but not the 6 month test (p = .11). The published³⁷ exercise results included analyses that used the values of those post-randomization exercise tests that were stopped by dyspnea and fatigue. This analysis is not clearly defined as a prospective analysis in the protocol. The Division of Cardio-Renal Drug Products typically requires all post-randomization exercise tests be included in the primary analysis (regardless of the reason for stopping the test) because of the difficulty in determining that the reason a patient stops is unrelated to drug therapy.

Other Issues

Combination Policy

Under the Federal Regulations, two or more drugs can be combined in a single dose form when each component makes a contribution to the claimed effect [CFR 300.50(a)]. Typically, this requires a comparison of the combination versus both monotherapy dose forms. Neither V-HeFT I or V-HeFT II includes monotherapy treatment regimens for a comparison to the combination. Thus, even if nitrate tolerance is perceived to not to be a problem when ISDN is co-administered with hydralazine, there is no information to determine that each component contributes to the effect of the combination. The determination of the contribution of each agent to a treatment effect will have to be based on clinical judgment.

Applicability of Results to the CHF Population

Because of the superior mortality effect with enalapril compared to H-ISDN in V-HeFT II, H-ISDN should not be considered as a first line therapy in all heart failure.

³⁶ for multiple comparisons

³⁷ NEJM 1991;325(5):303-310

If BiDil® is approved, it should be clear in the label that female patients and NYHA Class IV were not included in the primary efficacy and safety trial.

Nitrate Tolerance

There is insufficient evidence to unequivocally conclude that hydralazine prevents tolerance to the vasodilator effect of ISDN. The published clinical trial³⁸ supporting the prevention of nitrate tolerance with hydralazine was only one day in duration and appears to be unblinded. The incidence of headache in the H-ISDN group in V-HeFT I is initially high and then approaches the incidence of placebo after 3 months suggesting some tolerance to the vasodilator effect. If nitrate headache is dissociated from the intracardiac hemodynamic effects of nitrates, then the decrease in headache is not helpful in addressing the question of nitrate tolerance.

Comparison of V-HeFT II H-ISDN to V-HeFT I Placebo

The sponsor performed analyses³⁹ (see appendix page 17) that compare the placebo results from V-HeFT I to the H-ISDN results from V-HeFT II. According to the authors of the V-HeFT II publication⁴⁰, the rationale that supports this comparison includes:

- the criteria for entry into the two studies and the H-ISDN treatment regimens were identical;
- the homogeneity of the patient populations in the two trials (i.e. same centers, similar demographics); and,
- the reproducibility of the survival curves (i.e. overlap of the H-ISDN survival curves of V-HeFT I and V-HeFT II).

Although this appears to be an appealing exercise, it is insufficient to be considered as confirmatory of the V-HeFT I results for the following reasons.

- First, it assumes that the placebo event rate in the two trials is exactly the same. This is an assumption that can never be tested. Even for studies performed at the same centers, there would be some variability in event rate with the same treatment. The observation that the H-ISDN curves from V-HeFT I and II appear to overlap does not support the notion that placebo curves would also be superimposable.
- Second, these analyses ignore the enalapril results in V-HeFT II. If the same centers and same entry criteria suffice as determinants of reproducibility, then a one treatment arm trial (i.e. an uncontrolled trial) with H-ISDN would have provided the same information as V-HeFT II for this type of analysis.
- Third, it assumes that there were no other diagnostic, procedural or therapeutic interventions available to physicians in the latter half of the decade that would have influenced outcome in a placebo group.

In keeping with the evaluation of other positive control trials that have come to the Committee (e.g., reteplase, May 1996), an analysis that would more appropriately support the results of V-HeFT I is one that incorporates the expected effect of enalapril on mortality. Would H-ISDN in V-HeFT II have beaten a putative placebo and maintained at least 50% of enalapril's treatment effect (enalapril vs. placebo) in a placebo controlled mortality trial? This can be done by comparing the risk ratios for mortality of H-ISDN and placebo compared to enalapril. The risk ratios for the placebo vs. enalapril comparison are obtained from the SOLVD Treatment Trial. Table S.2 lists the risk ratio for Placebo from SOLVD and H-ISDN from V-HeFT II compared to enalapril.

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³⁸ JACC 1995; 26(7):1575-1580

³⁹ December 13, 1996 submission

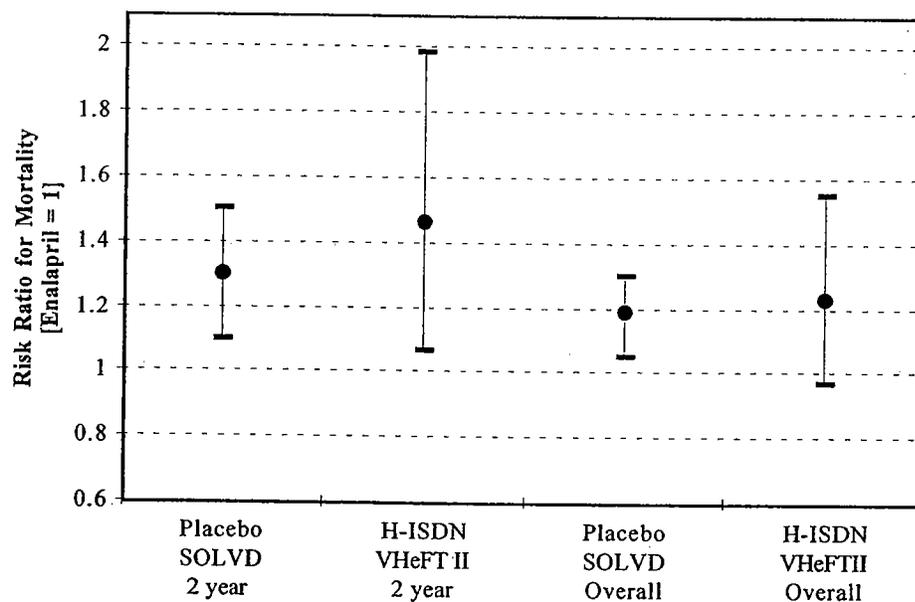
⁴⁰ Cohn JN, Johnson G, Ziesche S et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. NEJM 1991;325(5):303-310

Table S.2. Risk Ratio for Mortality from SOLVD and V-HeFT II.

