BACKGROUND INFORMATION:

About JANUVIA®

JANUVIA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Selected Safety Information About Sitagliptin

JANUVIA is contraindicated in patients who are hypersensitive to any components of this product. 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.

"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.[i] 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).**Erreur ! Signet non défini.**

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]).**Erreur ! Signet non défini.** 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]).**Erreur ! Signet non défini.**

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).**Erreur ! Signet non défini.** 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).**Erreur ! Signet non défini.**

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=1.02; 95% CI [0.90-1.15]).**Erreur ! Signet non défini.** 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]).**Erreur ! Signet non défini.**

The proportion of patients with non-CV death was 2.3 percent in both treatment groups.**Erreur ! Signet non défini.** Death due to infection was 0.6 percent and 0.7 percent in the sitagliptin and placebo groups, respectively.**Erreur ! Signet non défini.** 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 ± 18.4 mL/min/1.73m^2 in the sitagliptin group compared to -2.8 ± 18.3 mL/min/1.73m^2 for placebo.**Erreur ! Signet non défini.**

“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 MSD 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.[i] 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.**Erreur ! Signet non défini.** This resulted in an overall difference of -0.29 percent in patients treated with sitagliptin versus placebo.**Erreur ! Signet non défini.** 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).**Erreur ! Signet non défini.**

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 MSD.[i] A total of 14,735 patients from 38 countries were randomized between December 2008 and July 2012.**Erreur ! Signet non défini.** 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.**Erreur ! Signet non défini.**

Patients enrolled in the trial had type 2 diabetes with established CV disease in the coronary, cerebral, or peripheral arteries.**Erreur ! Signet non défini.** 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.**Erreur ! Signet non défini.** Participants were randomly assigned to treatment with sitagliptin 100 mg daily (50 mg daily if baseline eGFR was ≥30 and <50 mL/min/1.73m^2) or matching placebo.**Erreur ! Signet non défini.**

The primary non-inferiority hypothesis was assessed by determining whether the upper bound of the 95 percent confidence interval for 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.**Erreur ! Signet non défini.** If non-inferiority on the primary composite CV endpoint was met, superiority was to be evaluated in the ITT population.**Erreur ! Signet non défini.**

Important Selected Safety Information About Sitagliptin (continued)

• There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA.

• There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter.

• There is an increased risk of hypoglycemia when JANUVIA is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.

• There have been post-marketing reports of serious allergic and hypersensitivity reactions in patients treated with JANUVIA such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUVIA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes.

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

• Adverse reactions reported in 5% of patients treated with JANUVIA and more commonly than in patients treated with placebo are: upper respiratory tract infection nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with JANUVIA compared to placebo.

About MSD

Today's MSD is a global healthcare leader working to help the world be well. MSD is a tradename of Merck & Co., Inc., with headquarters in Kenilworth, N.J., U.S.A. 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.

MSD 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 MSD’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; MSD’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 MSD/Merck patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

MSD/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 MSD’s/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).

Please see Prescribing Information for JANUVIA® (sitagliptin) at 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.

# # #

Green JB et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2015 June.

[1] Green JB et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American Heart Journal. 2013 Dec;166(6):983-989.e7.

Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)
Background and Timeline

TECOS is an event-driven safety study conducted in adults with type 2 diabetes and a history of cardiovascular (CV) disease, which is designed to assess the CV safety of long-term treatment with JANUVIA® (sitagliptin) as part of usual diabetes care[a] compared with usual care without JANUVIA. The primary hypothesis of the TECOS CV safety trial is to confirm that JANUVIA plus usual care shows no increased risk (non-inferiority) for the primary endpoint of time to first significant confirmed CV event, or MACE+ (a composite of CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, and unstable angina requiring hospitalization)[b] compared to placebo plus usual care. If JANUVIA plus usual care is found to be non-inferior to placebo plus usual care with respect to CV outcomes, the superiority of JANUVIA compared to placebo with respect to CV outcomes will be evaluated.[ii]

- Achieving similar glucose control (glycemic equipoise) between treatment groups is a design element of the TECOS CV safety trial that is intended to minimize any effect that differences in glucose control might have on CV results.
- The TECOS CV safety trial enrolled 14,724 participants from 38 countries between December 2008 and July 2012. The median patient follow-up for TECOS is expected to be approximately three years.[iii]

The TECOS CV safety trial is being 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 is being sponsored by MSD.[ii] The study's academic leaders are:[iv]

