CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
19-787/S-007

Medical Review(s)

Dave Raeder

MEMORANDUM

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

DATE: APR 22 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Amlodipine PRAISE Labeling Change

TO: Dr. Raymond Lipicky

Dr. [redacted] comments are worth considering. There has been some discussion in other settings of whether a trial that hoped to show an advantage for an agent can be used to show "equivalence." I believe the answer is clearly yes, although there is perhaps a statistical penalty to pay.

It is not clear to me whether there was an intent to analyze by etiology, but this may not matter as, in the end, the steering committee considered the subset finding inconclusive.

Dr. [redacted] wonders about the last paragraph of p. 17 and I do too. It seems to say that because the power for testing the non-ischemic subset was low, the finding could have occurred by chance.

I may be missing something but that conclusion seems entirely illogical. The P value of 0.03 tells you that the chance of observing the difference between groups seen if there really was no difference is 3% (assuming no need to correct for multiple testing, which, of course is not true: there were two strata and a combined analysis, giving more than 2 independent tests and a need for correction of at least 2+).

If that paragraph represents a combined med/stat conclusion, I think some remedial work is needed.

Robert Temple, M.D.

cc: (with [redacted] Letter)
Dr. Chi

NDA-19-787
HFD-110
HFD-110/CSO

Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Pfizer

Central Research

April 16, 1996

Department of Clinical Research

CONFIDENTIAL/TRADE SECRET INFORMATION SUBJECT TO 18-USC-1905 AND TO WHICH ALL CLAIMS OF PRIVILEGE AND CONFIDENTIALITY ARE ASSERTED IN BOTH STATUTORY AND COMMON LAW. FURTHER DISSEMINATION MAY ONLY BE MADE WITH THE EXPRESS WRITTEN PERMISSION OF PFIZER INC.

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research HFD #110
Office of Drug Evaluation I
ATT: DOCUMENT CONTROL ROOM #16B-30
5600 Fishers Lane
Rockville, MD 20857

Dear Doctor Lipicky:

RE: NDA-19-787 - NORVASC® (amlodipine), Oral

Reference is made to our April 25, 1995, NORVASC labeling change supplement. Reference is also made to your primary Medical Reviewer's comments on this labeling change supplement received from the Division on February 26, 1996, and comments from the secondary Medical Reviewer and yourself which were kindly provided on April 2, 1996.

We forwarded a copy of the Division's comments on the submission to [redacted] As you are aware, Dr. [redacted] and his group served as the [redacted] for the PRAISE Data Safety Monitoring Board. Dr. [redacted] has returned comments to us and we are providing them to you herewith as many of the comments may be useful as we begin to finalize the labeling. Please note that the page numbers indicated in Dr. [redacted] letter refer to comments from the primary review, however, we believe that many of these comments are relevant to the other reviews as well.

Thank you for the opportunity to read and comment on the review comments to date. We hope Dr. [redacted] comments are helpful and we look forward to the opportunity to meet with you and Dr. Temple in the near future to finalize the labeling.

Please include this information in our file for NDA-19-787.

Sincerely yours,

/S/

William R. Murphy, Ph.D.
Associate Director II
Regulatory Affairs - Liaison

CC: Dr. R. Temple

enclosure
Serial No.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION **Public Health Service**

Division of Cardio-Renal Drug Products

Memorandum

DATE : APR 17 1996

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

SUBJECT: NDA 19-787/S-007, Amlodipine, CHF, PRAISE, labelling.

TO : Director, Office of Drug Evaluation 1, HFD-101

We need no meeting; your labeling recommendations look fine to us. Regarding your question about the p-values, they do appear to be rather odd. Dr. Nuri has looked at them carefully and assures me that they are correct. He would be happy to discuss the issue with you in detail if you wish, but I don't believe that it is relevant to the decision that has to be made.

cc:
Orig. NDA
HFD-110
HFD-110/CSO

MEMORANDUM

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

DATE: APR 16 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: NDA 19-787/S-007 (Amlodipine CHF labeling revision)

TO: Dr. Raymond Lipicky, HFD-110

The tertiary, secondary, and primary reviews are very clear. It appears that amlodipine, despite being a dihydropyridine CCB, has little, if any, net adverse effect on patients with CHF, even severe CHF, presumably because whatever modest negative inotropic effect it has is countered by its arterial dilator effect. The CHF symptom studies are a wash, with one suggesting benefit, two not (and one of those trended the wrong way). The PRAISE study, an ambitious effort, showed no overall adverse effect on the combined endpoint of mortality or other cardiovascular outcomes and even in NYHA Class IV patients, there was no real suggestion of problems. I agree that the non-ischemic subset data are unpersuasive and should not be presented in labeling; they could only mislead.

I have modified the labeling changes and we probably need to discuss this. I believe the results of PRAISE and the symptom studies deserve somewhat more prominence than you seem to; they seem pretty reassuring to me, especially PRAISE. Unless we take the position that all CCB's need to be avoided in CHF no matter what the clinical data show, a position that seems to me to make more than it should of a simple name for a complex electrophysiologic property, Pfizer seems to have done what should be done to explore safety in CHF. There is, however, one question with respect to the generally reassuring data. The distribution of cardiac events (MOR, p. 16) is interesting, with near-significantly more CHF deterioration on Norvasc, and near-significantly less ventricular arrhythmia on Norvasc. Should <u>this</u> subset response be noted in labeling? It has a pretty strong "prior".

There is something odd in the p-values given for various comparisons (MOR, p. 18). In looking at cardiac events by etiology, the non-ischemic patients, for life-threatening ventricular arrhythmias, were 6 placebo vs 2 Norvasc, which is said to be significant at p=0.023. That is not plausible; 6 vs 2 must be NS. In contrast, for deterioration of heart failure, it's 5 placebo vs 16, said to be p=0.231. That seems far too high a p-value. (Note that 18 vs 10 is p=0.06 for life threatening arrhythmias, MOR p. 23.) Are those values correct?

/S/

Robert Temple, M.D.

cc:
NDA 19-787
HFD-110
HFD-110/Project Manager

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : APR - 1 1996

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 19-787/S-007, Amlodipine, CHF, PRAISE, labelling.

TO : Director, Office of Drug Evaluation 1, HFD-101

Attached are the primary and secondary reviews of Supplement 007 for NDA 19-787. The documentation contains the reviews of PRAISE as well as that of 3 other clinical trials that evaluated the utility of amlodipine in CHF. Study 053-121 was the ETT study contained in the original amlodipine NDA submission and led to statements in the current package insert as well as to many advertisements. Needless to say, it could not be duplicated (does that lead you to wonder what a p of 0.025 means and whether one ought to trust a single trial?; no need to answer that).

The reason for sending this package to you is because there are labelling issues. I do not think that my approach to labelling would be consonant with yours. The labelling that has been suggested by the sponsor and by Dr. Karkowsky are nicely documented in pages 1 through 7 of Dr. Karkowsky's attachment to his March 4, 1996 memorandum. Mine are below.

There is little need to sift through the data. Of the 3 ETT (do patients feel better) trials, one of 3 had statistically significant findings. The other two (both larger) trend, if anything, slightly in the wrong direction (that's not really a fair statement; the means are almost identical). So, one can reasonably conclude that for symptoms and ETT, amlodipine has no measurable adverse effect.

PRAISE, a randomized, double-blind, placebo-controlled trial with morbidity/mortality endpoints found no statistically significant effect with respect to its primary end-point. A retrospective (in that it was not mentioned anywhere in the protocol) analysis raises the hypothesis that patients with non-ischemic heart disease fare well with amlodipine. From my point of view, that suggestion should appear nowhere in the package insert (if PRAISE appears at all). So there is little to study or even to argue about. The question is what prose should be written.

Under Clinical Pharmacology suggestion, all new words.

DRAFT

Under Pharmacokinetics my suggestion (add the 6 bolded words).

Elderly patients, patients with hepatic insufficiency DRAFT
have decreased clearance of amlodipine with a resulting increase in AUC between 40 and 60% and a lower initial dose may be required.

Under Precautions: Use in Patients with Congestive Heart Failure, my suggestion.

DRAFT

The reason for no more words here are tables XX (page 16 medical/statistical review) and XXX (page 20 medical/statistical review). There was a trend for worsening of heart failure in PRAISE. So, this is consistent with good advice.

Summary

I have no more to say. It seems to me that my suggestions make it clear that bunches of controlled trials were done, that amlodipine certainly did not benefit patients with heart failure, did not overtly harm patients with heart failure, but all-in-all, it seems wise to avoid amlodipine in heart failure.

cc:
Orig. NDA
HFD-110
HFD-110/CSO

MEDICAL/STATISTICAL REVIEW

JAN 30 1996

NDA #: 19787/S-007 CHF Safety Supplement
DRUG NAME: Norvasc® (Amlodipine Besylate)
SPONSOR: Pfizer Inc.
TYPE OF DOCUMENT: Supplemental NDA
DATE RECEIVED: Document 04/26/1995, Data tape 04/26/1995
DATE REVIEW COMPLETED: 1/11/1996
MEDICAL REVIEWER: Juan Carlos Pelayo, M.D.
STATISTICIAN: Walid Nuri, Ph.D.

INTRODUCTION

This is a supplemental NDA submitted by the sponsor to support a revision to the labeling of Norvasc® (Amlodipine Besylate). Norvasc® has previously been approved for the treatment of angina and hypertension in the United States (NDA # 19787, approved on 07/31/92). According to the sponsor, the data presented herein "support the use of Norvasc® as a safe therapeutic option for the treatment of hypertension and/or angina in patients with congestive heart failure." This supplemental NDA submission centers around a mortality/morbidity trial, known as the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation), as the pivotal investigation. In addition to the PRAISE study, the sponsor has also included results from nine clinical studies, two investigating the hemodynamic effect(s) and one investigating the pharmacokinetics of amlodipine in patients with congestive heart failure (CHF), and three were exercise tolerance studies. The three remaining studies were extension of the hemodynamic and exercise tolerance studies. The new proposed labeling, in its entirety, has been incorporated to the appendix of this review.

The document has been evaluated jointly by the Division of Cardio-Renal Drug Products and the Division of Biometrics as a combined Medical/Statistical review.

GENERAL INFORMATION

Name of Drug:
Generic: Amlodipine Besylate
Trade: Norvasc®
Chemical: (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine-dicarboxylate benzensulphonate.

Pharmacologic Category: Amlodipine Besylate is a dihydropyridine calcium antagonist (i.e., slow Ca^{++} channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.

Proposed Indication: Therapeutic option for treating angina and hypertension in patients with clinical evidence of congestive heart failure.

Dosage Form(s) and Route(s) of Administration: 5 mg tablets; 1 tablet p.o. qd or 2 tablets p.o. qd.

