Investigational data from IMPROVE-IT to be announced in Featured Clinical Research Session II

Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that new data from two trials of the company’s cardiovascular medicines will be presented at the 2015 American College of Cardiology Annual Scientific Sessions (ACC.15), March 14-16 in San Diego. In all, eleven data presentations from company-sponsored studies will be presented at ACC.15, including new data from the investigational IMPROVE-IT (IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial) study of VYTORIN (ezetimibe/simvastatin) and exploratory sub-analyses of the TRA 2ºP TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial of ZONTIVITY (vorapaxar).

“The American College of Cardiology's 64th Annual Scientific Sessions provide an opportunity for Merck to share new data from two of the largest cardiovascular outcomes trials of recent years,” said Dr. Daniel Bloomfield, vice president, Cardiovascular Diseases, Merck Research Laboratories. “We are pleased to share new data from these important studies with the scientific community.”

The primary results from the IMPROVE-IT trial of VYTORIN, which combines simvastatin with the non-statin ZETIA® (ezetimibe), were presented in November 2014. VYTORIN and ZETIA are indicated for use along with a healthy diet to reduce elevated LDL cholesterol in patients with hyperlipidemia. The current U.S. Prescribing Information for VYTORIN and ZETIA states that the effect of ezetimibe on cardiovascular morbidity and mortality, alone or
incremental to statin therapy, has not been determined.

The TRA 2°P TIMI 50 study of ZONTIVITY (vorapaxar) supported the May 2014 approval of that medicine for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or in patients with peripheral arterial disease (PAD). In TRA 2°P TIMI 50, ZONTIVITY was shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke and urgent coronary revascularization. The U.S. Prescribing Information for ZONTIVITY includes a boxed warning regarding bleeding risk, which states that ZONTIVITY is not for use in patients with a history of stroke, transient ischemic attack (TIA) or intracranial hemorrhage (ICH), or active pathological bleeding. Antiplatelet agents, including ZONTIVITY, increase the risk of bleeding, including ICH and fatal bleeding.

The following data will be presented at ACC.15:

**IMPROVE-IT Data in Featured Clinical Research Session II**

- (Abstract #414-03) Reduction in Total (First and Recurrent) Cardiovascular Events with Ezetimibe/Simvastatin compared with Simvastatin Alone post-Acute Coronary Syndromes in the IMPROVE-IT Trial. S. Murphy
  - Monday, March 16 12:30 PM-12:45 PM PT. Location: Room 6E.

**TRA 2°P TIMI 50 Trial**

- (Abstract #1131M-11) Vorapaxar and Acute Limb Ischemia: Insights from the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-TIMI 50 Trial. A. Gutierrez
  - Saturday, March 14; 11:00 AM-11:10 AM PT. Location: Vascular Medicine Moderated Poster Theater, Poster Hall B1.
- (Abstract #905-04) The role of Vorapaxar in Patients with Coronary Artery Bypass Grafting: Findings from the TRA 2P-TIMI 50 Trial. E. Kosova
  - Sunday, March 15; 10:57 AM-11:08 AM PT. Location: Room 7B.
- (Abstract #1131M-05) Vorapaxar and Peripheral Revascularization: Insights from the TRA2P-TIMI 50 Trial. I. Gilchrist
- (Abstract #1131M-03) Statin Intensity and Outcome in Patients with Peripheral Artery Disease: Insights from the TRA2P-TIMI 50 Trial. I. Gilchrist
  - Saturday, March 14; 10:00 AM-10:10 AM PT. Location: Vascular Medicine Moderated Poster Theater, Poster Hall B1.
Additional Merck-sponsored Data

- (Abstract #1125M-09) Baseline LDL-C and Clinical Outcomes with Addition of Ezetimibe to Statin in 18,144 Patients Post ACS. R. Giugliano
  - Saturday, March 14; 10:45 AM-10:55 AM PT. Location: Acute Coronary Syndromes Moderated Poster Theater, Poster Hall B1.

- (Abstract #1125M-07) Risk Stratification for Cardiovascular Events in the IMPROVE-IT Trial. E. Bohula
  - Saturday, March 14; 10:30 AM-10:40 AM PT. Location: Acute Coronary Syndromes Moderated Poster Theater, Poster Hall B1.