	SOLVD Treatment (6/86 - 9/89)			V-HeFT II (3/86 - 9/90)		
	Enalapril (N = 1283)	Placebo (N = 1284)	Risk Ratio	Enalapril (N = 403)	H-ISDN (N = 401)	Risk Ratio
2 Year Crude Mortality	21.6%	26.8%	1.30 ^A (1.1 - 1.5) ^B	16.9%	23.7%	1.46 (1.07 - 1.99) ^B
Overall Crude Mortality	35.2% ^C	39.2% ^C	1.19 ^A (1.05 - 1.3) ^B	32.8% ^D	38.2% ^D	1.23 (.97 - 1.6) ^B

¹ NEJM 1991;325(5):293 - 302. ; ^A calculated from risk reduction in NEJM; Risk Ratio = 1 / (1 - risk reduction);
^B 95% C.I. calculated by the log rank test; ^C follow-up ranged from 22 - 55 months, average = 41.4 months;
^D follow-up ranged from 6 - 68 months, average = 30 months

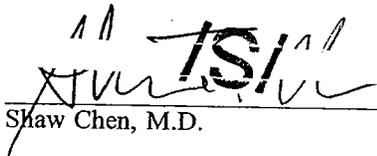
Figure S.1 graphically displays the risk ratios from table S.2. The H-ISDN (V-HeFT II) treatment effect compared to enalapril cannot be distinguished from the treatment effect of Placebo (SOLVD) compared to enalapril. From this framework of reference, the mortality results of V-HeFT II do not support the results of V-HeFT I.

Figure S.1. Risk Ratios for Mortality for Placebo (SOLVD) and H-ISDN (V-HeFT II) Compared to Enalapril at 2 Years and Overall.

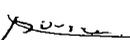
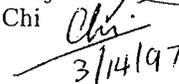
Graphical display for mortality risk expressed as the risk ratio (point estimate and 95% confidence interval) for SOLVD Placebo patients and V-HeFT II H-ISDN patients compared to enalapril (relative risk = 1) for 2 years and overall follow-up. The 95% confidence intervals (C.I.) are also provided.

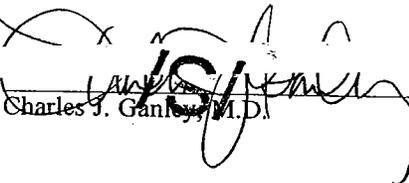
Conclusions

- In V-HeFT I, the only mortality analysis that might achieve statistical significance is the one-sided p value calculated for 2-year mortality. The determination of significance is dependent on the adjustments made for the interim analyses and the multiple endpoints.
- In V-HeFT I, the increase in ejection fraction with H-ISDN is significantly different compared to placebo.
- In V-HeFT I, there was no significant difference in maximum oxygen consumption or exercise duration between treatment groups. Multivariate repeated measures analyses with various models suggest a trend toward possible improved maximum O₂ consumption (unadjusted p-value ranging from 0.05 to 0.12) and exercise duration (unadjusted p-value ranging from 0.073 to 0.089) in the H-ISDN group.
- V-HeFT II does not support the mortality results of V-HeFT I. The most compelling observation in V-HeFT II is the risk reduction of 22% in 2-year mortality (Logrank p = .019) in favor of enalapril compared to H-ISDN.
- The interpretation of the exercise test data in V-HeFT II is dependent on the analysis chosen. A multivariate repeated measures analysis for maximum oxygen consumption showed no significant difference between treatments. Treatment comparisons of the individual visits suggests H-ISDN may be superior to enalapril at some visits⁴¹. These results are analysis dependent and are not consistent with the results observed in V-HeFT I⁴².
- In V-HeFT II, any perceived effect on exercise tolerance does not correlate with the mortality results.

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 James Hung, Ph.D.

Concur: Mahjoob   b 03/05/97
Chi  3/14/97

 Charles J. Ganley, M.D.

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HFD-110 file
HFD-110 / CSO / C. Ganley/S.Chen/R.Lipicky
HFD- 710/ J.Hung/K.Mahjoob/G.Chi

41 page appendix attached

⁴¹ assumes no correction for multiple comparisons

⁴² Multivariate analysis for exercise endpoints in V-HeFT I trended in favor of H-ISDN. Multivariate analysis for exercise endpoints in V-HeFT II showed no significant difference between treatments.

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Unger P, Berkenboom G, Fontaine J. Interaction between hydralazine and nitrovasodilators in vascular smooth muscle. Cardiovascular Pharm. 1993;21:478-483.	24
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Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
104006	placebo	1/7/86	20
101021	placebo	12/17/85	26
101028	placebo	12/16/85	23
32005	placebo	12/13/85	30
32018	placebo	12/13/85	23
33003	placebo	12/13/85	35
42010	placebo	12/13/85	29
53012	placebo	12/13/85	26
53018	placebo	12/13/85	21
23025	placebo	12/12/85	12
24005	placebo	12/12/85	32
32021	placebo	12/12/85	18
33012	placebo	12/12/85	26
123019	placebo	12/12/85	15
64018	placebo	12/9/85	24
81008	placebo	12/9/85	27
101020	placebo	12/9/85	26
33010	placebo	12/6/85	27
44009	placebo	12/6/85	21
44014	placebo	12/6/85	15
53016	placebo	12/6/85	22
54002	placebo	12/6/85	35
71009	placebo	12/6/85	23
73021	placebo	12/6/85	21
101033	placebo	12/6/85	21
12014	placebo	12/5/85	18
22018	placebo	12/5/85	28
82008	placebo	12/5/85	33
101007	placebo	12/5/85	30
102016	placebo	12/5/85	31
102021	placebo	12/5/85	30
123011	placebo	12/5/85	23
12016	placebo	12/4/85	15
83012	placebo	12/4/85	15
121013	placebo	12/4/85	23
82005	placebo	12/3/85	32
114030	placebo	12/3/85	20
121021	placebo	12/3/85	19
121022	placebo	12/3/85	19
123017	placebo	12/3/85	18
42020	placebo	12/2/85	26
61033	placebo	12/2/85	18
112022	placebo	12/2/85	23

