Press Release

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Takeda EXAMINE Cardiovascular Safety Outcomes Trial of Alogliptin Met Primary Endpoint of Non-Inferiority Compared to Placebo in Addition to Standard of Care Showing No Increase in Cardiovascular Risk in Type 2 Diabetes Patients at High-Risk for Cardiovascular Events

Clinical Data Published in the New England Journal of Medicine and Presented at the ESC Congress 2013

Amsterdam, The Netherlands and Osaka, Japan, September 2, 2013 – Takeda Pharmaceutical Company Limited (Takeda) today announced results of the EXAMINE (**EX**amination of C**A**rdiovascular Outco**M**es: Aloglipt**IN** vs. Standard of Car**E** in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) cardiovascular (CV) safety outcomes trial, showing the primary endpoint of non-inferiority compared to placebo in addition to standard of care was met with no increase in CV risk in a Type 2 diabetes patient population at high-risk for CV events. These data, published in the *New England Journal of Medicine* (*NEJM*) and also presented at the ESC Congress 2013, demonstrate that alogliptin does not increase CV risk in Type 2 diabetes patients at high-risk for major adverse cardiac events (MACE) due to a recent acute coronary syndrome (ACS). The trial's primary objective was to evaluate non-inferiority of CV risk based on a primary composite endpoint of CV death, nonfatal myocardial infarction and nonfatal stroke. The primary endpoint occurred at similar rates in the alogliptin and placebo groups (in 11.3% of patients vs. 11.8% of patients during a median follow-up period of 18 months; hazard ratio, 0.96; one-sided repeated confidence interval [CI] bound, 1.16). Alogliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of Type 2 diabetes in adults to improve glycemic control as an adjunct to diet and exercise.

"There is a need for safer glucose lowering therapies in patients with diabetes who are at an elevated risk for cardiovascular disease," stated William B. White, MD, FASH, FAHA, FACP, principal investigator of the EXAMINE trial. "Given the EXAMINE study design and high-risk patient population evaluated, these results provide key insights to clinicians treating diabetes patients with coronary disease."

The global EXAMINE trial is an important evaluation as it assesses CV safety in patients known to be at an elevated risk of cardiovascular disease (CVD), the leading cause of morbidity and mortality in the Type 2 diabetes patient population. A global, large, randomized, double-blind, placebo-controlled clinical trial, EXAMINE was designed to evaluate CV safety following treatment with alogliptin in addition to standard of care, versus placebo in addition to standard of care alone, in patients with Type 2 diabetes and a recent ACS.

During the EXAMINE trial, patients were randomly assigned to receive alogliptin or placebo in addition to standard of care medications for diabetes and CVD. A total of 5,380 patients were randomly assigned and followed for a median of 18 months and up to 40 months. The rate of premature discontinuation of the study drug was similar in the alogliptin and placebo groups. Patients also received high levels of standard of care for treatment of Type 2 diabetes and CV risk factors.

"The EXAMINE trial design and importantly, the safety outcomes measured make it a uniquely informative study for diabetes treatment in some of the most high-risk patients," said Ajay Ahuja, MD, Vice President, Global Medical Affairs, Takeda. "Over the past 20 years, Takeda has built a strong foundation in and maintained a robust focus on diabetes. EXAMINE reinforces our ongoing commitment to the science behind alogliptin and the diabetes community."

The principal secondary safety endpoint was the primary composite with the addition of hospitalization for unstable angina that required coronary revascularization within 24 hours of hospital admission. Testing of the secondary composite endpoint of CV death, myocardial infarction, stroke and unstable angina with urgent revascularization showed no difference in rates on alogliptin versus placebo (12.7% vs. 13.4%; hazard ratio, 0.95; one-sided repeated CI bound, 1.14).

Other secondary endpoints included CV death alone and death from any cause. CV death occurred in 112 patients treated with alogliptin (4.1%) and 130 patients treated with placebo (4.9%) for a hazard ratio of 0.85 (95% confidence limits [CL] of 0.66 to 1.10, p=0.21). All-cause mortality (death from any cause) occurred in 153 patients treated with alogliptin (5.7%) and 173 patients treated with placebo (6.5%) for a hazard ratio of 0.88 (95% CL of 0.71 to 1.09, p=0.23). Overall, rates of death from any cause and CV death were not statistically significantly different between alogliptin and placebo groups.

Additional safety endpoints included angioedema, hypoglycemia, pancreatitis, malignancy, and results of laboratory testing. Rates of hypoglycemia, malignancy, pancreatitis, dialysis, and serum aminotransferase elevations were similar for the alogliptin and placebo groups. No events of pancreatic cancer were reported during the trial. The alogliptin and placebo groups did not differ significantly with regard to rates of serious adverse events (33.6% and 35.5%, respectively, p=0.14).

About EXAMINE

A global, large, randomized, double-blind, placebo-controlled clinical trial, EXAMINE was designed to evaluate CV safety following treatment with alogliptin in addition to standard of care, versus placebo in addition to standard of care alone, in patients with Type 2 diabetes and a recent ACS (within 15 to 90 days prior to randomization). The trial had a primary composite endpoint of CV death, nonfatal myocardial infarction and nonfatal stroke.