- (Abstract #1133M-05) Cholesterol in Remnant-Lipoproteins as Measured by Different Methods. P. Toth
  - Saturday, March 14; 10:15 AM-10:25 AM PT. Location: Stable Ischemic Heart Disease Moderated Poster Theater, Poster Hall B1.

  - Sunday, March 15; 9:45 AM-10:30 AM PT. Location: Poster Hall B1.

- (Abstract #1211-119) Low LDL-Cholesterol Target Achievement in Statin-Treated Patients in Clinical Practice in China and Europe: Results of the Dyslipidemia International Study (DYSIS) A. Gitt

- (Abstract # 1261-347) Effect of Beta-Blockade on Cardiovascular Event Rates in Patients with Asymptomatic Aortic Stenosis C. Bang
  - Monday, March 16; 9:45 AM-10:30 AM PT. Location: Poster Hall B1.

About VYTORIN® (ezetimibe/simvastatin)

VYTORIN contains ezetimibe and simvastatin. VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, and non-HDL cholesterol, and to increase HDL cholesterol in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia when diet alone is not enough.

The Prescribing Information for VYTORIN states that no incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. VYTORIN is not indicated to reduce cardiovascular events in patients who have presented with acute coronary syndromes.

VYTORIN (ezetimibe/simvastatin) should not be taken with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin,
clarithromycin, telithromycin, nefazodone, and cobicistat-containing products); or with gemfibrozil, cyclosporine, or danazol. VYTORIN also should not be taken by anyone with active liver disease, unexplained persistent elevations of hepatic transaminase levels, or hypersensitivity to the product; or by women who are pregnant, nursing or may become pregnant.

**Selected cautionary information about VYTORIN**

All patients starting therapy with VYTORIN, or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to promptly report any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing VYTORIN. VYTORIN should be discontinued immediately if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. VYTORIN contains simvastatin, which occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with CK levels above 10 times ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. The risk of myopathy, including rhabdomyolysis, is dose related.

The 10/80 mg dose of VYTORIN should not be started in new patients. The risk of myopathy, including rhabdomyolysis, is greater in patients taking simvastatin 80 mg compared with other statin therapies with similar or greater LDL cholesterol lowering efficacy, and with lower doses of simvastatin. The 10/80 mg dose of VYTORIN should be used only in patients who have been taking that dose chronically (e.g., for 12 months or more) without evidence of muscle toxicity. If a patient who is currently tolerating the 10/80 mg dose needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin or statin-based regimen with less potential for the drug-drug interaction. Please read Warnings and Precautions in the Prescribing Information for additional information.

In addition to drugs that are contraindicated because of an increased risk of myopathy/rhabdomyolysis, grapefruit juice should be avoided. Use caution when prescribing VYTORIN with a fenofibrate, and immediately discontinue both drugs if myopathy is diagnosed or suspected. Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be used when prescribing VYTORIN (ezetimibe/simvastatin) with colchicine.

The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving verapamil, diltiazem or dronedarone, and 10/20 mg daily in patients receiving amiodarone, amlodipine or ranolazine. For patients with homozygous familial hypercholesterolemia (HoFH) taking lomitapide, the dose should not exceed 10/20 mg/day (or 10/40
mg/day for patients who have previously taken simvastatin 80 mg/day chronically, e.g., for 12 months or more, without evidence of muscle toxicity); patients initiating lomitapide should have their dose of VYTORIN reduced by 50%. The benefits of combined use of VYTORIN with these drugs, other fenofibric acid derivatives, or niacin (≥1 g/day) should be carefully weighed against the potential risk of myopathy/rhabdomyolysis. Caution should be used when Chinese patients taking niacin (≥1 g/day) are coadministered doses of VYTORIN exceeding 10/20 mg/day; Chinese patients should not receive VYTORIN 10/80 mg with niacin.

Persistent elevations in hepatic transaminase can occur. Liver function tests should be performed at treatment initiation and thereafter when clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment, therapy should be interrupted promptly and not restarted unless an alternate etiology is found.

