

June 10, 2015

**TECOS, the Trial Evaluating Cardiovascular Outcomes with JANUVIA<sup>®</sup>  
(Sitagliptin), Met Primary Endpoint in Patients with Type 2 Diabetes**

Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced the primary results of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), a placebo-controlled study of the cardiovascular (CV) safety of Merck's DPP-4 inhibitor, JANUVIA<sup>®</sup> (sitagliptin), added to usual care in more than 14,000 patients at the 75th Scientific Sessions of the American Diabetes Association on June 8. The study achieved its primary composite CV endpoint of non-inferiority (defined as the time to the first confirmed event of any of the following: CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina) compared to usual care without sitagliptin. These data were also published in the *New England Journal of Medicine*.

Sitagliptin was co-developed for the Japanese market by ONO and MSD K.K. (formerly Banyu Pharmaceutical Co., Ltd.; "MSD") under the licensing agreement signed by ONO and Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. in November 2004.

Glactiv<sup>®</sup> (ONO) and JANUVIA<sup>®</sup> (MSD) were launched in December 2009 as the first DPP-4 (dipeptidyl peptidase-4) inhibitor in Japan.

Attached from the following page is the press release made by Merck for your information.

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**FOR IMMEDIATE RELEASE**

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## **TECOS, Merck's Cardiovascular Safety Trial of JANUVIA (sitagliptin), Met Primary Endpoint in Patients with Type 2 Diabetes**

**Findings Published in the *New England Journal of Medicine* and Presented at the American Diabetes Association Scientific Sessions**

### **Treatment with Sitagliptin Did Not Increase the Risk of Major Adverse Cardiovascular Events in the Primary Composite Endpoint, or Hospitalization for Heart Failure, Compared with Placebo**

KENILWORTH, N.J., June 8, 2015 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the primary results of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), a placebo-controlled study of the cardiovascular (CV) safety of Merck's DPP-4 inhibitor, JANUVIA<sup>®</sup> (sitagliptin), added to usual care in more than 14,000 patients. The study achieved its primary composite CV endpoint of non-inferiority (defined as the time to the first confirmed event of any of the following: CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina) compared to usual care without sitagliptin. Overall, the primary endpoint occurred in 11.4 percent (n=839) of sitagliptin-treated patients compared with 11.6 percent (n=851) of placebo-treated patients in the Intention-to-Treat (ITT) analysis (HR=0.98; 95% CI [0.89-1.08]), and in 9.6 percent of patients (n=695) in both the sitagliptin and placebo groups in the Per Protocol (PP) analysis (HR=0.98; 95% CI [0.88-1.09]; p<0.001 for non-inferiority).<sup>1</sup> In addition, there was no increase in hospitalization for heart failure and rates of all-cause mortality were similar in both treatment groups, which were two key secondary endpoints. These data were presented today at the 75<sup>th</sup> Scientific Sessions of the American Diabetes Association and were also published in the *New England Journal of Medicine*.

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<sup>1</sup> The primary hypothesis of non-inferiority of sitagliptin vs. placebo for the composite CV endpoint was based on the Per Protocol (PP) analysis.

## **Indications and Limitations of Use for JANUVIA® (sitagliptin) 25 mg, 50 mg and 100 mg tablets**

JANUVIA is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus. JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. JANUVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while taking JANUVIA.

### **Selected Important Risk Information about JANUVIA**

JANUVIA is contraindicated in patients with a history of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or with any other antidiabetic drug.

“Patients with type 2 diabetes need antihyperglycemic medicines to help control their blood sugar. Because these patients are at increased risk for cardiovascular complications, understanding the cardiovascular safety of these medicines is important,” said study co-chair, Rury Holman, Professor of Diabetic Medicine and Diabetes Trials Unit Director, University of Oxford. “The results from TECOS showed that sitagliptin did not increase the risk of cardiovascular events in a diverse group of patients with type 2 diabetes at high cardiovascular risk.”

### **Additional Findings from the TECOS CV Safety Trial**

TECOS was an event-driven study designed to assess the long-term CV safety of the addition of sitagliptin to usual care, compared to usual care without sitagliptin, in patients with type 2 diabetes and established CV disease. In addition to showing no increased risk for the primary composite CV endpoint, sitagliptin also met the secondary composite CV endpoint (defined as the time to the first confirmed event of any of the following: CV-related death, nonfatal MI, or nonfatal stroke), showing non-inferiority compared to usual care without sitagliptin (HR=0.99; 95% CI [0.89-1.11];  $p < 0.001$  for non-inferiority).

In additional secondary endpoints assessing time to first confirmed event, hospitalization for heart failure was reported in 3.1 percent (n=228) of sitagliptin-treated patients and 3.1 percent (n=229) of placebo-treated patients (HR=1.00; 95% CI [0.83-1.20]). All-cause mortality was similar in both treatment groups, occurring in 7.5 percent (n=547) of patients in the sitagliptin group and 7.3 percent (n=537) in the placebo group (HR=1.01; 95% CI [0.90-1.14]).

Acute pancreatitis was uncommon, occurring in 0.3 percent of patients in the sitagliptin group (n=23) and 0.2 percent of patients in the placebo group (n=12); the difference was not statistically different between groups ( $p=0.065$ ). Pancreatic cancer was also uncommon,

occurring in 0.1 percent of patients in the sitagliptin group (n=9) and 0.2 percent of patients in the placebo group (n=14), and was not statistically different between groups (p=0.322).

