CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 10/23-24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 10/23-24/97

AGENDA

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Drug Products
82nd Meeting
October 23-24, 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.

October 23, 1997

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

9:00 a.m. DISCUSSION

Basic Statistical Considerations for the Evaluation of Active Controlled Clinical Trials.

9:05 a.m. View of the Cardiorenal Division Regarding Positive Controlled Trials: Robert R. Fenichel, M.D., Ph.D., Deputy Director HFD-110.

9:25 a.m. "If That is Your View", Then This is What You Have to Think About: Rory Collins, M.D., University of Oxford.

9:45 a.m. "If These Are The Circumstances", This is How to Calculate Things: David DeMets, Ph.D., University of Wisconsin.

10:05 a.m. BREAK

10:20 a.m. GENERAL DISCUSSION

1:00 a.m. ADJOURN

The committee will meet in **closed session** from 2:00 p.m. to 5:00 p.m. at the Hyatt Regency Hotel in Bethesda Maryland.

October 24, 1997

9:00 a.m. NDA 20-839, clopidogrel (Plavix), Sanofi Pharmaceuticals, Inc., to be indicated for the prevention of vascular ischemic events in patients with a history of symptomatic atherosclerosis.

SPONSOR'S PRESENTATION (Agenda attached)

11:00 a.m. BREAK

11:15 a.m. COMMITTEE DISCUSSION AND REVIEW

FDA Medical Reviewers: Robert R. Fenichel, M.D., Ph.D.
Charles Ganley, M.D.

FDA Statistical Reviewer: James Hung, Ph.D.

FDA Biopharmaceutical Reviewers: Venkata Ramana S. Uppoor, Ph.D.
Patrick J. Marroum, Ph.D.
Ameeta Parekh, Ph.D.

1:00 p.m. COMMITTEE RECOMMENDATIONS

Committee Reviewer: Dan Roden, M.D.C.M.

ADJOURN

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

CHAIRPERSON

Packer, Milton, M.D. 06/30/01
Chief, Division of Circulatory Physiology
Columbia University
College of Physicians and Surgeons
630 West 168th Street
New York, New York 10032

EXECUTIVE SECRETARY

Standaert, Joan C.
Center for Drug Evaluation and Research
Food and Drug Administration
234 Summit Street, Room 117
Toledo, Ohio 43604
419/259-6211 FAX 419/259-6353

MEMBERS

Grines, Cindy, M.D. 06/30/99
Director, Cardiac Catheterization
Division of Cardiovascular Diseases
William Beaumont Hospital
3601 West Thirteen Mile Road
Royal Oak, Michigan 48073-6769

Lindenfeld, JoAnn, M.D. 06/30/99
Professor of Medicine, Division of Cardiology
University of Colorado Health Science Center
4200 East Ninth Avenue, B-130
Denver, Colorado 80262

Moye, Lemuel, M.D., Ph.D. 06/30/99
Associate Professor of Biometry
University of Texas Health Science Center at Houston
Coordinating Center for Clinical Trials
1200 Herman Pressler Street, Suite 801
Houston, Texas 77030

Thadani, Udho, M.D. FRCP 06/30/99
Professor of Medicine
Division of Cardiology
Oklahoma University Health Sciences Center
920 S.L. Young Boulevard, 5-SP-300
Oklahoma City, Oklahoma 73104

Califf, Robert, M.D. 06/30/00
Professor of Medicine/Director, Duke Clinical
Research Center
Duke University Medical Center
2024 West Main Street, Box 31123
Durham, North Carolina 27707

DiMarco, John, M.D. 06/30/00
Professor of Medicine
Cardiovascular Division
University of Virginia Hospital, Box 3608
Hospital Drive, 5th Floor
Private Clinic, Room 3608
Charlottesville, Virginia 22908

Konstam, Marvin, M.D. 06/30/00
Professor of Medicine
New England Medical Center
750 Washington Street, Box 108
Boston, Massachusetts 02111

Roden, Dan, M.D.C.M. 06/30/00
Vanderbilt University
Division of Clinical Pharmacology
532C Medical Research Building 1
23rd and Pierce Avenue
Nashville, Tennessee 37232-6602

CONSUMER REPRESENTATIVE

Graboys, Thomas, M.D. 06/30/01
Director Lown Cardiovascular Center
Brigham and Women's Hospital
Associate Clinical Professor of Medicine
Harvard Medical School
21 Longwood Avenue
Brookline, Massachusetts 02146

Pina, Ileana, M.D. 06/30/01
Director, Cardiac Rehabilitation
Temple University Hospital
Cardiology Section
3401 North Broad Street
904 Parkinson Pavilion
Philadelphia, Pennsylvania 19140

Agenda
24 October 1997
Cardiovascular and Renal Drugs Advisory Committee Meeting

NDA 20-839, PLAVIX®

Introduction	George A. Clay, Ph.D.
Overview of CAPRIE	J. Donald Easton, M.D.
Statistical Interpretation of CAPRIE	Lloyd Fisher, Ph.D.
Clinical Interpretation of CAPRIE	Alison Pilgrim, M.D., Ph.D.
Conclusions	George A. Clay, Ph.D.

Sanofi's Speaker List:

George Clay, Ph.D.
Vice President, Regulatory Affairs
Sanofi Pharmaceuticals, Inc.

J. Donald Easton, M.D.
Professor And Chairman,
Department Of Clinical Neurosciences
Brown University Medical School
Providence, Rhode Island
CAPRIE Steering Committee
CAPRIE Central Validation Committee

Lloyd Fisher, Ph.D.
Professor, Associate Chair
Director Of Graduate Program
Department Of Biostatistics
University Of Washington
Seattle, Washington

Alison Pilgrim, M.D., Ph.D.
Vice President,
Cardiovascular Clinical Research
Sanofi Recherche

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: CARDIOVASCULAR and RENAL DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 10/23-24/97

QUESTIONS

Questions

clopidogrel

24 October 1997

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

Clopidogrel is an inhibitor of platelet aggregation, chemically similar to ticlopidine (TICLID®, Roche Laboratories). Sanofi Pharmaceuticals proposes that clopidogrel be approved for the prevention of atherothrombotic events in patients at high risk of such events.

Essentially all that is directly known of the clinical efficacy of clopidogrel comes from the CAPRIE trial, in which clopidogrel was compared to aspirin. To decide whether or not clopidogrel is effective (*i.e.*, superior to placebo), you will need to interpret the results of CAPRIE in the light of what is known about the effectiveness of aspirin in similar patients.

For clopidogrel to be approved, the demonstration that it is superior to placebo must be as convincing as those which, in other clinical settings, have usually been provided by two or more successful clinical trials. Recent discussions have emphasized that the the expectation of two successful trials is not absolute, but that is only because a single trial can sometimes provide evidence of similar strength.

Despite the required strength of the overall evidence of superiority to placebo, some of the components contributing to the overall argument might — at least in principle — be much weaker. If you believe that aspirin is far superior to placebo, then clopidogrel could be superior to placebo even if clopidogrel were no better than aspirin, and, in fact, even if clopidogrel were slightly *inferior* to aspirin. Similarly, if you believe that clopidogrel is far superior to aspirin, then clopidogrel could be superior to placebo even if the effect of aspirin were neutral or slightly adverse.

Even though you might recommend approval of clopidogrel without being satisfied that CAPRIE had provided strong evidence of superiority to aspirin, the relative efficacy of clopidogrel and aspirin will, if clopidogrel is approved, be of great clinical interest.

Before permitting comparative claims in any drug's labeling, FDA has generally insisted on the evidentiary equivalent of two or more successful trials. Additionally, FDA has required that the comparator regimen have not been handicapped by inadequate dosage or other unfair burden.

FDA is occasionally asked to pass judgment on claims of relative cost-effectiveness, but these judgments are not the responsibility of the Division or this Committee.

The issues today are relatively complex, and the approach taken by these Questions is one of many that might have been taken. The strategy we chose asks you in this order

- How persuasive are the several findings of CAPRIE?
- Are you willing to make inferences by combining the CAPRIE data with those of the aspirin trials?
- How persuasive are the several findings of the aspirin trials?
- How persuasively can the CAPRIE and aspirin results be combined to demonstrate the efficacy of clopidogrel in various populations?
- Should clopidogrel be approved for use in some population? If so, which one?

In an attempt to avoid leading questions, we have used parallel constructions that end up including a few options that we regard as far-fetched.

In keeping with the above strategy, the first few questions are concerned with clopidogrel/aspirin, without regard to the relative efficacy of clopidogrel (or aspirin) and placebo.

1. In the overall CAPRIE population, clopidogrel appeared to be superior to aspirin. This apparent finding is

1(A). not meaningful, because of heterogeneity among subgroups of patients.

1(B). probably attributable to the play of chance.

1(C). a plausible finding, but weaker than that of a typical successful trial.

1(D). as persuasive as the finding of a typical successful trial.

1(E). as persuasive as a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of patients after they had discontinued receiving study drug?

2. The CAPRIE protocol specified that the results would be tested for homogeneity of effect among the three recruitment groups. When this test was performed, the clopidogrel/aspirin results appeared to be significantly heterogeneous. This apparent finding is

2(A). probably attributable to the play of chance.

2(B). a plausible finding, but weaker than that of a typical successful trial.

2(C). as persuasive as the finding of a typical successful trial.

2(D). as persuasive as a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of patients after they had discontinued receiving study drug?

The test of homogeneity was protocol-specified, but follow-on analyses to obtain estimates of effect size in the three recruitment groups were not. Are such analyses legitimate? *Post hoc* analyses of subsets are always problematic, as shown by the wry Zodiacal analyses in the report of ISIS-2 nine years ago. On the other hand, because the three recruitment groups were identified in the CAPRIE protocol for the homogeneity analysis, using them in separate *post hoc* analyses of effect size is not utterly arbitrary. The subset problem is central to the next two questions; you may wish to discuss the general problem before turning to the specific questions.

3. Among patients recruited into CAPRIE on the sole basis of **peripheral arterial disease**, clopidogrel's margin of superiority over aspirin was much greater than what was seen in the overall CAPRIE population. This apparent finding is

3(A). probably attributable to the play of chance.

3(B). a plausible finding, but weaker than that of a typical successful trial.

3(C). as persuasive as the finding of a typical successful trial.

3(D). as persuasive as a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of patients after they had discontinued receiving study drug?

4. Among patients recruited into CAPRIE on the sole basis of a recent **myocardial infarction**, clopidogrel appeared to be indistinguishable from (or slightly inferior to) aspirin. This apparent finding is

4(A). probably attributable to the play of chance.

4(B). a plausible finding, but weaker than that of a typical successful trial.

4(C). as persuasive as the finding of a typical successful trial.

4(D). as persuasive as a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of patients after they had discontinued receiving study drug?

5. To draw a regulatory conclusion about clopidogrel/placebo, one must somehow combine the CAPRIE data with the accumulated data from trials that compared aspirin to placebo. There are obvious pitfalls to any process that attempts to merge data across populations, years, and styles of concomitant therapy. Are you willing to engage in such a process? (If not, the remainder of the questions should be skipped.)

6. (The next two questions are concerned with aspirin/placebo, without regard to clopidogrel.) In the overall analysis of the pooled aspirin/placebo trials whose patients were similar to those of CAPRIE, aspirin was superior to placebo. This apparent finding is

6(A). not meaningful, because of heterogeneity among subgroups of patients.

6(B). probably attributable to the play of chance.

6(C). a plausible finding, but weaker than that of the typical successful trial.

6(D). as persuasive as the finding of a typical successful trial.

6(E). as persuasive as a package of two or more typical successful trials.

7. In the pooled aspirin/placebo trials whose patients were similar to those of the **peripheral-arterial-disease** group in CAPRIE, aspirin was not distinguishable from placebo. This apparent finding is

7(A). probably attributable to inadequate sample size.

7(B). a plausible finding, although weakened by inadequate sample size.

8. (The remaining questions try to bring it all together. What are the populations (if any) in whom there is persuasive evidence of clopidogrel's superiority to placebo?) Clopidogrel seemed to be superior to aspirin in the overall analysis of CAPRIE, and aspirin seemed to be superior to placebo in the overall analysis of the pooled trials with CAPRIE-like patients. From these facts, one might conclude that clopidogrel is superior to placebo in all patients similar to those of CAPRIE. This reasoning

8(A). is specious, since there is no proper way to draw conclusions from these disjoint bodies of data.*

8(B). is misleading, because of heterogeneity among subgroups of patients within the aspirin trials, and again among the subgroups of CAPRIE.

8(C). is attractive, but some links in the chain are so weak that the positive result is probably attributable to the play of chance.

8(D). leads to a plausible conclusion, but one supported by evidence weaker than that provided by a typical successful trial.

8(E). leads to a plausible conclusion, supported about as persuasively as the finding of a typical successful trial.

8(F). leads to a plausible conclusion, supported as persuasively as the findings of a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of CAPRIE patients after they had discontinued receiving study drug?

9. (This and the next two questions may be superfluous, depending on your answer to Question 8.) From the results of CAPRIE and those of the aspirin/placebo trials, the sponsor has argued that clopidogrel must be superior to placebo in patients like those who entered CAPRIE because of a recent **myocardial infarction.** This reasoning

9(A). is specious, since there is no proper way to draw conclusions from these disjoint bodies of data.

9(B). is attractive, but some links in the chain are so weak that the positive result is probably attributable to the play of chance.

9(C). leads to a plausible conclusion, but one supported by evidence weaker than that provided by a typical successful trial.

