Table XLVIII. (continued)

Amlodipine	174 7840004	45	Worsening CHF
	174 7880003	6	Increasing Angina
	174 7880012	51	Severe Left Leg Pain
	174 8890002	68	Ventricular Tachycardia
Placebo	174 5180015	28	Fatigue
	174 6170002	69	Worsening CHF
	174 6060005	57	SOB
	174 7600003	77	Cardiac Arrest
	174 7840005	36	Ankle Fracture
	174 7910008	14	Dyspnea on Exertion/Worsening CHF
	174 7920004	16	CA Larynx, Sore Throat, Pharyngitis

In total, thirteen patients in the amlodipine group, and 8 patients in the placebo group were discontinued from the study. Among the amlodipine treated patients that were discontinued three subjects defaulted. One patient in each group was discontinued because they died.

Case Summaries of Patients with Fatal Events
Patient 053-174-617-0006 (RUS5311): This 69-year-old diabetic male was treated with amlodipine for congestive heart failure. Study drug was administered orally at a dose of 10 mg/day from December 7, 1992, to February 19, 1993. On February 19 while driving, he became weak and short of breath, pulled to the side of the road and collapsed. He was taken to the emergency room in acute respiratory distress requiring bag-assisted ventilation. His vital signs continued to deteriorate and on February 20, 1993, he went into third degree heart block, eventually becoming asystolic and expiring The cause of death was listed as myocardial infarction. Concomitant medications included potassium chloride, furosemide, digoxin, and glipizide.
Patient 053-174-656-0002 (RUS4448): This 66-year-old male was treated with double-blind placebo for congestive heart failure. Study drug was administered orally from July 29, 1992, to September 6, 1992. On September 7 he was found dead in bed. The cause of death per death certificate was coronary artery disease. Concomitant medications included furosemide, digoxin, allopurinol, enalapril, and potassium chloride. Other illnesses present at the time of death included gouty arthritis.

Summary: This was a randomized, parallel-group, double-blind, placebo-controlled, force-titration (5 mg to 10 mg once daily), 12 week study. The effects of orally administered amlodipine on exercise tolerance and safety were assessed in patients with mild to severe chronic heart failure (NYHA Class II to IV) receiving a combination of diuretics and digoxin, with or without an added ACE inhibitor.

Patient baseline characteristics were similar in the amlodipine and placebo treatment groups. For most of the patients the underlying cause of heart failure was ischemic heart disease or cardiomyopathy.

Administration of amlodipine for 12 weeks was not associated with any significant changes in either the primary clinical efficacy endpoint, i.e., symptom-limiting (dyspnea or fatigue) exercise time, or the other clinical endpoints, i.e., NYHA functional class, symptoms, LVEF, and quality of life (including a six minute walk test). Except for peripheral edema, there appeared to be no differences between amlodipine and placebo in the incidence of side effects. However, there was twice as many patients discontinued because of worsening of heart failure in the amlodipine group as compared with the placebo group.

The factual interpretation of this study is that it provides no support for a presumably beneficial effect of treatment with amlodipine to patients with heart failure.

***Protocol* #053-175:** This was a randomized, double-blind, placebo-controlled, parallel group, 12 week study to evaluate the safety and efficacy of a fixed dose (10 mg once daily) of amlodipine on exercise tolerance in patients with mild to severe heart failure NYHA Class II to IV (LVEF ≤35%), receiving a combination of diuretics, digoxin, and ACE inhibitor. An exercise tolerance test was performed every 4 weeks and at the end of the double-blind treatment period.

The purposes of this investigation were to:

i) determine the effects of amlodipine on exercise tolerance.
ii) ascertain the effects of amlodipine on functional status and cardiac function
iii) assess the safety of amlodipine

Efficacy:

The primary endpoint was:

-symptom-limiting exercise time.

Secondary endpoints consisted of:

-NYHA and clinical symptoms,
-LVEF,
-Assessment of autonomic regulation and,
-Quality of life.

Safety:

Safety evaluation included clinical side effects, laboratory parameters, ECG, twenty-four hour ambulatory electrocardiogram.

Inclusion and Exclusion Criteria: Subjects were eligible for the study if they met criteria described in protocol #053-173 (pages 5-6).

Results:

Initially, four hundred forty-nine subjects entered the single blind placebo stabilization period, and two hundred forty-five patients were randomized, 125 to placebo group and 120 to amlodipine group.

Baseline characteristics of the randomized patients are summarized in Table XLIX.

Table XLIX. Baseline Patient Characteristics

Variables	Placebo	Amlodipine
# of Patients	125	120
Race (n):		
White	87	76
Black	30	37
Other	8	7
Mean Age (in years)	63.5	62.8
Mean Duration of CHF (in years)	4.4	3.6
NYHA Class (n):		
II	72	64
III	53	55
IV	0	1

Sex distribution, i.e. male/female ratio, was 97/28 in the placebo group, and 94/26 in the amlodipine group.

The underlying cause of heart failure was idiopathic dilated cardiomyopathy/ischemic heart disease/hypertension 60/57/4 in the placebo group, and 48/61/5 in the amlodipine group. Three amlodipine-treated patients had unspecified heart failure, 1 amlodipine-treated and 2 placebo-treated patients had alcoholic cardiomyopathy, 1 placebo-treated patient had persistent heart failure despite a properly functioning prosthetic valve, 1 placebo-treated patient had Chaga's disease with heart involvement, and 2 amlodipine-treated patients had unspecified hypertensive heart disease. The cardiovascular medical history was similar between the groups. In the amlodipine group, thirteen (10.8%) patients were smokers, and 60 (50.0%) had had a myocardial infarction. Among patients receiving placebo, 17 (13.6%) were currently smokers, and 55 (44.0%) had had a myocardial infarction.

Every patient in the study, independent of group assignment, was concurrently medicated with diuretics, digoxin, and an ACE inhibitor. In both groups mean LVEF was 23% (range 4-35%).

Most patients in each group had a duration of therapy between 70 and 98 days [placebo, 102/125 (81.6%); amlodipine, 95/120 (79.2%)].

Efficacy:

The primary endpoint was symptom-limiting exercise time (Table L). In both groups exercise tolerance increased, the magnitude of this change was 11.3% in the placebo group and 10.8% in the amlodipine group. However, amlodipine therapy failed to improve significantly exercise tolerance .

Table L. Total Exercise Test (sec) Intent to Treat Analysis

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=117)	540.9±16.8	609.9±20.8	69.0±12.1	11.3	0.7156
Amlodipine (n=111)	544.2±16.6	588.3±18.7	44.1±12.3	10.8	

[Values were obtained from IND Vol. 11.3, Table 8A, page 56, and they are expressed as arithmetic means±S.E; *sponsor's analysis.]

There were several secondary endpoints, i.e., LVEF, NYHA class and clinical symptoms, assessment of autonomic regulation and, quality of life. When compared to placebo patients, subjects receiving amlodipine had a modest but statistically significant increase in LVEF (Table LI). The clinical significant of that improvement in LVEF is not clear. Since measures of clinical betterment, such as exercise tolerance and six minute walk tests (Tables L and LII, respectively), were not improved by amlodipine therapy.

Table LI. LVEF (%) Intent to Treat Analysis

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=104)	23.4	24.1	0.68±0.69	3	0.006
Amlodipine (n=100)	23.3	26.6	3.31±0.67	14.2	

[Values were obtained from IND Vol. 11.3, Table 8B, page 57, and they are expressed as arithmetic means±S.E, *sponsor's analysis.]

The results from the six minute walk test are summarized in Table LII. The difference observed between the two groups was not statistically significant (p=0.2817).

Table LII. Six Minute Walk Test (yards) Intent to Treat Analysis

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=102)	418.9±13.9	429.1±15.2	10.2±8.8	2.43	0.2817
Amlodipine (n=95)	394.3±12.6	400.8±11.1	6.5±10.4	1.64	

[Values were obtained from IND Vol. 11.3, Table 8F, page 61, and they are expressed as arithmetic means±S.E; *sponsor's analysis.]

Data in NYHA class changes for both treatment arms are summarized in Table LIII. Examination of the results indicates that 14/116 (12.1%) amlodipine-treated patients and 15/120 (12.5%) placebo-treated patients improved;

10/116 (8.6%) amlodipine-treated patients and 9/120 (7.5%) placebo-treated patients worsened. The changes were similar between the treatment arms.

Table LIII. NYHA Classification Changes Intent to Treat Analysis

		Final NYHA Class			
Group	Baseline NYHA Class	I (n)	II (n)	III (n)	IV (n)
Amlodipine	II	1	51	9	0
	III	0	12	41	1
	IV	0	1	0	0
Placebo	II	2	64	5	0
	III	0	13	32	4
	IV	0	0	0	0

[Values were obtained from IND Vol. 11.3, Table 10, page 63.]

Similarly, changes (data not shown) in the severity of heart failure symptoms were comparable in the amlodipine and placebo groups (IND Vol. 11.3, Table 11A, page 64).

Summary of quality of life parameters are shown in Table LIV. There were no significant differences between the groups.

Table LIV. Quality of Life Measures Intent to Treat Analysis

Quality of Life Variables	N	Baseline (mean)	Final (mean)	Change from Baseline (mean±SE)	p-Value*
Total					0.1914
Amlodipine	111	66.84	68.67	1.83±1.62	
Placebo	118	69.72	72.49	2.77±1.28	
Physical					0.1899
Amlodipine	111	61.02	62.50	1.48±1.99	
Placebo	118	64.56	66.95	2.39±1.75	
Emotional					0.3404
Amlodipine	111	71.20	74.58	3.38±2.15	
Placebo	117	74.08	77.95	3.87±1.46	
Health Care					0.4102
Amlodipine	105	3.69	3.66	-0.03±0.09	
Placebo	113	3.65	3.73	0.08±0.08	
Global Rating					0.7324
Amlodipine	110	2.82	2.99	0.17±0.15	
Placebo	117	2.97	3.11	0.15±0.10	
Health Perception					0.6034
Amlodipine	111	46.93	48.87	1.94±1.53	
Placebo	118	49.75	51.65	1.91±1.30	
Bed Days					0.7293
Amlodipine	108	0.54	0.68	0.14±0.17	
Placebo	112	0.76	0.92	0.16±0.26	
Alertness					0.5079
Amlodipine	110	84.84	85.13	0.29±1.81	
Placebo	117	83.31	85.53	2.22±1.58	

[Values were obtained from IND Vol. 11.3, Table 8D, page 59; *sponsor's analysis.]

Safety:

The number of side effects occurring per group is summarized in Table LV. There was an incidence of side effects of 16.7% in patients receiving amlodipine, and of 16.8% in placebo treated subjects.

Table LV. Incidence of Side Effects

Number of Patients	Placebo	10 mg Amlodipine
Evaluable	125	120
With Side Effects	21	20
Withdrawn with Side Effects	2	3

Peripheral edema was experienced more often by patients in the amlodipine group than by patients in the placebo group. The incidence of all remaining side effects was otherwise comparable between groups.

Table LVI is a summary of patients who were discontinued from double-blind therapy, and the reasons for theirs' discontinuation.

