Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
November 2, 2011

Location: Hilton Hotel Washington DC/Silver Spring. 8727 Colesville Road, Silver Spring, Maryland 20910.

Topic: The committee discussed supplemental new drug applications (sNDA) 21-687 and 21-445, VYTORIN (ezetimibe/simvastatin) and ZETIA (ezetimibe) tablets, respectively, MSP (Merck/Schering-Plough) Singapore Company, LLC. The proposed indication of ZETIA in combination with simvastatin or VYTORIN is to reduce major cardiovascular events in patients with chronic kidney disease based on the results of the Study of Heart and Renal Protection (SHARP).

These summary minutes for the November 2, 2011 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on 01/16/2012

I certify that I attended the November 2, 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/
Abraham Thomas, M.D., M.P.H.
(Committee Chair)

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 2, 2011

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on November 2, 2011. The verbatim transcript will be available in approximately six weeks, send to the Division of Metabolism and Endocrinology Products and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm252891.htm

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

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA Center for Drug Evaluation and Research, met on November 2, 2011 at the Hilton Washington DC/Silver Spring, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Merck & Co., Inc. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Chair), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 150 people in attendance. There was one Open Public Hearing speaker.

Issue: The committee discussed supplemental new drug applications (sNDA) 21-687 and 21-445, VYTORIN (ezetimibe/simvastatin) and ZETIA (ezetimibe) tablets, respectively, MSP (Merck/Schering-Plough) Singapore Company, LLC. The proposed indication of ZETIA in combination with simvastatin or VYTORIN is to reduce major cardiovascular events in patients with chronic kidney disease based on the results of the Study of Heart and Renal Protection (SHARP).

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Erica Brittain, Ph.D.; Eric Felner, M.D.; Edward Gregg, Ph.D.; Ellen Seely, M.D.; Ida Spruill, Ph.D., R.N. (*Consumer Representative*), Abraham Thomas, M.D., M.P.H. (*Chair*), Lamont Weide, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Vera Bittner, M.D.; David Capuzzi, M.D., Ph.D.

Acting Industry Representative to the Committee (Non-voting)
Edward B. Nelson, M.D., Ph.D. (*Acting Industry Representative*)

Temporary Members (Voting):
Susan Broyles, R.N. (Patient Representative), David Gordon, M.D., Ed Hendricks, M.D.; William Hiatt, M.D.; Lawrence Hunsicker, M.D.; Michael Lauer, M.D.; Julia Lewis, M.D.; Emil Paganini, M.D.; Robert Smith, M.D.

FDA Participants (Non-voting):
Eric Colman,M.D.; Mary H. Parks, M.D.; Curtis Rosebraugh, M.D., M.P.H.; James Smith, M.D., M.S.

Designated Federal Officer: Paul Tran, R.Ph

Open Public Hearing Speaker: Josef Coresh, M.D., National Kidney Foundation

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Abraham Thomas, M.D., M.P.H., FACP** Chair, 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 Products (DMEP) Office of Drug Evaluation (ODE) II Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER) Food and Drug Administration (FDA)
SPONSOR PRESENTATION	**Merck & Co., Inc.**
Introduction	**Jeffrey Tucker, M.D.** Regulatory Affairs Merck & Co., Inc.
Background and Rationale Study Results	**Professor Colin Baigent** SHARP Chief Investigator University of Oxford, United Kingdom
Key Design Issues	**Professor Rory Collins** University of Oxford, United Kingdom
Merck's Perspective on SHARP	**Thomas Musliner, M.D.** Clinical Research

	Merck & Co., Inc.
Clarifying Questions from the Committee	
BREAK	
FDA PRESENTATION	
Review of the SHARP Efficacy and Safety Data	**James P. Smith, M.D., M.S.** Clinical Reviewer DMEP, ODE II, OND, CDER, FDA
Clarifying Questions from the Committee	
LUNCH	
Open Public Hearing Session	
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Advisory Committee:

1. In the Study of Heart and Renal Protection (SHARP) trial, after a median follow-up of 4.9 years, 639 (15.2%) of 4193 Vytorin (10 mg ezetimibe/20 mg simvastatin)-treated patients and 749 (17.9%) of 4191 placebo-treated patients had a major vascular event (MVE), defined as cardiac death, myocardial infarction, any stroke, or revascularization (excluding dialysis access-related procedures); risk ratio of 0.84 (0.75, 0.93), 95% confidence interval (CI), log-rank p=0.001.

The risk ratios for the individual components of the primary composite endpoint are shown in the following table.

	Vytorin 10/20 N=4193	Placebo N=4191	Risk Ratio (95% CI)	p-value
MVE	639 (15.2%)	749 (17.9%)	0.84 (0.75, 0.93)	0.001
Cardiac death	235 (5.6%)	249 (5.9%)	0.94 (0.79, 1.13)	0.51
Non-fatal MI	128 (3.1%)	147 (3.5%)	0.86 (0.68, 1.10)	0.22
Any Stroke	148 (3.5%)	192 (4.6%)	0.77 (0.62, 0.95)	0.02
Revascularization	261 (6.2%)	327 (7.8%)	0.79 (0.67, 0.92)	0.004

In a subgroup analysis by baseline dialysis status, the risk ratio for MVE in the Vytorin 10/20 mg group versus the placebo group was 0.77 (0.67, 0.88) in pre-dialysis patients,

and the risk ratio in the Vytorin 10/20 mg group versus the placebo group was 0.94 (0.80, 1.11) in dialysis patients. The interaction p-value was 0.07.