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

In clinical trials, the most commonly reported side effects, regardless of cause, included headache (5.8 percent), increased ALT (3.7 percent), myalgia (3.6 percent), upper respiratory tract infection (3.6 percent), and diarrhea (2.8 percent).

VYTORIN tablets contain ezetimibe and simvastatin: 10 mg of ezetimibe and 10, 20, 40, or 80 mg of simvastatin (VYTORIN 10/10, 10/20, 10/40, or 10/80 mg, respectively). The usual dosage range is 10/10 mg/day to 10/40 mg/day; patients should not be titrated to the restricted 10/80-mg dose.

About ZETIA (ezetimibe)

ZETIA, administered alone or in combination with a statin, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, and non-HDL cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia when diet alone is not enough.

The Prescribing Information for ZETIA states that the effect of ZETIA on cardiovascular morbidity and mortality has not been determined. ZETIA is not indicated for use with a statin to further reduce cardiovascular events in patients who have presented with acute coronary syndromes.

ZETIA (ezetimibe) should not be taken by people with hypersensitivity to any component of the medication. Statin contraindications also apply when ZETIA is used with these drugs: statins are contraindicated in patients with active liver disease, unexplained persistent elevations in hepatic transaminase levels and in pregnant and nursing women. Refer to individual statin labels for details about who should not take that statin.
Selected cautionary information about ZETIA

When using ZETIA with a statin, also follow the label recommendations for that specific statin.

When ZETIA was coadministered with a statin, consecutive elevations in hepatic transaminase levels (greater than or equal to 3 times ULN) were slightly higher (1.3 percent) than those of statins alone (0.4 percent). Liver function tests should be performed when ZETIA is added to statin therapy and according to statin recommendations. Should an increase in ALT or AST greater than or equal to 3 times ULN persist, consider withdrawal of ZETIA and/or the statin.

Patients should be advised to promptly report muscle pain, tenderness, or weakness. Risk for skeletal muscle toxicity increases with higher statin doses, advanced age (>65), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs. Discontinue drug if myopathy is diagnosed or suspected.

ZETIA is not recommended in patients with moderate to severe hepatic impairment.

The coadministration of ZETIA with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. Exercise caution when using ZETIA and cyclosporine concomitantly because exposure to both drugs is increased. Cyclosporine concentrations should be monitored in these patients.

ZETIA should be used in pregnant or nursing women only if the benefit outweighs the risk.

In clinical trials, regardless of causality assessment, the most frequent side effects for ZETIA coadministered with a statin versus a statin alone included nasopharyngitis (3.7 percent vs 3.3 percent), myalgia (3.2 percent vs 2.7 percent), upper respiratory tract infection (2.9 percent vs 2.8 percent), arthralgia (2.6 percent vs 2.4 percent), and diarrhea (2.5 percent vs 2.2 percent); for ZETIA administered alone vs placebo: upper respiratory tract infection (4.3 percent vs 2.5 percent), diarrhea (4.1 percent vs 3.7 percent), arthralgia (3.0 percent vs 2.2 percent), sinusitis (2.8 percent vs 2.2 percent), pain in extremity (2.7 percent vs 2.5 percent), and fatigue (2.4 percent vs 1.5 percent).

About ZONTIVITY (vorapaxar)

ZONTIVITY is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or with PAD. ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization. ZONTIVITY inhibits the protease-activated receptor-1 (PAR-1), the primary receptor for thrombin, which is considered to be the most potent activator of platelets. The PAR-1 pathway participates in the formation of blood clots through the activation and aggregation of platelets.
ZONTIVITY is a once-daily tablet containing 2.08 mg vorapaxar, equivalent to 2.5 mg vorapaxar sulfate. ZONTIVITY was studied only as an addition to aspirin and/or clopidogrel and should be used with aspirin and/or clopidogrel according to their indications or standard of care. There is no experience with use of ZONTIVITY alone as the only administered antiplatelet agent.

**Additional selected safety information about ZONTIVITY**

ZONTIVITY is contraindicated in patients with a history of stroke, TIA, or ICH and in patients with active pathological bleeding such as ICH or peptic ulcer. Discontinue ZONTIVITY in patients who experience a stroke, TIA, or ICH.

