Two New Post-Hoc Analyses of TRA 2°P TIMI 50 Study Showed ZONTIVITY® (vorapaxar) Added to Aspirin and/or Clopidogrel Reduced Acute Limb Ischemia and Peripheral Revascularizations, Respectively, in Certain Patients with Peripheral Arterial Disease

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These and other post-hoc subgroup analyses from TRA-2°P are being presented at the 2015 American College of Cardiology Scientific Sessions

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced results from two post-hoc analyses of the TRA 2°P TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial of ZONTIVITY® (vorapaxar), one of the largest secondary prevention studies of an antiplatelet medicine. These data on additional endpoints in subgroups of patients with peripheral arterial disease (PAD) are being presented at the 2015 American College of Cardiology (ACC) Scientific Sessions in San Diego from March 14-16, 2015 along with other post-hoc subgroup analyses from the trial, with abstracts currently available online.

ZONTIVITY is indicated for the reduction of thrombotic cardiovascular (CV) events in patients with a history of myocardial infarction (MI) or in patients with PAD. The May 2014 U.S. approval of ZONTIVITY was based on the pivotal TRA 2°P TIMI 50 study, in which ZONTIVITY was shown to reduce the rate of a combined endpoint of CV death, MI, stroke and urgent coronary revascularization (UCR) when added to aspirin and/or clopidogrel. 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.

“As treating physicians, we are always concerned about our patients with PAD because of their risk for both systemic cardiovascular events as well as limb vascular events including acute limb ischemia and disease progression leading to peripheral revascularizations,” said Marc P. Bonaca, M.D., M.P.H., investigator, TIMI Study Group and associate physician at Brigham and Women's Hospital and Harvard Medical School in Boston, Mass. “Because there are limited options available to reduce the risk of limb vascular events, these exploratory subgroup analyses raise important hypotheses regarding the role of ZONTIVITY (vorapaxar) in the management of PAD.”

Previously Reported Efficacy and Safety Results from the TRA 2°P TIMI 50 Trial

The primary results of TRA 2°P TIMI 50 study have been previously reported. TRA 2°P TIMI 50 was a 26,449 patient, randomized, double-blind, placebo-controlled trial in which participants had a history of spontaneous MI within the prior two weeks to twelve months, ischemic stroke, or documented (symptomatic) PAD. Patients were followed for up to four years, with a median follow-up of 2.5 years. ZONTIVITY, when used daily with standard of care that included aspirin and/or a thienopyridine (principally clopidogrel), was superior to standard of care alone in reducing the incidence of both the primary combined endpoint of CV death, MI, stroke, and UCR (10.1% in the group randomized to ZONTIVITY vs. 11.8% in the placebo group; hazard ratio [HR] 0.83, p<0.001). For the key secondary composite efficacy endpoint of CV death, MI, and stroke, the study showed a 20% relative risk reduction through three years (7.9% in the group randomized to ZONTIVITY vs. 9.5% in the placebo group; HR 0.80, p<0.001).

Among randomized post-MI or PAD patients without a history of stroke or TIA who were treated with ZONTIVITY (n=10,059)
or placebo (n=10,049), adding ZONTIVITY to standard of care (including aspirin and/or a thienopyridine) was associated with an increased rate of GUSTO moderate or severe bleeding through three years (3.7%) compared to adding placebo (2.4%) (HR 1.55, 95% confidence interval [CI] 1.30-1.86). GUSTO severe bleeding occurred at a rate of 1.3% for ZONTIVITY versus 1.0% for placebo (HR 1.24, 95% CI 0.92-1.66). Any GUSTO bleeding (severe/moderate/mild) occurred at a rate of 27.7% for ZONTIVITY (vorapaxar) versus 19.8% for placebo (HR 1.52, 95% CI 1.43-1.61). The three-year rate of ICH was numerically higher for patients adding ZONTIVITY to standard of care, 0.6%, compared to 0.4% for patients adding placebo (HR 1.46; 95% CI 0.92-2.31). Fatal bleeding occurred at a three-year rate of 0.2% in both the ZONTIVITY and placebo groups, with a hazard ratio of 1.15 favoring the placebo group (95% CI 0.56-2.36). Clinically significant bleeding occurred at a three-year rate of 15.5% in the group taking ZONTIVITY, compared with 10.9% in the placebo group (HR 1.47, 95% CI 1.35-1.60).

There is no experience with ZONTIVITY as the only administered antiplatelet agent, because ZONTIVITY was studied only as an addition to aspirin and/or clopidogrel.

New post-hoc analyses results from the TRA 2°P TIMI 50 Trial

Data being presented at ACC include two post-hoc subgroup analyses that explored the use of ZONTIVITY in certain patients with established PAD. PAD is generally defined as obstruction of arteries supplying the lower extremities, most commonly due to atherosclerosis. People with PAD are at increased risk for heart attack, stroke, and CV death. People with PAD are also at risk for complications from ischemia involving the lower extremities, and this was the focus of the two subgroup analyses being presented. More specifically, these exploratory analyses looked at rates of:

1. acute limb ischemia (ALI), a serious condition caused by an abrupt interruption of blood flow to a limb due to embolic or thrombotic vascular occlusion, which can result in limb loss.
2. peripheral artery revascularization (PR), either a percutaneous (generally with stenting) or surgical procedure that restores blood flow to a limb that is supplied by blocked arteries.