Table LVI. Discontinuation of Therapy

Treatment Group	Patient ID	Duration of Therapy (days)	Event
Amlodipine	175 6070009	53	Pedal Edema, Rash, Achy, Joint Stiffness
	175 6070015	27	Asked to be Withdrawn from Study
	175 6070002	19	Stroke
	175 6570009	66	Worsening CHF
	175 6570011	17	Rash, Ankle Edema
	175 6570015	42	Bilateral Pneumonia
	175 7410006	3	Enlarged Liver and Spleen
	175 7440007	34	Chest Pain
	1757490010	21	Non Compliant
	175 7530004	47	Asked to be Withdrawn from Study
	175 7690014	59	Worsening CHF
	175 7720003	67	Pulmonary Edema
	175 7720007	35	Cardiac Arrest
	175 7780002	46	Worsening CHF
	175 7720006	57	Acute Renal Failure
	175 7460002	79	Lost to Follow-Up
Placebo	175 6310007	115	Patient Defaulted
	175 6570004	34	Non Compliant
	175 7460004	54	Patient Incarcerated
	175 7460006	24	Asked to be Withdrawn from Study
	175 7490013	28	Worsening Orthopnea, Chest Pain
	175 7520005	47	Myocardial Infarction
	175 7690017	61	Patient Fracture 13 Vertebrae/Accident
	175 7720001	14	Non-q Wave Myocardial Infarction
	175 7760002	27	Worsening CHF
	175 7760004	9	Worsening CHF
	175 7760006	36	Worsening CHF/Cardiac Transplant
	175 7770001	70	TIA/CVA
	175 8950016	91	Patient Run Out of Meds.

Four patients receiving amlodipine and three patients receiving placebo defaulted. Two patients in the placebo-treated group were discontinued for other reasons (i.e., incarceration; patients ran out of study medication). One patient in the amlodipine group (657-0015) was discontinued due to bilateral pneumonia and one placebo-treated patient (752-0005) was discontinued because they had a myocardial infarction. Three patients in the amlodipine group discontinued because they died (607-0017; 749-0003; 772-0007). There were not discontinuations due to laboratory abnormalities.

Case Summaries of Patients with Fatal Events
Patient 607-0017 (AEM 9403048) This 84-year-old white female, with a history of coronary artery disease, stated that she "felt great" at her study clinic visit on April 15, 1994. She went shopping with her daughter and played bridge later in the evening. During the bridge game, she suddenly slumped over; EMS was called and she was pronounced dead due to cardiac arrest secondary to congestive heart failure. She had received amlodipine (10 mg/day) for 67 days. Concurrent illnesses present at the time of death included Paget's disease, hyperlipidemia, temporal arteritis, and iron deficiency anemia. Concomitant medications included prednisone, digoxin, iron, cimetidine, captopril, potassium, and furosemide.
Patient 749-0003 (AEM RUS4926) This 56-year-old Hispanic female with idiopathic cardiomyopathy died December 20, 1992, due to cardiopulmonary arrest secondary to congestive heart failure. She had received 6 days of treatment with amlodipine (10 mg/day) prior to her death. No further information is available about this death. Concomitant medications at the time of death included digoxin, enalapril, warfarin, glibenciamide, and furosemide.
Patient 772-0007 (AEM RUS4284) This 52-year-old black male had a cardiac arrest on August 3, 1992, while shopping. He was intubated by EMS, defibrillated once, and lidocaine and dopamine drips were started, but he remained comatose. He was weaned from the infusions on August 4 and remained unresponsive on a ventilator. Acute myocardial infarction was ruled out. On August 17 he was transferred to a general medical floor where he remained unresponsive until his death on August 18, 1992. Death was attributed to underlying ischemic cardiomyopathy. Study drug had been permanently discontinued on August 3, 1992 at which point he had received 35 days of amlodipine (10 mg/day). Concurrent illnesses included chronic obstructive pulmonary disease, hypercholesterolemia, and arthritis. Medical history includes alcohol abuse x 15 years and a family history of ischemic heart disease. Concomitant medications included nitroglycerin, enalapril, potassium, lovastatin, warfarin, furosemide, digoxin, and acetaminophen.

Summary: This was a randomized, double-blind, placebo-controlled, parallel group, 12 week study to evaluate the safety and efficacy of a fixed dose (10 mg once daily) of amlodipine on exercise tolerance in patients with mild to severe heart failure NYHA Class II and IV (LVEF ≤35%), receiving a combination of diuretics, digoxin, and ACE inhibitor.

This study failed to show improvement in exercise tolerance (i.e., primary endpoint) by amlodipine treatment. The only result supportive of amlodipine efficacy was a statistically significant but rather meager increase in LVEF (11.2%, i.e., amlodipine-placebo effect).

***Protocol* #053-172:** This was an open-label, non-comparative, 2-week study of the hemodynamic and clinical effects of a fixed oral dose of amlodipine (10 mg once-daily) in patients with NYHA class III-IV congestive heart failure and a left ventricular ejection fraction <35%. Patients were concurrently maintained on a stable therapeutic regimen consisting of diuretics, digoxin and/or ACE inhibitors. The investigation was conducted at three clinical centers.

The purposes of this study were as follows:

i) To evaluate the safety of amlodipine as assessed by hemodynamic and clinical endpoints.
ii) To determine the time-effect relationship of amlodipine given acutely on hemodynamic parameters.

Cardiac hemodynamic parameters were obtained, by right heart catheterization, at baseline and after dosing for 24 hr. (i.e., acute effects), and following the two-week course (i.e., chronic effects) of amlodipine therapy. No formal statistical analysis involving hypothesis testing was performed. The data werer evaluated using descriptive statistics.

Efficacy:

The two primary endpoints were:

-pulmonary capillary wedge pressure (PCWP) and cardiac index (CI).

Secondary endpoints included:

-systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR).

Clinical endpoints consisted of:

-NYHA and clinical symptoms,
-body weight,
-and supine and standing systolic/diastolic blood pressures and heart rate.

Safety:

Safety evaluation included:

-clinical side effects,
-laboratory parameters, ECG and chest X-ray.

Inclusion and Exclusion Criteria: Subjects were eligible for the study if they met criteria described in protocol #053-173 (pages 5-6).

Results:

Sixteen subjects entered the single blind placebo run-in period and 14 were entered in the open label period. Table LVII summarizes baseline patient characteristics.

Table LVII. Baseline Patient Characteristics

Variables	Amlodipine
# of Patients	14
Race (n):	
White	7
Black	6
Other	1
Mean Age (in years)	60.9

Table LVII. (continued)

Mean Duration of CHF (in years)	5.6
NYHA Class (n):	
III	7
IV	7

There were 2 female and 12 male patients in the trial. Fifty percent of the patients were either in NYHA functional class III or IV, with a mean LVEF of <22% (range 11-33%). The etiology of heart failure was ischemic heart disease (n=7) or idiopathic dilated cardiomyopathy (n=7). Medications at baseline included cardiac glycosides (n=11), diuretics (n=14), and ACE inhibitors (n=8).

Table LVIII summarizes the acute hemodynamic effects of amlodipine in 11 patients. The only two hemodynamic responses to amlodipine treatment that merit mentioning are the changes in Pulmonary Vascular Resistance (PVR) and Systemic Vascular Resistance (SVR). There was a 17.2% fall in PVR while SVR decreased by only 7.3%.

Table LVIII. Acute Hemodynamic Effects Intent to Treat Analysis (n=11)

Hemodynamic Variables	Baseline (mean)	*Peak (mean)	Change from Baseline (mean±SE)
Pulmonary Capillary Wedge Pressure (mmHg)	18.5	17.76	-0.74±1.42
Cardiac Index (l/min/m^2)	2.02	2.17	0.15±0.12
Mean Right Atrial Pressure (mmHg)	7.36	7.38	0.02±0.82
Mean Arterial Pressure (mmHg)	83	83.1	0.10±1.78
Heart Rate (bpm)	83	85.33	2.33±1.47
Mean Pulmonary Artery Pressure (mmHg)	32.21	29.69	-2.52±1.08
Stroke Volume Index (ml/m^2)	24.54	25.8	1.26±1.53
Systemic Vascular Resistance (dyne.sec.cm^2)	1699.86	1576.36	-123.50±132.73
Pulmonary Vascular Resistance (dyne.sec.cm^2)	315.52	261.37	-54.15±30.54

[Values were obtained from IND Vol. 5.1, Table 8B, page 34; *Peak-Week 0, mean of measurements taken at 6, 9, 12 hr. post-dose.]

Assessment of the effects of amlodipine following the last dose were analyzed (Table LIX, Figures 1 and 2). The comparison of trough values with peak values is summarized in Table LIX. The documented changes were negligible, however pulmonary capillary wedge pressure (PCWP) increased by 13.7%.

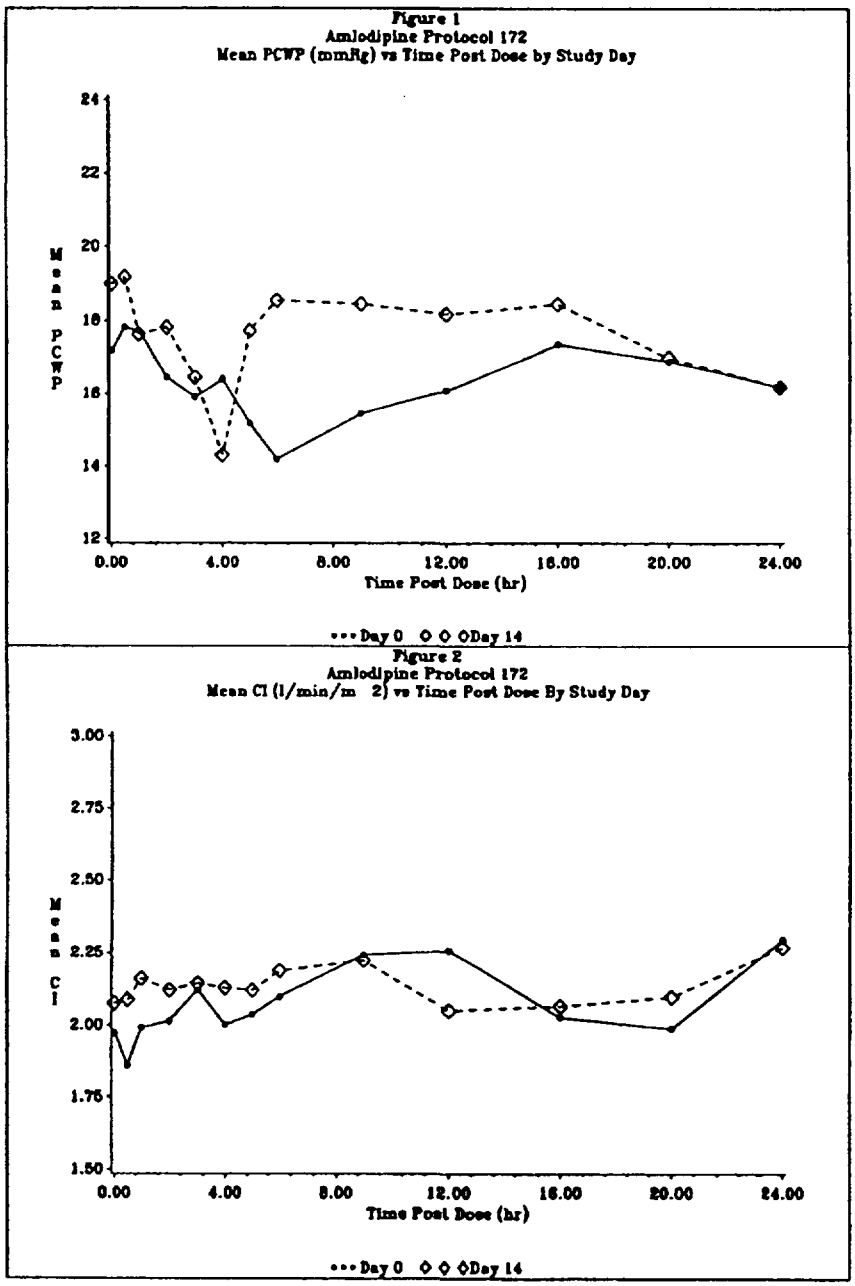
Table LIX. Chronic Hemodynamic Effects: Peak/Trough Intent to Treat Analysis (n=11)

Hemodynamic Variables	Trough (mean)	*Peak (mean)	Peak-Trough (mean±SE)
Pulmonary Capillary Wedge Pressure (mmHg)	16.18	18.39	2.21±1.20
Cardiac Index (l/min/m^2)	2.27	2.15	-0.12±0.10
Mean Right Atrial Pressure (mmHg)	7.82	7.88	0.06±0.79
Mean Arterial Pressure (mmHg)	84.18	81.82	-2.36±2.52
Heart Rate (bpm)	81.82	83.33	1.52±0.98
Mean Pulmonary Artery Pressure (mmHg)	29.27	30.33	1.06±1.15
Stroke Volume Index (ml/m^2)	27.82	25.94	-1.87±1.18
Systemic Vascular Resistance (dyne.sec.cm^2)	1519.28	1513.50	-5.78±98.37
Pulmonary Vascular Resistance (dyne.sec.cm^2)	263.00	258.97	-4.03±20.97

[Values were obtained from IND Vol. 5.1, Table 8C, page 35; *Peak-Week 2, mean of measurements taken at 6, 9, 12 hr. post-dose.]