- Rury Holman, FMedSci FRCP, Professor and Director, Diabetes Trials Unit, University of Oxford (study co-chair)
- Eric Peterson, M.D., MPH, Executive Director of the Duke Clinical Research Institute, Professor of Medicine, Division of Cardiology, Duke University (study co-chair as of March 25; replaced Robert Califf M.D., Vice Chancellor for Clinical and Translational Research, Professor of Medicine, Division of Cardiology, Duke University)
- Paul Armstrong, M.D., Professor of Medicine, Division of Cardiology, University of Alberta
- John Buse, M.D., Ph.D., Professor of Medicine, Chief of Division of Endocrinology, Executive Associate Dean for Clinical Research, University of North Carolina Chapel Hill
- Robert Josse, M.D., Professor, Department of Medicine, University of Toronto
- John Lachin, Sc.D., Research Professor of Biostatistics and Epidemiology, and Statistics, The Biostatistics Center, The George Washington University
- Darren McGuire, M.D., Professor of Internal Medicine and Director, Cardiology Clinical Trials Unit, University of Texas Southwestern Medical Center
- Eberhard Standl, M.D., Professor of Medicine, Munich Diabetes Research Group/Diabetes Research Institute
- Frans Van de Werf, M.D., Ph.D., Professor of Cardiology, Chair of the Division of Cardiology, Catholic University of Leuven

About JANUVIA® (sitagliptin)
JANUVIA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Selected Safety Information About Sitagliptin

JANUVIA is contraindicated in patients who are hypersensitive to any components of this product. 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.

Please see Prescribing Information for JANUVIA (sitagliptin) at [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**].**

a)Additional oral antihyperglycemic agents or insulin were to be added to target A1C goals based on current guidelines.
b) MACE is defined as Major Adverse Cardiac Events (a composite of CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, and unstable angina requiring hospitalization)

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TECOS CV Safety Trial Design[i]

- ***Primary hypothesis***: Confirm no increased risk (non-inferiority) for the primary endpoint of time to first significant confirmed CV event, or MACE+.[b]
- ***Study population***: Patients aged ≥50 years with type 2 diabetes; documented vascular disease in the coronary, cerebral, or peripheral arteries; and baseline $A1C^{1c}$ between 6.5 and 8.0 percent and dose-stable for at least 3 months on:
  - Monotherapy or dual combination therapy with metformin, pioglitazone, and/or a sulfonylurea, or
  - Insulin as monotherapy or in combination with stable dose of metformin
- ***Treatment arms***: JANUVIA + usual care[a] vs. placebo + usual care.
- ***Event-driven study***: Study completion based upon attainment of 1,300 patients with a confirmed primary outcome of CV events.[d,iii]
- ***Primary outcome***: Time from randomization to first confirmed MACE+ event.
- ***Key secondary outcomes***: Composite of time to first confirmed CV-related death, nonfatal MI, nonfatal stroke (MACE); time to occurrence of the individual components of the primary endpoint; time to all-cause mortality; time to hospital admission for adjudicated congestive heart failure (CHF).[b]

[a] Additional oral antihyperglycemic agents or insulin were to be added to target A1C goals based on current guidelines.
[b] MACE is defined as Major Adverse Cardiac Events (a composite of CV-related death, nonfatal myocardial infarction (MI), nonfatal stroke, and unstable angina requiring hospitalization)
[c] A1C is an estimate of a person's average blood glucose over a two- to three-month period.
[d] CV events will be adjudicated by an independent committee, blinded to study therapy.

TECOS Timeline

2006
- JANUVIA approved in the U.S. and Mexico.[v,vi]

2007
- Additional regulatory approvals of JANUVIA begin worldwide.[vii]

2008
- TECOS CV safety trial protocol is established by MSD, in partnership with an academic research collaboration between the University of Oxford Diabetes Trials Unit and the Duke University Clinical Research Institute.[viii]
- *November*: MSD announces TECOS CV safety trial to evaluate the cardiovascular (CV) safety of JANUVIA.[ix]
- *December*: First patient enrolled.[ii]

2010
- *September*: Protocol amended to permit insulin use at baseline

2012
- *July*: TECOS reached full patient enrollment.[x]

2013
- *October*: "Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease," published online by the *American Heart Journal* (published in print in December 2013.[ii]

2015
- *January*: "Regional, age, and sex differences in baseline characteristics of patients enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)," published online in *Diabetes, Obesity and Metabolism* in January 2015.[iii]
- *March 31*: Study complete[xi] (ClinicalTrials.gov Identifier: NCT00790205).

- *June*: The primary results of TECOS will be presented at the 75th Scientific Sessions of the American Diabetes Association in Boston on June 8, 2015.[ix]

[ii] Green JB et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American Heart Journal. 2013 Dec;166(6):983-989.e7.
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