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
81014	placebo	11/29/85	22
64001	placebo	11/27/85	36
81002	placebo	11/27/85	33
22012	placebo	11/26/85	29
22032	placebo	11/26/85	18
52003	placebo	11/26/85	34
101009	placebo	11/26/85	28
123018	placebo	11/26/85	15
61019	placebo	11/25/85	24
81023	placebo	11/25/85	15
23019	placebo	11/22/85	22
51015	placebo	11/22/85	20
71006	placebo	11/22/85	27
61013	placebo	11/21/85	27
61026	placebo	11/21/85	21
64006	placebo	11/21/85	33
73006	placebo	11/21/85	30
111006	placebo	11/21/85	32
73016	placebo	11/20/85	24
81006	placebo	11/20/85	28
114033	placebo	11/20/85	12
121019	placebo	11/19/85	19
101013	placebo	11/18/85	27
102019	placebo	11/18/85	30
112020	placebo	11/18/85	25
32015	placebo	11/14/85	24
111005	placebo	11/13/85	33
114005	placebo	11/13/85	33
83009	placebo	11/12/85	24
23026	placebo	11/8/85	12
31003	placebo	11/8/85	33
73025	placebo	11/8/85	19
22025	placebo	11/7/85	24
72005	placebo	11/7/85	30
73012	placebo	11/7/85	25
84009	placebo	11/7/85	32
101026	placebo	11/7/85	23
104003	placebo	11/7/85	27
42030	placebo	11/6/85	15
53020	placebo	11/6/85	15
61030	placebo	11/6/85	20
23007	placebo	11/5/85	28
42013	placebo	11/5/85	28
112026	placebo	11/5/85	20

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
121004	placebo	11/5/85	26
123013	placebo	11/5/85	21
44013	placebo	11/4/85	15
61024	placebo	11/4/85	22
114025	placebo	11/4/85	24
22029	placebo	11/1/85	20
23023	placebo	10/31/85	18
53002	placebo	10/31/85	31
73011	placebo	10/31/85	26
101035	placebo	10/31/85	19
121008	placebo	10/31/85	24
22035	placebo	10/30/85	12
42028	placebo	10/30/85	18
64015	placebo	10/30/85	25
71013	placebo	10/30/85	18
82006	placebo	10/30/85	30
114034	placebo	10/30/85	12
53023	placebo	10/29/85	9
82011	placebo	10/29/85	31
123002	placebo	10/29/85	26
112012	placebo	10/28/85	27
33019	placebo	10/24/85	12
74004	placebo	10/24/85	34
53004	placebo	10/23/85	29
12006	placebo	10/22/85	30
101042	placebo	10/22/85	12
23003	placebo	10/21/85	32
61015	placebo	10/21/85	26
51014	placebo	10/18/85	20
51012	placebo	10/17/85	25
51019	placebo	10/17/85	12
64020	placebo	10/17/85	19
101002	placebo	10/17/85	36
12008	placebo	10/16/85	27
72004	placebo	10/16/85	31
104007	placebo	10/15/85	20
112015	placebo	10/15/85	26
22020	placebo	10/11/85	26
51002	placebo	10/9/85	31
112006	placebo	10/9/85	29
42027	placebo	10/8/85	18
81018	placebo	10/8/85	19
73023	placebo	10/4/85	19
112028	placebo	10/4/85	9

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
114028	placebo	10/4/85	21
14007	placebo	10/3/85	28
42014	placebo	10/3/85	27
12005	placebo	10/2/85	31
112010	placebo	10/2/85	28
112002	placebo	10/1/85	34
101037	placebo	9/30/85	18
102014	placebo	9/30/85	31
83007	placebo	9/27/85	26
114024	placebo	9/25/85	24
102009	placebo	9/24/85	33
81011	placebo	9/19/85	23
33015	placebo	9/12/85	21
53006	placebo	8/6/85	28
61001	placebo	8/6/85	34
101011	placebo	7/11/85	26
81025	placebo	5/20/85	5
102005	placebo	3/18/85	32
72002	placebo	1/2/85	30
71004	placebo	9/15/83	20
114012	placebo	1/31/83	15
34007	placebo	2/12/82	7
61020	hydralazine/ISDN	10/21/86	23
101029	hydralazine/ISDN	12/13/85	22
22003	hydralazine/ISDN	12/12/85	34
53017	hydralazine/ISDN	12/12/85	22
102006	hydralazine/ISDN	12/12/85	35
104011	hydralazine/ISDN	12/12/85	12
121009	hydralazine/ISDN	12/12/85	24
121023	hydralazine/ISDN	12/12/85	19
23028	hydralazine/ISDN	12/6/85	12
101019	hydralazine/ISDN	12/6/85	26
112027	hydralazine/ISDN	12/6/85	12
114038	hydralazine/ISDN	12/6/85	12
61031	hydralazine/ISDN	12/4/85	20
121012	hydralazine/ISDN	12/4/85	23
123003	hydralazine/ISDN	12/4/85	26
51016	hydralazine/ISDN	12/3/85	18
101036	hydralazine/ISDN	12/3/85	19
102017	hydralazine/ISDN	12/3/85	31
101041	hydralazine/ISDN	12/2/85	15
104002	hydralazine/ISDN	12/2/85	28
112023	hydralazine/ISDN	12/2/85	22
52004	hydralazine/ISDN	11/29/85	33

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
24007	hydralazine/ISDN	11/27/85	30
74012	hydralazine/ISDN	11/27/85	32
83011	hydralazine/ISDN	11/27/85	15
12010	hydralazine/ISDN	11/26/85	27
12017	hydralazine/ISDN	11/26/85	15
23010	hydralazine/ISDN	11/26/85	27
23010	hydralazine/ISDN	11/26/85	27
23024	hydralazine/ISDN	11/26/85	15
103001	hydralazine/ISDN	11/26/85	36
114015	hydralazine/ISDN	11/26/85	28
64010	hydralazine/ISDN	11/25/85	29
42026	hydralazine/ISDN	11/22/85	19
81026	hydralazine/ISDN	11/22/85	12
12018	hydralazine/ISDN	11/21/85	15
22030	hydralazine/ISDN	11/21/85	20
32011	hydralazine/ISDN	11/21/85	26
61012	hydralazine/ISDN	11/21/85	27
81024	hydralazine/ISDN	11/21/85	15
102011	hydralazine/ISDN	11/21/85	33
104010	hydralazine/ISDN	11/21/85	18
114026	hydralazine/ISDN	11/20/85	23
114032	hydralazine/ISDN	11/20/85	19
22023	hydralazine/ISDN	11/19/85	25
23020	hydralazine/ISDN	11/19/85	21
101004	hydralazine/ISDN	11/19/85	32
71002	hydralazine/ISDN	11/16/85	32
31001	hydralazine/ISDN	11/14/85	34
42029	hydralazine/ISDN	11/8/85	15
82010	hydralazine/ISDN	11/8/85	32
102008	hydralazine/ISDN	11/8/85	34
12001	hydralazine/ISDN	11/7/85	34
44004	hydralazine/ISDN	11/7/85	30
53008	hydralazine/ISDN	11/7/85	28
101008	hydralazine/ISDN	11/7/85	28
121017	hydralazine/ISDN	11/7/85	21
22013	hydralazine/ISDN	11/6/85	28
64013	hydralazine/ISDN	11/6/85	26
112005	hydralazine/ISDN	11/6/85	30
114020	hydralazine/ISDN	11/6/85	25
22034	hydralazine/ISDN	11/5/85	15
101025	hydralazine/ISDN	11/5/85	23
42002	hydralazine/ISDN	11/4/85	36
74007	hydralazine/ISDN	11/4/85	33
34005	hydralazine/ISDN	11/1/85	31

