

COVINGTON & BURLING LLP

1201 PENNSYLVANIA AVENUE NW WASHINGTON
WASHINGTON, DC 20004-2401 NEW YORK
TEL 202.662.6000 SAN FRANCISCO
FAX 202.662.6291 LONDON
WWW.COV.COM BRUSSELS

PATRICK S. DAVIES
TEL 202.662.5274
FAX 202.778.5274
PDAVIES@COV.COM

September 4, 2008

CONFIDENTIAL TREATMENT REQUESTED

DELIVERED BY HAND

The Honorable John D. Dingell
Chairman
United States House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

The Honorable Bart Stupak
Chairman
United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
Washington, DC 20515-6115

Re: Request to Schering-Plough Corporation and Merck & Co., Inc.

Dear Chairman Dingell and Chairman Stupak:

This letter constitutes an initial response on behalf of Schering-Plough Corporation (“Schering-Plough”), Merck & Co., Inc. (“Merck”), and Merck/Schering-Plough Pharmaceuticals (collectively, “M/SP Pharmaceuticals”) to your requests dated August 21, 2008 for certain information and documents related to the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study.

M/SP Pharmaceuticals will continue to work diligently to gather further information and documents in response to these requests. We request that the Committee treat this letter and any subsequent information provided in response to the Committee’s August 21 requests as confidential, and that the Committee provide us with notice and an opportunity to object prior to making any portion of our response public.

Please see our responses to your specific requests below.

The Honorable John D. Dingell
The Honorable Bart Stupak
September 4, 2008
Page 2

Requests for Information

- 1. How much is Dr. Peto and his institute, the Clinical Trials Service Unit of Oxford University, being paid directly or indirectly by Merck, Schering-Plough, the joint venture, or their agents, attorneys, or lobbyists to conduct the SHARP trial?**

Merck, on behalf of the Merck/Schering-Plough joint venture, has a contract with Oxford University ("Oxford") for the conduct of the SHARP study, which is expected to randomize about 9,000 subjects. The contract provides that the study will be led by investigators affiliated with Oxford University's Clinical Trials Service Unit (CTSU) (Dr. Colin Baigent, Dr. Martin Landray and Professor Rory Collins), and that the CTSU will serve as an international coordinating center for SHARP. The CTSU is internationally recognized as a leading medical research institute focusing on large-scale clinical trials and epidemiological studies of chronic diseases such as cancer, heart attack and stroke. The CTSU has decades of experience in cancer epidemiology, in vascular and other trials, and in collaborative meta-analyses of other trials.

Under the contract with Oxford, Merck has agreed to pay a total of £ 34,789,231 over a seven-year period for the entire conduct of the study. These funds, which under the contract are allocated by Oxford, cover among other things the cost of clinical investigators, researchers, laboratory technicians, nurses and other staff at over 300 sites in about 20 countries, as well as the cost of meetings and travel, laboratory work, computers and equipment, and administrative overhead.

Counsel for M/SP Pharmaceuticals made clear to Committee staff as early as January 24, 2008, in the initial briefing on issues related to the ENHANCE study, that SHARP was one of several ongoing company-sponsored studies of Vytorin (along with SEAS and IMPROVE-IT). In addition, counsel for the companies provided detailed information on Dr. Peto in a July 22, 2008 briefing to Committee staff. As discussed in that briefing and as detailed in the transcript of the July 21, 2008 public press conference on the SEAS study (provided to staff on July 22), Dr. Peto is co-director of the CTSU, a Professor of Medical Statistics and Epidemiology at Oxford University, and a widely recognized leader in the field of cancer epidemiology. In his role as a leading statistician affiliated with the CTSU, Dr. Peto performed a meta-analysis of the cancer data from these three studies and submitted a report on his conclusions to FDA and European regulatory authorities on July 21.

In the July 22 briefing, counsel for the companies discussed Dr. Peto's report with Committee staff and stated that Dr. Peto prepared the report independently. Counsel also pointed out to staff the CTSU's statement, in its July 21 press release, that "[a]lthough

The Honorable John D. Dingell
The Honorable Bart Stupak
September 4, 2008
Page 3

CTSU is conducting the SHARP trial, it is doing so independently of the source of funding, and has a policy of not accepting honoraria or consultancy fees.”

In your letter of August 21, you acknowledge this July 22 briefing but express concern that Dr. Peto’s report “may not be as ‘independent’ as expected,” given that the CTSU is conducting the SHARP study and the SHARP study is funded by the companies.

Any suggestion that Dr. Peto’s report is biased or otherwise not independent is wholly without basis. In fact, Dr. Peto’s scientific conclusions are consistent with those of other independent third parties. The FDA stated in its “Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia),” posted on www.fda.gov on August 21, 2008, that the agency is investigating “a report from the SEAS trial . . . of a possible association between the use of Vytorin . . . and a potentially increased incidence of cancer,” but that “*to date, [the] findings in the SEAS trial plus the interim data from ongoing trials should not prompt patients to stop taking Vytorin or any other cholesterol-lowering drug*” (emphasis added). Also consistent with Dr. Peto’s report are the recommendations stated in a recent issue of *The Medical Letter on Drugs and Therapeutics* (August 25, 2008), a nonprofit publication aimed at practitioners. The *Medical Letter* noted the concerns raised by the SEAS cancer figures, but recommended that pending the conclusion of large ongoing clinical-endpoint studies, “drug treatment of hypercholesterolemia should continue to aim at achieving LDL-C levels below 100 mg/dL in high-risk patients and, if possible, below 70 mg/dL for patients at very high risk. For patients who cannot achieve these goals with a safe dose of statin alone, adding another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe continues to be a reasonable option.” As detailed in the transcript of the SEAS press conference on July 21, prominent cardiovascular specialists and cancer epidemiologists including Dr. Eugene Braunwald of Harvard Medical School, Dr. Robert Califf of Duke University, Dr. Terje Pedersen of Ulleval University Hospital in Oslo, and Dr. Rory Collins at Oxford all agree that ongoing studies of Vytorin such as SHARP and IMPROVE-IT should be continued. Finally, a *New England Journal of Medicine* editorial entitled “Ezetimibe and Cancer -- An Uncertain Association,” published online on September 2, 2008, discussed the uncertainty created by the SEAS cancer figures but concluded that “[i]t is appropriate that SHARP and IMPROVE-IT continue.”

