Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee
July 1 – 2, 2008

Summary Minutes of the
Endocrinologic and Metabolic Drugs Advisory Committee
July 1 - 2, 2008
Location: Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland.

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

These summary minutes for the July 1 - 2, 2008 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on _9/9/08_____

I certify that I attended the July 1 - 2, 2008 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**/s/**_____	_____**/s/**_____
Paul T. Tran, RPh.	Kenneth Burman, M.D.
Designated Federal Official, EMDAC	Acting Committee Chair

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The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 1 – 2, 2008 at the Hilton Hotel Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, 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 Kenneth Burman, M.D. (Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Official). There were approximately 250 persons in attendance. There were 3 speakers for the Open Public Hearing sessions.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Kenneth Burman, M.D., Katherine Flegal, Ph.D., Jessica Henderson, Ph.D., Thomas Bersot, M.D., Ph.D, Eric Felner, M.D., Allison Goldfine, M.D., Michael Proschan, Ph.D., Clifford Rosen, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-voting):
Enrico Veltri, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee Member (Voting)
Timothy S. Lesar, Pharm.D.

Special Government Employee Consultants Present (Voting):
Thomas Fleming, Ph.D., Ruth Day, Ph.D., Eric Holmboe, M.D., Marvin Konstam, M.D., Rebecca Killion (Patient Representative).

Regular Government Employee Consultants Present (Voting):
Judith Fradkin, M.D., Peter Savage, M.D.

Special Government Employee Consultants Present (Non-voting)
Saul Genuth, M.D.

Guest Speakers Present (Non-Voting):
Steven Nissen, M.D., Robert Califf, M.D., David Nathan, M.D., Robert Ratner, M.D., Hertzel Gerstein, M.D., Professor Rury Holman

FDA Participants:
Gerald Dal Pan, M.D, M.H.S., Robert Temple, M.D., John Jenkins, M.D., Curtis Rosebraugh, M.D., M.P.H., Mary H. Parks, M.D., Hylton Joffe, M.D.

Open Public Hearing Speakers:
Alan Moses, Corporate Vice President and Global Chief Medical Officer for Novo Nordisk,
Robert Vigersky, M.D., President-Elect, Endocrine Society
Farhad Zangeneh, M.D., Private Practice, Clinical Assistant Professor, George Washington University School of Medicine.

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Designated Federal Official:
Paul Tran, R.Ph.

Issue:

The committee discussed the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

The agenda was as follows:

Day One: July 1, 2008

Call to Order and Introductions	**Kenneth Burman, M.D.** Acting Chair, EMDAC
Conflict of Interest Statement	**Paul Tran, R.Ph.** Designated Federal Official EMDAC
Introduction/Background Overview of Day 1 Agenda	**Hylton Joffe, M.D., M.M.Sc.** Lead Medical Officer Diabetes Drug Group FDA/CDER Division of Metabolism and Endocrinology Products

Guest Speaker Presentations

Natural History of Type 2 Diabetes and Diabetes-Related Macrovascular Complications	**David Nathan, M.D.** Director of General Clinical Research Harvard Medical School
Hemoglobin A1c as a Surrogate For Glycemic Control and Microvascular Complications	**Robert Ratner, M.D.** Vice-President of Scientific Affairs, MedStar Research Institute
BREAK	
Evaluating Benefit and Risk in Type 2 Diabetes: Statistical Considerations	**Thomas Fleming, Ph.D.** Professor of Biostatistics University of Washington
Clinical Macrovascular Outcomes with Anti-Diabetic Drugs: What we already Know	**Professor Rury Holman** Professor of Diabetic Medicine Diabetes Trials Unit Director OCDEM, University of Oxford

Lunch

Clinical Macrovascular Outcomes with Anti-diabetic drugs: Ongoing studies	**Hertzel Gerstein, M.D.** McMaster University Department of Medicine Hamilton, Ontario, Canada
Need for Cardiovascular Assessment During the Approval Process for Anti-diabetic drugs	**Steven Nissen, M.D.** Medical Director, Cleveland Clinic, Cardiovascular Coordinating Center, Department of Cardiovascular Medicine

BREAK

Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes	**Robert Califf, M.D.** Vice Chancellor for Clinical Research Duke University

Clarifications/questions from the Panel to the Speakers/Discussion

ADJOURN

The meeting adjourned at approximately 5:30 p.m. on July 1, 2008

Day 2: July 2, 2008

Call to Order and Introductions	**Kenneth Burman, M.D.** Acting Chair, EMDAC
Conflict of Interest Statement	**Paul Tran, R.Ph.** Designated Federal Official EMDAC
Open Public Hearing	**Alan Moses, M.D.** Novo Nordisk **Robert Vigersky, M.D** Present-Elect, Endocrine Society **Farhad Zangeneh, M.D.** Private Practice, Clinical Assistant Professor George Washington University School of Medicine

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FDA Remarks/Introductions to Day 2 Session	**Mary H. Parks, M.D.** Director, FDA/CDER Division of Metabolism and Endocrinology Products

BREAK

Discussion/questions to the Committee

LUNCH

Continued discussion/questions to the Committee

ADJOURN
The meeting adjourned at approximately 4:30 p.m. on July 2, 2008

Questions to the committee:

1. Please discuss what changes you recommend be made to the current design and conduct of Phase 2 and 3 trials for anti-diabetic therapies that might enhance the Agency's ability to detect a cardiovascular (CV) safety signal prior to drug approval. Please include in this discussion the role of:

- an independent, blinded adjudication committee for CV events
- conducting a meta-analysis of safety data from all Phase 2/3 trials
- adequacy of current safety database (e.g., number of patients, duration of exposure) required for drug approval

The committee believed additional assessment for CV risk should be performed in Phase 2 and 3 clinical trials as compared to the present procedures. The committee agreed with using an independent, blinded adjudication committee for CV events. In addition, a majority of the committee members agreed that a meta-analysis of safety data from all Phase 2/3 clinical trials may be beneficial. The majority of the committee members felt there should be a standardization of data to help define safety signals and rule out CV risk.