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
53005	hydralazine/ISDN	11/1/85	29
102020	hydralazine/ISDN	10/31/85	30
114031	hydralazine/ISDN	10/28/85	19
32017	hydralazine/ISDN	10/25/85	23
33017	hydralazine/ISDN	10/25/85	21
14004	hydralazine/ISDN	10/24/85	30
42018	hydralazine/ISDN	10/24/85	26
81007	hydralazine/ISDN	10/24/85	27
62002	hydralazine/ISDN	10/23/85	34
64017	hydralazine/ISDN	10/23/85	24
44011	hydralazine/ISDN	10/22/85	20
51013	hydralazine/ISDN	10/22/85	22
73019	hydralazine/ISDN	10/22/85	22
112016	hydralazine/ISDN	10/22/85	26
42008	hydralazine/ISDN	10/18/85	29
24001	hydralazine/ISDN	10/17/85	34
32020	hydralazine/ISDN	10/17/85	20
101003	hydralazine/ISDN	10/17/85	35
114010	hydralazine/ISDN	10/17/85	30
42012	hydralazine/ISDN	10/16/85	28
12012	hydralazine/ISDN	10/10/85	24
22016	hydralazine/ISDN	10/10/85	28
33006	hydralazine/ISDN	10/10/85	30
51018	hydralazine/ISDN	10/10/85	12
22021	hydralazine/ISDN	10/9/85	26
14010	hydralazine/ISDN	10/8/85	22
101017	hydralazine/ISDN	10/8/85	26
52001	hydralazine/ISDN	10/4/85	35
33008	hydralazine/ISDN	10/3/85	28
53022	hydralazine/ISDN	10/3/85	12
81017	hydralazine/ISDN	10/3/85	20
44001	hydralazine/ISDN	10/2/85	36
22007	hydralazine/ISDN	10/1/85	31
53019	hydralazine/ISDN	10/1/85	18
71014	hydralazine/ISDN	9/30/85	9
33002	hydralazine/ISDN	9/26/85	34
83010	hydralazine/ISDN	9/25/85	22
53011	hydralazine/ISDN	9/24/85	25
74001	hydralazine/ISDN	9/17/85	34
81010	hydralazine/ISDN	8/23/85	24
73017	hydralazine/ISDN	8/13/85	22
81013	hydralazine/ISDN	3/28/85	20
22026	hydralazine/ISDN	1/4/85	18
42005	hydralazine/ISDN	12/12/84	30

Date of Last Clinic Visit for Survivors in V-HeFT I

Patient ID	Treatment	Last Clinic Visit	Visit #
44008	hydralazine/ISDN	8/31/84	15
71010	hydralazine/ISDN	11/15/83	4

Appears This Way
On Original

Survivors Discontinued Prematurely From Both Medications [Sponsor's Analysis]

Center	Patient #	Treatment	Day Discontinued	Reason Discontinued
2	2003	hydralazine/ISDN	1458	Patient's decision
2	2026	hydralazine/ISDN	399	Patient's decision
3	1001	hydralazine/ISDN	683	Adverse Event: dizziness or syncope, disorientation
3	2017	hydralazine/ISDN	30	Adverse Event: headache, dizziness or syncope, disorientation
3	3002	hydralazine/ISDN	697	Increased CHF
3	3006	hydralazine/ISDN	1100	Patient's decision
4	2002	hydralazine/ISDN	586	Adverse Event: arthralgias
4	2008	hydralazine/ISDN	926	Adverse Event
4	2029	hydralazine/ISDN	206	Adverse Event: headache, other
4	4004	hydralazine/ISDN	1354	Adverse Event: other, dizziness or syncope
4	4008	hydralazine/ISDN	200	other
6	1012	hydralazine/ISDN	1092	Patient's decision
6	2002	hydralazine/ISDN	1835	Patient's decision
6	4010	hydralazine/ISDN	1122	Increased CHF
7	1002	hydralazine/ISDN	1041	Cardiac Procedure
7	1010	hydralazine/ISDN	2	Patient's decision
7	1014	hydralazine/ISDN	24	Adverse Event: headache, dizziness or syncope
7	3017	hydralazine/ISDN	484	Adverse Event: other; Increased CHF
7	3019	hydralazine/ISDN	472	Patient's decision; other medical condition
7	4001	hydralazine/ISDN	315	Adverse Event: headache, dizziness or syncope, nausea
7	4007	hydralazine/ISDN	13	Adverse Event: headache, dizziness or syncope
12	3012	hydralazine/ISDN	299	Patient's decision
2	2025	placebo	622	Increased CHF
3	2005	placebo	276	Increased CHF
3	4007	placebo	27	Patient's decision
4	2010	placebo	946	Cardiac Procedure
4	2014	placebo	321	other
4	4013	placebo	305	other
5	1014	placebo	576	Patient's decision
5	3006	placebo	108	other medical condition
6	1001	placebo	1092	Patient's decision
6	1030	placebo	57	Patient's decision
7	1006	placebo	565	Adverse Event: dizziness or syncope, other
7	1009	placebo	724	Adverse Event: other
7	2002	placebo	48	Patient's decision
7	3012	placebo	23	Adverse Event: dizziness or syncope
8	1002	placebo	1534	Increased CHF
8	2006	placebo	1072	new or worsened angina
10	1007	placebo	1416	Adverse Event: embolism; another MD decision; other medical condition
10	1011	placebo	818	new or worsened angina
11	4012	placebo	285	Patient's decision

The following table includes patients who had zero capsules and pills prescribed on the final study medication case report form (form F). In addition, there were some patients who had greater than zero capsules and pills prescribed on their final form F but who had a discontinuation form (form P) completed at a later date that indicated discontinuation of therapy.

Patients Permanently Discontinued Prematurely From Both Medications Based on FDA Analysis.