The time course of changes in PCWP and cardiac index (CI) are graphically depicted in figures 1 and 2.

Figures 1 and 2. Amlodipine Protocol #172. Mean PCWP and CI vs. Time Post-Dose



[Figures were obtained from IND Vol. 5.1, Figures 1 and 2, page 49.]

Table LX summarizes the chronic effects following a 2-week course of amlodipine therapy. These effects were evaluated by comparing hemodynamic parameters taken prior to the first dose (week 0) and 24 hours after the last dose (week 2). Although minor the following hemodynamic changes are worth mentioning. PCWP fell by 5.8%, change that was associated with a 15.2% increment in CI. SVR and PVR fell by 14.9% and 21%, respectively.

Table LX. Chronic Hemodynamic Effects Intent to Treat Analysis (n=11)

Hemodynamic Variables	*Baseline (mean)	**Final (mean)	Change from Baseline (mean±SE)
Pulmonary Capillary Wedge Pressure (mmHg)	17.18	16.18	-1.00±1.37
Cardiac Index (l/min/m^2)	1.97	2.27	0.30±0.07
Mean Right Atrial Pressure (mmHg)	7.18	7.82	0.64±1.83
Mean Arterial Pressure (mmHg)	85.45	84.18	-1.27±2.68
Heart Rate (bpm)	79.64	81.82	2.18±1.26
Mean Pulmonary Artery Pressure (mmHg)	31.36	29.27	-2.09±1.76
Stroke Volume Index (ml/m^2)	25.01	27.82	2.81±0.86
Systemic Vascular Resistance (dyne.sec.cm^2)	1785.81	1519.28	-266.54±86.58
Pulmonary Vascular Resistance (dyne.sec.cm^2)	332.80	263.00	-69.80±25.22

[Values were obtained from IND{ }Vol. 5.1, Table 8A, page 33; * Baseline-Week 0, pre-dose, **Final-Week 2, 24 hr. post-dose.]

There were no changes in NYHA functional class (IND{ }Vol. 5.1, Table 8A, page 39). There were no changes in patients' symptoms whether assessed by a composite score index or individually. No changes in body weight were noted. No patient developed or experienced an increased edema. Standing systolic blood pressure fell by 3.5 mmHg and heart rate, both supine and standing, dropped by 2.7 and 6.1 bpm, respectively. Insofar as physical global evaluation and patient self-assessment, the investigators determined that overall clinical status was improved in 67% of the patients, and similarly 7 out of 12 patients reported an amelioration of symptoms.

Safety:

Patient 732-0002 developed ventricular arrhythmias. The severity of heart failure was reported to increase in two patients: 667-0003 and 732-0005. Patient 667-0002 was withdrawn from the study to undergo heart transplant. Patient 732-0001 experienced ventricular tachycardia and this resulted in discontinuation of the patient from the study drug. Neither major laboratory abnormalities nor fatal events were reported during the study.

Three patients were discontinued from the study:
-Patient 667-0002 was withdrawn from the study 12 hours after the first dose to undergo heart transplant when a donor heart became available.
-Patient 732-0001 was withdrawn on day 1 when he experienced episodes of ventricular tachycardia judge by the investigator to be treatment-related.
-Patient 732-0005 was withdrawn on day 7 due to worsening of heart failure judge by the investigator to be unrelated to treatment.

Summary: This was an open-label, non-comparative, 2-week study of the hemodynamic and clinical effects of a fixed oral dose of amlodipine (10 mg once-daily) in patients with NYHA Class III-IV congestive heart failure and a left ventricular ejection fraction <35%.

This study indicates that a short course of a fixed dose (10 mg once daily p.o.) of amlodipine does not exert detrimental effects in patients with severe heart failure as assessed by hemodynamic endpoints. No consistent changes in the main hemodynamic parameters, PCWP and CI, were found.

***Protocol* #053-176:** This was a 12-week randomized, placebo-controlled, double-blind, fixed-dose, parallel group study to investigate the hemodynamic effects of amlodipine treatment (5 mg and 10 mg once daily) versus placebo in patients with stable NYHA functional class II-IV receiving a combination of digoxin, diuretics and/or angiotensin converting enzyme inhibitors.

Cardiac hemodynamic parameters were obtained, by right heart catheterization, at baseline and at 0.5, 1, 4, 6, 8, 10 and 12 hours after dosing (i.e., acute effects), and following the two-week course (i.e., chronic effects) of amlodipine therapy.

Patients who successfully completed this study, without safety concerns, could be entered into an open-label extension trial (protocol #053-180).

The main purposes of this study were:

i) To determine the acute and chronic (12 weeks) hemodynamic activity and safety of amlodipine treatment (5 mg and 10 mg once daily).
ii) To assess the time-effect relationship of amlodipine on hemodynamic parameters.
iii) To ascertain the pharmacokinetics of amlodipine following single and multiple oral dosing.

Efficacy:

Primary Endpoints

-pulmonary capillary wedge pressure (PCWP) and cardiac index (CI).

Secondary Endpoints

-Mean right atrial pressure (MRAP), mean arterial pressure (MAP), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR).

Clinical endpoints

-NYHA functional class.
-Quality of Life.

Safety:

-Safety evaluation included clinical side effects, laboratory parameters, ECG, chest X-ray, and 24-hour ambulatory electrocardiogram.

Inclusion and Exclusion Criteria: Subjects were eligible for the study if they met a similar criteria to that described in protocol #053-173 (pages 5-6).

Results:

Two hundred six patients were entered in the single-placebo run-in period. Of those patients, one hundred forty-two were randomized to the double-blind therapy period. Baseline characteristics of these patients are summarized in table LXI.

Table LXI. Baseline Patient Characteristics

Variables	Placebo	Amlodipine 5 mg	Amlodipine 10 mg
# of Patients	49	48	45
Race (n):			
White	36	39	31
Black	13	8	12
Other	0	1	2

Table LXI. (continued)

Mean Age (in years)	61.7	60.8	63
Mean Duration of CHF (in years)	5.4	3.5	3.8
Mean LVEF (%)	24	23	23
NYHA Class (n):			
II	14	15	12
III	31	26	26
IV	4	7	7

The number/percentage of patients receiving all three background medications (i.e., digitalis, ACE inhibitor and diuretic) for CHF were similar in the three treatment groups: 35 of 49 patients (71.4%) receiving placebo, 37 of 48 patients (77.1%) in the 5 mg amlodipine group, and 33 of 45 patients (73.3%) receiving 10 mg amlodipine. Sex distribution, i.e. male/female ratio, among groups was placebo 38/11, amlodipine 5 mg 36/12, and amlodipine 10 mg 31/14. Mean LVEF was 23% in both amlodipine groups and 24% in the placebo group.

The distribution of underlying cause of heart failure, i.e., ischemic versus non-ischemic, was 23/25 for patients in the placebo group, 27/18 and 19/24 for patients receiving amlodipine 5 mg and 10 mg, respectively. The occurrence of other cardiovascular diseases was similar in each treatment group (IND( )Vol. 7.8, Tables 5a and 5b, pages 56-57). The number of patients that were current smokers and that had experienced a previous myocardial infarction was comparable among the treatment arms.

The mean (range) duration of double-blind therapy was 84.4 (12-121) days for 5 mg amlodipine, 81.6 (6-118) days for 10 mg amlodipine, and 80.2 (1-106) days for placebo.

Efficacy:

The acute effects of treatment on hemodynamic variables were ascertained by comparing the values obtained at baseline to the values obtained at peak (Table LXII). Amlodipine treatment, as compared with placebo, was associated with a small but significant reduction in mean arterial pressure. This response was associated with a decrease in systemic vascular resistance.

Table LXII. Acute Hemodynamic Effects Intent to Treat Analysis

Hemodynamic Variable	N	Baseline (mean)	Final (mean)	Change from Baseline (mean±SE)	p-Value*
Pulmonary Capillary Wedge Pressure (mmHg)					0.3021
Amlodipine 5 mg	40	20.70	19.77	-0.93±0.63	
Amlodipine 10 mg	36	20.64	19.83	-0.81±0.68	
Placebo	40	23.70	21.80	-1.90±0.72	
Cardiac Index (l/min/m^2)					0.0705
Amlodipine 5 mg	40	2.41	2.48	0.07±0.05	
Amlodipine 10 mg	36	2.30	2.53	0.23±0.07	
Placebo	40	2.08	2.17	0.08±0.07	
Mean Right Atrial Pressure (mmHg)					0.7522
Amlodipine 5 mg	40	8.42	8.08	-0.34±0.44	
Amlodipine 10 mg	36	9.59	9.40	-0.19±0.60	
Placebo	40	10.88	10.12	-0.76±0.47	

Table LXII. (continued)

Delayo 2/27/96

Mean Arterial Pressure (mmHg)			93.25		0.0012
Amlodipine 5 mg	40	94.65	94.57	-1.40±1.07	
Amlodipine 10 mg	36	96.38	97.60	-1.81±1.13	
Placebo	40	94.62	[illegible]	2.98±1.27	
Heart Rate (bpm)					0.422
Amlodipine 5 mg	40	78.40	80.88	2.47±0.93	
Amlodipine 10 mg	36	79.12	81.34	2.21±0.95	
Placebo	40	76.93	80.17	3.24±0.92	
Mean Pulmonary Artery Pressure (mmHg)					0.6447
Amlodipine 5 mg	40	30.82	30.38	-0.44±0.64	
Amlodipine 10 mg	35	36.26	34.09	-2.17±2.19	
Placebo	40	34.62	34.85	0.23±0.72	
Stroke Volume Index (ml/m^2)					0.36
Amlodipine 5 mg	40	31.90	31.89	-0.01±0.72	
Amlodipine 10 mg	36	30.22	32.49	2.26±0.73	
Placebo	40	27.58	28.04	0.45±0.93	
Systemic Vascular Resistance (dyne.sec.cm^2)					0.0131
Amlodipine 5 mg	40	1574.58	1504.35	-70.24±44.05	
Amlodipine 10 mg	36	1688.27	1537.04	-151.23±46.71	
Placebo	40	1801.29	1788.40	-12.88±66.59	
Pulmonary Vascular Resistance (dyne.sec.cm^2)					0.4131
Amlodipine 5 mg	40	191.95	203.72	11.77±10.49	
Amlodipine 10 mg	35	321.82	289.03	-32.79±44.46	
Placebo	40	253.56	276.08	22.52±16.78	

[Values were obtained from IND [illegible] Vol. 7.8, Table 8C, page 71; *sponsor's analysis. Baseline-Week 0, pre-dose. Peak-Week 0, mean of measurements taken at 6, 8, 10, 12 hrs post-dose.]

