

---

**Summary Minutes of the  
Endocrinologic and Metabolic Drugs Advisory Committee  
Hilton Hotel Washington DC/Silver Spring, Maryland  
8727 Colesville Road  
Silver Spring, Maryland  
May 19, 2011**

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

**These summary minutes for the May 19, 2011 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on 6/24/2011**

**I certify that I attended the May 19, 2011 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.**

\_\_\_\_\_  
**/s/**  
Paul T. Tran, R.Ph  
Designated Federal Officer, EMDAC

\_\_\_\_\_  
**/s/**  
Allison Goldfine, M.D.  
Committee Acting Chair

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research met on May 19, 2011 at the Hilton Hotel, Washington DC/Silver Spring, Maryland. Prior to the meeting, members and invited consultants had been provided the background material from the FDA and Abbott Laboratories. The meeting was called to order by Allison Goldfine, M.D. (Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph (Designated Federal Officer). There were approximately 175 persons in attendance. There were 3 speakers for the Open Public Hearing session.

**Attendance:**

**Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):**

Eric Felner, M.D., Allison Goldfine, M.D. (Acting Chair), Edward Gregg, Ph.D., Ida Spruill, Ph.D., R.N., (Consumer Representative), Lamont Weide, M.D., Ph.D.

**Endocrinologic and Metabolic Drugs Advisory Committee Members NOT Present:**

Vera Bittner, M.D., Thomas Bersot, M.D., Ph.D., David Capuzzi, M.D., Ph.D., Abraham Thomas, M.D., M.P.H.

**Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-voting):**

Enrico Veltri, M.D. (Industry Representative)

**Temporary Voting Members (Voting):**

Erica Brittain, Ph.D., William Cooper, Ph.D., Susan Heckbert, M.D., Ph.D., William Hiatt, M.D., Sanjay Kaul, M.D., Rebecca Killion (Patient Representative), David Oakes, Ph.D., Terry Smith, M.D.

**FDA Participants (Non-voting):**

Iffat Chowdhury, M.D., Eric Colman, M.D., Solomon Iyasu M.D., M.P.H., Mary H. Parks, M.D., Curtis Rosebraugh, M.D., M.P.H.

**Open Public Hearing Speaker:**

Diana Zuckerman, Ph.D., President, National Research Center for Women & Families, Cancer Prevention and Treatment Fund  
Anne Tybjærg-Hansen, M.D., D.M.Sc, Professor, Chief Physician, Section for Molecular Genetics, Rigshospitalet, Copenhagen University Hospital  
Eliot A. Brinton, M.D., F.A.H.A., F.N.L.A., Cardiovascular Genetics, University of Utah School of Medicine

**Designated Federal Officer:**

Paul Tran, R.Ph

Issue:

*The committee discussed the findings of the Action to Control Cardiovascular Risk in Diabetes-Lipid (ACCORD Lipid) trial as they relate to the efficacy and safety of the approved new drug application (NDA) 22224, TRILIPIX (fenofibric acid) delayed release capsules, manufactured by Abbott Laboratories.*

Call to Order and Introductions

**Allison B. Goldfine, M.D.**

*Acting Chair*

Endocrinologic and Metabolic Drugs Advisory  
Committee (EMDAC)

Conflict of Interest Statement

**Paul T. Tran, R.Ph**

Designated Federal Officer, EMDAC

Introduction/Background

**Eric C. Colman, M.D.**

Deputy Director

Division of Metabolism and Endocrinology Product  
(DMEP)

Office of Drug Evaluation (ODE) II

Office of New Drugs (OND)

Center for Drug Evaluation and Research (CDER)

Food and Drug Administration (FDA)

**GUEST PRESENTATION**

The ACCORD Lipid Trial: In Depth  
Examination of the Results

**Henry Ginsberg, M.D.**

Director Irving Institute for Clinical and  
Translational Research  
Columbia University

Clarification Questions for Guest Speaker

**BREAK**

**SPONSOR PRESENTATION**

**Abbott Laboratories**

Overview

**James Stolzenbach, Ph.D.**

Dyslipidemia Divisional Vice President  
Abbott Laboratories

Data Presentation

**Maureen Kelly, M.D.**

Dyslipidemia Project Director  
Abbott Laboratories

Clinician Perspective

**Peter Jones, M.D.**

Associate Professor  
Baylor College of Medicine

Closing Remarks

**James Stolzenbach, Ph.D.**

Dyslipidemia Divisional Vice President  
Abbott Laboratories

Clarifying Questions from the Committee to Sponsor

**LUNCH**

**FDA PRESENTATION**

Fibrate and Statin Concurrency Analyses

**Vicky Borders-Hemphill, Pharm.D.**  
CDR, USPHS Commissioned Corps  
Drug Utilization Analyst  
Division of Epidemiology II (DEPI)  
Office of Pharmacovigilance and Epidemiology  
Office of Surveillance and Epidemiology (OSE)  
CDER, FDA

Hospitalized Rhabdomyolysis with Combined Statin/Fibrate Use - Observational Evidence Submitted by the Sponsor in the Context of the Trilipix Postmarketing Requirement

**Christian Hampp, B.S. Pharm., Ph.D.**  
Epidemiologist  
Division of Epidemiology I (DEPI)  
Office of Pharmacovigilance and Epidemiology  
OSE, CDER, FDA

Statin-Fenofibrate Combination Therapy after the ACCORD-Lipid Trial

**Iffat Nasrin Chowdhury, M.D.**  
Clinical Reviewer  
Division of Metabolism and Endocrinology Product (DMEP)  
ODE II, OND, CDER, FDA

Clarifying Questions from the Committee to FDA

Open Public Hearing Session

Discussion/Questions to the Committee

**ADJOURNMENT**

**Questions to the Advisory Committee:**

1. Discuss your interpretation of the primary efficacy results from ACCORD-Lipid, specifically as they relate to Trilipix's indication for coadministration with a statin.