[last clinic visit = date last clinic visit form completed; last form F = last study medication (form F) completed; caps/day or tabs/day = the number of capsules or tablets prescribed on the last form F

On Sponsor list	Rx	Center	Patient #	last clinic visit	last form F	Visit	capsules disp	caps/day	tablets disp	tabs/day
yes	H-ISDN	2	2003	12/12/85	12/12/85	34	0	0	0	0
yes	H-ISDN	3	2017	10/25/85	10/25/85	23	0	0	0	0
yes	H-ISDN	3	3002	9/26/85	9/26/85	34	0	0	0	0
yes	H-ISDN	3	3006	10/10/85	10/10/85	30	0	0	0	0
yes	H-ISDN	4	2002	11/4/85	11/4/85	36	0	0	0	0
yes	H-ISDN	4	2008	10/18/85	10/18/85	29	0	0	0	0
yes	H-ISDN	4	2029	11/8/85	11/8/85	15	0	0	0	0
yes	H-ISDN	4	4004	11/7/85	11/7/85	30	0	0	0	0
yes	H-ISDN	6	2002	10/23/85	10/23/85	34	0	0	0	0
yes	H-ISDN	6	4010	11/25/85	11/25/85	29	0	0	0	0
yes	H-ISDN	7	1002	11/16/85	11/14/85	32	0	0	0	0
yes	H-ISDN	7	1007	1/16/85	10/10/84	19	0	0	0	0
yes	H-ISDN	7	1010	11/15/83	11/14/83	4	0	0	0	0
yes	H-ISDN	7	1014	9/30/85	6/21/85	5	0	0	0	0
yes	H-ISDN	7	3017	8/13/85	2/7/85	20	0	0	0	0
yes	H-ISDN	7	3019	10/22/85	10/22/85	22	0	0	0	0
yes	H-ISDN	7	4001	9/17/85	9/17/85	35	0	0	0	0
yes	H-ISDN	7	4007	11/4/85	11/4/85	33	0	0	0	0
yes	H-ISDN	12	3012	11/20/84	11/20/84	15	0	0	0	0
yes	H-ISDN	2	2026	1/4/85	1/4/85	18	840	8	840	8
yes	H-ISDN	4	4008	8/31/84	6/7/84	12	840	8	840	8
yes	H-ISDN	6	1012	11/21/85	8/6/85	25	280	8	280	8
yes	H-ISDN	7	2003	1/24/84	10/14/83	24	840	8	840	8
yes	placebo	1	1003	5/31/83	5/31/83	21	0	0	0	0
yes	placebo	3	2005	12/13/85	1/28/83	18	0	0	0	0
yes	placebo	3	4007	2/12/82	2/12/82	7	0	0	0	0
yes	placebo	4	1002	5/25/83	5/25/83	21	0	0	0	0
yes	placebo	4	2010	12/13/85	12/13/85	29	0	0	0	0
yes	placebo	4	2014	10/3/85	10/3/85	27	0	0	0	0
yes	placebo	5	3006	8/6/85	8/6/85	28	0	0	0	0
yes	placebo	6	1007	12/12/85	9/12/85	27	0	0	0	0
yes	placebo	7	1003	3/30/85	3/12/85	26	0	0	0	0
yes	placebo	7	1006	11/22/85	11/22/85	27	0	0	0	0
yes	placebo	7	1009	12/6/85	12/6/85	23	0	0	0	0
yes	placebo	7	2002	1/2/85	9/17/84	29	0	0	0	0
yes	placebo	7	3012	11/7/85	11/8/85	25	0	0	0	0
yes	placebo	7	3018	8/19/85	5/6/85	21	0	0	0	0
yes	placebo	7	4008	10/20/81	10/20/81	14	0	0	0	0
yes	placebo	7	4013	10/26/82	8/2/82	15	0	0	0	0
yes	placebo	8	1002	11/27/85	11/27/85	33	0	0	0	0
yes	placebo	8	2006	10/30/85	10/30/85	30	0	0	0	0

Patients Permanently Discontinued Prematurely From Both Medications Based on FDA Analysis.

[last clinic visit = date last clinic visit form completed; last form F = last study medication (form F) completed;
caps/day or tabs/day = the number of capsules or tablets prescribed on the last form F

On Sponsor list	Rec	Center	Patient #	last clinic visit	last form F	visit	capsules disp	caps/day	tablets disp	tabs/day
yes	placebo	10	1005	12/16/82	12/16/82	19	0	0	0	0
yes	placebo	10	1011	7/11/85	7/11/85	26	0	0	0	0
yes	placebo	10	2007	1/6/83	1/6/83	23	0	0	0	0
yes	placebo	11	4012	1/31/83	1/31/83	15	840	0	840	0
yes	placebo	5	1014	10/18/85	7/19/85	19	840	8	840	8
yes	placebo	6	1001	8/6/85	5/10/83	25	840	8	840	8
yes	placebo	6	1030	11/6/85	5/9/84	3	280	4	280	4
yes	placebo	10	1007	12/5/85	12/5/85	30	840	8	840	4
yes	placebo	3	2002	11/18/82	11/18/82	23	840	8	840	8
yes	placebo	4	4007	12/12/83	12/12/83	12	560	8	560	8
yes	placebo	8	3004	7/23/82	7/23/82	7	632	8	632	8
no	H-ISDN	3	2006	12/5/85	5/31/85	27	0	0	0	0
no	H-ISDN	4	2023	8/9/85	8/9/85	20	0	0	0	0
no	H-ISDN	4	2026	11/22/85	11/22/85	19	0	0	0	0
no	H-ISDN	5	1005	8/22/83	8/22/83	20	0	0	0	0
no	H-ISDN	6	1031	12/4/85	12/4/85	20	0	0	0	0
no	H-ISDN	7	3002	8/25/81	8/25/81	16	0	0	0	0
no	H-ISDN	8	1019	11/21/84	11/21/84	9	0	0	0	0
no	H-ISDN	8	2010	11/8/85	11/8/85	32	0	0	0	0
no	H-ISDN	8	4006	11/20/84	11/20/84	27	0	0	0	0
no	H-ISDN	10	4004	12/13/83	12/13/83	18	0	0	0	0
no	H-ISDN	11	4031	10/28/85	8/27/84	5	0	0	0	0
no	placebo	1	4005	1/4/83	3/16/82	7	0	0	0	0
no	placebo	3	2012	3/1/85	3/1/85	23	0	0	0	0
no	placebo	3	3007	1/3/84	1/3/84	21	0	0	0	0
no	placebo	3	3015	9/12/85	3/15/85	19	0	0	0	0
no	placebo	4	2007	7/11/82	6/1/82	9	0	0	0	0
no	placebo	4	4003	2/7/83	2/4/83	20	0	0	0	0
no	placebo	8	2003	8/6/82	11/3/82	21	0	0	0	0
no	placebo	8	2005	12/3/85	12/3/85	32	0	0	0	0
no	placebo	8	2008	12/5/85	12/5/85	33	0	0	0	8
no	placebo	8	4004	6/8/81	6/8/81	8	0	0	0	0
no	placebo	10	1021	12/17/85	12/17/85	26	0	0	0	0
no	placebo	10	1023	11/1/83	10/18/83	12	0	0	0	0
no	placebo	10	1031	12/14/84	12/14/84	18	0	0	0	0
no	placebo	10	2012	12/12/84	12/12/84	29	0	0	0	0
no	placebo	10	4006	1/7/86	1/7/86	20	0	0	0	0
no	placebo	11	2013	4/6/83	4/6/83	12	0	0	0	0
no	placebo	11	3006	10/17/84	10/17/84	29	0	0	0	0
no	placebo	11	4011	4/16/85	4/16/85	28	0	0	0	0

The following table includes patients who had zero capsules or pills prescribed on the final study medication case report form (form F).

