CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 02/27-28/97

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AGENDA

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products
80th Meeting, February 27-28, 1997
Cardiovascular and Renal Drugs Advisory Committee
National Institutes of Health
Clinical Center - Building 10
Jack Masur Auditorium
9000 Rockville Pike
Bethesda, Maryland

Parking in the Clinical Center visitor area is reserved for Clinical Center patients and their visitors. If you must drive please use an outlying lot such as Lot 41B. Free shuttle bus service is provided from Lot 41B to the Clinical Center every eight minutes. Free shuttle bus service from the subway is also available.

FEBRUARY 27, 1997

8:30 a.m. OPEN PUBIC HEARING
One hour allocated unless public participation does not last that long.

FDA Temporary Voting Members:
Jeffrey S. Borer, M.D.
Ralph D'Agostino, Ph.D.
FDA Invited Expert: Robert Cody, M.D.

NDA 20-727, BiDil (hydralazine HCl and isosorbide dinitrate), Medco Research Inc., to be indicated for congestive heart failure.

Sponsor's Presentation (Agenda attached)

10:30 a.m. Break

10:45 a.m. FDA Review
Medical Reviewers: Shaw Chen, M.D., Charles Ganley, M.D.
Biostatistical Reviewer: James Hung, Ph.D.
Biopharmaceutical Reviewer: Patrick J. Marroum, Ph.D.

11:45 a.m. Committee Review and Discussion
Committee Medical Reviewer: JoAnn Lindenfeld, M.D.
Committee Biostatistical Reviewer: Lemuel Moye, Ph.D.

12:30 p.m. Committee Recommendations

1:30 p.m. Lunch Break

2:15 p.m. NDA 20-297 s-001, Coreg (carvedilol) to be indicated for congestive heart failure.

Sponsor's presentation (Agenda attached)

3:15 p.m. Break

3:30 p.m. FDA Review
Medical Reviewer: Norman Stockbridge, M.D., Ph.D.
Biostatistical Reviewer: Lu Cui, Ph.D.

4:00 p.m. Committee Review and Discussion
Committee Medical Reviewer: Robert Califf, M.D.
Committee Biostatistical Reviewer: Ralph D'Agostino, Ph.D.

4:30 p.m. Committee Recommendations

FEBRUARY 28, 1997

8:30 a.m.	NDA 20-689, Posicor (mibefradil dihydrochloride) tablets, Hoffmann-La Roche Inc., to be indicated for hypertension and angina.
	Sponsor's Presentation (Agenda attached)
10:30 a.m.	Break
10:45 a.m.	FDA Review Medical Reviewers: Sughok K. Chun, M.D., Maryann Gordon, M.D., Knud Knudsen, M.D., and Juan Carlos Pelayo, M.D. Statistical Reviewers: James Hung, Ph.D., Kooros Mahjoob, Ph.D. Biopharmaceutical Reviewer: Emmanuel Fadiran, Ph.D. Pharmacology Reviewers: John Koerner, Ph.D., Anthony Proakis, Ph.D., Sidney Stolzenberg, Ph.D., Xavier Joseph, D.V.M.
11:30 a.m.	Committee Review and Discussion Committee Medical Reviewers: John DiMarco, M.D., Michael Weber, M.D.
12:30 p.m.	Committee Recommendations
1:30 p.m.	Lunch Break
2:15 p.m.	NDA 20-718, Integrilin (intrifiban), COR Therapeutics, Inc., to be indicated for adjunct antithrombotic therapy in PCTA.
	Sponsor's Presentation (Agenda attached)
3:30 p.m.	FDA Review Medical Reviewer: Lilia Talarico, M.D. Biostatistical Reviewer: A. J. Sankoh, Ph.D.
4:00 p.m.	Committee Review and Discussion Committee Reviewer: Marvin Konstam, M.D.
5:00 p.m.	Committee Recommendations

February 27, 1997
Cardiovascular and Renal Drugs Advisory Committee Meeting

NDA 20-727 BiDil Tablets
hydralazine hydrochloride and isosorbide dinitrate
Medco Research Inc.

Sponsors Presentation

Introduction	Cesare Orlandi, MD
Historical Overview, Clinical Efficacy	Jay Cohn, MD
Statistical Overview	Joseph Quinn, MSPH
Summary/Conclusions	Jay Cohn, MD

Cardiovascular and Renal Drugs Advisory Committee (February 27, 1997)

SmithKline Beecham Pharmaceuticals

Coreg™(Carvedilol) Tablets for the Treatment of Symptomatic Congestive Heart Failure

Agenda

Introduction	Robert L. Powell, Ph.D. Vice President Regulatory Affairs and Product Professional Services North America SmithKline Beecham Pharamaceuticals
Clinical Program	Neil Shusterman, M.D. Vice President and Director Clinical Research, Development, and Medical Affairs SmithKline Beecham Pharmaceuticals

Consultants in Attendance for Carvedilol in the Treatment of Symptomatic Congestive Heart Failure

Clinical

Michael Fowler, M.D.
Assistant Professor of Medicine
Falk Cardiovascular Research Center
Stanford University Medical Center
Stanford, CA 94305

Milton Packer, M.D.
Dickinson W. Richards Professor of Medicine
Professor of Pharmacology
College of Physicians & Surgeons of Columbia University
Chief, Division of Circulatory Physiology
Director, Center for Heart Failure Research
Columbia-Presbyterian Medical Center

Statistical

Lloyd Fisher, Ph.D.
Professor of Biostatistics
Associate Chair, Department of Biostatistics
University of Washington

Thomas Fleming, Ph.D.
Professor of Biostatistics
Chairman, Department Professor
University of Washington

Gary G. Koch, Ph.D.
Professor, Biostatistics
School of Public Health
University of North Carolina - Chapel Hill
Chapel Hill, NC 27599-7400

Presentation Agenda

Cardio-Renal Advisory Committee Meeting

February 28, 1997

NDA 20-689

Posicor®
(mibefradil dihydrochloride)

Hoffmann-La Roche Inc.