Related Drugs: Nifedipine.

CLINICAL STUDIES

PRAISE (Protocol # 053-173) was a long-term morbidity and mortality study in poorly compensated NYHA class III and IV patients. The protocol of the PRAISE clinical study is incorporated, in its entirety, to this review as part of the appendix (Appendix, pages 1A-58A).

In addition to the PRAISE study, the sponsor included results from eight Phase II and III clinical studies and one Phase I clinical study in CHF patients. In these clinical studies the effect(s) of amlodipine was evaluated on patients with heart failure NYHA class II and III for 2- to 12-weeks, including three exercise tolerance studies (121, 174 and 175) and two hemodynamic studies (172 and 176), as well as one pharmacokinetic study (009). Studies 174E, 175E and 180 were safety extensions of studies 174, 175, and 176, respectively. In these trials some patients were evaluated for up to a mean of 49 weeks.

PROTOCOL #053-173 (PRAISE Study)

Objectives of the Study: The primary objective of the PRAISE study was to compare the effect of treatment with amlodipine and placebo on combined mortality (cardiac and non-cardiac death) and cardiac morbid events in patients with clinical evidence of severe heart failure with left ventricular ejection fraction (LVEF) < 30%.

The secondary objectives of this study were:

i) To determine the effect of amlodipine on quality of life score and alteration of patient's NYHA functional status. Also, in a subset of patients, changes in neurohormonal plasma concentrations were to be assessed.

ii) To assess the safety of amlodipine in patients with severe heart failure treated with ACE inhibitors, digoxin and diuretics.

Rationale of the Study: Administration of calcium channel blockers to patients with hypertension and/or angina has been demonstrated to be beneficial. However, the presence of heart failure has precluded the use of this therapeutic option in the aforementioned clinical conditions, because of the concern of worsening ventricular function. Although, the precise mechanism by which calcium channel blockers in general could worsen heart failure in patients with ventricular dysfunction is not completely understood, the current thought is that by inhibiting Ca^{++} uptake in cardiac myocyte they might exert a significant negative inotropic effect. Because amlodipine is regarded as a poor calcium channel blocker in cardiac myocyte; it is claimed by the sponsor that Norvasc® administration should not have a clinically significant negative inotropic effect in patients with heart failure. Thus, the sponsor surmised that administration of Norvasc® to patients with heart failure should not be associated with hemodynamic and symptomatic deterioration due to a negative inotropic effect.

Experimental Design: This was a multicenter, randomized, placebo controlled, parallel, double-blind study with an initial estimated enrollment of approximately 800 patients with severe heart failure NYHA class III-IV (i.e., 400 patients in the amlodipine group and 400 patients in the placebo group). The study consisted of a screening visit, followed by a double-blind period of at least 24 weeks.

The study medication could be temporarily discontinued for any serious adverse event, whether related or not to the study drug, but after the patient had recovered from the event, treatment was to be re-instituted. Treatment with digoxin, diuretics, ACE inhibitors and other permitted medications was continued during the double-blind treatment period.

Study Periods:

I. Screening
II. Randomization
III. Double-Blind Treatment Phase
    a. Dose-Titration Phase (Week 0-2)
    b. Dose-Maintenance Phase (Week 2-end of study)

Four weeks, after screening evaluations were completed, was the maximum time allowed before patients were entered in the double-blind, forced-dose titration treatment period.

Subject Selection:

Inclusion Criteria
Patients must be at least 18 years of age.
Females must be non-lactating, without childbearing potential, e.g., postmenopausal or surgically sterilized.
Patients should have heart failure for $\geq$ 2 months.
Patients must be symptomatic (i.e., experience fatigue, palpitation or dyspnea) at rest, or upon minimal exertion (i.e., walking across a room or down the hallway) despite adequate treatment with ACE inhibitors, digoxin and diuretics for at least 2 months.
Predominant systolic dysfunction with left ventricular ejection fraction (LVEF), measured by radionuclide or contrast ventriculography, **lower than 30%** within the past three months. If LVEF was measured within three months, but there has been an intervening cardiac event, the LVEF measurement must be repeated prior to randomization. For patients with atrial fibrillation, the highest estimated value of ejection fraction corresponding to the optimally opacified beat must be **lower than 30%**.
Patients with properly functioning prosthetic heart valve.
The investigator was to obtain informed written consent from all patients.

Exclusion Criteria:

Exclusion Criteria
Women of childbearing potential, lactating and pregnant women.
NYHA Class II symptoms within two months.
Clinical evidence of impending myocardial infarction, i.e., patients who experience angina of increasing frequency, or duration.
Myocardial infarction within one (1) month.
PTCA or CABG within three (3) months.
Stroke within three (3) months.
Uncorrected primary valvular heart disease, with the exceptions indicated above.
Patients with congenital heart disease.
Arterial hypotension with a supine systolic blood pressure lower than 84 mmHg; **arterial hypertension** with a supine systolic blood pressure greater than or equal to 160 mmHg, or a supine diastolic blood pressure greater than or equal to 90 mmHg.
Clinical evidence of digitalis toxicity.
Patients with a history of sudden death, sustained (greater than 30 seconds and greater than or equal to 140 beats per minute) ventricular tachycardia, symptomatic ventricular tachycardia greater than or equal to 140 beats per minute), or ventricular fibrillation were not eligible unless these occurred within 24 hours of an acute myocardial infarction. However, patients with these events shall be eligible for the study if the events were treated with an effective antiarrhythmic intervention and there has been no recurrence of the event in the preceding twelve months.
Patients with second (Mobitz Type II) or third degree AV block were not eligible unless these rhythms have been treated with a properly functioning permanent pacemaker.
Patients who have received encainide, flecainide, disopyramide, propafenone, morizicine, *or sotalol** within two weeks.
Patients who have received **ß-blockers**, hydralazine, *flosequinan, vesnarinone*. pinacidil, minoxidil, **calcium channel blockers** (*including felodipine, and bepridil*), and oral levodopa (except when taken for Parkinson's disease as carbidopa/levodopa combination within two weeks). *Patients who have previously been treated with amlodipine or felodipine for any duration of time, or who have participated in an amlodipine double-blind trial are excluded from participation in this study.*
Severe primary lung disease or respiratory failure of any cause, cor pulmonale.
Sick sinus syndrome, except patients with a properly functioning permanent pacemaker.
Patients with clinically important hematologic, primary renal, hepatic, endocrine (other than diabetes mellitus) or neurologic (including all forms of epilepsy) disease. Patients with renal or hepatic impairment secondary to heart failure may be included in this study if the degree of impairment is consistent with the severity of the heart failure, and the values of serum creatinine, total bilirubin, alkaline phosphatase, SGOT (ASAT), SGPT (ALAT) are within the limits specified in the criteria for randomization.
Collagen vascular disease other than rheumatoid arthritis (e.g., SLE, PAN , scleroderma).
Active myocarditis.
Constrictive pericarditis.

Exclusion Criteria (continued)
Any medical condition which, in the investigator's opinion, required continued therapy with any prohibited medication, *or prohibits the continuation of triple background therapy (ACE Inhibitor, digoxin, diuretic).*
Patients that were under consideration for cardiac transplantation.
Planned CABG or PTCA during course study.
Significant drug allergy or intolerance to 1,4-dihydropiridines such as nifedipine.
Therapy with another investigational drug within one month prior to entry or concomitantly with the present study. Patients may not receive any other investigational drug until the study is complete.
Patients with known drug or alcohol dependence, or any other factors (such as the patients who will not reliably take the study medication or attend the planned study visits) which will interfere with the interpretation of the results.
Patients must not have a disease, other than heart failure, that can be expected to limit survival during the next three years.
Failure to give consent.
Patients that were considered intolerant to ACE Inhibitors, digoxin, or diuretics.

[*Amendments effected on March 23, 1993, are represented by *italics*.]

Criteria for Randomization: Potentially suitable patients who gave their informed consent were to undergo a complete medical history, full physical examination, chest x-ray, laboratory tests, and 12 lead ECG. LVEF was determined by radionuclide or contrast ventriculography. Ensuing the screening visit, qualifying and consenting patients were further required to satisfy the following laboratory/therapeutic criteria to qualify for randomization. The patient eligibility to enter the study was discussed between the investigator or coordinator and the randomization site before randomization.

1. Laboratory criteria:
    a. serum creatinine $\leq$ 3.0 mg/dl.
    b. WBC, MCH, hemoglobin, hematocrit within 30% of the normal range.
    c. total bilirubin and alkaline phosphatase $\leq$ 3 times the upper limit of normal.
    d. SGOT (ASAT) and SGPT (ALAT) $\leq$ 3 times the upper limit of normal.
    e. serum potassium $\leq$ 5.50 mEq/L and $\geq$ 3.50 mEq/L.
2. Patients must not have received intravenous diuretics or vasodilators within the previous 24 hours.
3. Patients must not have received intravenous positive inotropics agents within the previous 72 hours.
4. Patients must not have received any prohibited medication within the previous 2 weeks.

Randomization was **stratified** by etiology of heart failure:
Stratum I: Ischemic Heart Disease (Numbers 1-2000)
Stratum II: Non-Ischemic Heart Disease (Numbers 2001-4000)

Patient Population: Male and female patients with chronic severe congestive heart failure (i.e., NYHA Class III-IV) were to be enrolled in this study.

Demography: The patient population to be studied in this clinical investigation was from the US and Canada.

Clinical Characteristics: Patients recruited in the study were supposed to have substantiated clinical evidence of heart failure NYHA Class III-IV. Patients were also to be eligible if they had heart failure for at least 2 months. Their background therapy should have consisted of an angiotensin converting enzyme inhibitor, digoxin, and diuretics.

Dosing Strategy: There was a dose-titration phase and a dose maintenance phase during the double-blind period. The dose of the study drug was to be titrated from 1 tablet (5 mg) p.o. qd to 2 tablets (10 mg) p.o. qd two weeks after starting double-blind therapy. The dose of study drug could be decreased to 1 tablet p.o. qd, only if the patient developed an adverse event (i.e., a side effect or clinically important laboratory abnormality considered possibly related to the study drug), at any time during the double-blind period. However, **asymptomatic hypotension** was **not** considered to be an indication to reduce the dosage.

Follow-up: The analysis of the study was to be conducted on an intention-to-treat basis (i.e., all patients were to be followed-up for the occurrence of primary or secondary outcomes until study close irrespective of the duration of treatment). All patients were to be followed for a minimum of 6 months. The approach for the follow-up evaluation is depicted in table I.

Table I. Follow-up Evaluation.

Evaluation/Weeks	0	2	4	8	12	16	26	39	52	65	78	91	104	Every 12	Final Visit
Routine-Clinic Visit*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Cardiovascular-NYHA Status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of Life	x				x		x		x		x		x		x
Laboratory**	x		x	x		x	x	x	x	x	x	x	x	x	x

[*The flow chart in appendix describes in more detail patient's evaluation, Appendix, page 21A.]

[**Laboratory parameters included: chemistry panel, CBC with differential, urinalysis, and prothrombin time.]

Study Diet: Patients were to be instructed or reminded to restrict their dietary sodium and to maintain a constant sodium intake throughout the study.

Study Termination: Recruitment was to be terminated after 190 events of the primary endpoint in the placebo group. The trial was to be closed after all patients have completed at least six months of double-blind therapy. The Data Safety Monitoring Board could end the study, at any time, according to predetermine stopping guidelines.

Upon study termination, final visit evaluation needed to be completed for all patients before discontinuation of study medication.

Compliance: The mechanism(s) (i.e., counting pills at each visit, etc.) by which the sponsor did plan to asses compliance is not available within the text of the protocol. However, it is recognized by the sponsor that noncompliance in the intention-to-treat analysis would tend to dilute treatment effects while preserving randomization and minimizing bias in comparisons. This dilution of treatment effects would cause a loss of power and precision. Therefore, the sponsor outlined adjustments to the statistical analysis for noncompliance (Appendix, pages 36A-37A).

Withdrawal of Treatment: Patients could be withdrawn from drug treatment for the following reasons:

Reasons for Discontinuation from Study
Fatal endpoint
Clinically important side effect(s) (which persist after dose reduction)
Laboratory abnormality (which persist after dose reduction)
Patient quitted the study
Patient was lost to follow-up

Statistical Basis for Sample Size: A sample of 800 patients is required to detect a reduction of 25% in the combined event rate with the amlodipine treatment compared to placebo group. For the placebo group it was expected that 190 events be observed during the course of this trial. The sample size was based on the following assumptions:

1. One-year combined event rate in the placebo group was calculated to be 40%.
2. The total duration of the study was supposed to be 2 years with a recruitment period of 1.5 years. This gave a minimum follow-up of 6 months and a maximum follow-up of 2 years.
3. Time to event is exponentially distributed and the hazard rate is constant over time for both treatment groups.
4. These sample size estimates were based on <u>two-tailed</u> log-rank test with a power of 90% at $\alpha = 0.05$.

Primary Endpoint: The primary outcome was a combined **mortality** and **cardiac event**.

Primary Endpoint	
Mortality or Cardiac Event	-Cardiac and non-cardiac death -Hospitalization 24 hours or longer for: a. deterioration of heart failure as evidence by -acute pulmonary edema, or -the development of severe hypoperfusion (i.e., change in mental status or oliguria requiring i.v. positive inotropic agents) b. acute myocardial infarction c. life threatening ventricular arrhythmia requiring therapy, such as -sustained ventricular tachycardia (>30 seconds and ≥140 beats per minute), or -ventricular fibrillation

Additional Endpoints: The additional outcomes were defined as follows.

Additional Endpoints	
Change in NYHA functional class	Assessment of NYHA functional class was carried out at screening and every visit during double-blind therapy.
Patient self-assessment-quality of life score‡	Scoring was performed at baseline and week 12, 26, 52, 78, 104 and final visit of double-blind therapy.
Neurohormonal parameters, *TNFα and lipid peroxidation parameters**†	The neurohormonal measurements included atrial natriuretic factor and plasma norepinephrine.
*Mortality***	Separate (secondary) analyses were performed for i)mortality, all-cause; and ii)cardiac mortality.

[Amendments/Revisions to the protocol are represented by *italics*.]

[*Amendment effected on March 23, 1993.]

[†These variables were measured at baseline and at 8 weeks during double-blind period. TNFα and lipid peroxidation products were also measured at week 26.]

[**Amendment effected on January 27, 1993.]

[‡Quality of Life Assessment battery description, Appendix, pages 28A-29A.]

Documentation supporting the classification of a cardiac morbid event as a primary endpoint was evaluated by the Event Classification Committee. The committee made the definite determination of whether documentation supported the classification of a morbid cardiac event as a primary endpoint. Similarly, this committee made the conclusive assignment of death classification for all fatal events.

Organization of the Study: The PRAISE study was directed and coordinated in a manner independent of the sponsor. Autonomy was assured by two committees, [redacted] which together directed the study. The [redacted] assisted in the design and conduct of the trial including protocol development, patient recruitment and data completeness and ensured implementation of recommendations from the [redacted]

The [redacted] established the stopping guidelines which were included in the protocol. This committee was also responsible for periodic review of safety data to ensure the continued safety of patients for the duration of the trial.

[redacted] reported to the [redacted] and was accountable for the statistical analysis of data.

Statistical Analysis: The principal analysis was **intention-to-treat**; that is, all patients randomized were analyzed regardless of post randomization eligibility checks or compliance to assigned therapy. The statistical methodology utilized in this study as well as the general statistical considerations for repeated tests and adjustments for non-compliance are explained in detail in the attached appendix (Appendix, pages 30A-38A).

Interim Analysis: Interim statistical analyses of the study outcomes were planned to monitor patient safety and treatment efficacy (Appendix, page 39A).

The following is a list of variables that were supposed to be examined at interim analyses.

1. Combined all-cause total mortality and cardiac events
2. NYHA Functional Class
3. Quality of Life
4. Neurohormonal Parameters
5. Incidence of Adverse Events (i.e., clinical side effects and laboratory parameters such as chemistry panel, CBC with differential, urinalysis)

Protocol Amendments/Revisions: In July 20, 1992 the protocol was amended to include immediate reporting of significant adverse experience.

In January 27, 1993 the protocol was amended to include mortality as an additional endpoint.

In March 23, 1993 the protocol was amended primarily in the exclusion criteria and additional endpoints sections.

RESULTS OF PROTOCOL #053-173 (PRAISE STUDY)

The PRAISE study was designed to test the overall hypothesis that amlodipine could provide a safe therapeutic option for patients with clinical evidence of severe heart failure. Thus, the major aim of the study was to compare the two treatment groups (i.e., placebo group vs. amlodipine group) in a combined mortality and cardiac morbid event endpoint. The secondary aims were to compare the two treatment groups in changes in NYHA functional class, patient self-assessment-quality of life score, neurohormonal parameters, and TNFα and lipid peroxidation parameters. A separate (secondary) analysis was performed for mortality, non-cardiac and cardiac mortality.

[Reviewers' Note: Except for those that are indicated as provided by the sponsor, all table presented in this review were constructed by the reviewers, using the data submitted by the sponsor. In some of these constructed tables p-values, based on Chi-Square tests, are also reported. Since these tests were not statistically planned before the trial was conducted, one would not be able to assess the power of each of these tests. Therefore, one cannot make decisions on the basis of these p-values; instead, these p-values provide some information as to what extent the amlodipine and the placebo groups differ with respect to the specified categories.]

Patient Randomization: A total of 1483 patients were screened in the PRAISE study by 105 centers located in the US and Canada. In total 1153 patients were randomized, 571 to amlodipine and 582 to placebo. The first randomization of this study occurred on March 9, 1992, accrual was extended in November 1993, and the final randomization was on June 30, 1994. The study ended six month later in December 30, 1994.

The main reasons for excluding screened patients from randomization are summarized in table II.

Table II. Distribution of Causes Precluding Randomization of Screened Patients

Causes	Patients Screened but not Randomized (n=330) n(%)
LVEF >30%	140(42.4)
Not enough symptoms of heart failure	36(10.9)
Patient declined to participate	20(6.0)
Not on triple therapy	18(5.4)
Treatment with amlodipine or other Ca^{++} channel blocker	10(3.0)
↑ Creatinine	6(1.8)
> 30 days window for randomization	5(1.5)
Miscellaneous	95(28.8)

In over forty percent of the patients screened but not randomized, a LVEF >30% was the factor precluding their enrollment. Administrative reasons (i.e., transportation problems, unwillingness to enroll, etc.) comprised the largest category within the miscellaneous causes.

Baseline Demographic Data: Patients studied in this clinical investigation were extracted from the general population of the US and Canada.

Patient Characteristics: The following tables summarize patient baseline characteristics data, including percent of females, race and age distribution, previous medical conditions requiring therapy, history of medications used, etc.

Table III. Patient Baseline Characteristics

Variables	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
Sex (Female)	129(22.2)	149(26.1)

Table III. (continued)

Race (White)	439(75.4)	443(77.6)
(Black)	118(20.3)	106(18.6)
(Other)	25(4.3)	22(3.8)
Smoker (Yes)	100(17.2)	84(14.7)

The groups were reasonably well matched with regard to sex distribution, in that 26.1% and 22.2% of the patients were females in the amlodipine and placebo groups, respectively. The male to female ratio in this study, 73.9%/26.1% in the amlodipine group vs. 77.8%/22.2% in the placebo group, is consistent with similar ratios observed in multicenter studies on the subject. Over three-fourths of the patients in both groups under investigation were white. The percentage of patients that smoke was also similar between the groups.

Table IV shows the mean patient age, at the time of entry, for both treatment groups. The patients' mean age at the time of the study was identical between groups. Of note, the mean age of patients participating in the PRAISE study is in accordance with patients' mean age observed in other studies of CHF (i.e., AIRE and SAVE studies).

Table IV. Patient Age at Randomization

Age (in years)	
Placebo (mean±SD)	Amlodipine (mean±SD)
64.7±11.0	64.7±11.5

The next two tables describe the patients' medical history regarding previous medical conditions requiring therapy and previous cardiac medications. The percent of patients with relevant previous cardiac conditions and diabetes mellitus was almost identical in both treatment groups. Over fifty percent of the patients in either group had a history of hypertension or myocardial infarction.

Table V. Previous Medical Conditions Requiring Therapy

Previous Medical Condition	Placebo %	Amlodipine %
History of Myocardial Infarction	61.34	59.37
History of Angina	54.47	53.42
History of Hypertension	57.22	54.64
History of Ventricular Tachycardia	1.37	1.58
History of Atrial Fibrillation	2.41	2.28
History of Diabetes	35.57	38.53

As can be expected, the list of the major previous medications that randomized patients have previously received included nitrates, and antiplatelets. The percent of patients with a history of use of the aforementioned medications was comparable in both groups. An exception to that assertion is the history of antiarrhythmic usage, in that more patients in the placebo group were on that therapeutic regimen than patients in the amlodipine group (25.26% vs. 20.32%, respectively).

Table VI. History of Previous Medications

Previous Medication	Placebo %	Amlodipine %
History of Antiarrhythmic Use	25.26	20.32
History of Antiplatelet Use	49.48	50.44
History of Nitrate Use	51.37	47.46

Of importance to the interpretation of the data is to have knowledge about the baseline medications of the patient population being study. Baseline medications were defined by the sponsor as those taken at any time within 2 weeks prior to randomization. Table VII provides the percentage of patients for either group receiving the most common baseline medications. As one could have predicted, on the basis of the inclusion criteria, over 90% of the patients in either the placebo group or the amlodipine group were concurrently treated with ACE inhibitors, diuretics, and a digitalis preparation. Other prevalent baseline medications included anticoagulants, nitrates, and vasodilators. These treatments were evenly distributed between the groups.

Table VII. Baseline Medications

Medication	Placebo %	Amlodipine %
ACE Inhibitor	92.4	94.4
Digitalis Prep.	90.4	91.2
Diuretics	93.5	95.3
Anticoagulants	37.6	36.3
Antiarrhythmic	14.9	12.6
Nitrate	40.4	37.5
Vasodilators	31.3	28.9

The distribution of the number/percentage of patients according to study drug and etiology of heart failure is detailed in Table VIII. Randomization was stratified by etiology of heart failure in two stratum: ischemic-heart disease and non-ischemic heart disease. The largest number of patients (i.e., >60%) randomized to either placebo or amlodipine arm had ischemic-heart disease. This pattern of rate of occurrence of heart failure by etiology is in accordance with the current knowledge about this clinical entity. According to the sponsor, only twenty-two patients were randomized erroneously, in terms of baseline etiology of heart failure.

Table VIII. Etiology of Heart Failure at Randomization

Etiology of Heart Failure	Randomization Assignment	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
Non-Ischemic-Heart Disease	Randomized as Non-Ischemic	207(35.5)	200(35.0)
	Randomized as Ischemic	5(0.8)	9(1.6)
Ischemic-Heart Disease	Randomized as Ischemic	366(62.9)	358(62.7)
	Randomized as Non-Ischemic	4(0.7)	4(0.7)

[Erroneous randomization of heart failure by etiology is represented by the shadow font.]

In Table IX the mean duration, in years, of heart disease (i.e., CHF) prior to randomization is shown. Patients in the placebo group had a history of heart disease of 3.85 years duration, an interval which was not different from 4.21 years observed in the amlodipine group.

Table IX. Duration of Disease

Duration of Disease (in years)	
Placebo (mean±SD)	Amlodipine (mean±SD)
3.85±3.79	4.21±4.55

The degree of left ventricular dysfunction as assessed by left ventricular ejection fraction was well balanced at randomization between the two groups (Table X). LVEF was <21% in either group, denoting the severity of the heart failure.

Table X. Left Ventricular Ejection Fraction (LVEF) at Randomization

LVEF (in %)	
Placebo (mean±SD)	Amlodipine (mean±SD)
20.8±6.0	20.6±5.7

The number/percentage of patients in a given NYHA functional class at baseline is represented in Table XI. Approximately eighty percent of the patients recruited were clinically classified as NYHA class III and the remaining ~20% percent had NYHA class IV. Treatment groups were comparable in the distribution of NYHA functional class at baseline.

Table XI. NYHA Functional Class at Baseline

NYHA Functional Class	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
Unknown	0(0)	1(0.17)
I	1(0.17)	0(0)
II	0(0)	1(0.17)
III	464(79.72)	464(81.26)
IV	117(20.10)	105(18.39)

Table XII provides the number/percentage of patients in both groups which were concurrently treated with ACE inhibitors, diuretics, digitalis preparation, anticoagulants, antiarrhythmics, nitrate, and vasodilators. More than seventy seven percent of the patients in either group were medicated with ACE inhibitors, digoxin and diuretics for at least 2 months prior entry to study, as per inclusion criteria. Perusal of the results in Table XII indicates that with the exception of antiarrhythmics, the remaining of the medications were distributed evenly between groups. More subjects in the placebo group than in the amlodipine group were being treated with antiarrhythmics (22.3% vs. 18.0%, respectively).

Table XII. Concomitant Medication at Randomization

Medication	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
ACE Inhibitor	475 (81.6)	474 (83.0)
Digitalis Prep.	452 (77.7)	446 (78.1)
Diuretics	521 (89.5)	516 (90.4)
Anticoagulants	303 (52.1)	302 (52.9)
Antiarrhythmics	130 (22.3)	103 (18.0)
Nitrate	289 (49.7)	269 (47.1)
Vasodilators	220 (37.8)	216 (37.8)

In the aggregate, the analyses of the data indicate that both groups were well matched with regard to baseline characteristics, LVEF, NYHA functional class, etc. One exception to that interpretation of the data was the usage of antiarrhythmics which was more frequent in the placebo group than in the amlodipine group. Nevertheless, the fact that the groups were reasonably well balanced at randomization (i.e., absence of a significant confounding variable at baseline) should dissipate doubts about whether or not any difference observed between treatments reflects an actual treatment effect of the drug.

Patient follow-up: Of the 1153 patients initially enrolled in the PRAISE study, no patient was lost to follow-up. The minimum length of patient follow-up was 6 months. On average, the number of days (Mean±SD) in

treatment for patients who completed the study was 562.9±239.8 for the amlodipine group (n=349), and 553.8±241.8 for the placebo group (n=324). The status of randomized patients at study close is shown in Table XIII.

Table XIII. Status of Randomized Patients at Study Close

Patient Status	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
Alive, No Endpoint	336(57.7)	349(61.1)
Alive, Following Morbidity Endpoint	23(4.0)	32(5.6)
Dead, Subsequent to Morbidity Endpoint	31(5.3)	30(5.3)
Dead, No Prior Morbidity Endpoint	192(33.0)	160(28.0)
All	582(100.0)	571(100.0)

Patient Withdrawal: The incidence of withdrawal from study drug and the number of days in treatment before withdrawal, with the exclusion of patients who had died, are shown in Table XIV.

Table XIV. Patient Withdrawal:

Group	Patients Withdrawn n(%)	No. of Days in Treatment Before Withdrawal (mean±SD)
Placebo (n=582)	77(13.2)	253.9±240.4
Amlodipine (n=571)	68(11.9)	217.9±199.7

The total number of withdrawals and the average number of days in treatment before withdrawal were comparable between treatment arms (77 patients with 253.9 days in the placebo group, and 68 patients with 217.9 days in the amlodipine group). Reasons for patients' discontinuation are included in Appendix, pages 83A-86A.

***Compliance*:** The number of noncompliant patients per study visit is shown in Table XV.

Table XV. Number of Noncompliant Patients per Study Visit

Visit Number	Placebo n(%)	Amlodipine n(%)
2	94(16.2)	79(13.8)
4	106(18.7)	102(18.2)
8	142(26.1)	132(24.4)
12	139(26.2)	133(25.3)
16	139(26.9)	145(27.4)
26	169(36.8)	159(34.5)
39	139(36.1)	135(34.5)
52	120(40.0)	120(34.6)
65	123(48.6)	95(35.2)
78	85(41.0)	86(41.9)
91	61(43.9)	54(36.5)
104	39(40.6)	33(34.7)
116	19(41.3)	22(38.6)

Between visits 2 and 39 the degree of noncompliance was similar between the groups, however, thereafter there was a tendency for patients in the placebo group to be less compliant. Our analysis shows that on average 34.0% and 31.0% of the patients in the placebo and amlodipine groups, respectively, were noncompliant.

Dose of Study Drug During the Trial: Because differences in the dosage of study drug taken by the patients could potentially be a confounding factor on treatment efficacy as well as on the rate/type of adverse events, an analysis to determine the number of daily tablets taken by patients throughout and at the end of the study was performed (Tables XVI and XVII).

Table XVI. Number (dose in mg) of Daily Tablets Taken by Patients Throughout the Study

Visit#	Group	Dose 0.5/day (2.5 mg)	Dose 1.0/day (5 mg)	Dose 2.0/day (10 mg)	Dose 3.0/day (15 mg)	Unknown
2	Placebo	0	571	10	0	1
	Amlodipine	0	565	6	0	0
4	Placebo	0	42	510	1	13
	Amlodipine	0	24	526	0	9
8	Placebo	0	35	491	1	17
	Amlodipine	0	39	486	0	15
12	Placebo	1	33	476	0	20
	Amlodipine	0	42	452	0	31
16	Placebo	1	32	465	0	19
	Amlodipine	0	41	434	0	36
26	Placebo	1	27	411	0	21
	Amlodipine	0	37	393	0	31
39	Placebo	0	18	341	0	26
	Amlodipine	0	35	325	0	33
52	Placebo	0	8	276	0	16
	Amlodipine	0	28	296	0	23
65	Placebo	1	9	232	0	11
	Amlodipine	0	21	230	0	19
78	Placebo	0	11	187	0	9
	Amlodipine	0	18	171	0	16
91	Placebo	0	8	124	0	7
	Amlodipine	0	13	121	0	14
104	Placebo	0	6	84	0	6
	Amlodipine	0	11	74	0	10
116	Placebo	0	5	39	0	2
	Amlodipine	0	5	46	0	6

Table XVII. Number of Daily Tablets Taken by Patients at End of Study

Number of Daily Tablets (Dose in mg)	Placebo n(%)	Amlodipine n(%)
One (5 mg)	30(5.15)	46(8.05)
Two (10 mg)	323(55.49)	303(53.06)
Unknown	229(39.34)	222(38.87)

Most of the patients (i.e., ~ 90%), throughout the trial, in either the placebo or the amlodipine group were taken 10 mg/daily of study drug, as per protocol.

Primary Endpoint: The primary outcome was a combined mortality and cardiac morbidity endpoint. It comprised cardiac and no-cardiac deaths, or a cardiac morbid event, i.e., hospitalization for at least twenty-four hours because of deterioration of heart failure, or acute myocardial infarction, or life threatening ventricular arrhythmia requiring therapy.

The result of the sponsor's statistical analysis of this primary endpoint is shown in Table XVIII.

Table XVIII. Primary Endpoint All-Cause Mortality and Cardiac Morbidity

Etiology	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)	Hazard Ratio (95% CI)	p-Value*
Ischemic and Non-Ischemic	246(42.3)	222(38.9)	0.910 (0.756, 1.095)	0.31

[*Comparison between placebo and amlodipine groups on primary endpoint, using a Log-rank test. Sponsor's analysis.]

There were 246 of 582 patients in the placebo group experiencing a primary event and 222 of 571 patients in the amlodipine group. The log-rank test comparing the two groups gave a p-value of 0.31, and the relative hazard comparing amlodipine to placebo was 0.910 (95% confidence interval 0.756, 1.095). On the basis of this statistical analysis it could be concluded that the effect(s) of amlodipine on mortality and cardiac morbidity was not significantly different from placebo effect(s).

Because the primary endpoint is a combined endpoint, it is of interest to analyze each of its components separately to determine whether their changes were "unidirectional". Table XIX summarizes all-cause mortality (cardiac and non-cardiac causes of death).

Table XIX. All-Cause Mortality

Causes of Death	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)	p-Value*
Cardiac and Non-Cardiac	223(38.3)	190(33.3)	0.074

[*Comparison between placebo and amlodipine groups on all-cause mortality, using a Chi-Square test.]

In patients taking placebo there were 223 of 582 (38.3%) who died; in patients taking amlodipine there were 190 of 571 (33.3%) who died. The observed numerical difference between treatment groups didn't reach statistical significance at a p-value of 0.074.

The other component of the primary endpoint was cardiac morbidity, i.e., hospitalization for at least twenty-four hours because of deterioration of heart failure, or acute myocardial infarction, or life threatening ventricular arrhythmia requiring therapy. The distribution of cardiac events by treatment group is summarized below in Table XX.

Table XX. Distribution of Cardiac Events

Cardiac Event	Placebo n(%)	Amlodipine n(%)	p-Value*
Deterioration of Heart Failure	26(4.46)	45(7.88)	0.094
Acute Myocardial Infarction	10(1.71)	7(1.22)	0.309
Life Threatening Ventricular Arrhythmia	18(3.09)	10(1.75)	0.06

[*Comparison between placebo and amlodipine groups on cardiac events rates, using a Chi-Square test. The p-value for the overall comparison between the two groups, using a Chi-Square test is 0.025.]

There were no statistically significant differences between treatment groups in the number of cardiac morbid events. Of note, there were almost twice as many patients with deterioration of heart failure in the amlodipine group than in the placebo group (i.e., 7.88% vs. 4.46%, respectively; p-value = 0.094). Also, numerically there were more patients with life threatening ventricular arrhythmias in the placebo group than in the amlodipine group (i.e., 18 vs. 10, respectively; p-value = 0.06).

Patients' randomization was stratified by etiology of heart failure, i.e., stratum I: ischemic heart disease and stratum II: non-ischemic heart disease. When the model of analysis included etiology and treatment interaction terms, a significant treatment by etiology interaction for the combined endpoint was detected. Table XXI displays the results obtained from the statistical analysis of the primary endpoint stratified by etiology.

Table XXI. Primary Endpoint All-Cause Mortality and Cardiac Morbidity Stratified by Etiology

Etiology	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)	Hazard Ratio (95% CI)	p-Value*
Ischemic	168/370 (45.4)	164/362 (45.3)	1.037 (0.832, 1.292)	0.74
Non-Ischemic	78/212 (36.8)	58/209 (27.8)	0.694 (0.490, 0.982)	0.03

[*Comparison between placebo and amlodipine groups on primary endpoint, using a Log-rank test. Sponsor's analysis.]

In patients with heart failure of ischemic etiology, there were 168 of 370 patients with a primary event in the placebo group, compared to 164 of 362 in amlodipine-treated patients. Between treatment groups the significance for time to event is p = 0.74, with a hazard ratio of 1.037 and a 95% confidence interval of 0.832 and 1.292. In contrast, in heart failure patients with non-ischemic etiology taking amlodipine, there were 58 of 209 patients experiencing a primary event; in those patients taking placebo however there were 78 of 212 experiencing a primary event. Between treatment groups the significance for time to event is p = 0.03 with a hazard ratio of 0.694 and a 95% confidence interval of 0.490 and 0.982. This subgroup analysis suggests that amlodipine may have a salutatory effect in heart failure patients with non-ischemic etiology. The scientific reason(s) for the discrepancy in results between the subset of patients with ischemic versus those with non-ischemic etiology is unknown.

The study was designed to have a power of 90% (two-tailed) to detect a difference of 25% in event rate of the primary endpoint between the two treatment groups. The sample size was estimated to be 800, based on the assumption of a baseline one-year placebo event rate of 40%. Certainly, such a power would not be maintained when one considers the analysis of the primary endpoint by etiology (a subgroup analysis). In fact, the sponsor's results of a p-value = 0.03 for the non-ischemic group was not based on a design of a trial with a power of 90% for this subgroup. Based on a sample size of 209 patients for placebo and 212 for amlodipine, a post hoc calculation shows that a test which is expected to detect a difference of 25% in event rate of primary endpoint between the two groups would have a power of only 51%. Thus, a test having such a small power would not be able to detect the specified difference between the two treatment groups and this may mean that the significant results found above could have easily occurred by **chance**.

Table XXII summarizes the statistical results of the analysis of all-cause mortality when stratified by etiology.

Table XXII. All-Cause Mortality Stratified by Etiology

Etiology	Placebo (Total Deaths = 223) n(%)	Amlodipine (Total Deaths = 190) n(%)	Hazard Ratio (95% CI)	p-Value*
Ischemic	149(66.8)	145(76.3)	1.019 (0.807, 1.287)	0.87

Table XXII. (continued)

Non-Ischemic	74(33.2)	45(23.7)	0.540 (0.370, 0.788)	0.001

[*Comparison between placebo and amlodipine groups on primary endpoint, using a Log-rank test. Sponsor's analysis.]

This subgroup analysis on all-cause mortality stratified by etiology showed that, in heart failure patients with ischemic etiology taking placebo, 149 out of 370 randomized patients died, while in heart failure patients with ischemic etiology taking amlodipine, 145 out of 362 randomized patients died (p-value of 0.87). However, in heart failure patients with non-ischemic etiology taking placebo 74 out of 212 randomized patients died, while in heart failure patients with non-ischemic etiology taking amlodipine 45 out of 209 randomized patients died. Between treatment groups the significance for time to death is p-value of 0.001 with a hazard ratio of 0.540 and a 95% confidence interval of 0.370 and 0.788. Kaplan-Meier survival curves by patients' etiology of heart failure were produced and are incorporated in the appendix (page 59A).

Subgroup analysis was also carried out in order to determine whether there is a significant treatment by etiology interaction for cardiac and non-cardiac causes of death. The results, which are summarized in Table XXIII, failed to demonstrate a statistically significant difference between the two groups.

Table XXIII. Cardiac and Non-Cardiac Causes of Death Stratified by Etiology

Etiology	Causes of Death	Placebo (n=223) n(%)	Amlodipine (n=190) n(%)	p-Value*
Ischemic	Cardiac	57(25.5)	54(28.4)	0.921
	Non-Cardiac	92(41.3)	91(47.9)	0.938
Non-Ischemic	Cardiac	37(16.6)	20(10.5)	0.672
	Non-Cardiac	37(16.6)	25(13.2)	0.685

[*Comparison between placebo and amlodipine groups on all-cause mortality, using a Chi-Square test.]

Further subgroup analysis was performed to determine whether there is a significant treatment by etiology interaction for cardiac morbid events. The results summarize in Table XXIV, except for life threatening ventricular arrhythmia (p = 0.023), failed to demonstrate a statistically significant difference between groups. Of interest, in both etiologies there was a higher incidence of deterioration of heart failure in the amlodipine group than in the placebo group.

Table XXIV. Cardiac Events Stratified by Etiology

Etiology	Cardiac Event	Placebo n(%)	Amlodipine n(%)	p-Value*
Ischemic	Deterioration of Heart Failure	21	29	0.388
	Acute Myocardial Infarction	9	4	0.333
	Life Threatening Ventricular Arrhythmia	12	8	0.550
Non-Ischemic	Deterioration of Heart Failure	5	16	0.231
	Acute Myocardial Infarction	1	3	0.640
	Life Threatening Ventricular Arrhythmia	6	2	0.023

[*Comparison between placebo and amlodipine groups on cardiac events rates, using a Chi-Square test]

To test the hypothesis that there might be a difference between male and female patients in the rate of occurrence of death between the placebo and the amlodipine groups, gender subgroup analyses were performed. The results of the analyses of the potential modifying influence of gender on all-cause mortality, cardiac causes of death, and non-cardiac causes of death are shown in Tables XXV, XXVI, and XXVII, respectively. The analyses demonstrate that the incidence of death was not affected by gender in either the placebo group or the amlodipine group.

Table XXV. All-Cause Mortality by Gender

Group	Male n(%)	Female n(%)	p-Value*
Placebo (n=223)	176(78.9)	47(21.1)	0.787
Amlodipine (n=190)	152(80.0)	38(20.0)	

[*Comparison between placebo and amlodipine groups on all-cause mortality by gender, using a Chi-Square test]

Table XXVI. Cardiac Causes of Death by Gender

Group	Male n(%)	Female n(%)	p-Value*
Placebo (n=94)	76(80.8)	18(19.1)	0.221
Amlodipine (n=74)	65(87.8)	9(12.2)	

[*Comparison between placebo and amlodipine groups on cardiac causes of death by gender, using a Chi-Square test]

Table XXVII. Non-Cardiac Causes of Death by Gender

Group	Male n(%)	Female n(%)	p-Value*
Placebo (n=129)	100(77.5)	29(22.5)	0.643
Amlodipine (n=116)	87(75.0)	29(25.0)	

[*Comparison between placebo and amlodipine groups on non-cardiac causes of death by gender, using a Chi-Square test]

Additional (secondary) Endpoints: The following outcomes were defined prospectively by the sponsor as secondary endpoints: changes in NYHA functional class, patient self-assessment-quality of life score, neurohormonal, TNF_{α} and lipid peroxidation parameters, and mortality [separate (secondary) analyses were performed for i) mortality all-cause; and ii) cardiac mortality, see Tables XXII and XXIII, pages 17 and 18 respectively].

Table XXVIII summarizes the changes (from baseline) in NYHA functional class for each follow-up visit after randomization in both treatment groups. Examination of the data suggests that there was not a different pattern in the changes of NYHA functional class between the two treatment arms.

Table XXVIII. Changes (from baseline) in NYHA Functional Class

Visit	Group	Improved	No Change	Worsened	Unknown
2	Placebo	64	487	22	2
	Amlodipine	80	473	13	0
4	Placebo	109	414	24	2
	Amlodipine	101	420	24	8
8	Placebo	125	378	26	2
	Amlodipine	142	364	21	3
12	Placebo	159	332	20	4
	Amlodipine	165	323	17	4
16	Placebo	167	317	18	4
	Amlodipine	164	306	30	2
26	Placebo	166	242	29	1
	Amlodipine	162	258	23	0
39	Placebo	143	201	21	4
	Amlodipine	142	191	29	1
52	Placebo	123	167	14	5
	Amlodipine	122	163	26	0

Table XXVIII. (continued)

65	Placebo	95	130	15	2
	Amlodipine	107	133	15	0
78	Placebo	82	103	8	1
	Amlodipine	78	110	5	3
91	Placebo	55	64	9	1
	Amlodipine	62	71	7	0
104	Placebo	43	42	4	2
	Amlodipine	40	42	5	0
116	Placebo	20	23	2	1
	Amlodipine	20	30	2	0

The results of the patient self-assessment-quality of life score are incorporated as figures in the Appendix, pages 60A-65A. Plotting of the results of quality of life by alertness behavior scale, living with heart failure scale, and health perception scale demonstrated similar profiles for placebo and amlodipine groups.

The data obtained, in a subset of patients, at weeks 0 and 8 on plasma norepinephrine and ANF are included as figures in the Appendix, pages 66A-69A. Plotting of the neurohormonal results revealed comparable profiles for placebo and amlodipine groups.

The results on TNF_{α} and lipid peroxidation parameters could not be found either in the main body of this application or in the SAS dataset.

Hospitalizations: The number of patients hospitalized due to any reason as well as the total number of hospitalizations in each treatment arm are depicted in Table XXIX. The number/percentage of patients requiring hospitalization was very similar between groups. The total number of hospitalizations in each group were also comparable.

Table XXIX. Number of Patients Requiring Hospitalization and Number of Hospitalizations (for any reason)

Group	No. of Patients Requiring Hospitalization n(%)	No. of Hospitalizations n
Placebo (n=582)	428(73.5)	1646
Amlodipine (n=571)	416(72.8)	1593

[Reviewers' Note: These results on number of patients requiring hospitalization differ from the sponsor's account. According to the sponsor the number of patients requiring hospitalization were for placebo group=371 (63.74%) and for amlodipine group=376 (65.84%). The reason for the disparity in the data is not clear, since the results were derived from the SAS dataset provided by the sponsor.]

An analysis of the cardiovascular reasons for hospitalization was performed to determine whether there was a difference between groups (Table XXX).

Table XXX. Cardiovascular Reasons for Hospitalization

Causes	Placebo n(%)	Amlodipine n(%)
Worsening Heart Failure	387(23.5)	410(25.7)
Chest Pain	73(4.4)	51(3.2)
Cardiac Arrest	44(2.6)	24(1.5)

Table XXX. (continued)

Fibrillation Atrial	43(2.6)	33(2.1)
Pulmonary Edema	27(1.6)	43(2.7)
Angina Pectoris	42(2.5)	30(1.9)
Myocardial Infarction	37(2.2)	35(2.2)
Tachycardia Ventricular	35(2.1)	31(1.9)
Syncope	25(1.5)	31(1.9)
Cerebrovascular Disorder	24(1.4)	16(1.0)
Fibrillation Ventricular	22(1.3)	11(0.7)
Hypotension	14(0.8)	15(0.9)
Arrhythmia Atrial	15(0.9)	9(0.6)
Arrhythmia Ventricular	5(0.3)	5(0.3)

In keeping with the results from morbid cardiac events (i.e., heart failure deterioration, Table XX, page 16) there was a slight trend for patients in the amlodipine group to be hospitalized more often because of worsening of heart failure and pulmonary edema, and for patients in the placebo group to be admitted more repeatedly to the hospital for chest pain, cardiac arrest, or angina.

Safety/Adverse Events: The number of patients in each group that have experienced at least an adverse event is described below in Table XXXI.

Table XXXI. Patients Experiencing Any Adverse Event

	Placebo (n=582) n(%)	Amlodipine (n=571) n(%)
At Least One Adverse Event	545(93.6)	538(94.2)

The incident rates of clinical adverse events and laboratory abnormalities (with an incidence ≥1%), recognized in the PRAISE study by the sponsor, are given below in Table XXXII. Adverse events are tabulated in alphabetical order as the percentages of patients who reported the adverse event.

Table XXXII. Adverse Events from PRAISE Study

Adverse Events	Placebo (%)	Amlodipine (%)
Abdominal Pain	2.1	1.6
Abnormal Liver Function Tests	1.2	0.5
Anemia	2.1	3.5
Angina Pectoris	5.7	5.1
Ankle Edema	1.9	5.1
Arrhythmia Atrial	1.5	0.5
Arrhythmia Ventricular	0.7	1.1
Atrial Fibrillation	5.7	4.7
Bruise	1.5	0.9
Cardiac Arrest	4.6	4.2
Cardiac Failure	2.1	0.7
Cerebral Ischemia	0.9	0.9
Chest Pain	18.2	15.8
Congestive Heart Failure	5.8	6.7
Coughing	8.1	9.1

Table XXXII. (continued)

Edema Peripheral	7.9	11.7
Depression	2.2	3.5
Diarrhea	5.7	3.7
Dizziness	11.9	12.4
Dizziness Postural	0.7	2.5
Dyspnea	9.8	10.9
Fatigue	8.9	7.9
Headache	5.7	6.8
Hypertension	0.7	0.7
Hypotension	6.7	7.7
Hypotension Orthostatic	1.7	1.1
Insomnia	2.7	3.2
Muscle Cramps	1	1.4
Myocardial Infarction	2.9	2.8
Nausea	10.8	9.6
Nose Congestion	0.2	1.1
Palpitation	4.5	3.5
PTT Prolonged	1.4	0.7
Pulmonary Edema	10.0	14.7
Renal Failure Acute	1.4	4.4
Sudden Death	11.7	8.9
Supraventricular Tachycardia	0.5	1.1
Syncope	4.3	3.5
Ventricular Fibrillation	2.4	2.3
Ventricular Tachycardia	5.7	6.1
Vomiting	4	3.5
Weakness Generalized	4.1	6.1
Worsening Heart Failure	38.7	39.6

In general, no marked differences were observed in the incidence of most adverse events between treatment groups. However, there was a tendency for patients in the amlodipine group, as compared with subjects in the placebo group, to develop more frequently ankle and peripheral edema, pulmonary edema and acute renal failure. Peripheral and ankle edema are well established side effects of amlodipine treatment. However, the higher incidence of pulmonary edema and acute renal failure, which are not known to be particular side effects of amlodipine therapy, may be linked to the fact that more patients in the amlodipine group than in the placebo group had deterioration of their heart failure requiring hospitalization (Table XX, page 16).

SUMMARY OF PROTOCOL #053-173 (PRAISE STUDY)

The PRAISE study was the largest clinical trial reported in this supplemental NDA. This was a multicenter (105 centers from US and Canada), randomized, placebo controlled, parallel, double-blind study with an enrollment of 1153 patients with severe heart failure, 582 to placebo and 571 to amlodipine. Recruitment of subjects for the trial was slightly slower than planned. That resulted in one extension, in November 1993. The study consisted of a screening visit, followed by a double-blind period of at least 24 weeks. The dose of the study drug was titrated from 1 tablet (5 mg) p.o. qd to 2 tablets (10 mg) p.o. qd two weeks after starting double-blind therapy. The subjects in this clinical study had a mean age of 64.7 years, and congestive heart failure NYHA class III-IV, primarily due to ischemic (>62%) and non-ischemic (>35%) etiologies. Patients had a history of heart failure for at least two years prior to enrollment in the trial. Heart failure NYHA class III was diagnosed in 79.72% and 81.26% of the patients in the placebo and amlodipine groups, respectively. Thus, the number of randomized patients who had heart failure NYHA class IV, was less than for those with NYHA class III, 20.10% in the placebo group and 18.39% in the amlodipine group. One patient receiving placebo was class I, one patient was class II and in another subject the class was unknown in the amlodipine group. The mean duration of the disease prior to randomization was 3.85 and 4.21 years for placebo and amlodipine groups, respectively. The severity of the disease was validated clinically, and by a considerably low mean LVEF, i.e., <21% for both groups. Over ninety percent of the subjects at randomization were concurrently treated with diuretics, ACE inhibitors, and digoxin, as per protocol. Slightly more than 20% of the enrolled subjects in each group were females. Of note, the exclusion criteria was rather extensive (pages 5-6). In this regard, subjects with a history of stroke, myocardial infarction, **angina** of increasing frequency, or treatment with β-Blockers or calcium channel blockers, etc., and **hypertensive patients** were excluded from the study. The two treatment groups were well matched with regard to most baseline variables. However, an "imbalance" in the history of previous medications was noticed. More patients in the placebo group had a history of previous usage of antiarrhythmics than patients in the amlodipine group (25.26% vs. 20.32%, respectively). Patient withdrawal and compliance was similar between groups. Most of the patients (i.e., ≥90%) in either the placebo or the amlodipine group were, throughout the trial, taken 10 mg/daily of study drug, as per protocol.

The PRAISE study at its inception was an **efficacy** trial. The lack of results in support of an efficacy claim prompted the sponsor to rescue the effort by changing the study/application from an efficacy to a safety trial/claim.

The primary clinical endpoint was combined mortality (all-cause) and cardiac event. A cardiac morbid event was defined as hospitalization for at least twenty-four hours because of deterioration of heart failure, or acute myocardial infarction, or life threatening ventricular arrhythmia requiring therapy. This endpoint was reached by 246 (42.3%) of 582 placebo subjects and by 222 (38.9%) of 571 amlodipine subjects, a difference which was **not** statistically significant (p=0.31, using a log-rank test). The primary endpoint was a combined outcome, and the results were not modified by gender. Mortality and cardiac morbid events were therefore analyzed independently. Deaths (all-cause mortality) occurred to 223 (38.3%) placebo and 190 (33.3%) amlodipine patients. The observed numerical difference did not reach statistical significance (p=0.074). Of the 223 placebo group deaths, 94 were reported as cardiac deaths, and 129 were reported as non-cardiac deaths. In the amlodipine group, of the 190 deaths, 74 were reported as cardiac deaths, and 116 were reported as non-cardiac deaths. The second component of the combined primary endpoint, hospitalization 24 hours or longer for cardiac morbid events, was also analyzed separately. Hospitalization for deterioration of heart failure was required in 26 (4.46%) and 45 (7.88%) patients in the placebo and amlodipine groups, respectively (p=0.094). Ten (1.71%) patients in the placebo group and 7 (1.22%) patients in the amlodipine group were hospitalized because of acute myocardial infarction (p=0.309). Life threatening ventricular arrhythmias were accountable for the hospitalization of 18 (3.09%) subjects in the placebo group and 10 (1.75%) patients in the amlodipine group (p=0.06). The results indicate that treatment with amlodipine did not adversely affect, in a statistically significant manner, the number of deaths or hospitalizations due to cardiac morbid events. Nevertheless, there was a tendency for patients in the amlodipine group to experience more hospitalizations for deterioration of heart failure than patients receiving placebo. Patients receiving placebo were hospitalized more often than those receiving amlodipine due to life threatening ventricular arrhythmias. The latter might be the consequence of an imbalance in randomization (pages 11 and 13). However, the PRAISE study was not powered to determine a difference in the incidence of hospitalizations for deterioration of heart failure between groups.

Of note, albeit the PRAISE study was not powered for, randomization was stratified by etiology of heart failure (i.e., ischemic or non-ischemic). The sponsor's subgroup analysis showed that the time to event of the primary endpoint

was not significantly different (p = 0.74) between amlodipine and placebo groups in the ischemic subgroup. In heart failure patients with non-ischemic etiology taking amlodipine, there were 58 of 209 patients experiencing a primary event; in those patients taking placebo however there were 78 of 212 experiencing a primary event. In the non-ischemic patients, the sponsor's analysis showed significance for time to event (p = 0.03) with a hazard ratio of 0.694 and a 95% confidence interval of 0.490 and 0.982. This purported beneficial effect of amlodipine was confined to death (p = 0.001), since no statistically significant changes were observed in the analysis of cardiac morbid events (page 18). This subgroup analysis suggests that amlodipine may have a salutatory effect, reducing the incidence of mortality, in patients with heart failure of non-ischemic etiology. An alternate way to interpret the data is that a test having such a small power (51%) would not be able to detect the specified difference between the two treatment groups and this means that the significant results found above could have easily occurred by **chance** (page 17). It is also subject to controversy the mechanism(s) responsible for the differential effect of amlodipine. Be that as it may, the sponsor is in the process of carrying out an efficacy study with amlodipine, PRAISE II study, in patients with heart failure of non-ischemic etiology.

The number/percentage of subjects experiencing an adverse event was nearly identical in both groups (Table XXXI, page 21). In keeping with what is known about amlodipine, in the PRAISE study, more patients in the amlodipine group than in the placebo group had episodes of peripheral edema. Of note, pulmonary edema and acute renal failure were also adverse events more frequently experienced by subjects in the amlodipine group than by subjects in the placebo group (Table XXXII, page 21). The higher incidence of these latter adverse events might be related to the fact that there were almost twice as many patients with deterioration of heart failure in the amlodipine group than in the placebo group (Table XX, page 16).

ANCILLARY CLINICAL TRIALS

***Protocol* #053-121:** This was a randomized, parallel, double-blind, placebo-controlled study to evaluate the safety an efficacy of a fixed dose of amlodipine, in patients with mild to moderate heart failure (NYHA Class II and III) receiving diuretics and digoxin, with or without the addition of an ACE inhibitor.

The efficacy and safety of amlodipine was assessed as follows:

Efficacy:

-Symptom Rating
-Patient Self-Assessment (Quality of Life Questionnaire)
-Global Evaluation (Patient's clinical condition was evaluated by the principal investigator)
-Exercise Tolerance (as measured by treadmill exercise testing using the modified Naughton protocol), and Resting Radionuclide Imaging Left Ventricular Ejection Fraction

Safety:

-Clinical Side Effects
-Laboratory Parameters
-24-hour Holter Monitoring, Standard 12-lead ECG.

Inclusion and Exclusion Criteria: The eligibility criteria utilized in this study was within the context of that in protocol #053-173 (IND[redacted]Vol. 14.1, pages 655-656).

Results:

Following the stabilization-screening phase and the single-blind phase (2 weeks), patients were randomly assigned to either placebo (n=60) or amlodipine 10 mg/day (n=58) for a total of 8 weeks. Thus, in total 118 patients were enrolled to participate in this study. According to the sponsor, randomization was stratified according to the presence or absence of ACE inhibitor therapy.

The baseline characteristics of the patients randomized in the study are summarized in table XXXIII.

Table XXXIII. Baseline Patient Characteristics

Variables	Placebo	Amlodipine
# of Patients	60	58
Race (n):		
White	41	38
Black	16	12
Other	3	8
Mean Age (in years)	63.5	62.3
Mean Duration of CHF (in months)	25.8	33.8
NYHA Class (n):		
II	50	43
III	8	15
Unknown	2	0
ACE Inhibitor Therapy (n)	41	39
Cardiac Glycosides (n)	48	51
Loop Diuretics (n)	44	50

A total of 19 female and 99 male were enrolled in this study. Overall, both treatment arms were reasonably well balanced with regard to age, race and NYHA classification. Approximately half of the patients in each group had a history of myocardial infarction and/or angina pectoris, and symptoms of ischemic heart disease. As expected, the majority of the patients in either group were on diuretics, cardiac glycosides and ACE inhibitors. The groups were

similar in terms of the profile and severity of baseline disease(s) (IND Vol. 14.1, Tables 5a and 5b, pages 674-678). Mean duration of double-blind treatment for the placebo group was 50.9 days and for the amlodipine group was 50.2 days.

Efficacy:

Exercise tolerance , as assessed by treadmill exercise testing using the modified Naughton protocol, was one of the primary endpoints. Five patients in each group had only one exercise test during the single-blind placebo run-in period. However, these patients were not excluded from intent to treat analysis. In seven patients in the amlodipine group and one patient in the placebo group the baseline exercise tests were not within 15% of each other as required by the protocol. After 8 weeks of treatment, patients in the amlodipine group had a greater increase in exercise tolerance time than those treated with placebo (Table XXXIV).

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

Group	Baseline	Final	Change	% Change	p-Value
Placebo (n=54)	607.6±27.6	634.5±30.1	26.9±13.5	4.4	0.0225
Amlodipine (n=50)	559.2±31.0	631.5±32.9	72.3±18.1	12.9	

[Values were obtained from IND # Vol. 14.1, Table 9a, page 684, and they are expressed as arithmetic means±S.E.]

The table below summarizes the changes in NYHA class for both groups. There was no improvement in amlodipine treated patients as compared to the placebo group (p=0.229).

Table XXXV. NYHA Classification Changes Intent to Treat Analysis

Group	# of Patients Who Had			p-Value*
	Improved	No Change	Worsened	
Placebo (n=49)	10	31	8	0.229
Amlodipine (n=48)	12	33	3	

[Values were obtained from IND Vol. 14.1, page 662, and they are expressed as arithmetic means±S.E. *Cochran-Mantel-Hanszel test; sponsor's analysis. Baseline vs. 8 weeks.]

Treatment with amlodipine did not significantly modify LVEF as compared to placebo therapy (Table XXXVI).

Table XXXVI. LVEF (%) Intent to Treat Analysis

Group	Baseline	Final	Change	% Change	p-Value
Placebo (n=47)	26.4±1.0	28.4±1.2	2.0±0.8	7.5	0.1708
Amlodipine (n=47)	25.3±1.0	28.7±1.4	3.3±1.1	13.4	

[Values were obtained from IND Vol. 14.1, Table 9e, page 688, and they are expressed as arithmetic means±S.E.]

Of the originally proposed hormonal measurements, only data on plasma norepinephrine changes in a subset of patients are available. The results are summarized in Table XXXVII. Plasma norepinephrine levels decreased in patients treated with amlodipine, but increased on placebo treated subjects (p=0.0182).

Table XXXVII. Hormonal Data: Norepinephrine (pg/ml)

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=19)	410.1±48.7	587.3±128.3	177.2±99.5	43.2	0.0182
Amlodipine (n=20)	401.5±42.6	356.1±77.7	-45.4±60.5	-11.3	

[Values were obtained from IND Vol. 14.1, Table 9f, page 689, and they are expressed as arithmetic means±S.E. *Based on geometric means, two-tailed test; sponsor's analysis.]

According to the sponsor, the investigator's global assessment at the end of the study demonstrated that more patients improved on amlodipine than on placebo treatment (Table XXXVIII).

Table XXXVIII. Investigator's Global Assessment

Group	# of Patients Who Had			p-Value*
	Improved	No Change	Worsened	
Placebo (n=58)	17	31	10	0.027
Amlodipine (n=56)	31	15	10	

[Values were obtained from IND\ \Vol. 14.1, Table 9d, page 687. *Cochran-Mantel-Hanszel test; sponsor's analysis. Baseline vs. 8 weeks.]

Patient self assessment was completed on study weeks 2, 6, and 10. Table XXXIX summarizes the data for both groups. The total score p-value was equal to 0.06. However, patients receiving amlodipine reported an improvement in both dyspnea and fatigue (p=0.023 and p=0.022, respectively).

Table XXXIX. Patient's Congestive Heart Failure Quality of Life Questionnaire

Variables	n	Baseline	n	Endpoint	Slope	p-Value*
Dyspnea						0.023
Amlodipine	58	2.069±1.974	47	1.844±2.000	0.016	
Placebo	60	1.764±1.694	47	1.856±1.776	0.141	
Fatigue						0.022
Amlodipine	58	2.299±2.187	47	2.004±2.265	-0.020	
Placebo	60	1.895±1.801	47	1.764±1.701	0.108	
Affect						0.24
Amlodipine	58	2.033±1.885	47	1.826±2.147	0.003	
Placebo	60	1.514±2.024	47	1.268±1.871	0.087	
Locus of Control						0.412
Amlodipine	58	2.413±2.652	47	1.897±2.528	-0.040	
Placebo	60	1.931±2.414	47	1.365±1.962	0.048	
Sleep						0.234
Amlodipine	54	3.203±2.358	43	2.767±2.191	-0.048	
Placebo	57	3.053±2.341	47	3.106±2.846	0.037	
Life Satisfaction						0.357
Amlodipine	58	4.000±2.377	47	3.340±2.434	-0.037	
Placebo	60	3.817±1.846	47	3.532±1.965	0.036	
Index						0.062
Amlodipine	58	2.306±1.840	47	1.963±1.925	-0.015	
Placebo	60	1.932±1.522	47	1.759±1.624	0.089	

[Values were obtained from IND\ \Vol. 14.4, Table 5, page 2143, and they are expressed as arithmetic means±S.E. *Sponsor's analysis]

Safety:

The rate of occurrence of side effects is summarized in Table XL. There was an incidence of side effects of 41% in patients receiving amlodipine and of 30% in placebo treated subjects.

Table XL. Incidence of Side Effects

Number of Patients	Placebo	10 mg Amlodipine
Evaluable	60	58
With Side Effects	18	24
Withdrawn with Side Effects	2	4

Fourteen patients in the amlodipine group had peripheral edema, as compared to two patients with peripheral edema in the placebo group. Otherwise, the reported side effects were mild in severity and were evenly distributed between the groups (IND Vol. 14.1, Tables 15a-c and 16a-c, pages 703-708). One patient (6570012) in the amlodipine group was discontinued from the study because of an elevated alkaline phosphatase and GGT. However, both enzymes were elevated at screening and baseline periods. Analysis of data from the Holter monitoring and ECG was noncontributory to the interpretation of the study. In total, 11 patients in both the amlodipine and placebo groups were discontinued from the study. The distribution of the reasons for discontinuation by treatment arm is not contributory to the overall interpretation of the study (IND Vol. 14.1, Table 3, page 669).