Patients Permanently Discontinued Prematurely From Either Medication Based on FDA Analysis.

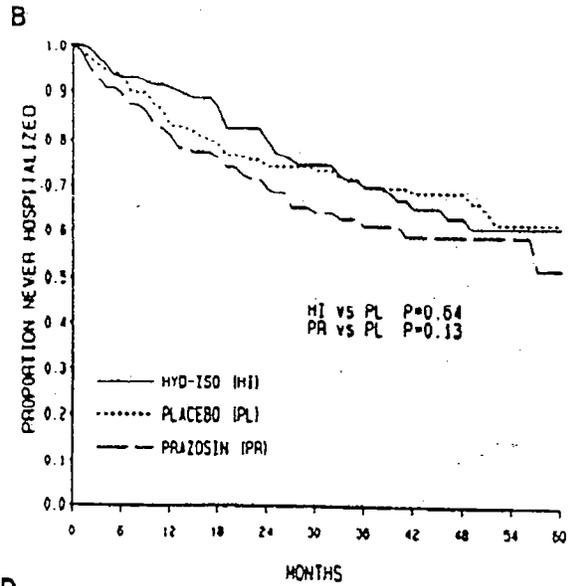
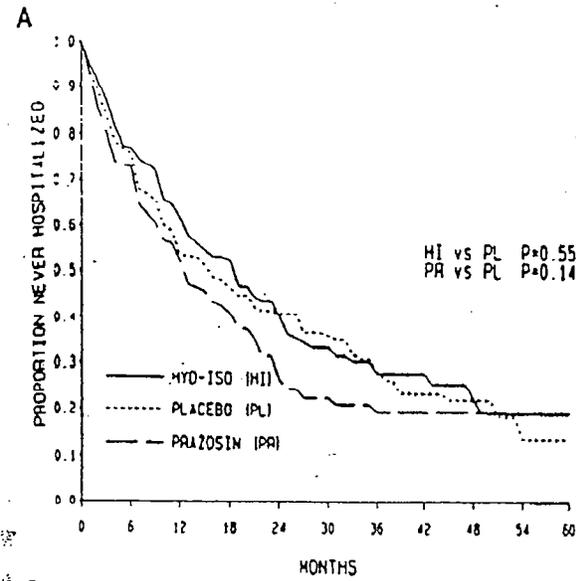
[last clinic visit = date last clinic visit form completed; last form F = last study medication (form F) completed; caps/day or tabs/day = the number of capsules or tablets prescribed on the last form F

On Sponsor List	R#	Center	Patient #	last visit	date of	visit	capsules disp	caps/day	tablets disp	tabs/day
no	H-ISDN	1	2001	11/7/85	11/7/85	34	0	0	840	8
no	H-ISDN	1	2004	6/18/84	6/18/84	27	0	0	840	8
no	H-ISDN	1	4010	10/8/85	10/8/85	22	840	8	0	0
yes	H-ISDN	3	4002	10/18/84	10/18/84	28	0	0	840	4
no	H-ISDN	4	2005	12/12/84	12/12/84	30	840	8	0	0
no	H-ISDN	4	2012	10/16/85	10/16/85	28	840	8	0	0
no	H-ISDN	4	2018	10/24/85	10/24/85	26	560	4	0	0
no	H-ISDN	4	3002	5/5/83	5/5/83	22	840	4	0	0
no	H-ISDN	4	4011	10/22/85	10/22/85	20	560	5	0	0
no	H-ISDN	5	1013	10/22/85	10/22/85	22	0	0	840	8
no	H-ISDN	5	2001	10/4/85	10/4/85	35	840	8	0	0
no	H-ISDN	5	2004	11/29/85	11/29/85	33	840	8	0	0
no	H-ISDN	5	3005	11/1/85	11/1/85	29	0	0	840	8
no	H-ISDN	5	3017	12/12/85	12/12/85	22	280	4	0	0
no	H-ISDN	5	3019	10/1/85	10/1/85	18	560	4	0	0
no	H-ISDN	5	3022	10/3/85	10/3/85	12	840	8	0	0
no	H-ISDN	6	1004	6/4/85	6/4/85	29	840	8	0	0
no	H-ISDN	6	1016	7/18/84	7/18/84	20	840	8	0	0
yes	H-ISDN	6	4003	10/28/81	10/28/81	19	0	0	840	8
no	H-ISDN	7	3022	9/5/85	7/1/85	18	840	8	0	0
yes	H-ISDN	8	2007	8/31/83	8/31/83	24	0	0	840	8
no	H-ISDN	8	3010	9/25/85	9/25/85	22	0	0	560	8
yes	H-ISDN	8	4003	11/8/82	11/8/82	21	0	0	840	8
no	H-ISDN	10	1025	11/5/85	11/5/85	23	840	6	0	0
no	H-ISDN	10	1029	12/13/85	12/13/85	22	0	0	840	8
no	H-ISDN	10	2008	11/8/85	11/8/85	34	840	8	0	0
no	H-ISDN	10	4002	12/2/85	12/2/85	28	840	8	0	0
no	H-ISDN	11	2005	11/6/85	11/6/85	30	560	0	0	0
no	H-ISDN	11	2027	12/6/85	12/6/85	12	0	0	840	6
yes	H-ISDN	11	3001	3/16/84	3/16/84	29	0	0	840	4
no	H-ISDN	11	4010	10/17/85	10/17/85	30	0	0	840	8
no	H-ISDN	12	3006	10/24/85	10/24/85	24	840	8	0	0
no	placebo	2	3025	12/12/85	12/12/85	12	0	0	840	8
no	placebo	4	4014	12/6/85	12/6/85	15	0	0	560	8
no	placebo	5	3004	10/23/85	10/23/85	29	840	8	0	0
no	placebo	5	3023	10/29/85	10/29/85	9	840	8	0	0
no	placebo	7	1004	9/15/83	9/15/83	20	840	8	0	0
no	placebo	7	3021	12/6/85	12/6/85	21	840	8	0	0
no	placebo	8	3007	9/27/85	9/27/85	26	840	8	0	0
no	placebo	11	1005	11/13/85	11/13/85	33	0	0	840	8
no	placebo	12	3017	12/3/85	12/3/85	18	840	8	0	0

Graphs from Circulation 1993; 87(6):VI-78 - 87

Graph A. Time to First Hospitalization for Any Reason (V-HeFT I).

