January 25, 2008

ENHANCE Chronology

Late 2000 / Early 2001

- Discussion of ENHANCE protocol as part of the ZETIA® (ezetimibe) clinical development program. Trial is designed to measure intima media thickness (IMT) using external ultrasound equipment. Consideration is also given to conducting an additional trial using intravascular ultrasound (IVUS) technology for imaging, but the decision is made subsequently not to conduct an IVUS trial. Approval of ZETIA is being sought on the strength of biomarkers (lowering total cholesterol, LDL, etc.). ENHANCE is intended as an intermediate post-market study with surrogate endpoints (relating to atherosclerosis), and it will be part of a broader development program with larger and longer term post-market studies focused on key cardiovascular clinical outcome endpoints. These include SEAS (patients with aortic stenosis) and SHARP (patients with chronic kidney disease), as well as IMPROVE-IT (discussed below).

April 2002

- ENHANCE protocol is finalized. The study will compare ezetimibe/simvastatin 10/80 mg versus simvastatin 80 mg in patients with Heterozygous Familial Hypercholesterolemia (HeFH), a rare condition that affects approximately 0.2 percent of the population. The protocol defines the primary endpoint as the change in IMT seen in B-mode ultrasound images of the carotid artery, measured as the average far wall IMT of the right and left common carotid artery (CCA), carotid bulb, and internal carotid arteries on a per patient basis, between baseline and endpoint. (The study also involves analysis of B-mode images of the femoral arteries, a secondary endpoint, and M-mode ultrasound images of the common carotid artery, an exploratory endpoint, but the discussion that follows relates to B-mode carotid images and the primary endpoint.)

June 2002

- First study site for ENHANCE is initiated.

August-September 2002

- ENHANCE is announced at the 24th Congress of the European Society of Cardiology, which was held between August 31 and September 4, 2002, in Berlin.

October 2002

- First patient randomized in ENHANCE.

- FDA approves ZETIA. ZETIA is a lipid-lowering compound approved on the basis of clinical studies showing that it reduces total cholesterol (total C), low-density lipoprotein (LDL) cholesterol, and apolipoprotein B (Apo B) in patients with hypercholesterolemia. Unlike statins, another class of lipid-lowering drug, which include simvastatin and which inhibit cholesterol synthesis in the liver, ZETIA inhibits the absorption of dietary cholesterol in the small intestine and reabsorption of cholesterol in the bile.

2002-2004

- Patient enrollment and study visits continue. The last patient entered the study in April 2004.

July 2004

- FDA approves VYTORIN® (ezetimibe/simvastatin), on the basis of clinical studies showing that it reduces total C, LDL-C, Apo B, and TG, and increases HDL-C, through dual inhibition of cholesterol synthesis absorption and synthesis in patients with hypercholesterolemia.

February 2005

- ENHANCE methods article published in the *American Heart Journal*. This article, authored by Kastelein (the principal investigator), Philip Sager (then at Schering-Plough), Eric de Groot (a medical director working for the principal investigator), and Enrico Veltri (Schering-Plough) describes the design and the rationale for the study.

Summer through End of 2005

- AHA Fall 2006 meeting is targeted for presentation of results, based on initiation of image reads at the reading laboratory in 2004 and anticipated completion of reads in May 2006.

- In September 2005, Merck and Schering-Plough (MSP) register (on the NIH website) the IMPROVE-IT study, which is a post-market double-blind study comparing VYTORIN and simvastatin. The primary objective of IMPROVE-IT is to evaluate the clinical benefit of VYTORIN, compared with simvastatin, defining clinical benefit as the reduction in the risk of the occurrence of the composite endpoint of cardiovascular death, major coronary events, and stroke. Trial will continue until a minimum of 5,250 subjects have an primary endpoint event and each patient is followed for a minimum of 2.5 years. Enrollment begins immediately, study start date is February 2006, and estimated study completion date is January 2011.

- Schering-Plough biostatisticians begin conducting routine data quality reviews of the initial blinded ENHANCE data, in anticipation of the completion of the study. These statistical reviews are performed for quality control/quality assurance purposes. The biostatisticians remain blinded as to treatment arm. In other words, they do not know whether a particular patient received ezetimibe/simvastatin or simvastatin, and they do not know how the group receiving ezetimibe/simvastatin compares to the group receiving simvastatin. The biostatisticians are unmasked as to patient and time sequence (i.e., they know that they are looking at the data for one particular patient and the proper time sequence for those data). The reviews are conducted batch by batch, and they identify concerns about the quality of the data based on the observations of results that appear biologically implausible. The initial concerns are raised by the review of the first batch and later confirmed by the review of the second and third batches.

January through April 2006

- The study team considers remedial measures to address data quality concerns, including a modified ultrasound image reading process for the study (referred to as "synchronous" reading) and additional quality control steps. Synchronous reading meant the reader at the laboratory would have the ability to see all images at the same time for one patient and artery segment, in order to ensure that the same anatomical segment was measured each time. The reader would be blinded as to treatment arm and time

sequence of patient visit. The reader would not know whether a particular patient had received ezetimibe/simvastatin or simvastatin. In March 2006, the Cholesterol Development Committee (CDC), a committee of the joint venture, reviews the data quality problems apparent from the Schering-Plough biostatisticians' review of data and the proposed remedial plan, including synchronous reading.