Subgroup analyses should be interpreted cautiously as differences can reflect the play of chance among a large number of analyses. The following are more specific details on the two presentations at ACC:

  
  Among the 3,787 patients whose qualifying diagnosis for the TRA 2°P TIMI 50 trial was symptomatic PAD (including 514 patients with a history of stroke or TIA in whom use of ZONTIVITY (vorapaxar) is contraindicated), a total of 109 ALI events occurred during the trial. The majority of ALI events were due to acute surgical graft thrombosis (54%) or in situ thrombosis in a native vessel (27%). In this post-hoc subgroup analysis, researchers found that in patients with symptomatic PAD, adding ZONTIVITY to standard care (which included aspirin and/or clopidogrel) yielded a 42% relative risk reduction in the incidence of ALI versus aspirin and/or clopidogrel alone (3-year event rates 2.3% vs. 3.9%, respectively; HR: 0.58, 95% CI 0.39–0.86).

  - **Saturday, March 14; 11:00 AM-11:10 AM PT. Location: Vascular Medicine Moderated Poster Theater, Poster Hall B1.**

- **(Abstract #1131M-05) Vorapaxar and Peripheral Revascularization: Insights from the TRA2P-TIMI 50 Trial. I. Gilchrist.**

  In this post-hoc subgroup analysis of 5,845 patients in TRA 2°P with a history of PAD (regardless of primary enrollment stratum), ZONTIVITY vs. placebo, added to aspirin and/or clopidogrel, showed a consistent pattern of reduction in the need for peripheral revascularization (PR) (via percutaneous or surgical procedures) among the various indications for PR captured by the analysis. This included a reduction in PR for the treatment of claudication (event rates 11.6% for placebo and 9.4% for ZONTIVITY; HR 0.84, 95% CI 0.71–0.99). Adding ZONTIVITY also reduced the rate of surgical PR procedures (event rates 7.7% for placebo and 4.5% for ZONTIVITY; HR 0.59, 95% CI 0.47–0.74). Approximately 20% of the 5,845 patients included in this analysis had a history of stroke or TIA, which are contraindications to use of ZONTIVITY.

  - **Saturday, March 14; 10:15 AM-10:25 AM PT. Location: Vascular Medicine Moderated Poster Theater, Poster Hall B1.**

These exploratory subgroup analysis abstracts in PAD patients do not include information about bleeding. In the overall trial population, among the subgroup of patients who qualified for the trial based on a diagnosis of PAD and who had no history of stroke or TIA, the annualized rate of GUSTO moderate or severe bleeding was 2.3% for those receiving ZONTIVITY compared with 1.5% for those receiving placebo (HR 1.60, 95% CI 1.15–2.21).

Additional subgroup analyses also being presented at ACC include:

- **(Abstract #905-04) Poster Session: The role of Vorapaxar in Patients with Coronary Artery Bypass Grafting: Findings from the TRA 2P-TIMI 50 Trial. E. Kosova.**

  In this post-hoc subgroup analysis of 2,942 post-MI or PAD patients with no history of stroke or TIA who had undergone coronary artery bypass grafting (CABG) prior to the trial, adding ZONTIVITY to aspirin and/or clopidogrel reduced the risk of CV death, myocardial infarction or stroke (event rate 11.9% for ZONTIVITY vs. 15.6% for placebo; HR 0.71, 95% CI 0.58–0.88). In these patients, ZONTIVITY increased the risk of GUSTO moderate or severe bleeding (6.8% for ZONTIVITY vs. 3.7% for placebo; HR 1.87, 95% CI 1.28–2.72). In another subgroup analysis, among 319 post-MI or PAD patients with no history of stroke or TIA who underwent a new CABG during the trial, the rates of TIMI major bleeding within 30 days of surgery were 6.0% for ZONTIVITY and 4.2% for placebo (HR 1.43, 95% CI 0.53–3.84). The authors state that the increased bleeding risk with ZONTIVITY in this small group undergoing CABG was similar to the increase in bleeding risk with ZONTIVITY in the overall study population.

  - **Sunday, March 15; 10:57 AM-11:08 AM PT. Location: Room 7B.**
About ZONTIVITY (vorapaxar)

ZONTIVITY is indicated for the reduction of thrombotic CV events in patients with a history of MI or with PAD. ZONTIVITY has been shown to reduce the rate of a combined endpoint of CV death, MI, stroke, and UCR. 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 (vorapaxar) 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.

Background antiplatelet therapies among PAD patients in the TRA-2P study

In TRA-2P, 88% of all patients who qualified for the trial with PAD were receiving background therapy with aspirin at enrollment, 37% were receiving a thienopyridine (principally clopidogrel), and 28% were receiving both. Among PAD patients with no history of stroke or TIA, 88% were receiving background therapy with aspirin at enrollment, 35% were receiving a thienopyridine (principally clopidogrel), and 27% were receiving both.

About Merck

Today’s Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside of 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 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 2014 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).

1 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. (GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries.)

2 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%).

3 CABG-related TIMI major bleeding: fatal bleeding, perioperative ICH, reoperation for bleeding, transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period, or chest tube output ≥2 L within a 24-hour period. (TIMI: Thrombolysis in Myocardial Infarction Study Group.)

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