*There was a general consensus that the trial did not demonstrate a significant benefit in coadministering fibrates and the statin in this particular group of patients. Many members expressed a concern that the trial was not specifically designed to address the questions at hand regarding coadministration with statin specifically in statin treated patients with high triglyceride- low HDL lipid profile, and thus did not provide adequate data with which to fully evaluate the benefits of coadministration. The committee stressed the need to avoid over- or under-interpretation of the data as it relates to individual subgroups within the trial. Of particular concern was the interpretation of data on two subgroups: women and the population of individuals with more dyslipidemic profiles. There were some concerns regarding accepting one subgroup analysis while*

*rejecting other subgroup analysis. The committee was also concerned about the use of surrogate endpoints for assessing clinical benefit in this trial and in metabolic trials in general, as the measure of clinical benefit is often vague. However, the consistency of results generated from the use of fibrates in this trial with that found in the clinical setting was reassuring.*

*Please see transcripts for detailed discussion.*

2. In the subgroup of women from ACCORD-Lipid, the incidence of MACE in patients randomized to simvastatin plus placebo was 6.6% compared to 9.1% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.01 vs. men).

Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

*The committee was concerned about overstating the significance of this finding derived from subgroup analysis but agreed that the implications should not be ignored. This finding was not seen previously in the fenofibrate monotherapy FIELD trial and there were insufficient number of women in other studies to perform this analysis. They agreed that the difficulty in interpreting the data resulted in much uncertainty.*

*Please see transcripts for detailed discussion.*

3. In the subgroup of patients from ACCORD-Lipid with baseline levels of TG  $\geq$  204 mg/dl and HDL-C  $\leq$  34 mg/dl, the incidence of MACE in patients randomized to simvastatin plus placebo was 17.3% compared to 12.4% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.06 vs. all others ).

Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

*The committee commented that subgroup analysis is always of concern when the trial as a whole is negative. They acknowledged that the findings from this subgroup are of a clinically important magnitude, consistent with other trials and with the current written risks indications. They acknowledged scientific plausibility for the lipid changes with fenofibrate added to statin to only benefit patients with high triglyceride-low HDL, but noted plausibility did not confirm the observation and further noted there were no corrections for multiplicity of testing, and agreed that the findings are not definitive.*

*Please see transcripts for detailed discussion.*

4. Discuss the safety profile of fenofibrate/fenofibric acid, specifically as it relates to Trilipix's indication for coadministration with a statin.

*The committee noted that coadministration did not yield any new safety concerns. Furthermore, they agreed that the reliability of the safety profile generated from the trial*

*is enhanced by the fact that the data is concurrent with years of observational data in the clinical setting. The committee did note that there was an increase in the risk of rhabdomyolysis but agreed that the risk of rhabdomyolysis or other adverse events was small and that the trial did not demonstrate a significant causal relationship between adverse events and coadministration.*

*Please see transcripts for detailed discussion.*

5. Discuss the benefit-risk profile of Trilipix when used in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD equivalent who are on optimal statin therapy to achieve their LDL-C goal.

*The committee felt that this question had been covered during the discussion of the preceding questions and agreed, as they did regarding the interpretation of data on other subgroups, that the data gathered from the trial does not support comprehensive subgroup analyses.*

*Please see transcripts for detailed discussion.*

6. Taking into account all relevant data and levels of evidence:

- A. Should FDA require the conduct of a clinical trial designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, add-on therapy with Trilipix versus placebo significantly lowers the risk for MACE.

**VOTE:      Yes: 13      No: 0      Abstain: 0**

Provide rationale for your recommendation

*The committee voted unanimously to require an additional clinical trial to obtain more comprehensive results that are more supportive of the effectiveness of add-on therapy with Trilipix in lowering the risk for MACE.*

*Please see transcripts for detailed discussion.*

- B. Which action do you recommend FDA take regarding Trilipix's indication for coadministration with a statin:

1. Allow continued marketing of Trilipix's indication for coadministration with a statin without revision of the labeling.

*Three members voted for number 1.*

2. Withdraw approval of Trilipix's indication for coadministration with a statin.

*Four members voted for number 2.*

3. Allow continued marketing of Trilipix's indication for coadministration with a statin with revision of the labeling to incorporate the principal findings from ACCORD-Lipid.

*Six members voted for number 3.*

**VOTE: 1, 2, or 3** and provide rationale for your recommendation.

*Many members indicated that they struggled with their decisions and could have voted for one of the other choices. Some members felt that there is not enough evidence to remove the indication while others felt the lack of evidence demonstrated from the trial warranted the removal of this indication until another trial could be conducted. Six members voted to revise the labeling to incorporate the findings from the ACCORD-Lipid trial in the clinical trial section of the labeling to allow clinicians to make informed treatment decision with their patients.*

*Please see transcripts for detailed discussions.*

*The meeting was adjourned approximately at 4:05 p.m.*