Graph B. Time to First Hospitalization for CHF (V-HeFT I).



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Table from Circulation 1993; 87(6):VI-78 - 87

TABLE I. Frequency and Duration of Hospitalization Within Treatment Groups for Vasodilator-Heart Failure Trial I

	Placebo (n=273)		Prazosin (n=183)		HYD-ISO (n=186)	
	No.	%	No.	%	No.	%
Hospitalized patients*						
Heart failure	65	24	54	30	45	24
Other cardiac	72	26	54	30	39	21
Noncardiac	107	39	88	48	78	42
Any reason	166	61	116	63	109	59
Hospitalizations†						
Heart failure	115	27	120	31	86	29
Other cardiac	104	25	89	23	60	20
Noncardiac	200	48	177	46	152	51
Any reason	419	100	386	100	298	100
	Median		Median		Median	
Total days hospitalized‡ (per patient)						
Heart failure	12		17		10	
Other cardiac	11		12		9.5	
Noncardiac	14		14.5		18	
Any reason	20		22		20	

*No significant differences between placebo and either prazosin or HYD-ISO.

†Total hospitalizations are the total number of clinic visit intervals in which a hospitalization was reported. Tests comparing frequency distributions showed no significant differences.

‡Total number of days hospitalized per patient is the sum of all the days a patient was reported hospitalized during follow-up.

HYD-ISO, hydralazine plus isosorbide dinitrate.

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Description of Simulation Utilizing Monte Carlo Randomization for Cox Regression

- 1) Patients with missing baseline values for the covariates used in the Cox Regression analysis have values imputed. The imputation strategy uses values from the patients who are not missing these baseline values. These imputed values are the mean, the maximum or the minimum values for ejection fraction or maximum oxygen consumption.
- 2) All placebo or H-ISDN patients are re-randomized to either placebo or H-ISDN. The survival data for a patient remains unchanged but their treatment assignment may change.
- 3) A Cox Regression analysis is performed on the re-randomized patients and a test statistic for the Cox Regression is calculated.
- 4) Steps #2 and #3 are performed 10,000 times (10,000 replications).
- 5) A simulation distribution is obtained from the test statistics of the 10,000 replications.
- 6) The Cox Regression test statistic for the actual V-HeFT I trial is compared to the simulation distribution. The number of test statistics from the simulation that are greater than the test statistic from V-HeFT I determines the p value. As an example, in the simulation for overall survival 384 of the 10,000 (10,000 replications plus 1 actual test result) test statistics in the simulation were greater than the actual test statistic calculated from the data of V-HeFT I. The p value is .038 (384/10,001).

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Description of Simulation Utilizing Monte Carlo Randomization for Logrank/Cox

- 1) Patients with missing baseline values for the covariates used in the Cox Regression analysis have values imputed. The imputation strategy uses values from the patients who are not missing these baseline values. These imputed values are the mean, the maximum or the minimum values for ejection fraction or maximum oxygen consumption.
- 2) All placebo or H-ISDN patients are re-randomized to either placebo or H-ISDN. The survival data for a patient remains unchanged but their treatment assignment may change.
- 3) Logrank test and Cox Regression analysis are performed on the re-randomized patients and test statistics for both analysis is calculated.
- 4) Steps #2 and #3 are performed 10,000 times (10,000 replications).
- 5) A simulation distribution is obtained by selecting the larger test statistic of the Logrank and Cox Regression for each replication (10,000 replications).
- 6) The Cox Regression test statistic for the actual V-HeFT I trial is compared to the simulation distribution. The number of test statistics from the simulation that are greater than the test statistic from V-HeFT I determines the p value. As an example, in the simulation for overall survival 509 of the 10,001 (10,000 replications plus 1 actual test result) test statistics in the simulation were greater than the actual test statistic calculated from the data of V-HeFT I. The p value is .051 (509/10,001).

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Summary of Mortality Analyses Results Submitted by Sponsor 12/13/96.

Table I
Summary of Mortality Analysis Results
VHeFT I and VHeFT II

<u>VHeFT I: H/ISDN vs. Placebo</u>		<u>p value</u>	<u>risk ratio</u>	<u>95% CI</u>
<i>2-Year Mortality:</i>				
Log rank test	N=459	0.0557	0.70	(0.49, 1.01)
Cox model (non-missing covariates)	N=404	0.0023	0.53	(0.35, 0.80)
Cox model (interpolated missing)	N=459	0.0335	0.67	(0.46, 0.97)
<i>Overall Mortality:</i>				
Log rank test	N=459	0.0925	0.78	(0.58, 1.04)
Cox model (non-missing covariates)	N=404	0.0053	0.63	(0.46, 0.87)
Cox model (interpolated missing)	N=459	0.0354	0.73	(0.54, 0.98)
<u>VHeFT II: H/ISDN vs. Enalapril</u>				
<i>2-Year Mortality:</i>				
Log rank test	N=804	0.0170	1.46	(1.07, 1.99)
<i>Overall Mortality:</i>				
Log rank test	N=804	0.0828	1.23	(0.97, 1.55)
<u>H/ISDN from VHeFT II vs. Placebo from VHeFT I</u>				
<i>2-Year Mortality:</i>				
Log rank test	N=674	0.0146	0.70	(0.52, 0.93)
<i>Overall Mortality:</i>				
Log rank test	N=674	0.0198	0.75	(0.59, 0.96)
Cox model (non-missing covariates)	N=620	0.0002	0.61	(0.47, 0.79)
Cox model (interpolated missing)	N=674	0.0002	0.63	(0.49, 0.81)
<u>H/ISDN patients from VHeFT II that did not participate in VHeFT I vs. Placebo in VHeFT I</u>				
<i>2-Year Mortality:</i>				
Log rank test	N=613	0.0269	0.71	(0.52, 0.96)
<i>Overall Mortality:</i>				
Log rank test	N=613	0.0206	0.74	(0.58, 0.96)
Cox model (non-missing covariates)	N=566	0.0007	0.62	(0.47, 0.82)
Cox model (interpolated missing)	N=613	0.0006	0.63	(0.48, 0.82)

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John Anthony Bauer, BSc, and Ho-Leung Fung, Ph.D., "Concurrent Hydralazine Administration Prevents Nitroglycerin-Induced Hemodynamic Tolerance in Experimental Heart Failure," Circulation, Volume 84, No. 1, July 1991:35-40.