Provide your interpretation of:

a. the primary efficacy result for MVE

Committee Discussion: *There was a general consensus from the committee that ezetimibe/simvastatin demonstrated efficacy with regard to the primary endpoint in the SHARP trial given the 16% reduction in the risk of a major vascular event (MVE) compared with placebo. Please see the transcript for details of the committee's discussion.*

b. the treatment effects for the individual components of the MVE endpoint

Committee Discussion: *Some members indicated that the trial was not designed to evaluate each of the individual components separately, thus it would not be prudent to evaluate the findings as such. Overall, the committee agreed that the treatment effects on the individual components were all going in the same direction as the primary result. There was a concern that revascularization was driving the results, but the committee noted that even if revascularization was removed from the primary composite endpoint, the results would still favor ezetimibe/simvastatin compared with placebo. Please see the transcript for details of the committee's discussion.*

c. the pre-dialysis versus dialysis subgroup result for MVE

Committee Discussion: *Some committee members noted that the best estimate of the treatment effect for each of the subgroups is the overall estimate of the treatment effect for the entire study population. However, other members stated that the results of the SHARP trial suggest that ezetimibe/simvastatin is likely beneficial in pre-dialysis patients but not in dialysis patients with regard to reducing MVE. Please see the transcript for details of the committee's discussion.*

2. Discuss whether you believe that the lack of lipid inclusion criteria in SHARP (e.g., low-density lipoprotein cholesterol [LDL-C]) was appropriate.

Committee Discussion: *The majority of the committee agreed that the lack of lipid inclusion criteria in the SHARP trial was appropriate. Some noted that previous statin trials have demonstrated benefit irrespective of baseline LDL-C. The committee commended the study for its inclusion of subjects regardless of the baseline LDL-C level, which improves generalizability.*
Please see the transcript for details of the committee's discussion.

3. The standard accepted definition of chronic kidney disease (CKD), according to National Kidney Foundation guidelines, is evidence of kidney damage (including proteinuria) or glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for $\geq$ 3 months. The inclusion criteria for SHARP were age > 40 years and a) pre-dialysis: plasma or serum

creatinine ≥150µmol/L (≥1.7 mg/dL) in men or ≥130µmol/L (≥1.5 mg/dL) in women, as measured at the most recent routine clinic visit AND at the SHARP screening visit or b) on dialysis (hemo or peritoneal).

These criteria led to approximately 94% of pre-dialysis SHARP participants having an estimated GFR <45 mL/min/1.73m^2. According to estimates based on the National Health and Nutrition Examination Survey (NHANES), individuals with an estimated GFR <45 mL/min/1.73m^2 represent 15% of the entire CKD population in the United States.

Discuss whether you believe that the criteria used for enrollment of pre-dialysis patients into SHARP provided an appropriate study population to generalize the results from SHARP to the population of all patients with pre-dialysis chronic kidney disease.

Committee Discussion: *The committee agreed that the inclusion criteria led to the recruitment of patients from a population for whom adequate data were not previously available. The committee did not have concerns with extrapolating the results to patients with less severe CKD. Some members expressed concern that only 4% of the patients enrolled are from the U.S. and that African Americans were underrepresented, particularly because African Americans have a disproportionately high incidence rate of CKD. Please see the transcript for details of the committee's discussion.*

4. Provide your interpretation of the safety data from the SHARP trial, in particular, the findings related to muscle, liver, and cancer.

Committee Discussion: *In general, the committee agreed that there were no major safety concerns and that the muscle and liver changes were predictable based on the pattern of changes seen previously with statin use. Some members noted that there could be an imbalance in the muscle findings; thus, this should be followed closely in the future. There was a consensus that it is difficult to interpret the data regarding cancer from a single study, but that SHARP did not appear to raise new safety concerns. The totality of data should be considered, such as the published analysis by Peto et al. that used interim data from both SHARP and IMPROVE-IT. Please see the transcript for details of the committee's discussion.*

5. Do the available efficacy and safety data provide substantial evidence to support approval of Vytorin 10/20 mg for the prevention of major vascular events in patients with:

a. pre-dialysis chronic kidney disease?

Vote: Yes: 16 No: 0

b. end-stage renal disease receiving dialysis?

Vote: Yes: 6 No: 10

Please provide your rationale for each vote.

Committee Discussion: *The committee unanimously agreed that there was substantial evidence to support approval of Vytorin (ezetimibe/simvastatin) 10/20 mg for the prevention of major vascular events (MVE) in patients with pre-dialysis chronic kidney disease. However, the majority of the committee concurred that the data do not provide substantial evidence to support approval Vytorin 10/20 mg specifically for end-stage renal disease patients receiving dialysis. Those who voted "No" for question #5b indicated that this subgroup analysis did not demonstrate significant efficacy, although some noted that they would not specifically exclude dialysis patients from the indication. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 4:20 p.m.