Introduction	Rudolph Lucek Group Director Drug Regulatory Affairs
Posicor - Efficacy and Tolerability in Hypertension and Angina	Dr. Isaac Kobrin Director Clinical Research
Posicor and Cardiac Repolarization	
Introduction	Dr. Isaac Kobrin
Drugs Affecting Cardiac Repolarization	Dr. Jeremy Ruskin Director Cardiac Arrhythmia Service Massachusetts General Hospital
Preclinical	Dr. Gordon Tomaselli Associate Professor of Medicine Johns Hopkins University
Clinical	Dr. Isaac Kobrin
Safety	Dr. Isaac Kobrin

Consultants

Dr. Denis Noble	Burdon Sanderson Professor of Cardiovascular Physiology University of Oxford Oxford, England
Dr. Michael Sanguinetti	Professor of Medicine Division of Cardiology University of Utah
Dr. Suzanne Oparil	Professor of Medicine University of Alabama at Birmingham
Dr. Craig Pratt	Professor of Medicine Baylor College of Medicine Houston, Texas

APPEARS THIS WAY
ON ORIGINAL

Agenda

Charles Homcy, M.D.	Executive Vice President of R&D *COR Therapeutics, Inc.*	Overview
David Phillips, Ph.D.	Principal Research Scientist *COR Therapeutics, Inc.*	Preclinical Pharmacology
Michael Kitt, M.D.	Vice President of Clinical Research *COR Therapeutics, Inc.*	Efficacy
Todd Lorenz, M.D.	Director of Clinical Research *COR Therapeutics, Inc.*	Safety
Charles Homcy, M.D.	Executive Vice President of R&D *COR Therapeutics, Inc.*	Closing Summary

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 02/27-28/97

QUESTIONS

Questions

carvedilol for
heart failure
27 February 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

In May 1996, after consideration of the data and analyses that were available at that time, the Advisory Committee recommended non-approval of carvedilol for the treatment of heart failure. Since that time, long-term follow-up from one study (Study 223) and new analyses of all multi-center studies have become available. These new data are all, to some degree, supportive of the benefit from treatment with carvedilol. This matter is once again brought to the Advisory Committee, so that all of the available data can be brought to bear on the final recommendation of the Committee.

The Advisory Committee's initial decision was based in part on the position that one cannot reach definitive conclusions about secondary end points from a study that fails to demonstrate effectiveness using its primary end point. This position requires careful consideration, as it is consistent neither with past Agency actions nor past Advisory Committee recommendations. For example, in 1993, the Advisory Committee recommended approval of enalapril for the treatment of asymptomatic left ventricular dysfunction on the basis of a single trial in which there was little evidence for support for benefit on the primary end point, mortality (p=0.3), but fairly strong evidence for a benefit on one of 8 pre-specified secondary end points, time to first hospitalization for congestive heart failure (p<0.001, with no statistically significant difference for all-cause hospitalizations). The Advisory Committee's recommendation of approval with regard to enalapril was somewhat controversial, but it was sustained by Agency action; prevention of hospitalization for congestive heart failure was added to the *Indications* section of enalapril's labelling.

In reconsidering carvedilol, the Committee is reminded that Federal law pertaining to approval simply calls for evidence of effectiveness, from adequate and well-controlled clinical trials, that is convincing to experts. Regulations do not specify two-sided p<0.05 on the primary end points in each of two studies, and some Agency approval decisions involving end points of irreversible harm or rare conditions have not had two such studies. Regulations also do not specify that the end points in such studies be the same. One effect of relying upon 2 (out of 2) studies with p<0.05 on their primary end points is that the likelihood of incorrectly identifying a treatment benefit is <0.0025. The degree of clinical confidence in the treatment benefit is often further enhanced by the observation of apparent treatment effects on pre-specified secondary end points and other study data, where these observations support a mechanism of action or are otherwise expected in association with favorable effects on the primary end point.

The questions that follow assume that the Committee does not wish to recommend a change in standard of approval, in the sense of specifying a different level of acceptable Type I error rate. Instead, the questions are intended to solicit the Committee's judgement about how the data from the carvedilol development program might support a regulatory decision with a degree of confidence equivalent to the usual standard. The first 3 questions suggest alternative strategies by which *specific* benefits might be said to have been established by the carvedilol development program. Failing that, the Committee is asked, in question 4, if *non-specific* benefit should be the basis for approval.

1. Most approvals are made on the basis of $p<0.05$ for primary end points representing clinical benefit in each of two adequate and well-controlled studies. A case can be made that carvedilol meets that standard with Studies 240 and 223.

1.1. Study 240 had a primary end point of time to the first event of sudden death, death from progression of heart failure, hospitalization for worsening heart failure, or sustained increase in a specified group of heart failure drugs. Elimination of the medications component of the end point from either the sponsor's analysis (which included cause-specific mortality and hospitalization) or the reviewers' analysis (which included all-cause mortality and hospitalization) greatly increases the *p*-value (from 0.003 to 0.029 and 0.04 to 0.378, respectively), suggesting that most of the statistical power lies in the medications component. What effect does this observation have on the clinical interpretation of the results of Study 240?

1.2. With regard to Study 223...

1.2.1. ...what clinical benefit was the primary end point in the *short-term* phase?

1.2.1.1. Identify the words in the protocol leading to that conclusion.

1.2.1.2. What analysis leads one to conclude there was a treatment benefit?

1.2.2. ...what clinical benefit was the primary end point in the *long-term* phase?

1.2.2.1. Identify the words in the protocol leading to that conclusion.

1.2.2.2. What analysis leads one to conclude there was a treatment benefit?

1.2.3. ...for what baseline prognostic factors should one adjust?

1.2.4. ...what adjustment in *p*-values is indicated for multiplicity of end points?

1.3. With appropriate consideration of the supporting evidence from primary and secondary end points of these and other clinical trials, should carvedilol be approved for the treatment of heart failure on the basis of $p<0.05$ on the primary end points in each of two adequate and well-controlled studies?

2. If not, carvedilol might be approvable on the basis of compelling evidence, from pre-specified secondary end points, of a *specific* benefit. The promotion of a secondary end point to the status of a primary end point and a potential basis of approval carries with it some implications with regard to the overall type I error rate. Below is a list of pre-specified secondary end points of clinical benefit for which the sponsor's analyses yielded a nominal $p<0.05$ in at least 1 adequate and well-controlled study.

- Physician's global assessment
- Patient's global assessment
- NYHA class
- Hospitalization for cardiovascular causes
- Heart failure signs and symptoms

2.1. For each such study and end point, how should the nominal *p*-value be adjusted for...

2.1.1. ...the number of the study's primary end points?

2.1.2. ...the number of the study's other pre-specified secondary end points?

2.2. For which secondary end points and studies, if any, is the evidence of benefit as convincing as the observation of $p<0.05$ for a primary end point analysis?

2.3. With appropriate consideration of the supporting evidence from primary and other secondary end points of these and other clinical trials, should carvedilol be approved on the basis of compelling evidence of clinical benefit in some *specific* secondary end point or some combination of such end points?

3. If not, carvedilol might be approvable on the basis of compelling evidence, from *retrospectively-defined* end points, of a *specific* benefit. The promotion of a retrospective end point to the status of a primary end point and a potential basis of approval carries with it some presumably more serious implications with regard to the overall type I error rate. Below is a list of some retrospective end points of clinical benefit for which analyses yielded a nominal $p<0.05$ in at least one adequate and well-controlled study.

- Heart failure mortality and hospitalization for heart failure
- All-cause mortality
- All-cause mortality and hospitalization for heart failure
- All-cause mortality and hospitalization for cardiovascular causes
- All-cause mortality and all-cause hospitalization

3.1. For each such study and end point, how should the nominal *p*-value be adjusted for...

3.1.1. ...the number of the study's primary end point?

3.1.2. ...the number of the study's pre-specified secondary end points?

3.1.3. ...the number of the study's other retrospective end points?

3.2. For which retrospective end points and studies is there evidence of benefit at least as convincing as the observation of $p<0.05$ for a primary end point analysis?

3.3. With appropriate consideration of the supporting evidence from primary, secondary, and other retrospective end points of these and other clinical trials, should carvedilol be approved on the basis of compelling evidence of *specific* clinical benefit with respect to some respectively-defined end point or some combination of such end points?

4. If not, carvedilol might be approvable on the basis of compelling evidence of clinical benefit, without naming the specific benefit. For example, one might conclude that, overall, some set of measurements pertaining to symptomatic heart failure was indicative of benefit, but one might be unable to conclude that any specific measurement met standards that would permit it to be named as the expected benefit of treatment.

4.1. What analysis pertains to the assessment of an overall benefit?

4.1.1. What weight was given to primary end points?

4.1.2. How did that analysis adjust for each study's multiple pre-specified end points?

4.1.3. How did that analysis include retrospectively defined end points?

4.2. Should carvedilol be approved on the basis of compelling evidence of an overall clinical benefit?

Questions

mibefradil

28 February 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardiorenal Advisory Committee

1. Does mibefradil reduce the blood pressure of patients with mild to moderate **hypertension**? If so,

   1(A). Which trials convince you that this is so?

   1(B). What is the smallest dose that is consistently superior to placebo?

   1(C). What is the largest useful dose? Did you choose this dose because larger doses

      1(C)(1). were not studied?

      1(C)(2). had no greater effects?

      1(C)(3). are associated with dose-limiting annoyances (cough, edema, and the like)?

      1(C)(4). are associated with dose-limiting hazards (arrhythmia, major hemorrhage, and the like)?

   1(D). Has mibefradil been shown to be consistently more efficacious than alternative therapy?

2. Does mibefradil decrease ischemia and increase exercise tolerance in patients with **chronic stable angina**? If so,

   2(A). Which trials convince you that this is so?

   2(B). What is the smallest dose that is consistently superior to placebo?

   2(C). What is the largest useful dose? Did you choose this dose because larger doses

      2(C)(1). were not studied?

      2(C)(2). had no greater effects?

      2(C)(3). are associated with dose-limiting annoyances (cough, edema, and the like)?

      2(C)(4). are associated with dose-limiting hazards (arrhythmia, major hemorrhage, and the like)?

2(D). Has mibefradil been shown to be consistently more efficacious than alternative therapy?

3. Are there mibefradil-associated repolarization changes in human electrocardiograms? (If not, the next three questions should be skipped.)

4. Some electrocardiographic changes are ominous, but others are harmless anomalies. Do the available data (including the morphology of the observed changes, the results of electrophysiologic bench studies, the results of studies in whole animals, and the incidences of adverse events in clinical trials of mibefradil and other drugs) allow you to conclude that the mibefradil-associated repolarization changes must be harmless, and that their occurrence is therefore of no concern, regardless of dose? (If so, the next two questions may be skipped.)

5. At what doses of mibefradil do repolarization changes occur? Are these doses so much higher than the therapeutically effective doses that the repolarization changes are no longer of concern? (If so, the next question may be skipped.)

6. Is it reassuring to compare the mibefradil-associated repolarization changes to those seen with other drugs? In particular,

6(A). Can you conclude that the mibefradil-associated repolarization changes are **no different** from those seen with other drugs that are known **not** to induce malignant ventricular arrhythmias? If so,

6(A)(1). Which other drugs? At what doses of those drugs are repolarization changes seen?

6(A)(2). Are those other drugs' doses so close to therapeutic doses, and are those drugs known to be so safe at therapeutic doses, that the mibefradil-associated repolarization changes are no longer of concern?

6(B). Can you conclude that the mibefradil-associated repolarization changes are **different** from those seen with other drugs that **are** known to induce malignant ventricular arrhythmias? If so,

6(B)(1). What are the mibefradil-associated data that convince you that this is so?

6(B)(2). What are the other-drug-associated data that convince you that this is so?

7. Besides the effect upon repolarization, does mibefradil have other electrophysiologic effect(s) upon the heart? If so, what are those effects, and at what doses do they occur?

8. Are there any other safety concerns pertinent to the approval of mibefradil?

9. Should mibefradil be approved for the treatment of hypertension? If so,

   9(A). What dose(s) should be recommended for use?

   9(B). Are the mibefradil-associated repolarization changes still sufficiently worrisome that labeling should relegate mibefradil to second-line use for hypertension, to be used only by patients who do not respond to other therapy? The only antihypertensive products now approved as second-line therapy are (a) minoxidil, which was not approved until minoxidil had been shown to be effective in patients who were refractory to maximal therapy with various other agents; and (b) various fixed-dose combinations, none of which was approved until the combination had been shown in adequate trials to be superior to its component monotherapies. If mibefradil were approved as second-line therapy for hypertension, in what population is there reason to believe it would be effective?

10. Should mibefradil be approved for the treatment of chronic stable angina? If so,

   10(A). What dose(s) should be recommended for use?

   10(B). Are the mibefradil-associated repolarization changes still sufficiently worrisome that labeling should relegate mibefradil to second-line use for angina, to be used only by patients who do not respond to other therapy? The only antianginal product now approved as second-line therapy is bepridil, which was not approved until bepridil had been shown in an adequate trial to be superior to diltiazem in patients whose angina had been previously found to be refractory to diltiazem. If mibefradil were approved as second-line therapy for angina, in what population is there reason to believe it would be effective?

11. If mibefradil is approved, what should the labeling say about mibefradil-associated repolarization changes? For example,

   11(A). How should those changes be described?

   11(B). Should the dose be reduced in patients in whom these changes appear?

   11(C). How should mibefradil be used in patients who *for other reasons* have, or are at risk of, QT prolongation or other repolarization changes?

Questions

BiDil® for
heart failure
27 February 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Advisory Committee is asked to consider the approval of BiDil®, a fixed-dose combination of hydralazine and isosorbide dinitrate (ISDN), in the treatment of congestive heart failure. The to-be-marketed formulations of BiDil contain hydralazine/ISDN doses of 37.5/10, 37.5/20, 75/20, and 75/40 mg.

The two studies that support the use of hydralazine and ISDN in the treatment of congestive heart failure were performed by Dr. Jay Cohn and the V.A. Cooperative Study Group. V-HeFT I was a pioneering trial that influenced the design of modern heart failure trials. Placebo-controlled V-HeFT I began enrollment in 1980 and was terminated because of curtailment of funding. V-HeFT II ran from 1986 to 1991 and compared enalapril with hydralazine plus ISDN.

Both hydralazine and ISDN are approved and marketed drugs. Ordinarily, the approval of the fixed-dose combination product would require evidence that both drugs contribute to the therapeutic effect. There are no such data for BiDil. When such a situation has arisen, the Agency has said it would consider approval if there were compelling evidence that the combination favorably affected some irreversible end point, like mortality. The Division would, however, like the Committee to consider the following concerns:

- **Multiplicity:** The V-HeFT studies each had 6 "major" end points, but the studies were sized to detect an effect on mortality, and the protocols fairly clearly indicated that the primary objective was to study the effects of hydralazine and ISDN on mortality. Both studies also listed cardiovascular hospitalization as another "major" end point, and both studies measured maximum oxygen consumption during treadmill exercise and other indices of exercise capacity.
- **Bioequivalence:** The formulations of hydralazine and ISDN were not bioequivalent between the V-HeFT I and II studies, and the BiDil formulation is not bioequivalent to that used in either study.
- **Tolerance:** During repetitive dosing in patients with chronic stable angina, nitrate administration without a 12-hour nitrate-free interval ordinarily leads to tolerance.

V-HeFT I

1. Factors that might affect interpretation of the mortality results include the following:
   - There were 4 interim analyses, conducted by O'Brien/Fleming rules.
   - The protocol outlined three possible comparisons in the primary analysis using the log-rank test. The comparisons included (1) each active treatment arm to each other, (2) the combined vasodilator arms to placebo, and (3) each active treatment arm to placebo. Each of these analyses was performed at least once during the course of the study.
   - There were two other analyses, (1) a protocol-specified Cox regression, intended to identify covariates that were important, and (2) a retrospective Cox regression analysis (placebo vs. hydralazine-ISDN) using baseline covariates specified by the Division. The Cox regression analyses require the somewhat arbitrary imputation of values for missing baseline covariates.
   - Mortality was specified to be evaluated as either total mortality over the duration of the study or as two-year mortality.

The published description of the study and the NDA submission reported nominal *p*-values. In interpreting the *p*-values for mortality analyses in V-HeFT I, by what factor, if any, should the nominal *p*-value be inflated for...

1.1. ...multiple primary end points?

1.2. ...multiple interim analyses?

1.3. ...multiple treatment-arm-to-treatment-arm and pooled-to-control comparisons?

1.4. ...multiple statistical test methods?

1.5. ...multiple durations for assessment?

2. What is the appropriate factor for the overall adjustment of the nominal *p*-value for mortality in V-HeFT I?

3. In the Cox regression analysis of mortality in V-HeFT I, what is the appropriate method for imputing values for missing baseline covariates?

4. Was there a statistically significant effect found in V-HeFT I for...

4.1. ...mortality during the entire study period?

4.2. ...2-year mortality?

5. Was there a statistically significant effect found for hospitalizations for cardiovascular causes in V-HeFT I?

6. There were 3 measures of exercise tolerance in V-HeFT I. For which of these were there statistically significant treatment effects?

- Maximum oxygen consumption at peak exercise during a maximal exercise tolerance test.
- Total duration of symptom-limited exercise for a maximal exercise tolerance test.
- Submaximal exercise duration.

7. Was there a statistically significant effect found for Quality of Life in V-HeFT I?

8. Was there a statistically significant effect found for left ventricular ejection fraction in V-HeFT I?

9. Are the effects on headache and blood pressure in V-HeFT I consistent with the development of tolerance to isosorbide dinitrate?

V-HeFT II

V-HeFT II had no placebo control group. The Division and the Advisory Committee have held that a successful active comparator trial requires one to conclude

- that the new treatment would have beaten placebo, had there been a placebo group, and
- that the estimated effect size of the new treatment is not less than half of the effect size for the comparator agent.

10. One way in which it could be concluded that hydralazine-ISDN was superior to placebo would be if the combination were superior to enalapril in V-HeFT II. Was hydralazine-ISDN superior to enalapril for any of the mortality or exercise end points?

11. If hydralazine-ISDN was not superior to enalapril, it might still be superior to placebo.

11.1. The sponsor argues that an answer to that question would be best derived by comparing the hydralazine-ISDN group to the placebo group in V-HeFT I. The Division argues that the best comparison would be with the results of SOLVD Treatment (where the magnitude of treatment effect of enalapril was demonstrated) or with a combination of the results of SOLVD Treatment and V-HeFT I. What is the appropriate placebo group for comparison?

11.2. Had placebo been present, is it likely that the effect of hydralazine-ISDN would have been greater than that of placebo?

11.3. How does one show that a new treatment has at least half of the effect size of an active comparator? Does this mean...

11.3.1. ...that the point estimate of effect size is at least half as great?

11.3.2. ...that the confidence limits exclude an effect half as great?

11.4. Was the effect of hydralazine-ISDN at least half that of enalapril?

11.5. Like V-HeFT I, V-HeFT II had multiple end points, multiple time points (2 and 5 years) for evaluation of mortality, and interim analyses. What is the appropriate adjustment to the nominal *p*-value for multiple end points and comparisons, and for interim analyses?

12. Do the mortality results of V-HeFT II confirm the findings of V-HeFT I?

13. Exercise capacity was measured by maximum oxygen consumption at peak exercise and total duration of maximum exercise. Results of both measures of exercise capacity, in both the Division's and sponsor's view, gave similar results. One analysis of exercise duration included only those subjects who stopped exercise (post-randomization) for dyspnea or fatigue.

13.1. Should this be the pivotal analysis for determining whether there was a treatment effect on exercise capacity?

13.2. By the appropriate analysis, was there a statistically significant treatment effect on exercise duration?

13.3. For maximum oxygen consumption at peak exercise, was there a statistically significant treatment effect, favoring hydralazine-ISDN?

14. With regard to hospitalizations for cardiovascular causes...

14.1. ...was there a statistically significant effect, favoring hydralazine-ISDN?

14.2. If not, are the data supportive of some related benefit of hydralazine-ISDN?

15. Was there a statistically significant treatment effect on ejection fraction, favoring hydralazine-ISDN?

16. How compelling is the evidence that hydralazine prevents the occurrence of tolerance to ISDN?

17. If the combination product were to be approved, ...

17.1. ...what are the appropriate dosing interval and instructions for titration of dose?

17.2. ...what are the specific benefits of treatment to be named in the label?

17.3. ...should use be restricted to patients who cannot tolerate ACE inhibitors?

17.4. ...should it be for use with an ACE inhibitor?

18. Should *BiDil* be approved for use in the treatment of congestive heart failure?

Cardiorenal Drugs Advisory Committee
February 28, 1997

Questions re: Integrilin for PTCA

COR Therapeutics has requested approval of Integrilin (Intrifiban) injections as adjunctive therapy in patients undergoing percutaneous transluminal coronary angioplasty (balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty or excimer laser angioplasty) for the prevention of acute cardiac ischemic complications (death, myocardial infarction, need for urgent revascularization) related to abrupt closure of the treated coronary vessel. The sponsor recommends that Integrilin be administered at the dose of 135 ug/kg bolus injection followed by an infusion of 0.50 ug/kg-min for 20-24 hours. The drug would be administered concomitantly with heparin and aspirin. Support for the claimed indication is based mainly on the results of a single, large clinical trial, the IMPACT II study.

1. The primary endpoint of IMPACT II was death, AMI, or urgent intervention at 30 days from randomization. The specified alpha level was 0.035 to correct for the multiple comparison (high and low infusion groups), less than a Bonferroni because the comparisons were not fully independent (shared placebo group). At 24 hours, the low infusion group showed a 31% reduction ($p=0.006$). High infusion rate showed a 28% reduction ($p=0.014$). For the 30 day primary endpoint, the low infusion group showed a reduction of 22% ($p=0.035$). High infusion rate showed a 14% reduction (NS: $p=0.179$).
Does the IMPACT II study show a significant clinical benefit of Integrilin on acute ischemic events following PTCA or on its primary endpoint?

2. Since IMPACT II is the main support for the proposed indication, is that single study sufficiently persuasive to support approval? If so, indicate what makes it persuasive as a single study, e.g., supportive trend in IMPACT I, both treatment groups significant at 24-48 hours, low p-value at 24-48 hours (marginal at 30 days), similar direction of combined endpoint components.
Note that a large randomized controlled trial in Unstable Angina is almost complete. Would a negative result in that study affect your conclusion?

3. If Integrilin is recommended for approval, should it be indicated as first line therapy in PTCA and for all risk level patients?

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 02/27-28/97

SUMMARY MINUTES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

80TH MEETING

MINUTES

THURSDAY, FEBRUARY 27, 1997
FRIDAY, FEBRUARY 28, 1997

Jack Masur Auditorium
Building 10, Clinical Center
National Institutes of Health

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Joan C. Standaert, Executive Secretary
Robert Califf, M.D.
John DiMarco, M.D.
Cindy Grines, M.D.
Marvin Konstam, M.D.
JoAnn Lindenfeld, M.D.
Lemuel Moye, M.D., PH.D.
Cynthia Raehl, Pharm.D.
Dan Roden, M.D.C.M.
Udho Thadani, FRCP
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Michael Kitt, M.D.
Kerry Lee, M.D.
Todd Lorenz, M.D.
David Phillips, M.D.
James Tcheng, M.D.

The 80th meeting of the Cardiovascular and Renal Drugs advisory Committee was called to order by the chair. Dr. Barry Massie, at 8:30 a.m., on Thursday February 27, 1997. He introduced the committee members, temporary voting members, guests and FDA staff. Conflict of interest determinations were addressed by the executive secretary, Joan Standaert.

Full waivers had been granted to Drs. Lindenfeld, Moye, Konstam and Roden which permitted them to participate in all matters concerning Bidil. Dr. Robert Califf was excluded from discussion of Bidil.

Dr. Marvin Konstam was granted a waiver which permitted him to participate in the discussion of Coreg. Dr Califf's employer, Duke University Medical Center, has interests that could create the appearance of a conflict of interest. However, the agency has determined that the interest of the government in Dr. Califf's participation outweighs any appearance of a conflict. Accordingly, Dr. Califf may participate in all matters pertaining to Coreg. Drs. Massie, Lindenfeld and Thadani were excluded from the discussion of Coreg.

The committee then began review of NDA 20-727, Bidil, Medco Research Inc., a fixed dose combination of hydralazine (H) and isosorbide dinitrate (ISDN) in the treatment of congestive heart failure as an adjunct to digitalis and diuretics. The formulations of Bidil proposed for marketing were (H)/ISDN doses of 37.5/10, 37.5/20, 75/20, and 75/40 mg.

Both H and ISDN are approved and marketed drugs. Ordinarily, the approval of fixed dose combination products would require evidence that both drugs contribute to the therapeutic effect. There is no such data for Bidil. In this case approval could be based on compelling evidence that the combination had a favorable effect on an irreversible endpoint such as mortality.

The two studies in support of this application were presented by Dr. Jay Cohn. V-Heft I was a double-blind, placebo controlled trial begun in 1980, that randomized 642 male patients, at eleven VA centers to placebo (N=272), H-ISDN (N=186) and prazosin (N=183).

Six major and six minor endpoints were specified in the protocol. The major endpoints were overall mortality, 2-year mortality, number and duration of cardiovascular hospitalizations, maximum oxygen consumption during peak exercise, maximum treadmill exercise time on graded test and duration of exercise on submaximal tests. Sample size calculations were based on the mortality endpoints.

The study was conducted from 1980 to 1985. The mean follow-up was 2.3 years and ranged from six months to 5.7 years. Four interim analyses were performed conducted by O'Brian/Fleming rules. None achieved a significance that warranted stopping the trial. The primary analysis for survival was a log rank test where the survival curves could be tested

by a single test each active treatment arm to each other, the combined vasodilator arms to placebo and each active treatment arm to placebo.

Mortality was to be evaluated as total mortality over the entire study or as two year mortality. Two other analyses were conducted. A Cox protocol specified regression analysis intended to identify important covariates and a retrospective Cox analysis (placebo vs-ISDN) using baseline covariates specified by FDA.

V-Heft II was a double-blind placebo controlled trial that randomized 804 male patients with congestive heart failure to enalapril (N=403) or H-ISDN (N=401) at 13 VA centers. These patients included 15-20% of patients who survived V-Heft I.

Six major and four minor endpoints were specified in the protocol. Major endpoints included overall mortality, two year mortality, number and duration of cardiovascular hospitalizations, maximum oxygen consumption at anaerobic threshold and changes in quality of life, Sample size calculations were based on the mortality endpoint.

Dr. Cohn recommended approval of Bidil for congestive heart failure on the basis of a survival benefit in V-Heft I and trends for increased exercise tolerance and long term ejection fraction in both trials. The committee discussed these benefits.

In V-Heft I, the only mortality analysis that could achieve statistical significance was a one sided p value calculated for 2-year mortality. This p value was subject to adjustments for interim analyses and the multiple endpoints. There were suggestions of a trend toward possible improved maximum oxygen consumption. The increase in ejection fraction was significant for H-ISDN compared to placebo.

For V-Heft-2 study results showed a risk reduction in mortality for enalapril. Interpretation of exercise tolerance results were dependent on the analysis chosen. Overall the results were not consistent with V-Heft-I.

Although the primary endpoint in both trials was said to be mortality, both committee biostatiscians recommended that there were too many variables specified in the protocol as primary endpoints. They did not believe these data could be interpreted with any degree of certainty.

The members of the committee began a response to FDA questions, a copy of these questions is appended to these minutes. The committee unanimously recommended that there was no statistically significant effect on mortality for V-Heft-I at two years or over the entire study. They recommended 11-no, 1-abstention, that an effect on hospitalizations had been demonstrated, unanimously no, that there was a statistically significant effect on maximum oxygen consumption at peak exercise during maximal exercise tolerance test and unanimously yes that a significant effect on ejection fraction had been demonstrated.

Moving on to V-Heft-II issues they recommended that peak oxygen consumption at 3 and 6 months was not improved by a vote of 8-no, 4-yes. They could not identify a placebo group to which the results of this study could be compared. The committee had already voted that there was no mortality effect in V-Heft I, therefore question 12 was moot. Question 13 had been answered in the affirmative. There was no difference for hospitalizations and some effect for H-ISDN at 3 months. Tolerance was not discussed. In their final vote the committee recommended 9-no, 3-yes that Bidil be approved for use in congestive heart failure.

Following a lunch break the committee began a discussion of NDA 20-297, s-001, Coreg (carvedilol), SmithKline Beecham, to be indicated for congestive heart failure. Dr. Barry Massie stepped down from the chair and the meeting was conducted by Dr. John DiMarco. The sponsor's presentation was begun by Dr. William Powell, and continued by Dr. Neil Shusterman, who reminded the committee that on May 2,1996, they had recommended nonapproval of carvedilol, finding the totality of evidence insufficient to support approval for congestive heart failure. However, at that time they did recommend that study 240 supported the efficacy of carvedilol in worsening heart failure.

Study 240 randomized 366 patients to placebo (134) or carvedilol (232). The primary endpoint was the combined risk of morbidity and mortality. Events indicative of the progression of heart failure were death due to heart failure or sudden death, hospitalization for worsening heart failure or worsening heart failure requiring a greater than 50% increase in background medication or initiation of background medication for more than 30 days. Double blind therapy was to be maintained for 12 months. However this study was terminated early because of an unexpected finding of an effect on mortality.

Additional data from study 223, an Australian/New Zealand trial had become available since the May meeting. Study 223 had two phases: a short term phase of 6-12 months designed to evaluate hemodynamic and symptomatic endpoints and a long term phase of 18-24 months to evaluate morbidity and mortality. Other than morbidity and mortality, secondary endpoints were not clearly specified in the original protocol.

Final results for study 223, were presented. They were not significant for exercise tolerance but were significant for the long term prespecified endpoint of morbidity/mortality. The sponsor also presented data showing consistent effects on improvement of symptoms, New York Heart Association Class and global assessment.

Additional analyses were requested by FDA for studies 220, 221 (two components of the U.S. multicenter trial program) and 223 for secondary endpoints of morbidity and mortality. These placebo controlled multicenter trials had primary endpoints of exercise tolerance. The results of the morbidity/mortality reanalyses for all three trials were statistically significant.

The committee proceeded to answer questions directed by the FDA. A copy of these questions is appended to these minutes. The first question related to the significance of the results for study 240, when the medications component is removed and p values increase 10 fold. Since the medications component was prespecified in the protocol the committee recommended that the study maintained its power although clinical significance was diminished.

The committee also recommended that while ejection fraction was definitely improved, the short term phase of 223 did not provide evidence of any substantial clinical benefit. The long term phase had three poorly defined endpoints. One endpoint which combined mortality and morbidity, achieved statistical significance.

Question 1.3 was discussed and reformulated. The committee voted on a recommendation to approve carvediolol on the basis of the primary and secondary endpoints from studies 240 and 223. This was not recommended by a vote of 9-no, 1-yes. When the committee voted on this motion as originally presented with the an evaluation of the two study results and endpoints from other trials the committee voted 8-yes, 2-no, to recommend that carvedilol be approved for use in congestive heart failure. The other additional evidence the committee found persuasive was the consistency of the morbidity and mortality results, improvements in New York Association Class, subjective and objective scores and progression of heart failure.

Other questions were not discussed. However FDA staff did attempt to explore the exact nature of the data, outside of study 240, which led the committee to their recommendation. No combined endpoints involving death and morbidity or hospitalizations were protocol specified for any of the other clinical studies in the NDA. The U.S. multicenter trials had a secondary endpoint of hospitalizations for cardiovascular causes but this was not coupled with a prespecified endpoint of death. The committee was apparently persuaded by effects on mortality, however this effect remained an unconfirmed, not prespecified finding of 240. The meeting was adjourned at 6:20 p.m.

Reconvening in open session at 8:30 a.m. on Friday February 28, 1997, Dr. Massie chairing, the committee was to discuss NDA 20-689, Posicor (mibefradil dihydrochloride) tablets to be indicated for hypertension and angina. The executive secretary, Joan C. Standaert, entered the conflict of interest statement into the record.

Full waivers had been granted to Drs, Barry Massie, Lemuel Moye and Robert Califf, permitting them to participate in all official matters concerning Posicor. Dr. Thadani had a limited waiver allowing him to participate in discussions of Integrilin but he would be excluded from voting on this matter. Dr. Cindy Grines and Dr. Robert Califf would be excluded from discussion of and voting on recommendations for Integrilin.

Dr. Califf and his institution, the Duke University Medical Center have interests which do not constitute a financial interest within the meaning of 18 U.S.C. 208 (a) but which could

create the appearance of a conflict of interest. The agency has determined that the government's interest in Dr. Califf's participation outweighs the concern that the integrity of the agency's programs may be questioned. Therefore, Dr. Califf has been permitted to participate on all matters relating to Posicor.

Dr. Massie, stating some concerns about his participation in studies, not included in his waiver, elected to participate in the discussion of mibefradil but would not vote on recommended action. He introduced Dr. Rudolph Lucek, Hoffmann La-Roche, who began the sponsor's presentation.

Mibefradil is the first of a new class of calcium ion influx inhibitors. Compared with other calcium channel blockers currently available, mibefradil is a vasodilator without reflux increase in heart rate and has no appreciable negative inotropic activity at therapeutic concentrations. Mibefradil has been evaluated for efficacy in hypertension and angina.

Mibefradil has been evaluated as antihypertensive treatment in 10 clinical trials including 2,805 patients. The therapeutic trials were summarized in attachment 1. Superiority of mibefradil over placebo was demonstrated in 4 double-blind, parallel, placebo controlled studies in 1,123 patients with hypertension, 933 of whom received mibefradil at dosages of 6.25-200 mg/day.

The drug was evaluated as a treatment for chronic stable angina in 7 clinical trials of 1,698 patients, summarized in attachment 2. Superiority of mibefradil over placebo was demonstrated in 5 double blind, parallel, placebo controlled studies in 860 patients, 560 of whom received mibefradil at dosages of 25-150 mg/day. Tolerance after 12 weeks of mibefradil treatment was examined in 1 placebo controlled, randomized, withdrawal study of 102 patients and long term efficacy was supported by 1 open label, 12 month follow-up of 567 patients. The drug was compared with other antianginal agents amlodipine and diltiazem SR in two active controlled trials with 454 patients.

Treatment effects were assessed with standard exercise tolerance (ETT) and primary efficacy endpoints were defined as changes in the following ETT times from baseline measured at the end of the dosing interval for the primary endpoint of total symptom-limited exercise duration, time to onset of angina and time to less than 1 mm of ST-segment depression.

Mibefradil at 100-150 qd increased total symptom limited exercise duration and time to onset of moderate angina on ETT. The changes were modest but were seen in patients who were not treated with other antianginal agents. Antiischemic effects were evident and shown by increases in time to ST changes. Mibefradil was also effective in patients receiving betablockers as background therapy.

Safety concerns for possible proarrhythmic effects of mibefradil were generated by observations of QTc prolongation in hypertensive subjects dosed at 200 mg.. The sponsor devoted much of their presentation to examination of these effects with mibefradil and other

drugs. Dr. Jeremy Ruskin addressed the electrophysiologic effects of mibefradil and the electrocardiographic changes seen with the drug. When compared to agents known to cause torsades like quinidine, sotolol and bepridil, mibefradil demonstrates different characteristics. It does not affect or shorten action potential duration and has no measurable effect on atrial muscle or ventricular muscle refractoriness.

Dr. Gordon Tomaselli discussed the morphological changes in the electrocardiogram observed with mibefradil. At recommended doses of 50-100 mg mibefradil is associated with a decrease in repolarization time which is consistent with a decrease in the length of the myocardial action potential. Mibefradil was associated with dose-related morphologic changes in the T-U wave which led to an apparent increase in the mean QTc interval with the 200 mg dose. These changes were also observed with verapamil and diltiazem.

Mibefradil is currently being studied for use in congestive heart failure in a mortality study, MACH -1. The steering committee of this study conducted a special safety assessment, in which arrhythmic and potentially arrhythmic events were evaluated. They found no reason to discontinue this trial.

Dr. Massie asked committee reviewers to respond to questions posed by FDA. Dr. Weber said that studies K13003, EC14479 and BC14044 supported efficacy for hypertension. The 50 mg dose was consistently better than placebo and 100 mg seems like the highest useful dose. Mibefradil appears to be superior to diltiazem and nifedipine but no difference was demonstrated for amlodipine.

Dr. DiMarco said that studies K1300 and BC14047 demonstrated efficacy for 50-100 mg of mibefradil for angina pectoris. There are changes in the surface ECG which appear to be non-QT prolongation. This appears to be a new phenomenon, whose mechanism is unknown.

The advisory committee voted on approval of mibefradil. They recommended 5-yes, 3-no that the drug be approved for use in hypertension and angina. Mibefradil should not be used in patients receiving other drugs, like terfanidine, astemizole cisapride and cyclosporin, patients with LV dysfunction or in association with drugs known to produce changes in QT associated with morbidity.

The advisory committee reconvened after a brief lunch break to consider NDA 20-718, Integrilin (intriban), COR Therapeutics, Inc. to be indicated for adjunct antithrombotic therapy in percutaneous transluminal coronary angiplasty (PTCA). Integrilin is an antithrombotic agent that exerts an antiplatelet effect at the final common pathway of platelet aggregation. It is proposed to prevent abrupt closure and reduce ischemic events in patients undergoing PCTA.

The efficacy of Integrilin is primarily based on the results of the IMPACT II (Integrilin to Manage Platelet Aggregation and Prevent Coronary Thrombosis) study. These results were

presented by Dr. Michael Kitt.

The study was placebo controlled, randomized, double-blind, enrolling 4,010 patients at 82 sites in the U.S.. Integrilin was administered in two dosing regimens, a bolus dose of 135 um/kg prior to angioplasty followed by infusion of 0.5 um/kg or 0.75 um/kg for 20-24 hours. All patients also received aspirin (325mg) and heparin.

The primary endpoint was death (any cause), myocardial infarction (new Q wave and/or prespecified elevation of cardiac enzymes), severe symptomatic myocardial ischemia necessitating urgent coronary revascularation (CABG, repeat coronary angioplasty or stent placement for abrupt closure), within 30 days of coronary intervention. Precise definitions of clinical events were pre-specified to ensure consistent event determinations over the entire patient population. The occurrence of a clinical event was determined by the investigator and reviewed by a Clinical Events Committee. Composite endpoints were compared between each Integrilin dosing regimen and placebo using pairwise comparisons.

Patients enrolled in the study were randomized according to a computer generated schedule. Randomization was stratified by predicted clinical risk within each investigational site. "High-risk" patients were defined as those experiencing either unstable angina or non-Q wave MI or acute MI. Any patient not meeting these criteria was deemed "low risk" or elective.

Of the 4010 patients randomized, 3871 received study drug. The treated population was used for the primary analysis of efficacy. A statically significant reduction in the composite primary endpoint was observed at 24 hours for both Integrilin regimens. At 30 days, the reduction remained statistically significant for the low dose Integrilin regimen which achieved marginal statistical significance. The majority of events which occurred within the first 30 days were within 24 hours and were enzymatically defined.

The long term effect of Integrilin was assessed at six months. The endpoint for this assessment was reduction of death, MI and any revascularization procedure as opposed to urgent procedures for the primary endpoint. More Integrilin treated patients required required hospitalization for chest pain and angina than placebo patients.

At the conclusion of the sponsor's presentation the chair directed the committee to respond to FDA questions regarding this trial. The committee recommended by a vote of 6-yes, 2-no that this trial achieved statistical significance for the prespecified endpoint. They then unanimously recommended that Impact II was not sufficient evidence to support approval of Integrilin for the proposed indications. The meeting was adjourned at 4:30 p.m.

I certify that I attended the February 27, 28, 1997 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Barry Massie M.D.
Chairman Cardiovascular and Renal Drugs Advisory Committee