The chronic effects of amlodipine treatment, as compared to placebo, on hemodynamic parameters are summarized in Table LXIII. PCWP decreased comparably in all treatment arms (p=0.7737). CI was significantly albeit modestly increased by 8.2% in the amlodipine 10 mg arm as compared with placebo arm (0.0219). PVR fell significantly in both amlodipine groups (p=0.01).

Table LXIII. Chronic Hemodynamic Effects Intent to Treat Analysis

Hemodynamic Variables	N	Baseline (mean)	Drug (mean)	Change from Baseline (mean±SE)	p-Value*
Pulmonary Capillary Wedge Pressure (mmHg)					0.7737
Amlodipine 5 mg	40	20.70	18.60	-2.10±1.03	
Amlodipine 10 mg	36	20.64	18.86	-1.78±1.41	
Placebo	40	23.70	19.90	-3.80±1.34	
Cardiac Index (l/min/m^2)					0.0219
Amlodipine 5 mg	40	2.41	2.52	0.11±0.08	
Amlodipine 10 mg	35	2.31	2.50	0.19±0.08	
Placebo	39	2.07	2.18	0.10±0.09	
Mean Right Atrial Pressure (mmHg)					0.3774
Amlodipine 5 mg	40	8.42	7.65	-0.77±0.70	
Amlodipine 10 mg	36	9.59	8.06	-1.53±0.84	
Placebo	40	10.88	9.83	-1.05±0.67	

Mean Arterial Pressure (mmHg)					0.4276
Amlodipine 5 mg	40	94.65	90.93	-3.72±1.64	
Amlodipine 10 mg	36	96.38	88.34	-8.04±2.15	
Placebo	40	94.62	90.52	-4.10±1.58	
Heart Rate (bpm)					0.6852
Amlodipine 5 mg	40	78.40	78.54	0.14±1.41	
Amlodipine 10 mg	36	79.12	74.14	-4.99±1.57	
Placebo	40	76.93	76.32	-0.61±1.78	
Mean Pulmonary Artery Pressure (mmHg)					0.0901
Amlodipine 5 mg	40	30.82	28.46	-2.37±1.17	
Amlodipine 10 mg	35	36.26	29.33	-6.92±2.49	
Placebo	40	34.62	32.39	-2.23±1.57	
Stroke Volume Index (ml/m^2)					0.1719
Amlodipine 5 mg	40	31.90	32.76	0.85±1.18	
Amlodipine 10 mg	35	30.12	34.43	4.32±1.19	
Placebo	39	27.54	29.86	2.32±1.23	
Systemic Vascular Resistance (dyne.sec.cm^2)					0.1324
Amlodipine 5 mg	40	1574.58	1440.48	-134.11±49.52	
Amlodipine 10 mg	35	1686.50	1441.99	-244.51±83.81	
Placebo	39	1796.26	1599.30	-196.96±76.65	
Pulmonary Vascular Resistance (dyne.sec.cm^2)					0.01
Amlodipine 5 mg	40	191.95	174.50	-17.45±16.13	
Amlodipine 10 mg	34	320.11	205.82	-114.29±42.33	
Placebo	39	255.71	257.82	2.12±32.22	

[Values were obtained from IND Vol. 7.8, Table 8A, page 68; *sponsor's analysis. Baseline-Week 0, pre-dose. Final-Week 12, 24 hrs post-dose.]

Table LXIV summarizes chronic hemodynamic effects (peak/trough). Examination of the results indicates that there was not a clear pattern of response to be discerned for all the groups.

Table LXIV. Chronic Hemodynamic Effects: Peak/Trough Intent to Treat Analysis

Hemodynamic Variables	N	Trough (mean)	Peak (mean)	Peak-Trough (mean±SE)	p-Value*
Pulmonary Capillary Wedge Pressure (mmHg)					0.9394
Amlodipine 5 mg	40	18.60	18.60	0.00±0.61	
Amlodipine 10 mg	36	18.86	19.09	0.23±0.65	
Placebo	40	19.90	20.01	0.11±0.69	
Cardiac Index (l/min/m^2)					0.21
Amlodipine 5 mg	40	2.52	2.56	0.04±0.05	
Amlodipine 10 mg	35	2.52	2.54	0.01±0.05	
Placebo	40	2.18	2.19	0.01±0.04	
Mean Right Atrial Pressure (mmHg)					0.2229
Amlodipine 5 mg	40	7.65	8.02	0.37±0.38	
Amlodipine 10 mg	36	8.06	7.91	-0.15±0.42	
Placebo	40	9.83	10.17	0.34±0.42	
Mean Arterial Pressure (mmHg)					0.0032
Amlodipine 5 mg	40	90.93	90.86	-0.07±0.97	
Amlodipine 10 mg	36	88.34	88.58	0.24±0.96	
Placebo	40	90.52	93.89	3.37±1.09	

Table LXIV. (continued)

Heart Rate (bpm)					0.5305
Amlodipine 5 mg	40	78.54	81.35	2.81±0.87	
Amlodipine 10 mg	36	74.14	76.69	2.56±0.78	
Placebo	40	76.32	79.50	3.18±0.96	
Mean Pulmonary Artery Pressure (mmHg)					0.3418
Amlodipine 5 mg	40	28.46	29.25	0.80±0.70	
Amlodipine 10 mg	36	29.58	30.38	0.80±0.59	
Placebo	39	32.33	33.40	1.08±0.83	
Stroke Volume Index (ml/m^2)					0.319
Amlodipine 5 mg	40	32.76	32.26	-0.50±0.63	
Amlodipine 10 mg	35	34.90	33.97	-0.93±0.58	
Placebo	40	29.86	28.88	-0.98±0.50	
Systemic Vascular Resistance (dyne.sec.cm^2)					0.0064
Amlodipine 5 mg	40	1440.48	1419.99	-20.49±36.73	
Amlodipine 10 mg	35	1423.93	1446.88	22.95±31.41	
Placebo	40	1599.30	1707.70	108.40±43.10	
Pulmonary Vascular Resistance (dyne.sec.cm^2)					0.0086
Amlodipine 5 mg	40	174.50	183.28	8.78±12.72	
Amlodipine 10 mg	35	201.78	223.53	21.75±11.77	
Placebo	39	259.28	286.34	27.06±21.18	

[Values were obtained from IND\ \Vol. 7.8, Table 8F, page 75; *sponsor's analysis. Trough-Week 12, 24 hrs post-dose. Peak-Week 12, mean of measurements taken at 6 ,8 ,10 , 12 hrs post-dose.]

Acute changes in Cmax, Tmax and AUC are summarized in Table LXV. Cmax and AUC mean values doubled from 5 mg to 10 mg amlodipine treatment. Tmax remained stable from 5 mg to 10 mg amlodipine therapy.

Table LXV. Acute Pharmacokinetic Parameters Intent to Treat Analysis

Group	Cmax (ng/ml)	Tmax (hr)	AUC (ng.hr/ml)
Amlodipine 5 mg/day (n=17)	3.30±1.22	5.44±2.20	51.12±15.86
Amlodipine 10 mg/day (n=18)	6.91±1.79	4.73±1.73	106.35±31.88

[Values are mean±SD, and were obtained from IND\ \Vol. 7.8, Table 8D, page 73.]

NYHA class changes was a secondary clinical endpoint (Table LXVI). Forty-five patients receiving 5 mg amlodipine, 40 receiving 10 mg amlodipine, and 43 receiving placebo were analyzed for changes in NYHA functional class. Overall, there were no differences in NYHA class changes across treatment groups.

Table LXVI. NYHA Classification Changes Intent to Treat Analysis

		Final NYHA Class		
Group	Baseline NYHA Class	II (n)	III (n)	IV (n)
Amlodipine 5 mg	II	14	1	0
	III	3	21	0
	IV	0	2	3
Amlodipine 10 mg	II	11	0	0
	III	2	18	3
	IV	0	3	3
Placebo	II	8	4	0
	III	2	24	1
	IV	0	3	1

[Values were obtained from IND\ \Vol. 7.8, page 85.]

Summaries of results of quality of life variables are shown in Table LXVII. Data from physical, health perception, and bed days indicate statistically significant treatment effects in favor of amlodipine treatment.

Table LXVII. Quality of Life Measures Intent to Treat Analysis

Quality of Life Variables	N	Baseline (mean)	Final (mean)	Change from Baseline (mean±SE)	p-Value*
Total					0.0259
Amlodipine 5 mg	39	53.80	63.58	9.78±2.57	
Amlodipine 10 mg	37	52.99	54.74	1.75±2.14	
Placebo	38	59.75	56.65	-3.09±3.07	
Physical					0.0101
Amlodipine 5 mg	39	42.34	56.92	14.59±3.24	
Amlodipine 10 mg	37	42.70	47.63	4.92±2.88	
Placebo	38	51.52	48.36	-3.16±3.86	
Emotional					0.288
Amlodipine 5 mg	39	60.51	68.82	8.31±3.79	
Amlodipine 10 mg	37	56.97	59.49	2.51±3.22	
Placebo	38	66.47	64.21	-2.26±3.56	
Health Care					0.3257
Amlodipine 5 mg	36	3.25	3.64	0.39±0.18	
Amlodipine 10 mg	37	3.51	3.62	0.11±0.19	
Placebo	37	3.41	3.49	0.08±0.20	
Global Rating					0.0834
Amlodipine 5 mg	39	1.85	2.28	0.44±0.19	
Amlodipine 10 mg	37	1.86	2.49	0.62±0.21	
Placebo	38	2.26	2.21	-0.05±0.25	
Health Perception					0.05
Amlodipine 5 mg	39	42.18	45.19	3.01±1.66	
Amlodipine 10 mg	37	42.94	44.19	1.25±2.03	
Placebo	38	42.37	39.61	-2.76±2.12	
Bed Days					0.0297
Amlodipine 5 mg	38	1.05	0.84	-0.21±0.30	
Amlodipine 10 mg	32	2.31	2.22	-0.09±0.43	
Placebo	37	0.76	1.86	1.11±0.34	
Alertness					0.9074
Amlodipine 5 mg	38	79.72	82.53	2.81±3.11	
Amlodipine 10 mg	37	78.42	78.99	0.57±3.00	
Placebo	38	81.07	82.53	1.46±3.26	

[Values were obtained from IND Vol. 7.8, Table 8J, page 80; *sponsor's analysis.]

Safety:

Five of the 48 patients (10.4%) receiving 5 mg of amlodipine, 5 of the 45 patients (11.1%) receiving 10 mg amlodipine, and 2 of 49 patients (4.1%) receiving placebo experienced treatment related adverse events. Side effects in the 5 mg amlodipine group were mild in four cases (dependent edema, worsening heart failure, rash, headache) and moderate in two cases (dependent edema, pleural effusion). In the 10 mg amlodipine group, there were two incidents of severe worsening of heart failure, one severe muscle cramps, one severe pruritus and severe anorexia. The remaining side effects were mild in two cases (somnolence, fatigue) and moderate in four cases (edema, dependent edema, rash, nocturia). There was a case of severe hypotension and one case of moderate confusion in the placebo treatment group.

Patients' discontinuations and the reasons for withdrawal are summarized in Table LVIII.

Table LVIII. Discontinuation of Therapy

Treatment Group	Patient ID	Duration of Therapy (days)	Event
Amlodipine 5 mg	176 5150014	56	Died
	176 6560003	43	Worsening CHF
	176 6780008	59	Asked to be Withdrawn from Study
	176 7640006	14	Asked to be Withdrawn from Study
	176 7650008	85	Worsening CHF
	176 7650010	12	Increased Angina
	176 7680001	22	Worsening CHF
Amlodipine 10 mg	176 5150013	88	Asked to be Withdrawn from Study
	176 6780002	84	Hemoptysis, Pulmonary Infarct
	176 7000001	18	Pulmonary Edema
	176 7320001	51	Worsening CHF
	176 7360014	35	Lost to Follow-Up
	176 7640003	6	Worsening CHF
	176 7650011	41	Increased Pedal Edema, Nocturia
	176 7890011	49	Asked to be Withdrawn from Study
	176 6470001	56	Died
	176 7670002	26	Chest Pain, Worsening CHF
Placebo	176 5150015	68	Died
	176 5170002	78	Worsening CHF
	176 6340010	4	Patient C/O "Mental Confusion"
	176 7320012	27	Bradyarrhythmia
	176 7360008	91	Died
	176 7430001	1	Onset Pulmonary Edema
	176 7640004	14	Unstable Angina
	176 7650013	57	Died
	176 5150010		Died
	176 7670003	36	Worsening CHF

There were no discontinuations due to laboratory test abnormalities. One patient in each amlodipine arm and four patients in the placebo group were discontinued because they died. The case summaries of those patients with fatal events is summarized below.

Case Summaries of Patients with Fatal Events
176-515-0014 (RUS4263) This 51 -year-old markedly obese white male with severe heart failure (NYHA Class IV) secondary to ischemic heart disease was randomized to amlodipine 5 mg daily on 6/3/92. His medical history included palpitations, angina and possible myocardial infarction. His left ventricle was diffusely hypokinetic (ejection fraction was 23%) and he was awaiting a heart transplant. Baseline hemodynamic evaluation revealed PCWP 35 mmHg and CI 2.48 Umin/M2. Concomitant therapies included digoxin, furosemide, and nitroglycerin. After 56 days (7/29/92) of therapy he collapsed and family members initiated CPR. Paramedics found the patient in ventricular fibrillation, continued CPR, attempted cardioversion and witnessed conversion to asystole. The patient was transported to a hospital Emergency Room, but continued therapeutic interventions were unsuccessful and he died. The investigator listed probable acute myocardial infarction secondary to congestive heart failure as the cause of this patient's sudden death.
176-647-0001 (RUS4725) This 73-year-old male with moderately severe heart failure (NYHA Class III) secondary to idiopathic dilated cardiomyopathy was randomized to amlodipine 1 0 mg on 7/23/92. His medical history was significant for atrial fibrillation and hypertension. The left ventricular ejection fraction was 32%. Concomitant medications included furosemide, enalapril, and digoxin. He completed the double-blind treatment phase as scheduled with the last dose of double-blind amlodipine being taken on 1 0/1 5/92. The following day he was started on commercially available amlodipine. He was seen in clinic on 10/27/92 and was without complaint. On 11/9/92, after a day of physical exertion, he experienced sudden death. The investigator indicated sudden death unrelated to amlodipine therapy was the cause of death.

Case Summaries of Patients with Fatal Events (continued)
176-515-0010 (RUS4202) This 74-year-old white female with moderately severe heart failure (NYHA Class 111) and a history of ventricular tachycardia was randomized to placebo on 2/4/92. Concomitant medications included mexiletine, lisinopril, bumetanide, and digoxin. She completed the double-blind trial, without event, on 5/5/92 and died 22 days later (5/27/92). No autopsy was performed, but the investigator listed acute myocardial infarction secondary to cardiac arrhythmia (non-sustained VT) as the probable cause of death.
176-736-0008 (RUS4537) This 56-year-old black male with a primary diagnosis of moderately severe heart failure (NYHA Class 111) secondary to idiopathic cardiomyopathy was randomized to placebo on 7/7/92. The left ventricular ejection fraction was 30% and medical history included coronary artery bypass graft surgery and hypertension. Concomitant therapies included digoxin, captopril, and hydrochlorothiazide. After 91 days (1 0/6/92) he was found, unresponsive, by his brother. The investigator listed underlying myocardial infarction, unrelated to study drug, as the cause of death.
176-765-0013 (RUS4151) This 41 -year-old black male with a primary diagnosis of moderately severe heart failure (NYHA Class 111) secondary to idiopathic cardiomyopathy began a four-week placebo stabilization period on 3/26/92 and was randomized to placebo on 5/8/92. The left ventricular ejection fraction was 1 1 % and past medical history was noncontributory. Concomitant therapies included captopril, furosemide and amiloride. After 57 days of placebo (7/3/92) he was found in bed (7/4/92), unresponsive, by his sister. The investigator listed sudden death secondary to arrhythmia as the cause of death.
176-515-0015 (RUS4660) This 77-year-old white female with moderately severe heart failure (NYHA Class 111) secondary to ischemic heart disease was randomized to placebo on 8/29/92. Her medical history was significant for anterior and inferior myocardial infarctions and coronary artery bypass graft surgery. The left ventricular ejection fraction was 24%. Concomitant therapies included digoxin, fosinopril, furosemide and nitroglycerin. After 56 days she was hospitalized (1 0/1 9/92) for epigastric discomfort and myocardial infarction was ruled out. The hospitalization was uneventful and she was scheduled for discharge. During routine nursing assessment on the morning of 1 1 /4/92 she was noted to be cold and pasty. ABGs revealed metabolic acidosis and blood glucose was 15 mg/dl. She received glucose and sodium bicarbonate, but suddenly experienced respiratory arrest followed by cardiac arrest. Resuscitative efforts were unsuccessful. The investigator listed ischemic cardiomyopathy and respiratory and cardiac arrest as the cause of death.

Summary: This was a 12-week randomized, placebo-controlled, double-blind, fixed-dose, parallel group study to investigate the hemodynamics effects of amlodipine treatment (5 mg and 10 mg once daily) versus placebo in patients with stable NYHA functional class II-IV receiving a combination of digoxin, diuretics and/or angiotensin converting enzyme inhibitors.

The results from cardiac catheterization, evaluating acute and chronic effects of amlodipine on cardiac hemodynamic parameters, were significant only for mean arterial pressure and systemic vascular resistance. Both variables were significantly decreased by the administration of amlodipine. No significant changes in NYHA classification were observed. Quality of life measures, e.g., physical, health perception, bed days, were modified favorably and significantly by amlodipine therapy.

***Protocol* #053-009:** This was an open, randomized, crossover study to compare the pharmacokinetic profiles and absolute bioavailability of amlodipine administered both intravenously and orally to patients with heart failure and patients with mild to moderate hypertension (i.e., diastolic blood pressure between 95 and 114 mmHg in both the standing and supine position). One dose was to be 2.5 mg intravenously and the other was to be 10 mg given orally.

The main purpose of this study was to compare in hypertensive patients and patients with congestive heart failure:

i) the pharmacokinetic profile of acute intravenous administration of amlodipine.
ii) the pharmacokinetic profile achieved with oral administration of amlodipine.
iii) the bioavailability of amlodipine in patients with congestive heart failure in reference to hypertensive controls.

Pharmacokinetics:

-Plasma samples were to be drawn just before oral or intravenous administration of amlodipine, at the completion of the intravenous infusion, and at the following times after oral administration or completion of the infusion: 0.17, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 160 hours.

Safety:

-Safety evaluation included clinical side effects, laboratory parameters, ECG, chest X-ray, and 24-hour ambulatory electrocardiogram.

Results:

Baseline patient characteristics are summarized in Table LIX.

Table LIX. Baseline Patient Characteristics

Variables	Hypertension	# CHF
# of Patients	12	13
Race (n):		
White	0	0
Black	12	12
Other	0	1
LVEF (%)	-	40

There were 8 female patients in the hypertension group and 7 female patients in the CHF group. The LVEF was 29% for the 6 male patients and 49% for the 7 female patients in the CHF group. The mean value for LVEF in this group was 40%.

Table LX is a summary of the results on Cmax, Tmax, terminal phase rate constant (Kel), systemic clearance (Clp), and volumes of distribution at steady state (Vdss) for oral and intravenous administration in hypertensive and heart failure patients.

Table LX. Pharmacokinetics Parameters in Patients with Hypertension or CHF Following Oral or Intravenous Amlodipine Administration

Parameter	Group	N	Mean	Mean Difference (HTN - CHF)	95% Confidence Limits*	p-Value*
Oral Administration:						
Cmax (ng/ml)	Hypertensive	12	6.5	1.1	(-0.93, 3.17)	0.2664
	CHF	10	5.4			

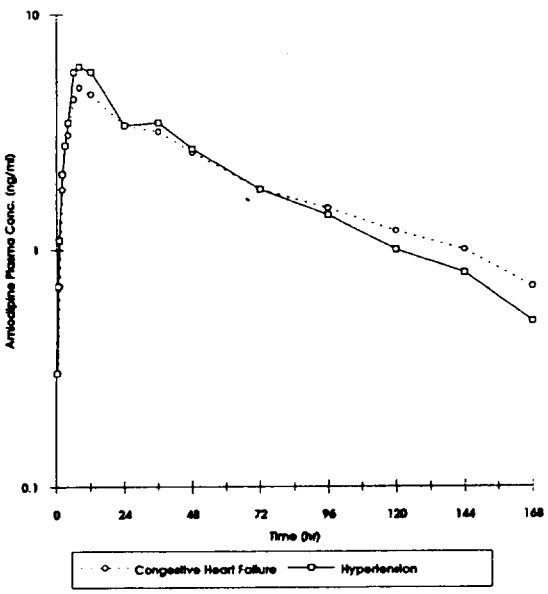
Table LX. (continued)

Tmax (hr)	Hypertensive CHF	12 10	9.0 12.0	-3.0	(-21.98, 15.98)	0.3190
AUC (ng•hr/ml)	Hypertensive CHF	12 9	386.1 412.3	-26.2	(167.00, 114.62)	0.7014
Kel (hr^{-1})	Hypertensive CHF	12 9	0.0134 0.0133	0.0000	(-0.003, 0.003)	0.9770
i.v. Administration:						
Clp (ml/min/kg)	Hypertensive CHF	12 10	4.65 3.87	0.78	(-0.74, 2.30)	0.2968
Vdss (L/kg)	Hypertensive CHF	12 10	19.2 17.5	1.7	(-2.56, 6.00)	0.4121
Kel (hr^{-1})	Hypertensive CHF	12 10	0.0141 0.0125	0.002	(-0.002, 0.005)	0.3527

[* Represents a p-value obtained from a two-sample t-test; sponsor's analysis.]

The mean Cmax was similar between groups, in the hypertensive patients was 6.5 ng/ml and 5.4 ng/ml for the heart failure group (Table LX, Figure 3). The corresponding mean estimates for Tmax were 9.0 and 12.0 hours in the hypertensive patients and the heart failure group, respectively. The numerical difference in Tmax was probably due to the unusual absorption observed in one patient (658-0017) for whom the Tmax was 36 hours.

Figure 3. Mean Plasma Concentrations of Amlodipine Following Oral Administration of a 10 mg Capsule to Patients with Mild to Moderate Hypertension or Congestive Heart Failure*

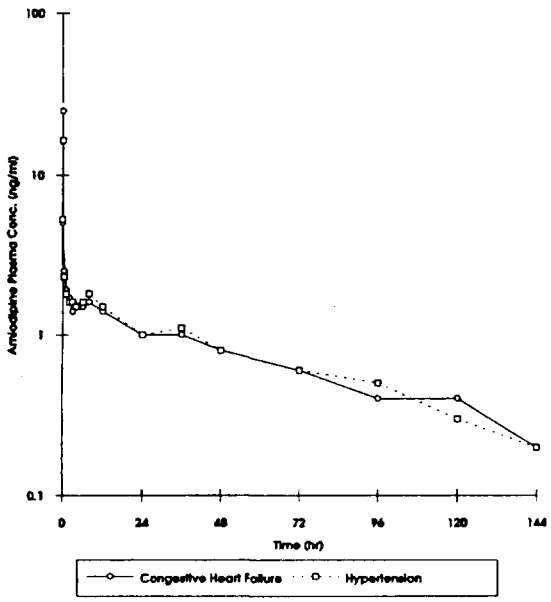


[*This figure was obtained from IND Vol. 12.1, Figure 1, page 23.]

The mean results for AUC (0-∞) were similar between groups. Similarly, the means for the terminal phase rate constant (Kel) for the oral administration were nearly identical in the hypertensive and heart failure patients, 0.0134 hr^{-1} and 0.0133 hr^{-1}, which corresponded to mean half-lives of 51.7 and 52.1 hours, respectively. In the aggregate, the data indicate that the pharmacokinetic profiles attained with oral administration were not significantly different between the two group of patients.

Figure 4 depicts the plasma concentrations of amlodipine over time following intravenous administration in heart failure and hypertensive patients.

Figure 4. Mean Plasma Concentrations of Amlodipine Following Intravenous Administration of a 2.5 mg Infusion to Patients with Mild to Moderate Hypertension or Congestive Heart Failure*



[*This figure was obtained from IND Vol. 12.1, Figure 2, page 24.]

The mean systemic clearance (Clp) was similar between groups, in the hypertensive group was 4.65 ml/min/kg versus 3.87 ml/min/kg in the heart failure group (Table LX). The volumes of distribution at steady state (Vdss) for the two groups were similar (Table LX). The mean Kel value was 0.0141 hr^{-1} for the hypertensive patients and 0.0125 hr^{-1} for the heart failure group, corresponding to elimination half-lives of 49.2 hours and 55.5 hours, respectively. The mean AUC (0-∞) following i.v. administration was 128.6 ng•hr/ml for the hypertensive group and 136.2 ng•hr/ml for the heart failure patients. Thus, the values of Clp, Vdss, and Kel, calculated after i.v. administration, were not significantly different between hypertensive and heart failure patients.

Oral bioavailability (i.e., oral/intravenous) for hypertensive and heart failure patients was 75% and 77%, respectively.

Safety:

Two patients with CHF (658-0017 and 658-0020) experienced mild dizziness and asthenia both just following the intravenous infusion. Two additional patients with CHF suffered chest pain and asthenia, that occurred subsequent to dosing. Laboratory test abnormalities developed in four patients, all in the CHF group, and consisted of mild elevations in serum creatinine and GGT.

Two hypertensive patients (658-0018 and 658-0038) were discontinued from the study after receiving the oral dose but before receiving the intravenous dose. Patient 658-0018 was discontinued due to a protocol violation (participation in another investigational trial). Patient 658-0038 suffered an acute myocardial infarction four days before the oral dose of amlodipine was administered.

Summary: This was an open, randomized, crossover study to compare the pharmacokinetic profiles and absolute bioavailability of amlodipine administered both intravenously and orally to patients with heart failure and patients

with mild to moderate hypertension (i.e., diastolic blood pressure between 95 and 114 mmHg in both the standing and supine position). The intravenous dose was 2.5 mg intravenously, and the oral dose was10 mg.

The results from this investigation indicate that the pharmacokinetic profiles obtained with oral or intravenous administration were similar between hypertensive and heart failure patients. Similarly, oral bioavailability was nearly identical between the groups. On the basis of the observed results, it can be concluded that the disease state of heart failure does not significantly modify the pharmacokinetics of amlodipine in comparison to a hypertensive state. Extrapolation of these conclusions however, to a patient population like the one in the PRAISE study might not be accurate. Since the mean LVEF in the patients with heart failure in this study was almost twice as high as to the LVEF documented for patients with heart failure in the PRAISE study (i.e., 40% vs. <21%, respectively). There were no fatal events reported in this study,

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***Protocol* #053-174E:** This study was a double-blind, placebo-controlled, 40 week extension of protocol #053-174 (pages 29-32) to assess primarily the safety of amlodipine therapy (10 mg daily) in patients with chronic mild to severe heart failure (NYHA Class II and IV) receiving diuretics and digoxin, and/or an ACE inhibitor.

For inclusion in the study patients must have previously participated in and successfully completed protocol #053-174.

Efficacy:

Clinical endpoints
-NYHA functional class.
-Cardiopulmonary symptomatic status.

Safety:
-Safety evaluation included clinical side effects, morbidity/mortality, laboratory parameters, ECG, and chest X-ray.

Results:

In total fifty-one patients at 10 centers entered the double-blind extension protocol.

Table LXI. Baseline Patient Characteristics

Variables	Placebo	Amlodipine
# of Patients	27	24
Race (n):		
White	20	22
Black	3	3
Other	1	2
Mean Age (in years)	63.2	64.7
Mean Duration of CHF (in years)	3.2	3.5
NYHA Class (n):		
II	19	17
III	8	7
Mean LVEF (%)	27	25

A total of 9 female and 42 male were enrolled in this study. Four female were enrolled in the placebo group, and five female were randomized to the amlodipine group.

The underlying causes of heart failure were idiopathic dilated cardiomyopathy/ischemic heart disease/hypertension /other, with the following distribution: 9/17/1/0 in the placebo group, and 7/15/0/2 in the amlodipine group. Seventeen patients in the placebo group and ten patients in the amlodipine group had a history of previous myocardial infarction.

The mean duration of double-blind therapy (beginning with the start of the parent study) was 347.6 days for patients receiving amlodipine and 306.9 days for patients receiving placebo. Of note, twenty of the 24 patients receiving amlodipine and 19/27 receiving placebo were treated for more than 40 weeks.

Efficacy:

Table LXII. NYHA Classification Changes

Group	Baseline NYHA Class	Final NYHA Class			
		I (n)	II (n)	III (n)	IV (n)
Amlodipine	II	3	11	2	1
	III	0	4	3	0
Placebo	II	3	14	2	0
	III	0	5	2	1

Table LXIV. (continued)

The results in Table LXII indicate that NYHA classification of the majority of patients did not change during the study. Seven amlodipine-treated patients (29.2%) and 8 placebo-treated patients (29.6) improved; 3 amlodipine-treated patients (12.5%) and 3 placebo-treated patients (11.1%) worsened.

Examination of the results of the overall assessment of heart failure symptoms (dyspnea at rest, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and fatigue) revealed small decreases in the overall mean symptom scores and these changes were of similar magnitude in both treatment groups (IND Vol. 11.1, Table 10, page 31).

Safety:

A list of the side effects classified by the investigators related to study drug or concomitant therapy is provided in Table LXIII.

Table LXIII. Side Effects Related to Study Drug or Concomitant Therapy All Patients

Organ System/Side Effect	Placebo (n=27)	Amlodipine (n=24)
Cardiovascular:		
Edema legs	1	2
Edema Dependent	2	3
Central Nervous:		
Vertigo	0	1
Gastrointestinal:		
Constipation	0	1
Abdominal Pain	2	0
Nausea	3	1
Respiratory:		
Coughing	1	0
Hematopoietic:		
Purpura	0	1
General:		
Fatigue	1	0

All adverse events are summarized in Table LXIV.

Table LXIV. All Adverse Events

Treatment Group	Patient ID	Event Onset (days)	Event
Amlodipine 5 mg	174E 6640003	315	Angina Pectoris
Amlodipine 10 mg	174E 6640004	179/333	Syncope/Pneumonia/Shortness of Breath

Table LXIV. (continued)

	174E 6430002	197	URI
	174E 5150001	206	Cold Symptoms
	174E 5150003	93	Chest & Abdominal Discomfort/Dysuria
	174E 5150005	31/89	Orthopnea/Weight Gain
	174E 5180004	66/69	Vertigo/Ankle Edema/Petechial Rash
	174E 5720002	242	Bronchitis
	174E 5720003	198	Uncontrolled IDDM
	174E 6640002	31	Lower Extremities Edema
	174E 6640006	116/260/373	Vestibular Disorder/Fatigue/Arrhythmia Atrial
	174E 5720008	139	Hyperqueratosis, Papular Rash
	174E 7380001	109/337	Dizziness/SOB, Chest Pain
	174E 7380008	81/135	L. Arm Pain/Abdom. Pain
	174E 7380009	222	TIA
	174E 7880001	151/174	AF/Hives/Abdom. Pain Severe
	174E 7920002	294	Accidental Injury
	174E 7920003	157-274	Blurry Vision
	174E 7920007	56	Back Pain
Placebo	174E 5150002	86-234	Chest Pain, Dyspnea, Edema/Inc. BP
	174E 5150004	178/246	Headache, URI/SOB, URI
	174E 5150006	16	Leg Pain
	174E 5180003	154	Cough
	174E 5720001	106/294	Pedal Edema, Arthralgia/Sinusitis
	174E 6060002	47/246	Joint Pain
	174E 6170004	137182	UTI, Vaginitis/Abdom. Cramps
	174E 6170005	148-460	URI/Worsening CHF/AF/Abdom. Discomfort
	174E 6430004	356	Lightheadeness
	174E 6430001	101	Fatigue
	174E 6430005	238	Ankle Edema, BPH
	174E 6640001	140-368	Ankle Edema/Weakness/Cardiac Arrest
	174E 6640004	58-130	Ankle Edema/Worsening CHF/Cardiac Arrest
	174E 6640005	176/315	Back Discomfort/Ankle Edema
	174E 7380002	39-284	Headache/Nausea/Back & Muscle Pain
	174E 7380003	138-280	Vertigo/Nausea/Palp./SOB/Headache/Ab.Pain
	174E 7880002	91-360	Worsening CHF/URI/Dizziness/Ankle Edema
	174E 7880008	204	Cardiac Arrest
	174E 7920001	140	Pneumonia
	174E 7920008	126-384	Cellulitis/Faintness/Edema/Arrhythmia/Sync.

There were no reported treatment-related laboratory test abnormalities.

Seventeen patients (70.8%) of the 24 patients receiving amlodipine and sixteen (59.2%) of the 27 patients receiving placebo completed the extension protocol. One patient receiving amlodipine and two receiving placebo defaulted. Five patients in the amlodipine group and six patients in the placebo group were discontinued by the sponsor (the reasons for such action are not available). One patient in the amlodipine group and three patients in the placebo group were discontinued because they died.

Case Summaries of Patients with Fatal Events
Patient ID No: 053-174E-788-0001 (Safety Reference No: RUS5112) This 83-year-old female patient received amlodipine for congestive heart failure. Study drug was administered orally 1 0 mg once daily from October 30, 1992 to January 25, 1993, for a total of 88 days. On January 25, she was hospitalized with acute abdominal pain. Exploratory laparotomy revealed small bowel obstruction due to ischemia of the bowel. She was transferred to the intensive care unit where she deteriorated and died. Death occurred on January 26, 1993, and was attributed to necrosis of the small bowel due to an abdominal embolus. The patient also had a history of hypothyroidism, atrial fibrillation, subendocardial infarction, and 3-vessel coronary artery bypass surgery. Relevant concomitant medications included digoxin, furosemide, thyroxine, and aspirin.
Patient ID No: 053-174E-788-0008 (Safety Reference No: RUS5613) This 76-year-old male patient received placebo for congestive heart failure. Study drug was administered orally from December 30, 1992 to April 27, 1993, for a total of 118 days. On April 28, 1993, the patient died due to cardiac arrest secondary to the cardiomyopathy. The patient also had a history of hyperglycemia. Concomitant medications included digoxin, furosemide, fosinopril, warfarin, potassium, and glibenclamide.
Patient ID No: 053-174E-664-0004 (Safety Reference No: RUS4682) This 84-year-old male patient received placebo for congestive heart failure. Study drug was administered orally from September 25, 1992 to November 6, 1992, for a total of 43 days. On November 7, he was found dead at home by family. Two days prior to his death, he complained of increasing shortness of breath. The cause of death was cardiac arrest due to cardiomyopathy secondary to ischemic heart disease. The patient also had a history of chronic atrial fibrillation. Relevant concomitant medications included digoxin, metolazone, potassium, and furosemide.
Patient ID No: 053-174E-664-0001 (Safety Reference No: RUS5435) This 87 year old male patient received placebo for congestive heart failure. Study drug was administered orally from June 10, 1992 to March 21, 1993, for a total of 285 days. On march 21, he collapsed at home. He was admitted to the hospital that day and died on March 22, one day after discontinuing study drug. The cause of death was anoxic encephalopathy. Aspiration pneumonia also contributed to the death. The patient also had a history atrial fibrillation. Relevant concomitant medications included digoxin, lisinorpil, aspirin, potassium, and furosemide.

Summary: This study was a double-blind, placebo-controlled, 40 week extension of protocol #053-174 (pages 29-32) to assess the safety of amlodipine therapy (10 mg daily) in patients with chronic mild to severe heart failure (NYHA Class II and IV) receiving diuretics and digoxin, and/or an ACE inhibitor.

This trial extension is of course noncontributory to the efficacy of amlodipine in patients with CHF. In regard to the contribution of this study to the overall interpretation of the safety of amlodipine in heart failure patients, not many patients were followed to permit a valid assessment.

***Protocol* #053-175E:** This clinical investigation was a double-blind, placebo-controlled, parallel group, 40-week extension of study #053-175 (page 33-37) to assess the safety of amlodipine therapy (10 mg daily) in patients with chronic, stable, heart failure, receiving digoxin, diuretics, and ACE inhibitors. Accordingly all qualifying patients should have met the inclusion/exclusion criteria for protocol #053-175.

Upon completion of protocol #053-175, patients were to undergo a complete physical examination and have laboratory tests performed. Patients were to be maintained on the same double-blind medication they were assigned in protocol #053-175.

Efficacy:

Clinical Endpoints
-NYHA functional class.
-Cardiopulmonary symptomatic status.

Safety:
-Safety evaluation included clinical side effects, morbidity/mortality, laboratory parameters, ECG, and chest X-ray.

Results:

In total, thirty-seven patients were entered in this double-blind extension trial. The baseline characteristics of the enrolled patients is given in Table LXV.

Table LXV. Baseline Patient Characteristics

Variables	Placebo	Amlodipine
# of Patients	17	20
Race (n):		
White	14	13
Black	3	6
Other	0	1
Mean Age (in years)	60.7	64.3
Mean Duration of CHF (in years)	3.4	4.0
NYHA Class (n):		
II	7	14
III	10	6
Mean LVEF (%)	24	25

A total of 25 male and 12 female (5 in the placebo group and 7 in the amlodipine group) patients from protocol #053-175 entered the extension study.

The underlying causes of heart failure were idiopathic dilated cardiomyopathy/ischemic heart disease/hypertension /other, with the following distribution: 6/10/0/1 in the placebo group, and 6/12/1/1 in the amlodipine group. Seven patients in the placebo group and sixteen patients in the amlodipine group had a history of previous myocardial infarction.

The medications taken during the study were also similar. In this regard, all patients enrolled in the study were receiving digoxin, a diuretic, and an ACE inhibitor at the beginning and through the extension period (IND Vol. 11.12, page 10).

The mean duration of double-blind therapy (beginning with the start of the parent study) was 332.6 days for patients receiving amlodipine and 291.4 days for patients receiving placebo. Sixteen of the 20 patients receiving amlodipine and 10/17 receiving placebo were treated for more than 40 weeks.

Efficacy:

The results for the changes in NYHA class for both treatments arms are summarized in Table LXVI. Three amlodipine-treated patients (15%) and four (23.5%) patients receiving placebo improved. Three (15%) patients receiving amlodipine and no placebo-treated patients worsened .

Table LXVI. NYHA Classification Changes Intent to Treat Analysis

		Final NYHA Class	
Group	**Baseline NYHA Class**	II (n)	III (n)
Amlodipine	II	11	3
	III	3	3
Placebo	II	7	0
	III	4	6

[Values were obtained from IND Vol. 11.12, Table 9, page 30.]

Evaluation of the results of the overall assessment of heart failure symptoms (dyspnea at rest, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and fatigue) revealed small decreases in the overall mean symptom scores. However, these changes were of similar magnitude in both treatment groups (IND Vol. 11.12, Table 10, page 31).

Safety:

Side effects during double-blind treatment which were considered by the investigators to be related to study drug or concomitant treatment are given in Table LXVII.

Table LXVII. Side Effects Related To Study Drug or Concomitant Therapy All Patients

Organ System/Side Effect	Placebo (n=17)	Amlodipine (n=20)
Cardiovascular:		
Worsening Heart Failure	0	1
Centr. & Periph. Nerv.:		
Ataxia	1	0
Cramps Legs	0	1
Psychiatric:		
Anorexia	0	1
Impotence	0	1
Gastrointestinal:		
Nausea	1	0
Diarrhea	1	0
Respiratory:		
Coughing	1	0
General:		
Asthenia	0	1

Table LXVIII is a summary of serious adverse events for placebo and amlodipine groups.

Table LXVIII. Serious Adverse Events

Treatment Group	Patient ID	Event Onset (days)	Event
Amlodipine 5 mg	175E 6070004	5	Worsening Congestive Heart Failure

Table LXVIII. (continued)

Amlodipine 10 mg	175E 5150005	222	Worsening Congestive Heart Failure
	175E 6070004	75	Abdominal Pain
	175E 6070004	158	Chest Pain
	175E 6070008	298	Worsening Congestive Heart Failure
	175E 6070013	100	Fever of Unknown Etiology
	175E 7460003	54	Pulmonary Edema
	175E 7760003	2	TIA
	175E 7810001	136	Irregular Heart Beats
	175E 7830008	118	Worsening Congestive Heart Failure
Placebo	175E 5150004	40	Pancreatic Pseudocyst
	175E 5150008	120	Cardiac Arrest
	175E 6070003	121	Antral/Duodenal/Gastric Ulcers
	175E 6070003	265	Pneumonia
	175E 6070011	228	Pneumonia
	175E 6070016	68	Asystole, Ventricular Fibrillation
	175E 7780008	268	Acute Myocardial Infarction
	175E 7690003	96	Worsening Congestive Heart Failure

Three patients receiving amlodipine and 1 patient receiving placebo defaulted. Four patients receiving amlodipine and 5 receiving placebo were discontinued for other reasons. There were not discontinuations due to laboratory abnormalities. Four patients in the placebo group and 1 patient in the amlodipine group died.

Case Summaries of Patients with Fatal Events
Patient ID No.: 053-175E-607-0008 (Safety Reference No: RUS5603) This 72-year-old male in the US received amlodipine for treatment of heart failure. Study drug was administered orally 10 mg daily from July 1, 1992 to April 14, 1993 for a total of 298 days. On April 24, 1993, eight days after completing the study, he was hospitalized with increased congestive heart failure. He died on April 29, 1993, 15 days after discontinuing study drug, due to an acute myocardial infarction. The investigator attributed death to coronary artery disease and cardiomyopathy. The patient also had a history of ventricular ectopy. Concomitant medication during the study and up until his death were procainamide, aspirin, nitroglycerin, and pentoxifyline.
Patient No.: 053-175E-607-0016 (Safety Reference No.: 9390033) This 69-year-old male in the US. received placebo for heart failure. Study drug was administered orally each day from September 16, 1993 to November 22, 1993 for a total of 68 days. On November 22, 1993 the patient was found dead at home. An autopsy was not performed and death was attributed by the investigator to ventricular fibrillation and cardiac asystole due to coronary artery disease. The patient had a history of arrhythmias and concomitant medications included digoxin, procainamide, furosemide and captopril. Other concomitant medications taken were gemfibrozil, famotidine, coumadin, and allopurinol.
Patient ID No.: 053-175E-607-0003 (Safety Reference No.: RUS6887) This 63-year-old male in the U.S. received placebo for heart failure. Study drug was administered orally each day from February 18, 1993 to November 9, 1993 for a total of 265 days. On November 9, he was hospitalized for pneumonia and study drug was discontinued. During hospitalization he developed gram negative sepsis and claudication of his legs. Severe congestive heart failure with low cardiac output also occurred. On November 14, five days after discontinuing study drug, he expired due to sepsis. Blood culture was positive for gram negative rods and the sputum grew pneumococcus. The patient also had a history of angina pectoris, ventricular ectopy, hypercholesterolemia, and gastrointestinal bleeding. Concomitant medication included aspirin, nitroglycerin, misoprostol, metolazone, captopril, furosemide, digoxin, and pravastatin.
Patient No.: 053-175E-515-0008 (Safety Reference No.: RUS5185) This 46-year-old male in the U.S. received placebo for congestive heart failure. Study drug was administered orally each day from August 4, 1992 to December 1, 1992 for a total of 120 days. On December 1, 1992, he was found slumped over the wheel of his truck and was taken to the emergency room by ambulance. Cardiopulmonary resuscitation was attempted, but it was unsuccessful. The patient was pronounced dead due to cardiac arrest. The patient had a history of myocardial infarction, coronary artery bypass graft and hypertension. Concomitant medications included furosemide, digoxin, and benazepril.
Patient No.: 053-175E-778-0008 (Safety Reference No.: 9403501) This 71 -year-old female received placebo for congestive heart failure. Study drug was administered orally each day from August 9, 1993 to May 2, 1994 for a total of 291 days. On May 2, she was found unresponsive and the Emergency Medical Service was called. She was given 1 mg of atropine and developed ventricular fibrillation. She was defibrillated and transferred to the hospital. An initial creatine kinase (CK) was unremarkable, but the second CK was 7,000 and a diagnosis of acute myocardial infarction was made. She was maintained with life support; however, she expired on May 5, 1994, four days after discontinuing study drug. The patient also had a history of atrial fibrillation and cerebral vascular accident. Concomitant medication included coumadin, enalapril, digoxin, and furosemide.

Summary: This clinical investigation was a double-blind, placebo-controlled, parallel group, 40-week extension of study #053-175 to assess the safety of amlodipine therapy (10 mg daily) in patients with chronic, stable, heart failure, receiving digoxin, diuretics, and ACE inhibitors.

As was the case for study #053-174E, this trial extension does not lend support to the concept of amlodipine being beneficial in patients with CHF. As far as the contribution of this study to the overall interpretation of the safety of amlodipine in heart failure patients, not many patients were followed to permit a valid assessment.

***Protocol* #053-180**: This was an open-label, 40 week study. Following completion of double-blind efficacy trial 053-174, 175, or 176, patients were to undergo a complete physical examination and have laboratory tests performed. All qualifying patients should have met the inclusion/exclusion criteria listed in protocols #053-174, 175, and 176.

The purpose of this investigation was to evaluate the safety of long-term amlodipine treatment in patients with chronic, stable heart failure receiving digoxin, diuretics, and/or angiotensin converting enzyme inhibitors.

Efficacy:

Clinical Endpoints:

-NYHA functional class.
-Cardiopulmonary symptomatic status.

Safety:

-Safety evaluation included clinical side effects, morbidity/mortality, laboratory parameters, and ECG.

Results:

A total of forty five patients from 8 centers were enrolled in this open-label extension study. Fourteen patients were recruited from protocol #053-174, 11 from protocol #053-175, and 20 from protocol #053-176.

Patient Baseline Characteristics are provided in Table LXIX.

Table LXIX. Patient Baseline Characteristics

Variables	N Amlodipine
# of Patients	45
Race (n):	
White	36
Black	7
Other	2
Mean Age (in years)	60.6
Mean Duration of CHF (in years)	4.6
NYHA Class (n):	
I	1
II	24
III	19
IV	1
Mean LVEF (%)	20

Eight (17.8%) females entered this extension protocol. All cardiovascular diseases present at baseline and cardiovascular history were representative of the original population from which this subset of patients originated from. As expected, all patients were on diuretics and most of them were also on digoxin and an ACE inhibitor.

The mean (range) duration of drug exposure was 240.8 (24-376) days.

Efficacy:

Results in Table LXX indicate that the NYHA classification did not change significantly during follow-up.

Table LXX. NYHA Classification Changes Intent to Treat Analysis

		Final NYHA Class			
Group	**Baseline NYHA Class**	I (n)	II (n)	III (n)	IV (n)
Amlodipine	I	0	1	0	0
	II	1	18	5	0
	III	1	6	12	0
	IV	0	0	0	1

[Values were obtained from IND Vol. 12.2, Table 9, page 28.]

The overall assessment of heart failure symptoms (dyspnea at rest, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and fatigue) revealed a modest increase (i.e., worsening) of 17.7% in the overall mean symptom scores (IND Vol. 12.2, Table 10, page 29).

Safety:

Tables LXXI and LXXII summarized adverse events with an onset prior to the start of open-label therapy and all adverse events, respectively.

Table LXXI. Adverse Events with an Onset Date Prior to the Start of Open-Label Therapy

Patient ID	Therapy at Onset	Event
680-4008	Amlodipine 10 mg	Pedal Edema
680-6012		Facial Rash
713-4004		Sinus Congestion
713-4007		Upper Airway Congestion/Leg Cramps
765-6001		R. Pleural Effusion
889-4004		Joint Pain
713-4003	Double-blind Placebo	Impacted 1st. R. Molar
765-6009		Nausea
889-4005		R. Leg Ulcer

Table LXXII. All Adverse Events

Dose at Onset	Patient ID	Event Onset (days)	Event
Amlodipine 5 mg-10 mg	6676002	32-238	Diff. Sleeping, Edema, Worsening CHF
	6676010	25-84	↑ SOB, Chest Pain, Ankle Edema
	7134006	166/230	Conjuctival Hemorrhage/Pneumonia
	7134007	19/111	Cold/Mitral Insufficiency
	7725002	10-132	Ear Ringing, Gouty Arthritis
Amlodipine 5 mg	6676003	23-29	Worsening CHF, Pulm. Edema, ↑ BUN
	6676004	19-96	Bronchitis, Cough, Worsening CHF
	6676005	111	Dizziness
	6676008	29	Ankle Edema
	6676001	63/143	Worsening CHF
	7134001	189/241	Hyperglycemia/Keratosis
	7134002	1-284	Edema, Chest, Pain, Rash, UTI, Myalgia, Insomnia
	7134003	207-294	Sinusitis, Edema
	6676009	55-140	Diarrhea, Chest Tightness, Cardiac Arrest

Table LXXII. (continued)

Amlodipine 5 mg	7134004	165-166	Chest Pain
	7134005	29/87	Muscle Weakness/Sinusitis
	7656001	24	Arrhythmia
	7656003	245	Worsening CHF
	7656004	65-249	Syncope, Chest Pain, Worsening CHF, Bronchitis
	7656005	6-79	Tonsillitis, Worsening CHF, Gout, Skin Eruption
	7656006	168	Diarrhea, URI
	7656007	5/56	Fatigue/Headache, Rosacea
	7656009	28/40	Epididymitis, Hernia/Dizziness
	7656012	187/202	Joint Pain/Hematuria
	7656014	58	URI
	7725005	28	DI Discomfort
	7725009	15	Rash
	8894004	30-237	Abd. Discomfort, URI, Gastric Ulcer
	8894005	13-270	Fatigue, Sinusitis, Edema, UTI
	8894008	35/94	Dizziness/Dizziness
	8894008	95	Accidental Injury
	8964001	18	Dizziness
	6676012	37-241	Leg Cramps, Visual Abnormality, Abscess
Amlodipine 10 mg	6804001	156	URI
	6804008	46-280	URI, Edema, Worsening CHF
	6806012	96-207	Fatigue, Rash, URI
	7715002	232	URI
	7725004	35	Rash
	7725008	118/253	Lightheaded/Cardiac Arrest
	7725010	107	Infection
	7725014	215	Worsening CHF
	7725016	170	Insomnia
	8894003	3-155	Abdominal Discomfort, Flu, Rash, Palpitations

Of note, 95% of the patients enrolled in the study reported at least one adverse event during the course of therapy. Twenty-eight (65%) patients were only receiving 5 mg/daily of amlodipine at the time of the adverse event. Worsening of congestive heart failure was one of the serious adverse events reported in 9 (21%) patients.

Table LXXIII is a summary of discontinuation of therapy.

Table LXXIII. Discontinuation of Therapy

Dose at Time of Withdrawal	Patient ID	Duration of Therapy (days)	Event
Amlodipine 5 mg	180 6676001	149	Pt. d/c'd per Request from Pfizer
	180 6676003	32	Worsening CHF/Pulmonary Edema
	180 6676004	145	Died
	180 6676009	140	Died
	180 7656001	24	Died
	180 7656002	282	Asked to be Withdrawn from Study
	180 7656004	257	Asked to be Withdrawn from Study

Table LXXIII. (continued)

Amlodipine 5 mg	180 7656005	29	Worsening CHF
	180 7656006	236	Asked to be Withdrawn from Study
	180 7656007	57	Asked to be Withdrawn from Study
	180 7656009	119	Asked to be Withdrawn from Study
	180 7656012	254	Asked to be Withdrawn from Study
	180 7656014	120	Asked to be Withdrawn from Study
Amlodipine 10 mg	180 7725008	252	Died
	180 6676002	238	D/c'd Due to Lack of Efficacy

Five patients died during open-label therapy.

Case Summaries of Patients with Fatal Events
Patient 180-667-6004 (RUS4936) This 73-year-old male received amlodipine as treatment for congestive heart failure. Study drug was administered orally at a dose of 5 mg daily from August 4, 1992 to December 26, 1992. On December 26, 1992 he collapsed at a store and died; the cause of death was congestive heart failure secondary to end-stage cardiomyopathy. Concurrent illnesses are unknown. Concomitant medications included allopurinol, enalapril, salbutamol, metolazone, potassium chloride, furosemide, digoxin, and aspirin.
Patient 180-667-6001 (RUS4527) This 65-year-old male received amlodipine as treatment for congestive heart failure. Study drug was administered orally at a dose of 5 mg daily from April 20, 1992 to September 15, 1992. On September 26,1992, he died "peacefully" at home due to refractory congestive heart failure and cardiac arrest. Concurrent illnesses included diabetes mellitus, sulfa drug allergy, and a previous stroke (1 990). Concomitant medications included insulin, glyburide, captopril, furosemide, digoxin, and quinidine.
Patient 180-765-6001 (RUS4150) This 85-year-old male with a pacemaker in place received amlodipine as treatment for congestive heart failure. Study drug was administered orally at a dose of 5 mg daily from June 10, 1992 to July 3, 1992. He collapsed on July 3 and never revived. The cause of this sudden death was attributed to arrhythmia (unspecified). Concurrent illnesses included atrial fibrillation and allergies to tetanus toxin and penicillin. Concomitant medications included metolazone, enalapril, warfarin, bumetanide, diphenhydramine, quinidine, and digoxin.
Patient 180-667-6009 (RUS5452) This 58-year-old male received amlodipine as treatment for congestive heart failure. Study drug was administered orally at a dose of 5 mg daily from November 6, 1992 to Study drug was administered orally at a dose of 5 mg daily from November 6, 1992 to March 25, 1993. On March 25 his wife found him unconscious and took him to the emergency room where he was pronounced dead on arrival. The causes of death were given as cardiopulmonary arrest, ischemic cardiomyopathy, and ventricular fibrillation. Concurrent illnesses included diabetes mellitus, coronary artery disease and hypertension. Concomitant medications included nitroglycerin, enalapril, potassium chloride, metoprolol, allopurinol, furosemide, digoxin, aspirin, and glipizide.
Patient 180-772-5008 (RUS5758) This 55-year-old male received amlodipine as treatment for congestive heart failure. Study drug was administered orally at a dose of 1 0 mg daily from September 17, 1992 to May 26,1993. On May 27 he was found dead at home by his son. The underlying cause of this sudden death was attributed to arteriosclerotic cardiovascular disease. Concurrent illnesses included atrial fibrillation and the above mentioned ASCD. Concomitant medications included digoxin, lisinopril, warfarin, potassium chloride, and furosemide.

Summary: This was an open-label, 40 week study. Following completion of double-blind efficacy trials #053-174, 175, or 176. All qualifying patients met the inclusion/exclusion criteria listed in protocols #053-174, 175, and 176.

The two purported efficacy endpoints, that is NYHA class and heart failure symptoms, were not significantly affected by amlodipine treatment. The incidence of adverse events although appears to be in keeping with the results of the PRAISE study, is difficult to adequately evaluate because of the small number of patients being followed and the uncontrolled open-label nature of the study.

THE CLAIMS/PACKAGE INSERT

This section of the review focus on the revisions to the package insert of amlodipine proposed by the sponsor. The statements that in the view of the reviewers need to be eliminated or significantly modify are shown in ~~strikethrough~~ font. The revisions proposedby the sponsor entail changes in the following sections:

DRAFT LABELING

---PROPOSED---

DRAFT LABELING

Reviewers' comments: The proposed changes suggested by the sponsor appear to be supported by the data.

REVIEWERS' CONCLUSIONS/RECOMMENDATIONS

1) The application is approvable.

2) The package insert requires modifications to accurately reflect the significant findings.

NOTE

It is to be noted that the statistical reviewer has only reviewed the statistical results of the PRAISE study (Protocol #053-173).

/S/

Walid A. Nuri, Ph.D.
Mathematical Statistician

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Walid Nuri, Ph.D.

/S/

Juan Carlos Pelayo, M.D.

Concur:
Dr. Hung 01/29/96
Dr. Chi 1/30/96

cc:
orig.
HFD-110
HFD-110 / CSO / J.C. Pelayo / S. Chen / A. Karkowsky
HFD-344 / Dr. Lisook
HFD-701 / Dr. Anello
HFD-710 / Mr. Orticke
HFD-710 / W. Nuri / G. Chi / J. Hung
HFD-710 /chron

13 pages redacted from this section of the approval package consisted of draft labeling