Gogia Harinder, M.D., et al., "Prevention of Tolerance to Hemodynamic Effects of Nitrates with Concomitant Use of Hydralazine in Patients With Chronic Heart Failure," Journal of the American College of Cardiology, December 1995:1575-80.

Thomas Munzel, et al., "Hydralazine Prevents Nitroglycerin Tolerance by Inhibiting Activation of a Membrane-bound NADH Oxidase," The Journal of Clinical Investigation, Volume 98, No. 6, September 1996:1465-1470.

P. Unger, G. Berkenboom, and J. Fontaine, "Interaction Between Hydralazine and Nitrovasodilators in Vascular Smooth Muscle," Journal of Cardiovascular Pharmacology, Volume 21, No. 3, 1993:478-483.

Hospitalizations in V-HeFT II.

	Hydralazine/ ISDN	enalapril
# randomized	401	403
# patients hospitalized at least once (as a percent of # randomized)	264 (65.8%)	276 (68.5%)
total # hospitalizations (any cause)	678	706
# hospitalizations / # randomized	1.69	1.75
# hospitalizations for heart failure ^A	189	189
# patients hospitalized at least once for CHF (as a percent of # randomized)	110 (27.3%)	112 (27.8%)
# hospitalizations for heart failure /# patients hospitalized at least once for CHF	1.72	1.69
duration of hospitalization for CHF (median)	8	7
duration of hospitalization for CHF (mean)	11.3 ± 13.4	10.3 ± 8.8
# hospitalizations for other cardiac cause ^A	215	175
# patients hospitalized at least once for other cardiac cause (as a percent of # randomized)	133 (33.2%)	126 (31.3%)
# hospitalizations for CHF or other cardiac cause ^{A,*}	389	348
# patients hospitalized at least once for CHF or other cardiac cause (as a percent of # randomized)	198 (49.4)	191 (47.4%)
# hospitalizations / # randomized	.97	.96
# hospitalizations for other cause ^A	324	388
# patients hospitalized at least once for other cause (as a percent of # randomized)	162 (40.4%)	200 (49.6%)

^A Each hospital admission may have more than one reason for hospitalization. Thus, the sum of the hospitalization for CHF, cardiac cause and other cause will be greater than the total # of hospitalizations.
 * Major Endpoint

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Medical Review

NDA #: 20-727/BZ

Drug Name: BiDil

Sponsor: Medco

Type of Document: response to request for information

Correspondence Date: 1/13/97

Date Received: 1/15/97

Date Completed: 2/14/97

This submission contained communications between the Operations Committee statistician and the Operations Committee. It also includes the results of data analyses provided to the Committee members. Table 1 list the results of the many analyses performed during the conduct of the trial.

Table 1. Analyses Presented to the Operations Committee.

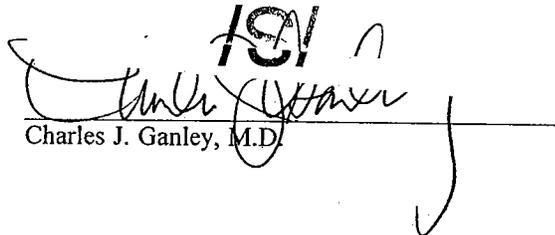
[All analysis are for overall survival except for those in shaded rows.]

Date	N	Comparison of all Three Treatments		Combined Vasodilators vs. Placebo		H-ISDN vs. Placebo		Prazosin vs. Placebo	
		Test	P value	Test	P value	Test	P value	Test	P value
10/81	195	Wilcoxon	.39						
		Savage	.59						
9/82	310	Wilcoxon	.38						
		Savage	.53						
4/83	393	logrank	.242	logrank	.18	logrank	.088		
6/83	433			logrank	.032	logrank	.0062		
				Wilcoxon	.240	Wilcoxon	.0073		
						exponential	.0066		
720 days							.066		
900 days							.0006		.042
9/83	420					logrank	.0074		
						Cox ¹	.0061		
9/83	456	logrank	.0165	logrank	.0104	logrank	.0042	logrank	.166
						exponential	.0041	exponential	.1666
		Wilcoxon	.1479	Wilcoxon	.1140	Wilcoxon	.0421	Wilcoxon	.5237
1 year				t-test	.2985	t-test	.1048	t-test	.8266
2 year				t-test	.0472	t-test	.024	t-test	.21
2.5 years				t-test	.0082	t-test	.0038	t-test	.0875
2/84	499	logrank	.053	logrank	.037	logrank	.013	logrank	.321
				exponential	.035	exponential	.015	exponential	.284
1 year						t-test	.062	t-test	
2 year						t-test	.052	t-test	.359
2.5 years						t-test	.008	t-test	.348
10/84	560					logrank	.0256		
				exponential	.095	exponential	.024	exponential	.626
1 year						t-test	.039		
2 year						t-test	.012		
2.5 years						t-test	.005		
5/95	627					logrank	.077	logrank	.627
10/85	642					logrank	.055	logrank	.95
						Wilcoxon	.040	Wilcoxon	.94

¹ see appendix page A28

Observations

- In September of 1982, the statistician first proposed the O'Brien Fleming rule for providing sequential monitoring guidelines. (see appendix A10) The timing of the first two analysis had already passed at the time that these rules were proposed.
- The third interim analysis at 420 randomized patients was performed for the H-ISDN vs. placebo comparison only. This comparison, however, was chosen because the results of the other comparisons¹ had less impressive p values after 456 patients².


 Charles J. Ganley, M.D.

cc: orig.
 HFD-110
 HFD-110 / CSO / C. GANLEY/S.CHEN
 HFD- 725/J.HUNG

Appendix Pages A1 - A43

Communications and selected analyses provided to the Operations Committee from the Statistician.

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¹ prazosin vs. placebo, combined vasodilator vs. placebo and comparison of all three treatments

² The analyses for 456 patients and 420 patients was provided at the same time to the committee (see appendix page A24; table 11.1 - 11.4 and table 12). The only reason to focus on the H-ISDN vs. placebo comparison is that this showed the most impressive difference of the analyses performed on 456 patients.

43 Page(s) Withheld



§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling