Food and Drug Administration
Center for Drug Evaluation and Research

Hilton Washington DC/North Hotel, Gaithersburg, Maryland

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on April 26, 2006, 1:00 PM – 5:00 PM session.

The committee discussed "Placebo in Hypertension Adverse Reaction Meta-Analysis" (PHARM) Study, a meta-analysis of more than 80,000 patients in placebo-controlled trials of antihypertensive medications, which evaluated the risk of irreversible harm in conducting placebo-controlled trials in patients with hypertension.

These summary minutes for the April 26, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on May 3, 2006,

I certify that I attended the April 26, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

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William R. Hiatt, M.D.
(Committee Chair)

FINAL SUMMARY MINUTES
Cardiovascular and Renal Drugs Advisory Committee Meeting
April 26, 2006 PHARM Study

A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

(1:00 P.M. – 5:00 P.M.)
Issue: The committee discussed "Placebo in Hypertension Adverse Reaction Meta-Analysis" (PHARM) Study, a meta-analysis of more than 80,000 patients in placebo-controlled trials of antihypertensive medications, which evaluated the risk of irreversible harm in conducting placebo-controlled trials in patients with hypertension.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
David L. DeMets, Ph.D.
Steven D. Findlay, M.P.H. (Consumer Representative)
John M. Flack, M.D., M.P.H.
Robert A. Harrington, M.D., F.A.C.C.
William R. Hiatt (Committee Chair)
Frederick J. Kaskel M.D., Ph.D.
Michael A. Lincoff, M.D.
Thomas G. Pickering, M.D, D.Phil.
Ronald J. Portman, M.D.
John R. Teerlink, M.D.
Lynn Warner-Stevenson, M.D.

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
John F. Neylan, M.D. (Industry Representative)

Guest Speakers (Non-Voting):
Raymond Lipicky, M.D.
Dennis Mangano, Ph.D., M.D.
Sana M. Al-Khatib, M.D., M.H.S.

Special Government Employee Consultant (Non-Voting):
Steven P. Glasser, M.D.

FDA Participants:
Robert Temple, M.D.
Norman Stockbridge, M.D., Ph.D.

Executive Secretary:
Cathy A. Groupe, R.N., B.S.N.

Open Public Hearing Speakers
None

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The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met from approximately 1:00 P.M. to 5:00 P.M. on April 26, 2006, at the Hilton Washington DC/North Hotel, Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by William R. Hiatt, M.D., (Committee Chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 65 persons in attendance. There were no speakers for the Open Public Hearing sessions.

The agenda was as follows:

Call to Order and Introductions	**William R. Hiatt, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee

Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director Division of Cardiovascular and Renal Products FDA Center for Drug Evaluation and Research
	Open Public Hearing

FDA Presentations:

Placebo-Controls in Short-Term Clinical Trials of Hypertension	**Sana M. Al-Khatib, M.D., M.H.S.** Electrophysiologist Department of Medicine – Division of Cardiology Duke University Medical Center
A Report on the PHARM Study	**Raymond Lipicky, M.D.** Principal Investigator Lipicky Consulting
Serious Clinical Events in the PHARM Study	**Dennis Mangano, Ph.D., M.D.** Principal Scientist/Founder/CEO Ischemia Research and Education Foundation
	Committee Discussion
	Break
	Questions to the Committee
	Adjournment

Questions to the Committee:

The Committee is asked to opine on the continued use of placebo in studies of antihypertensive drugs. If antihypertensive drugs, regardless of class, can be expected to reduce death and stroke, and possibly myocardial infarction and other irreversible outcomes as well, how can it be ethical to continue the current practice of including a placebo control in studies of new agents?

1. To address the risk, there are two meta-analyses. The first was conducted by Dr Al-Khatib and colleagues and based on published reports of placebo-controlled trials. Combining death, stroke, MI, and CHF among 25 trials, they found a net placebo-active difference of 0, ruling out a difference as high as 0.6 per 1000 patients enrolled.

    1.1. Assuming these trials were on the order of 8 weeks duration, the upper limit corresponds to about 0.1 per 1000 patient-years, which is considerably smaller than the benefit of treatment is expected to be. How do you explain that?

Committee comments included:

- *Infrequent events in a short observation time*
- *Events only occurred in [4] trials so most trials contributed no event information*
- *This observation is not reflective of the truth; the small numbers are not particularly trustworthy*
- *Concerns raised about the omission of data on risk during the withdrawal phase*

1.2. Are you concerned about …

1.2.1. …publication bias for the component studies?

- *The committee was generally not concerned about publication bias*

1.2.2. ...the effectiveness of agents employed?

- *The committee was not significantly concerned, though some concern was raised about the population exposed to the agents*
- *The committee also cited concerns about what happens to patients before and after the study period*

1.2.3. …other adverse effects not part of the end point?

- *The committee had no additional concerns*

(See transcripts for detailed discussion

2. The second meta-analysis (PHARM) was based on 93 NDAs (590 studies and 86137 randomized patients).

2.1. Are you concerned about …

2.1.1. …studies in INDs that never led to NDAs (analogous to publication bias)?

- *The committee discussed potential concern for studies that never led to NDA but clarifying comments added that these would be very small numbers and would bias in the opposite direction, therefore there is little need for concern.*

2.1.2. …trends in safety of active agents over 1973-2001?

- *The committee was in general agreement that there was not need for concern*

(See transcripts for detailed discussion)

The table below is based on the PHARM report. It is sorted by the absolute value of the "Excess" column, which shows the placebo minus active treatment difference in events per 1000 patient-years.

Event	Placebo	Active	RR	Excess
Any	3056	6580	1.33	+251
Treatment failure	1266	1384	2.53	+246
Other cardiovascular	52	417	0.33	-28
Hypertensive emergency	134	145	2.75	+26
Administrative	840	2241	1.09	+23
Other adverse event	653	2081	0.87	-18
Arrhythmia	17	73	0.64	-2
CHF	15	29	1.47	+2
Angina pectoris	27	72	1.07	+1
Myocardial infarction	22	55	1.06	+1
Stroke	12	28	1.43	+0.8
Death	10	33	0.72	-0.4
Transient ischemic attack	8	22	0.81	-0.2

2.2. The primary analysis was the relative risk for simply any reason for withdrawal, an analysis that counted treatment failure and MI equally. Was this reasonable?

- *While most of the committee did not felt that total withdrawal was a reasonable analysis, at few of them did, commenting it was reasonable and appropriate to use as an endpoint, citing that this was a retrospective data mining study*

2.3. The overwhelming majority of events in the PHARM analysis were discontinuations for treatment failure, not surprisingly much more common on placebo than on drug. Is this alone reason for concern about the use of placebo, or is it just a reflection that trial procedures appropriately caught most cases of need for treatment?

- *The FDA clarified that events should be worded "excess events"*
- *Overall, the committee was not concerned*
- *The committee commented there was more concern about withdrawals*

- *The committee also stated this does not change the perception of placebo trials; it is an important issue concerning informed consent and who should be included in these trials; there are groups of people where risks are higher and they will need to be identified.*

The second most important class of events contributing to differences in overall event rates was other cardiovascular events, which included such things as angioedema, dependent edema, hypotension, syncope, and nonspecific chest pain or ECG changes. These events were more common on active drug.

2.4. The third biggest contributor to placebo-active treatment was hypertensive emergency events. The clear intent was to capture a class of withdrawal more ominous than the treatment failures. Did it do that?

2.4.1. Hypertensive emergencies were defined by the combination of clinical signs or symptoms and blood pressure criteria.

2.4.1.1. The clinical presentation was supposed to include new end-organ damage or symptoms plausibly related to blood pressure. Were these criteria sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures?

- *The committee was in consensus that these criteria were not sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures*
- *The committee commented on the varied and inconsistent definitions available for a 'hypertensive emergency'*
- *The committee also cited that, of the total ER visits, there were very few hospitalizations, therefore questioning the true nature of the 'hypertensive emergency'.*

2.4.1.2. Which of the following cited evidence of end organ involvement should have been the basis for declaring hypertensive emergency?

- Retinopathy
- Eye hemorrhage
- Visual disturbance
- CNS alteration
- Headache
- Chest pain
- Palpitations
- Dizziness
- Edema
- Shortness of breath
- Erectile dysfunction
- Flu-like syndrome
- Rash
- Vomiting

- *The committee generally agreed that retinopathy (acute vs. chronic), eye hemorrhage (acute), CNS alterations would be appropriate, adding that chest pain would fall under the angina protocol and edema/shortness of breath would be captured under CHF protocol.*
- *The committee commented on the need to differentiate between transient versus permanent symptoms*
- *The committee questioned the fact that there were no reported observations of renal events*

2.4.1.3. The blood pressure criteria were either a diastolic pressure greater than 120 mmHg or a rise by 10 mmHg to >110 mmHg. Were these criteria sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures?

- *The majority of the committee members agreed that the criteria were not sufficient, as defined, to establish that the hypertensive emergency events were clearly worse than the treatment failures.*

(See transcripts for detailed discussion)

2.5. Please comment on the Mangano analysis of "hypertensive emergency" and "other cardiovascular" events.

2.5.1. What was the rationale for looking at those two classes in isolation?

2.5.2. Different 0-10 severity grading systems were employed for hypertensive emergency and other cardiovascular events, and then the scores were combined. Was this reasonable?

2.5.3. What scores represented permanent end-organ damage? How many of these events were there?

2.5.4. Is it appropriate to consider a threshold for severity, or is some integral appropriate?

2.5.5. What was an appropriate threshold score for considering events to be severe?

2.5.6. What would be an appropriate nominal p-value for considering a relative risk to be significant?

- *The Agency clarified that they may make 'general' comments on all portions of 2.5 but were not required to directly address them*
- *The committee commented that it was rational and appropriate to look at categories of events to provide additional insights about what the data means*
- *The committee commented that scaling is critical but there are limitation to how far one should take the scaling. The committee also noted that these analyses were exploratory and post hoc in nature.*
- *The committee suggested that this would be an informative addition to database*

(See transcripts for detailed discussion)

2.6. The fourth biggest contributor to placebo-active treatment differences was administrative events. This was the category with the largest number of total events. Why do you think these events were somewhat more common on placebo (p=0.03)?

- *The committee agreed that this would be very difficult to know; difficult to interpret*
- *The committee added that this may be confounded by treatment failures*

The fifth biggest contributor to placebo-active treatment differences was other adverse events, which included headache, lab abnormalities, rash, and fatigue. These were more common on active treatment than placebo.

2.7. The next largest contributor to placebo-active treatment differences is 10-fold less common, but generally the remaining event classes (arrhythmia, heart failure, angina, myocardial infarction, stroke, death, and transient ischemic attack) represent serious, often fixed, outcomes, mostly those that one would expect to be better on drug than on placebo.

2.7.1. The net excess on placebo is about 2 events per 1000 patient-years, Is this what one should expect for the benefits of active treatment?

2.7.2. Together, death, stroke, and myocardial infarction (not quite the Al-Khatib end point) give a relative risk of 1.03 (p=0.9). Is that what one should expect for the benefits of active treatment?

- *The committee commented that there was too short an exposure period and a low number of events to get a reliable endpoint*
- *The committee cited Dr. Lipicky's 'levels of risk', suggesting cutoffs for enrollment even in the short-term*
- *The committee commented that it is very difficult to detect absolute level of risk*
- *The committee also suggested that informative data should be included in informed consent information that is provided to patients during enrollment*
- *There is a need to define 'placebo population' so it is possible to get to equipoise, in light of the associated risks of patients on placebo for more than a month*

(See transcripts for detailed discussion)

3. If placebo-controlled studies continue, what do you advise to minimize risk?
   3.1 Minimize the duration of exposure to placebo
   3.2 Avoid study of patients at high risk because of high blood pressure or other risk factors
   3.3 Minimize the time between visits
   3.4 Set more strict criteria for remaining in study
   3.5 Others?
   - *The committee was in general agreement that 3.1 and 3.2 should be advised to minimize risk*

   Additional comments from the committee included:
   - *The need for a total risk assessment versus blood pressure along*
   - *The need for rigorous oversight and informed consent – DSMB involvement*
   - *Inclusion of patients only on monotherapy to help decrease dropout*
   - *A systematic database for early withdrawal data*

4. Under which, if any, of the following circumstances should placebo controls be discouraged?

   4.1 Dose-ranging studies for a new molecular entity
   NO: 11 YES: 0

   4.2 Withdrawal studies intended to show long-term effectiveness
   NO: 10 YES: 1

   4.3 Factorial studies for approved drugs
   NO: 11 YES: 0

   4.4 Others?
   - The committee recommended that monitoring should be setup for withdrawals

(See transcript for detailed discussion)

The committee adjourned at approximately 5:00 P.M.