Antiplatelet agents, including ZONTIVITY, increase the risk of bleeding, including ICH and fatal bleeding. ZONTIVITY increases the risk of bleeding in proportion to the patient’s underlying bleeding risk. Physicians should consider the underlying risk of bleeding before initiating ZONTIVITY.

General risk factors for bleeding include older age, low body weight, reduced renal or hepatic function, and history of bleeding disorders. Use of certain concomitant medications (e.g., anticoagulants, fibrinolytic therapy, chronic nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors) also increases the risk of bleeding. Avoid concomitant use of warfarin or other anticoagulants.

Withholding ZONTIVITY for a brief period will not be useful in managing an acute bleeding event because, due to its long half-life, significant inhibition of platelet aggregation remains four weeks after discontinuation. There is no known treatment to reverse the antiplatelet effect of ZONTIVITY.

Strong CYP3A inhibitors increase and inducers decrease ZONTIVITY exposure. Avoid concomitant use of ZONTIVITY with strong CYP3A4 inhibitors or inducers.

Based on the increased inherent risk of bleeding in patients with severe hepatic impairment, ZONTIVITY is not recommended in these patients.

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction with ZONTIVITY (vorapaxar). Among post-MI or PAD patients with no history of stroke or TIA, three-year bleeding rates (shown with hazard ratios and 95% confidence intervals) in patients who added ZONTIVITY (vorapaxar) or placebo, respectively, to aspirin and/or clopidogrel were:

—GUSTO moderate or severe bleeding, a 3.7% vs 2.4%, HR 1.55 (1.30-1.86)

—GUSTO severe bleeding, a 1.3% vs 1.0%, HR 1.24 (0.92-1.66)
—Any GUSTO bleeding (severe/moderate/mild), a 27.7% vs 19.8%, HR 1.52 (1.43-1.61)

—ICH, 0.6% vs 0.4%, HR 1.46 (0.92-2.31)

—Fatal bleeding, 0.2% vs 0.2%, HR 1.15 (0.56-2.36)

—Clinically significant bleeding, b 15.5% vs 10.9%, HR 1.47 (1.35-1.60)

Additional Information about the IMPROVE-IT Trial

IMPROVE-IT was a multi-center, randomized, double-blind active comparator trial of 18,144 high-risk patients presenting with acute coronary syndromes (ACS), including unstable angina (UA), non-ST-segment elevation acute myocardial infarction (NSTEMI), and ST-segment elevation acute myocardial infarction (STEMI). Patients were randomized to receive ezetimibe/simvastatin (VYTORIN) or simvastatin alone, and were followed for up to nine years, with a median clinical follow-up of approximately six years. The primary efficacy endpoint was the composite of cardiovascular death, non-fatal MI, non-fatal stroke, re-hospitalization for ACS, or coronary revascularization (occurring 30 days or more after the initial event).

Additional Information about the TRA 2°P TIMI 50 Trial

TRA 2°P TIMI 50 was a multi-center, randomized, double-blind, placebo-controlled trial of 26,449 patients with a history of spontaneous MI within the prior two weeks to twelve months, ischemic stroke, or documented (symptomatic) PAD. Among all randomized patients, 20,170 had a history of MI or PAD and had no history of stroke or TIA (contraindications for ZONTIVITY include a history of stroke or TIA). Patients were randomized to receive daily treatment with ZONTIVITY or placebo in addition to standard of care that included aspirin and/or a thienopyridine (principally clopidogrel), and were followed for up to four years, with a median follow-up of 2.5 years. The primary efficacy endpoint was the composite of CV death, MI, stroke, and UCR, and the key secondary efficacy endpoint was the composite of CV death, MI, and stroke.

About Merck

Today’s Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.
Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck’s management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck’s 2013 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).


Please see Prescribing Information, including Boxed Warning, for ZONTIVITY (vorapaxar) at http://www.merck.com/product/usa/pi_circulars/z/zontivity/zontivity_pi.pdf and Medication Guide for ZONTIVITY at
a GUSTO severe bleeding: fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention; GUSTO moderate bleeding: bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise.

b Clinically significant bleeding: bleeding requiring medical attention including ICH, or clinically significant overt signs of hemorrhage with a drop in Hgb ≥3 g/dL (or, when Hgb is not available, an absolute drop in Hct ≥9%).

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