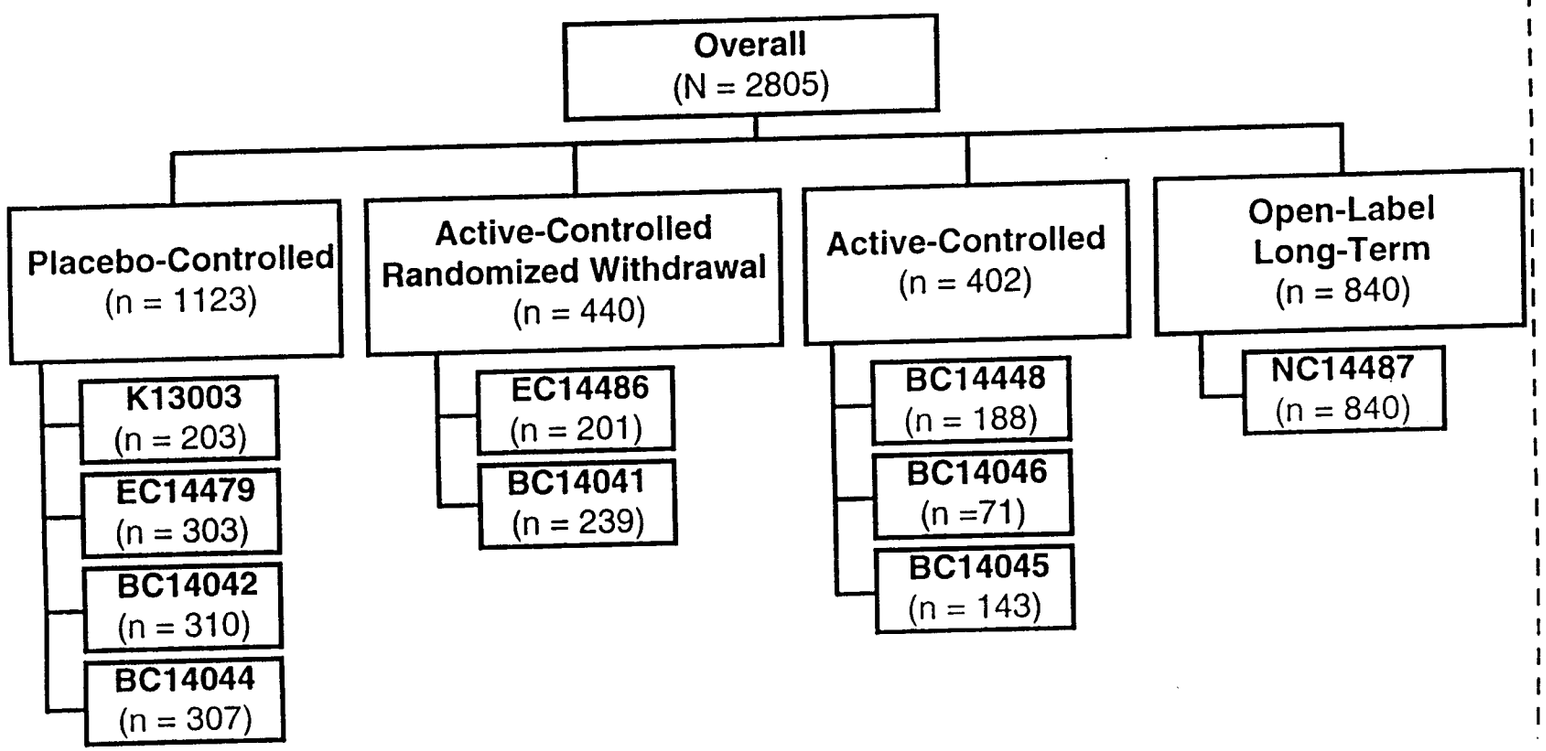
John DiMarco, M.D., Chairman

APPEARS THIS WAY
ON ORIGINAL

Joan C. Standaert, M.S.
Executive Secretary

APPEARS THIS WAY
ON ORIGINAL

Therapeutic Studies
Hypertension



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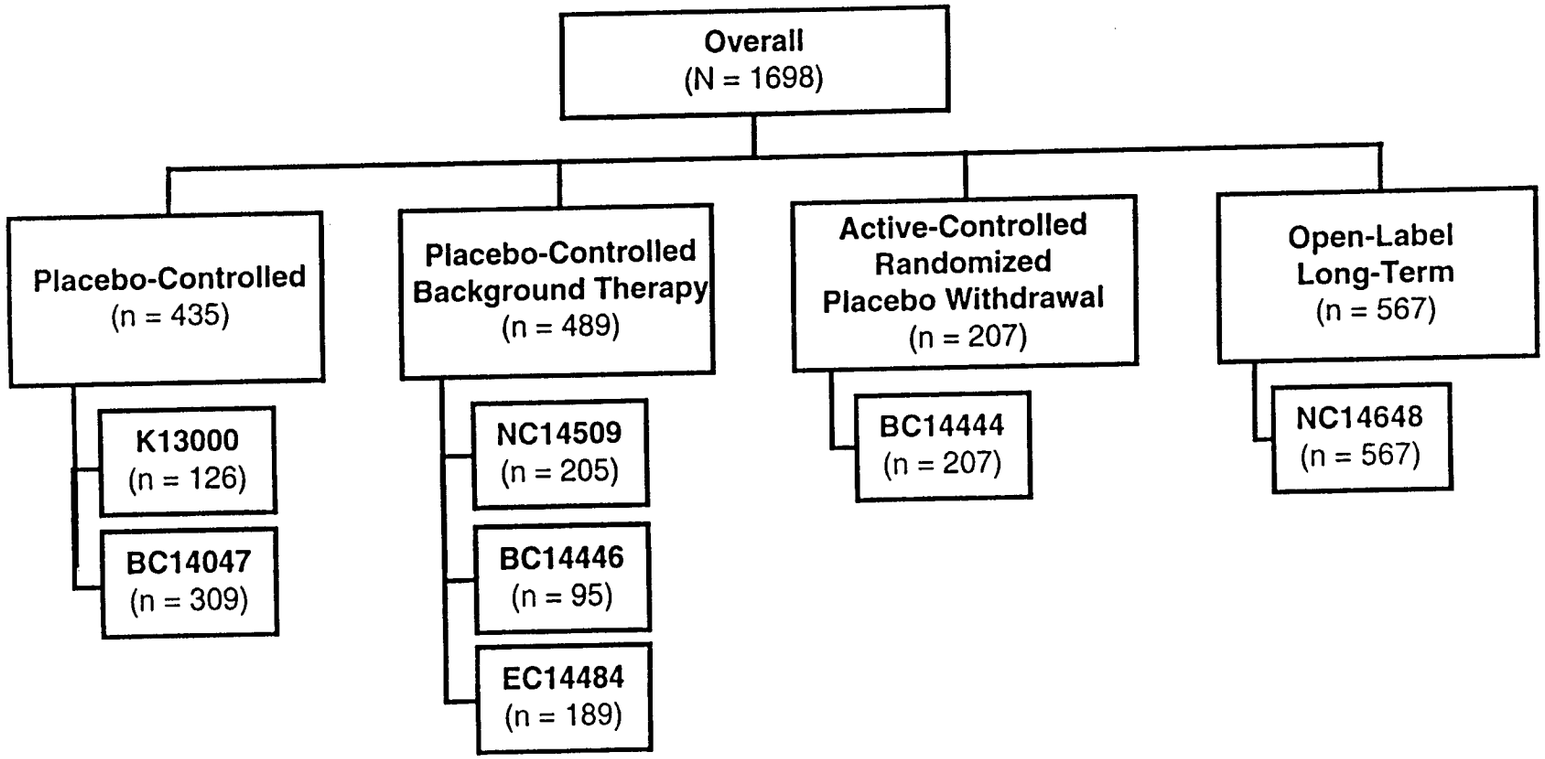
Therapeutic Studies
Chronic Stable Angina Pectoris



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