Two patients (5720003 and 6440010) in the amlodipine group and one patient (6490014) in the placebo group died during the study.

Case Summaries of Patients with Fatal Events
PATIENT 121 5720003 (amlodipine): This was a 52 year old white male with a history of chronic obstructive pulmonary disease and end stage congestive heart failure secondary to cardiomyopathy, presumably due to hypertension and chronic alcohol abuse. He received 10 mg of amlodipine for 10 days and no ACE inhibitors. The patient collapsed at home and underwent CPR for a lengthy time before being transferred to the hospital. He developed severe hypoxic encephalopathy and died. The Investigator stated that the patent's death was not related to amlodipine, but was due to his underlying, long-standing congestive cardiomyopathy and COPD.
PATIENT 121 6440010 (amlodipine): This was a 69 year old white male with a primary diagnosis of chronic heart failure and a history of an acute anterior MI in March, 1988. After receiving amlodipine 10 mg daily for 13 days, he had an MI, followed by cardiac arrest and anoxic encephalopathy and expired. The investigator concluded that the patient's death was possibly related to amlodipine treatment. Plasma potassium at the time of death was decreased, and it was initially the sponsor's assessment that this could have been due to amlodipine. While this was being investigated, the study was placed on hold. This was initially reported in a Safety Report filed September 21, 1988 (NDA-1 9,787, Serial Number S-16; IND Serial Number 306). However, as indicated in a Safety Report filed October 19, 1988 (NDA-19,787, Serial Number S-21); (IND Serial Number 309) further review of all available data indicated that this patient's terminal event e.g., acute myocardial infarction, was not associated with the use of amlodipine and the study was resumed.
PATIENT 121 6490014 (placebo): This was a 64 year old white male with a primary diagnosis of ischemic cardiomyopathy. He had a history of chronic renal insufficiency and of a possible MI in 1987. After receiving seven days of therapy with placebo and ACE inhibitors, he was found slumped over and unresponsive by his wife. Paramedics were called and he was found to be in ventricular fibrillation. He was successfully defibrillated, intubated and treated with I.V. lidocaine and transferred comatose to a hospital, where he died the next day. No autopsy was performed. The investigator indicated that while the exact cause of death was uncertain, his low ejection fraction (7%) put him at high risk for sudden death. He further stated that there was no reason to suspect that this death was related to study drug, but felt that it occurred coincidentally during the study.

Summary: It should be noticed, that the results of protocol #053-121 were previously presented to the FDA, and its interpretation is reflected in the current package insert for amlodipine. In any event, protocol #053-121 was a double-blind study evaluating, for 8 weeks, the efficacy and safety of amlodipine in patients with heart failure NYHA class II-III. In total, 118 subjects were recruited to two treatment arms, placebo or amlodipine (10 mg/daily). Patients' baseline characteristics were fairly well balanced between groups.

Briefly, the study showed that in patients with NYHA class II-III heart failure and LVEF <30%, amlodipine therapy modestly increased (by 12.9%) exercise tolerance time, and improved dyspnea and fatigue by patients' self assessment, and had no effect on NYHA class or LVEF. In the short period of clinical follow-up allowed by the protocol, no major safety issues were detected.

***Protocol* #053-174:** 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 evaluated 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.

Following a single-blind placebo stabilization period with a baseline exercise tolerance test (Naughton protocol), qualified patients entered double-blind therapy with 1 tablet (i.e., 5 mg amlodipine or placebo) for 2 weeks followed by an increase to 2 tablets (i.e., 10 mg amlodipine or placebo) for the remainder of the study. Exercise tolerance test was performed every four weeks and at the end of the double-blind treatment period.

Patients who successfully completed this study without safety concerns could be entered into a double-blind (protocol #053-174E) or open-label (protocol #053-180) extension trials.

Efficacy:

-The primary clinical efficacy endpoint was symptom-limiting (dyspnea or fatigue) exercise time.
-Other clinical endpoints were NYHA functional class, symptoms, LVEF, and quality of life (including a six minute walk test).

Safety:

-Clinical Side Effects.
-Laboratory Parameters.
-Other Safety Endpoints (i.e., Morbidity/mortality, body weight, blood pressure and heart rate, 12-lead electrocardiogram, 24 hour ambulatory EKG).

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

Results:

Three hundred and thirty five patients entered single-blind placebo run-in period, and 192 patients were randomized to enter the double-blind period. Baseline characteristics for those randomized patients are summarized in Table XLI.

Table XLI. Baseline Patient Characteristics

Variables	Placebo	Amlodipine
# of Patients	98	94
Race (n):		
White	74	66
Black	18	22
Other	6	6
Mean Age (in years)	66.1	63.4
Mean Duration of CHF (in years)	3.7	3.7
NYHA Class (n):		
II	62	51
III	35	40
IV	1	3
Digitalis & ACE inhibitor & Diuretic (n):	66	62

A total of 48 female and 144 male were enrolled in this study. Twenty seven female were enrolled in the placebo group, and twenty one female were randomized to the amlodipine group. In the aggregate, the distributions according to age, race, and other baseline patient characteristics were similar between groups. In this regard, the mean LVEFs

were 24% (8-35%) for the patients on amlodipine, and 23% (10-37%) for those on placebo. The number of patients receiving all three background medications was also similar between groups.

The primary underlying causes of heart failure included ischemic (57 and 56 patients in placebo and amlodipine groups, respectively), and idiopathic dilated cardiomyopathy (38 and 33 patients in placebo and amlodipine groups, respectively). The distribution of all cardiovascular diseases present at study entry was similar between placebo and amlodipine groups (IND\ \Vol. 7.1, Tables 5a and 5b, pages 43-46). Among patients treated with amlodipine, 17/94 (18.1%) were currently smokers and 40/94 (42.6%) had a history of myocardial infarction. Among patients receiving placebo, 15/98 (15.3%) were currently smokers, and 55/98 (56.1%) had a history of myocardial infarction.

Drug exposure times were comparable between groups, 82.7 (1-117) days for patients receiving amlodipine and 83.6 (14-118) days for patients on placebo.

Efficacy:

Symptom-limiting exercise time was the primary endpoint of this study. Contrary to what was seen in the results of protocol #053-121, amlodipine therapy in this study did not significantly improve exercise tolerance. Table XLII shows negligible increases in exercise tolerance time in both groups. There was not a statistically significant difference between the two treatment arms.

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

Group	Baseline	Final	Change	% Change	p-Value
Placebo (n=95)	557.7±19.6	618.7±24.1	61.0	10.9	0.4634
Amlodipine (n=91)	545.1±21.4	607.8±25.0	62.7	11.5	

[Values were obtained from IND\ \Vol. 7.1, Table 8A, page 57, and they are expressed as arithmetic means±S.E.]

The statistical analyses of the secondary endpoints follows. Insignificant increases in LVEF were documented for patients in both treatment groups; however, between group comparison did not show a statistically significant difference (Table XLIII).

Table XLIII. LVEF (%) Intent to Treat Analysis

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=83)	23.1	25.7	2.6	11.2	0.3175
Amlodipine (n=75)	23.1	26.6	3.5	15.1	

[Values were obtained from IND\ \Vol. 7.1, Table 8B, page 58, and they are expressed as arithmetic means; *sponsor's analysis.]

Table XLIV summarizes the results for the changes in NYHA classification from baseline to end of study. Amlodipine treatment failed to significantly alter the NYHA classification at baseline as compared with placebo therapy (p=0.311).

Table XLIV. NYHA Classification Changes Intent to Treat Analysis

Group	# of Patients Who Had			p-Value*
	Improved	No Change	Worsened	
Placebo (n=96)	17	69	10	0.311
Amlodipine (n=92)	20	65	7	

[Values were obtained from IND\ \Vol. 7.3, page 955. *Cochran-Mantel-Hanszel test; sponsor's analysis.]

A summary of the results of overall assessment of heart failure symptoms is provided in Table XLV. Negligible decreases were seen in overall symptom scores in both groups, but the changes were not significantly different from each other.

Table XLV. Overall Assessment of Heart Failure Symptoms Intent to Treat Analysis

Group	Baseline	Final	Change	p-Value*
Placebo (n=97)	3.7	3.43	-0.27	0.9295
Amlodipine (n=93)	3.71	3.44	-0.27	

[Values were obtained from IND(Vol. 7.1, Table 11A, page 65, and they are expressed as arithmetic means; *sponsor's analysis.]
[Symptoms include: dyspnea at rest, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, fatigue.]

Other secondary clinical endpoint was a six minute walk test (Table XLVI). There was not a significant change from baseline to final in the distance walk in six minutes by patients in either group (p=0.1547). The result of this analysis is in accordance with the result from the exercise tolerance test.

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

Group	Baseline	Final	Change	% Change	p-Value*
Placebo (n=79)	403.5±18.6	420.0±16.9	16.5	4.1	0.1547
Amlodipine (n=71)	431.6±21.7	438.9±22.7	7.3	1.7	

[*Values were obtained from IND(Vol. 7.1, Table 8F, page 62, and they are expressed as arithmetic means±S.E; *sponsor's analysis.]

Statistical analysis of quality of life measures (intent to treat analysis) obtained the following p-values for those measured variables as follows: Total p=0.8964, Physical p=0.8933, Emotional p=0.6038, Health Care p=0.2075, Global Rating p=0.8410, Health Perception p=0.0885, Bed Days p=0.1882, Alertness p=0.1095 (IND( )Vol. 7.1, Table 8D, page 60). The results suggest that the responses to the self assessment questionnaire of quality of life was not modified by amlodipine therapy.

Safety:

The number of side effects occurring per group is summarized in Table XLVII. There was an incidence of side effects of 19.1% in patients receiving amlodipine, and of 17.3% in placebo treated subjects.

Table XLVII. Incidence of Side Effects

Number of Patients	Placebo	10 mg Amlodipine
Evaluable	98	94
With Side Effects	17	18
Withdrawn with Side Effects	2	3

Peripheral edema was experienced by eleven patients in the amlodipine group, and by four patients in the placebo group. The incidence of all remaining side effects otherwise, was comparable between groups.

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

Table XLVIII. Discontinuation of Therapy Due to Side Effects

Treatment Group	Patient ID	Duration of Therapy (days)	Event
Amlodipine	174 6430003	61	Lower Extremity Edema
	174 6880008	32	Ankle Edema
	174 6310005	47	Worsening CHF
	174 6310008	62/54	Renal Failure/Worsening CHF
	174 6440001	45	Fatigue, Lightheaded, Worsening CHF