Finally, we note that no attorneys or lobbyists of Merck, Schering-Plough, or M/SP Pharmaceuticals have paid any funds to conduct the SHARP trial or any other clinical trial sponsored by the companies.

The Honorable John D. Dingell
The Honorable Bart Stupak
September 4, 2008
Page 4

2. Which data referenced above (SEAS or CTSU) are the correct data from which health care providers should base their clinical judgment?

This question references two press releases issued on July 21: one issued by the SEAS Steering Committee (headed by Dr. Terje Pedersen) entitled “Results From the SEAS Study,” and one issued by the CTSU entitled “Independent Analyses of the SEAS, SHARP and IMPROVE-IT Studies of Ezetimibe.” These press releases were prepared by the SEAS Steering Committee and the CTSU respectively. Therefore, we cannot comment on how information was selected for inclusion in these releases, including (as noted in your letter) the inclusion of a *p*-value related to cancer events in the SEAS release but not the CTSU release.

The SEAS Steering Committee’s press release stated that 93 patients in the SEAS treatment arm and 65 patients in the placebo arm “were recorded with a serious adverse event attributed to cancer.” The CTSU release stated that “total cancer incidence” in the SEAS trial was “102 vs. 67 cancer cases” in the treatment arm vs. placebo. As detailed in the transcript of Dr. Peto’s discussion at the July 21 public press conference on SEAS (which we provided to staff on July 22), the 93 vs. 65 figure refers to patients who were reported as developing cancer while participating in the study “or up to 15 days after stopping.” After that time, reports of serious adverse events were no longer being solicited, but reports of death were. Therefore a cancer event might not be captured unless the patient died. The 102 vs. 67 figure captures an additional 11 cancers that were reported in patients who died after the active solicitation of adverse events had concluded (9 among subjects from the treatment group and 2 among subjects in the placebo arm).

Dr. Terje Pedersen, the SEAS lead investigator, presented the SEAS results to the scientific community on September 2, 2008 at the European Society of Cardiology Conference in Munich, Germany. The companies expect that health care providers will make clinical judgments in light of all available data, including the data presented to date by the SEAS investigators and the CTSU; FDA’s August 21 “Early Communication” described above; and the articles on ezetimibe studies, including SEAS, that were published online in the New England Journal of Medicine on September 2.

3. What are the complete data for the number of randomized patients, as well as the number of cancers and cancer deaths, in each treatment arm of the SEAS, SHARP, and IMPROVE-IT trials?

The SEAS trial randomized 1873 patients into two treatment arms: an active treatment arm (944 patients) and a placebo arm (929 patients). The figures for the total number of patients with cancer in SEAS are set forth above in the response to question #2. The reported number of cancer deaths among study subjects was 39 in the active treatment arm and 23 in the placebo arm.

The Honorable John D. Dingell
The Honorable Bart Stupak
September 4, 2008
Page 5

Because the SHARP and IMPROVE-IT trials are ongoing and remain blinded, the companies do not have access to unblinded data from these trials beyond the data presented to the public at the July 21 press conference. We provided copies of the transcript of that press conference and the accompanying slide presentations to Committee staff over one month ago.

4. **Upon completion of the SHARP and IMPROVE-IT trials, will Merck, Schering-Plough, or its joint venture, conduct another full analysis of the relationship between Vytorin and cancer and cancer deaths based upon complete versus preliminary data?**

The companies, the Steering Committees, and the data safety monitoring boards for these studies will determine what additional analyses on the incidence of cancer and cancer deaths are appropriate upon the completion of the SHARP and IMPROVE-IT trials based on the data and state of scientific knowledge available at that time.

Requests for Records

M/SP Pharmaceuticals is producing with this letter a copy of the SHARP contract (with amendments) and its associated schedules. These materials bear Bates stamp numbers MSPP 356066 - MSPP 356215 and are responsive to the Committee's August 21 request for "[a]ny and all contracts or agreements between Merck, Schering-Plough, or the joint venture and Dr. Peto or the Oxford University Clinical Trials Service Unit for any work related to Vytorin or for any other reason."

M/SP Pharmaceuticals is working diligently to identify other records responsive to the Committee's August 21 requests and, as agreed to by Committee staff, will make those records available to the Committee on a rolling basis. We also have been in discussions with Committee staff concerning the scope of the requests for records in the Committee's August 21 letter and look forward to a continuing dialogue.

Sincerely,

By:


Patrick S. Davies
*Counsel to Schering-Plough
Corporation, Merck & Co., Inc., and
Merck/Schering-Plough
Pharmaceuticals*

Enclosures