In additional secondary analyses of the composite of time to first hospitalization for heart failure or CV death, the first confirmed hospitalization for heart failure or CV death occurred in 7.3 percent (n=538) in the sitagliptin group compared with 7.2 percent (n=525) for placebo (HR=1.01; 95% CI [0.90-1.14]). The proportion of patients with CV death was 5.2 percent (n=380) in the sitagliptin group compared with 5.0 percent (n=366) in the placebo group (HR 1.03; 95% CI [0.89-1.19]).

The proportion of patients with non-CV death was 2.3 percent in both treatment groups. Death due to infection was 0.6 percent and 0.7 percent in the sitagliptin and placebo groups, respectively. A slight reduction in eGFR (estimated glomerular filtration rate), a measure of renal function, was observed in both treatment groups during the study: at month 48, mean change from baseline in eGFR was  $-4.0 \pm 18.4$  mL/min/1.73m<sup>2</sup> in the sitagliptin group compared to  $-2.8 \pm 18.3$  mL/min/1.73m<sup>2</sup> for placebo.

“We believe the results of TECOS provide important clinical information about the cardiovascular safety profile of sitagliptin,” said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. “The TECOS CV safety trial reflects the best efforts of clinical scientists at the University of Oxford, the Duke Clinical Research Institute and Merck on behalf of patients around the world who suffer from type 2 diabetes.”

To minimize any potential effect that differences in glucose control might have on CV outcomes, the study aimed to achieve similar glucose control (glycemic equipoise) between treatment groups. At four months, mean HbA1c level was 0.4 percent lower in the sitagliptin group compared with placebo, and this narrowed to 0.1 percent lower during patient follow-up. This resulted in an overall difference of -0.29 percent in patients treated with sitagliptin versus placebo. Compared with patients treated with placebo, fewer patients treated with sitagliptin received additional antihyperglycemic agents during the study period (1,591 vs. 2,046 patients, respectively; p<0.001) and were less likely to start chronic insulin therapy (542 vs. 744 patients, respectively; p<0.001).

## **Study Methods and Design**

TECOS was led by an independent academic research collaboration between the University of Oxford Diabetes Trials Unit (DTU) and the Duke University Clinical Research Institute (DCRI), and was sponsored by Merck. A total of 14,735 patients from 38 countries were randomized between December 2008 and July 2012. Of these, 14,671 were included in the ITT analysis population, with 7,332 assigned to sitagliptin and 7,339 to placebo, in addition to existing therapy. The median patient follow-up was three years, with a maximum follow-up of 5.7 years.

Patients enrolled in the trial had type 2 diabetes with established CV disease in the coronary, cerebral, or peripheral arteries. Patients were at least 50 years of age, had a baseline HbA1c between 6.5 and 8.0 percent, and were dose-stable for at least three months on either: monotherapy or dual combination therapy with metformin, pioglitazone or a sulfonylurea; or insulin as monotherapy or in combination with a stable dose of metformin. Participants were randomly assigned to treatment with sitagliptin 100 mg daily (50 mg daily if baseline eGFR was  $\geq 30$  and  $< 50$  mL/min/1.73m<sup>2</sup>) or matching placebo.

The primary non-inferiority hypothesis was assessed by determining whether the upper bound of the 95 percent confidence interval around the hazard ratio for the risk of the primary composite CV endpoint (time to first event) between the sitagliptin and placebo groups in the PP population did not exceed 1.3, with a key supporting analysis in the ITT population. If non-inferiority on the primary composite CV endpoint was met, superiority was to be evaluated in the ITT population.

### **Selected Important Risk Information about JANUVIA® (continued)**

There have been postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiating JANUVIA, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA and initiate appropriate management.

Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis. Caution should be used to ensure that the correct dose of JANUVIA is prescribed.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin.

When JANUVIA was used in combination with a sulfonylurea or insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

The incidence (and rate) of hypoglycemia based on all reports of symptomatic hypoglycemia were: 12.2 percent (0.59 episodes per patient-year) for JANUVIA 100 mg in combination with glimepiride (with or without metformin), 1.8 percent (0.24 episodes per patient-year) for placebo in combination with glimepiride (with or without metformin), 15.5 percent (1.06 episodes per patient-year) for JANUVIA (sitagliptin) 100 mg in combination with insulin (with or without metformin), and 7.8 percent (0.51 episodes per patient-year) for placebo in combination with insulin (with or without metformin).

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA® (sitagliptin), such as anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUVIA.

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or with any other antidiabetic drug. In clinical studies, the adverse reactions reported, regardless of investigator assessment of causality, in greater than or equal to 5 percent of patients treated with JANUVIA as monotherapy and in combination therapy, and more commonly than in patients treated with placebo, were upper respiratory tract infection, nasopharyngitis and headache.

## **About Merck**

Today's Merck is a global health care 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 health care through far-reaching policies, programs and partnerships. For more information, visit [www.merck.com](http://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 U.S. 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 except as required by applicable law. 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](http://www.sec.gov)).

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Please see Prescribing Information for JANUVIA® (sitagliptin) at [http://www.merck.com/product/usa/pi\\_circulars/j/januvia/januvia\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf) and Medication Guide for JANUVIA at [http://www.merck.com/product/usa/pi\\_circulars/j/januvia/januvia\\_mg.pdf](http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_mg.pdf).