9(D). leads to a plausible conclusion, supported about as persuasively as the finding of a typical successful trial.

9(E). leads to a plausible conclusion, supported as persuasively as the findings of a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of CAPRIE patients after they had discontinued receiving study drug?

---

* This option is somewhat redundant with Question 5, but it is provided for members of the Committee who voted No to Question 5, but were outvoted.

10. From the results of CAPRIE and those of the aspirin/placebo trials, the sponsor has argued that clopidogrel must be superior to placebo in patients like those who entered CAPRIE because of a recent **stroke.** This reasoning

10(A). is specious, since there is no proper way to draw conclusions from these disjoint bodies of data.

10(B). is attractive, but some links in the chain are so weak that the positive result is probably attributable to the play of chance.

10(C). leads to a plausible conclusion, but one supported by evidence weaker than that provided by a typical successful trial.

10(D). leads to a plausible conclusion, supported about as persuasively as the finding of a typical successful trial.

10(E). leads to a plausible conclusion, supported as persuasively as the findings of a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of CAPRIE patients after they had discontinued receiving study drug?

11. From the results of CAPRIE and those of the aspirin/placebo trials, the sponsor has argued that clopidogrel must be superior to placebo in patients like those who entered CAPRIE because of **peripheral arterial disease.** This reasoning

11(A). is specious, since there is no proper way to draw conclusions from these disjoint bodies of data.

11(B). is attractive, but some links in the chain are so weak that the positive result is probably attributable to the play of chance.

11(C). leads to a plausible conclusion, but one supported by evidence weaker than that provided by a typical successful trial.

11(D). leads to a plausible conclusion, supported about as persuasively as the finding of a typical successful trial.

11(E). leads to a plausible conclusion, supported as persuasively as the findings of a package of two or more typical successful trials.

To what extent was your answer affected by concerns as to followup of CAPRIE patients after they had discontinued receiving study drug?

12. From the results of CAPRIE and those of the aspirin/placebo trials, one might generalize that clopidogrel is likely to be superior to placebo in any patient with **atherosclerosis** (*e.g.*, in a patient with a remote history of myocardial infarction). This generalization

12(A). is no more than a hypothesis in need of testing.

12(B). is attractive, but the evidence supporting it is weaker than that provided by a typical successful trial.

12(C). is supported about as persuasively as the finding of a typical successful trial.

12(D). is supported as persuasively as the findings of a typical package of two or more trials.

To what extent was your answer affected by concerns as to followup of CAPRIE patients after they had discontinued receiving study drug?

13. Should clopidogrel be **approved** for prevention of atherothrombotic events (acute myocardial infarctions, strokes, and vascular deaths) in some population of patients at high risk?

14. If clopidogrel is approved, how should the labeling and advertising identify the patients for whom clopidogrel is indicated (that is, the patients in whom clopidogrel has been shown to be better than **placebo**)?

14(A). Patients with atherosclerosis.

14(B). Patients similar to those enrolled in CAPRIE.

14(C). Patients similar to those enrolled in CAPRIE, excluding the MI group.

14(D). Patients similar to those enrolled in CAPRIE, excluding the stroke group.

14(E). Patients similar to those enrolled in CAPRIE, excluding the peripheral-arterial-disease (PAD) group.

14(F). Patients similar to those enrolled in the MI group in CAPRIE.

14(G). Patients similar to those enrolled in the stroke group in CAPRIE.

14(H). Patients similar to those enrolled in the PAD group in CAPRIE.

15. If clopidogrel is approved, how should the labeling and advertising characterize the clopidogrel/**aspirin** comparison?

15(A). In patients with atherosclerosis, clopidogrel was significantly superior to aspirin in preventing atherosclerotic events.

15(B). In patients meeting the enrollment requirements of CAPRIE, clopidogrel was significantly superior to aspirin in preventing atherosclerotic events.

15(C). In patients meeting the enrollment criteria of CAPRIE, clopidogrel was significantly superior to aspirin in preventing atherosclerotic events, but the effect was heterogeneous among subgroups. The two treatments were not distinguishable in patients whose sole indication of risk was a recent history of MI.

15(D). In patients meeting the enrollment criteria of CAPRIE, clopidogrel was significantly superior to aspirin in preventing atherosclerotic events, but the effect was heterogeneous among subgroups. In patients whose sole indication of risk was a recent history of MI, clopidogrel seemed to be a little bit *inferior* to aspirin.

15(E). In patients meeting the enrollment criteria of CAPRIE, clopidogrel was superior to aspirin in preventing atherosclerotic events, but the effect was heterogeneous among subgroups and of marginal statistical significance, and it has not been replicated.