- In March and April 2006, the director of an alternate reading laboratory is contacted regarding his laboratory's qualifications, and his feedback is sought on a selection of images from four patients. The laboratory is not retained, but the consultant will eventually serve as one of the expert panelists in November 2007.

- In April 2006, the CDC approves the plan to read images using the synchronous reading process and to adopt other quality control steps. It approves a six-week pilot study (involving the original reading laboratory and an alternate laboratory) to assess the reproducibility and quality of reader measurements, at the end of which one lab will be selected to perform readings for the entire study.

- Delays are incurred as a result of installation of new computer equipment required for synchronous reading and the training of readers on the new reading procedures.

- April 2006, last patient last visit in ENHANCE study.

- It is recognized that the AHA meeting deadline will not be met, and the ACC March 2007 meeting is identified as the target for presentation of the data.

<u>June 2006</u>

- Six-week pilot synchronous reading study begins (referred to as the "Vanguard" study).

<u>August 2006</u>

- The CDC reviews the results of the pilot synchronous reading study and selects the original laboratory to perform the readings for the entire study going forward.

<u>August through December 2006</u>

- Reading of images using the synchronous process continues. Considerable effort is made to meet early January deadline for submission of abstract for presentation of study results at March 2007 ACC meeting.

- In December 2006, primary reading process completed at the laboratory. Initial statistical review of the final received dataset (still blinded as to treatment arm) indicates that data quality problems still exist.

- Two primary data issues are raised. The first is significant fluctuations in IMT (in individual patients) within short periods of time and over time, which would not be expected to occur in nature, and which some have referred to as "biologically implausible" data. The other primary issue relates to "missing" data, essentially data gaps because specific images were rejected for quality reasons — for example, because the sonographer inaccurately captured the image, or because the reader deemed it outside the protocol or found it unreadable.

January 2007

- Hiring of two independent contractors (a project manager and a data manager) to work with the laboratory on data management issues. Advice also sought from an independent consultant, who reviews the data and issues a report on January 26. Report considers data quality similar to that in other IMT trials, but acknowledges desire to improve data quality and recommends a number of ways to improve the data and reduce "missingness." This consultant will serve as one of the expert panelists in November 2007.

- Schering-Plough begins the process of "querying" outlier data based on objectively defined criteria.

February through June 2007

- Independent contractors perform assessment of data and quality control processes at the core laboratory. Procedures put in place to address data management concerns and institute an outlier data query process, with the assistance of an expert consultant.

- Sponsor and consultants visit reading lab periodically to monitor activities.

- Efforts to address missing images are tried as a pilot exercise, including through a so-called neighboring, or adjacent, image analysis. These efforts are determined not to be a productive approach.

- The deadline for the March 2007 ACC meeting is not met, and the AHA November 2007 meeting is targeted for presentation of the data.

July 2007

- Outlier querying process completed and reviewed. Data quality problems still exist. Data remain blinded as to treatment arm.

August 2007

- MSP reviews data quality issues with the principal investigator and decides to convene an independent expert panel. Five experts, chosen primarily from a list supplied by the principal investigator, agree to sit on the panel. Principal investigator recuses himself from the meeting itself in order to help ensure that the panel members feel open to provide critical observations concerning the study, the principal investigator, and the core reading laboratory affiliated with the principal investigator.

November 2007

- The deadline for the November AHA meeting is not met, and the March 2008 ACC meeting is targeted for presentation of the data.

- On November 16, independent expert panel convenes. Consensus reached that despite significant methodological issues, total re-reading of the ENHANCE images is not recommended, since the assumption is that re-reading will not resolve problems in the ultrasound images themselves. Consensus also reached that the common carotid artery (CCA) provided the most reliable and consistent measurements in ENHANCE and that the sponsor should therefore consider changing the primary study endpoint to measurements of the CCA.

- On November 19, the joint venture issues a press release describing the expert panel's recommendations.

- On November 26, the CDC approves changing the primary endpoint and amending the study protocol. The original primary endpoint (the mean change in IMT measured at the three sites in the carotid arteries) would have been presented as a secondary endpoint.

- On November 30, MSP meets with US and ex-US expert advisory boards. Some members of both boards express the view that the primary endpoint should not be changed.

December 2007

- On December 11, MSP announces that it will not change the primary endpoint in the ENHANCE study. The primary endpoint and the protocol are not changed.

- Data quality control reviews conclude and transmission of final carotid artery data from the imaging reading lab to the sponsors.

- ENHANCE study is unblinded on December 31 to a small group of scientists.

January 2008

- Additional personnel at the companies were made aware of the findings during the first two weeks of January, 2008.

- On January 14, MSP issues press release announcing results from ENHANCE study. There was no statistically significant difference between the treatment groups on the primary endpoint. There was also no statistically significant difference between the treatment groups on each component of the primary endpoint, including the common carotid artery (CCA). The overall incidence of treatment-related adverse-events, serious adverse events, and adverse events leading to discontinuation were generally similar between treatment groups. The safety profiles of the two products (VYTORIN and simvastatin) were generally similar and consistent with their approved labeling. There was a significant difference in LDL cholesterol lowering between the treatment groups: 58 percent lowering at 24 months on VYTORIN 10/80, compared to 41 percent lowering at 24 months on simvastatin 80 mg.

- Submission of "Late Breaker Place Holder Abstract" (a shell abstract, without the trial results) to ACC to reserve a spot for March 2008 meeting of the ACC.

# # #