(Please see transcripts for detailed discussions)

2. Please discuss the following aspects of design and conduct of a long-term cardiovascular trial with an anti-diabetic therapy.

- Should the trial's objective be to show cardiovascular benefit of a new drug or to rule out an unacceptable increase in cardiovascular risk?

  The committee agreed it would be appropriate to conduct clinical trials to rule out an unacceptable increase in cardiovascular risk rather than be required to demonstrate CV benefit. Such a trial should have prespecified specific endpoints (including CV events).

  - An objective to show cardiovascular benefit should be discussed in the context of the fact that conclusive evidence of cardiovascular benefit has not been demonstrated for any of the currently available therapies for type 2 diabetes, despite the fact that several large, long-term trials have been conducted with this objective.

  - If the objective is to rule out a prespecified increase in cardiovascular risk (i.e., a non-inferiority trial), what magnitude of additional risk should be excluded? Is a relative risk (or hazard ratio) of 1.2 to 1.4, observed in several recently-designed cardiovascular safety trials, an acceptable non-inferiority margin?

  The majority of the committee members felt that the hazard ratio of 1.2 to 1.4 is reasonable, given the benefits of lowering HbA1c and decreasing microvascular complications are well-known. There was active discussion by the committee of possible hazard ratios. It was thought to be difficult to specify one size or duration of trial for all drugs. These factors would depend on the type and number of adverse events that had already been demonstrated in the development program and what other benefits the new drug was offering.

  (Please see transcripts for detailed discussions)

- What should the primary endpoint(s) be (e.g., total mortality; composite clinical endpoints such as nonfatal myocardial infarction, CV death and stroke)?

  The committee suggested using hard endpoints, composite clinical endpoints as well as capturing total mortality while keeping individual endpoints (e.g., nonfatal MI, stroke) in mind.

- Please comment on the size and duration of these long-term CV trials.

  The committee recommended trials with the duration between 3 – 5 years although the precise duration may vary based on individual specific considerations.

- What type of patient population should be enrolled (e.g., pre-diabetes, non-diabetics, high-risk for CV events such as patients with acute coronary syndrome)?

  The committee suggested enrolling diabetic patients; including focusing on the higher risk patients in these trials. There was general consensus from the committee not to enroll pre-diabetic and non-diabetic patients into these seminal trials, in part, because the ability to accrue sufficient endpoints would be low. It was recognized that the effect of an individual anti-diabetic medication on the frequency CV events may, in fact, be different in diabetic patients with a high risk of CV events as compared to diabetic patients with a low risk of CV events and in the longer term both groups of patients should be studied.

- As it is unlikely that such a study will be able to randomize study participants to placebo only, please discuss the possible comparator group(s) (e.g., Drug x vs. Drug y; Drug x added to standard of care vs. placebo added to standard of care; Drug x added to standard of care vs. Drug y added to standard of care). For add-on to standard therapy trials, how should standard therapy be defined?

  The majority of the committee members agreed with using Drug X added onto the standard of care vs. Drug Y added to standard of care and using a predefined step-wise approach to add-on therapy. Most committee members felt using placebo only was inappropriate because of the risks of acute and chronic hyperglycemia and the increased risks of microvascular events.

  (Please see transcripts for detailed discussion)

- How should deteriorating glycemic control be defined and handled (include a discussion of escape criteria and how to include patients who have been withdrawn due to worsening diabetes in the efficacy analysis)?

  The majority of the committee members agreed with following current standards for assessing glycemic control and treating hyperglycemia. There was discussion whether patients withdrawn from the study due to worsening diabetes should be included in the efficacy analysis and it was thought these patients should be included and analyzed in the efficacy analysis with appropriate application of statistical methods.

- Should investigators be encouraged to manage blood pressure, lipid profiles, aspirin use, and other cardiovascular factors to current guidelines (which will not necessarily ensure comparability across treatment groups) or should algorithms be used post-randomization to ensure that these risk factors are equalized across treatment groups?

  There was general consensus from the committee members that investigators should be encouraged to manage blood pressure, lipid profiles, aspirin use and other cardiovascular factors to current guidelines and these parameters should be comparable in different groups.
  (Please see transcripts for detailed discussions)

3. It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics **without** such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote **yes/no** requested).

Yes: 14 **No: 2** **Abstain: 0**

If "yes", please discuss when such a study should be conducted?

- Pre-approval
- Post-approval. If a long-term CV trial is required post-approval, please discuss whether this study should be ongoing at the time of approval (i.e., trial already initiated at time of approval).

  The majority of the committee members suggested starting the study during the pre-approval period and completing the study during the post-approval period.

  (Please see transcripts for detailed discussions)

4. As no currently marketed anti-diabetic therapy has established evidence of macrovascular benefit and most have not been tested for lack of cardiovascular harm, please discuss how any suggestion for a requirement for a long-term CV trial in question 3 above for drugs or biologics seeking an indication for the treatment of type 2 diabetes mellitus should be applied to existing anti-diabetic therapies.

The committee does not believe the FDA should require testing against existing agents unless there were specific adverse signals. There was discussion regarding relevant techniques to help detect a possible adverse signal in marketed agents.

(Please see transcripts for detailed discussions)