In the alogliptin group, 71.4% of patients received 25 mg, 25.7% received 12.5 mg, and 2.9% received 6.25 mg daily. Alogliptin doses were adjusted according to renal function: estimated glomerular filtration rate (eGFR) by the Modification in Diet in Renal Disease formula ≥ 60 ml/min, 25 mg daily; < 60 ml/min but ≥ 30 ml/min, 12.5 mg daily; and < 30 ml/min, 6.25 mg daily. Premature discontinuation of the study drug was similar in the alogliptin and placebo groups (20.9% of patients vs. 22.6%). The median duration of exposure to study drug was 533 days (interquartile range, 280 to 751 days). By the end of the study, the mean change from baseline in HbA1c was -0.33% and 0.03% in the alogliptin and placebo groups, and the least square means difference in HbA1c between alogliptin and placebo was -0.36% (95% CI, -0.43, -0.28, p<0.001). In the analysis of the components of the primary endpoint, the hazard ratios were consistent with the overall result. Hazard ratios for death from any cause and CV death were consistent with the primary composite endpoint.

Takeda conducted the global EXAMINE trial in accordance with the United States (U.S.) Food and Drug Administration's (FDA) 2008 Guidance, titled "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," for all new Type 2 diabetes treatments. As a global trial, EXAMINE results will be shared with regulatory agencies upon completion of all analyses, as appropriate.

About Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes affecting millions of people globally. Type 2 diabetes is a progressive and chronic condition and patients should work with a healthcare professional to manage and monitor their disease. In addition to diet and exercise, patients often need to take one or more medications in order to help them manage their blood glucose levels. According to the International Diabetes Federation, the global health care expenditures for diabetes (both Type 1 and 2) were estimated at more than $471 billion USD in 2012.[i] By 2030, this number is projected to exceed $595 billion.[ii]

About Alogliptin

Alogliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4i) for the treatment of Type 2 diabetes in adults as an adjunct to diet and exercise. DPP-4is are designed to slow the inactivation of incretin hormones GLP-1 and GIP. As a result, an increased amount of active incretins enables the pancreas to secrete insulin in a glucose-dependent manner, thereby assisting in the management of blood glucose levels. A New Drug Application (NDA) for NESINA (alogliptin) was approved in April 2010 by the Japanese Ministry of Health, Labour and Welfare for the treatment of Type 2 diabetes, and the therapy is available under the same brand name in Japan. NESINA (alogliptin) was approved by the U.S. FDA as a free-dose therapy and also in fixed-dose combination (FDC) with pioglitazone (OSENI) and metformin HCl (KAZANO) in January 2013 for the treatment of Type 2 diabetes in adults as adjuncts to diet and exercise. Alogliptin as a free-dose therapy is currently approved for use in 6.25 mg, 12.5 mg, and 25 mg dose tablets. For patients with moderate renal impairment (creatinine clearance [CrCl] ≥ 30 to < 60 mL/min), the dose of alogliptin is 12.5 mg once daily and for patients with severe renal impairment (CrCl ≥ 15 to < 30 mL/min) and for patients with end-stage renal disease (ESRD) (CrCl < 15 mL/min or requiring hemodialysis), the dose of

alogliptin is 6.25 mg once daily.

Alogliptin is not currently licensed or available in Europe. VIPIDIA (alogliptin), VIPDOMET (alogliptin and metformin FDC) and INCRESYNC (alogliptin and pioglitazone FDC) are currently undergoing regulatory review by the European Medicines Agency (EMA), having received positive opinions for use by the Committee for Medicinal Products for Human Use (CHMP) in July 2013. Alogliptin is also approved for use in China, Mexico and South Korea, though the therapy is not yet available in those markets.

The efficacy of alogliptin was studied as an adjunct to diet and exercise as an add-on therapy to several other classes of anti-diabetic medications, including metformin, pioglitazone, insulin and sulfonylureas. In these studies, alogliptin 25 mg tablets taken once-daily, demonstrated clinically and statistically significant reductions in HbA1c, with a good overall tolerability profile and low incidence of hypoglycemia compared with active control or placebo. Study results indicated that alogliptin co-administered with either metformin or pioglitazone produced significant improvements in glycemic control compared with the respective free-dose therapies.

About Takeda Pharmaceutical Company Limited
Located in Osaka, Japan, Takeda is a research-based global company with its main focus on pharmaceuticals. As the largest pharmaceutical company in Japan and one of the global leaders of the industry, Takeda is committed to strive towards better health for people worldwide through leading innovation in medicine. Additional information about Takeda is available through its corporate website, www.takeda.com.

This press release contains forward-looking statements. Forward-looking statements include statements regarding Takeda's plans, outlook, strategies, results for the future, and other statements that are not descriptions of historical facts. Forward-looking statements may be identified by the use of forward-looking words such as "may," "believe," "will," "expect," "project," "estimate," "should," "anticipate," "plan," "assume," "continue," "seek," "pro forma," "potential," "target," "forecast," "guidance," "outlook" or "intend" or other similar words or expressions of the negative thereof. Forward-looking statements are based on estimates and assumptions made by management that are believed to be reasonable, though they are inherently uncertain and difficult to predict. Investors are cautioned not to unduly rely on such forward-looking statements.

Forward-looking statements involve risks and uncertainties that could cause actual results or experience to differ materially from that expressed or implied by the forward-looking statements. Some of these risks and uncertainties include, but are not limited to, (1) the economic circumstances surrounding Takeda's business, including general economic conditions in Japan, the United States and worldwide; (2) competitive pressures and developments; (3) applicable laws and regulations; (4) the success or failure of product development programs; (5) actions of regulatory authorities and the timing thereof; (6) changes in

exchange rates; (7) claims or concerns regarding the safety or efficacy of marketed products or product candidates in development; and (8) integration activities with acquired companies.

The forward-looking statements contained in this press release speak only as of the date of this press release, and Takeda undertakes no obligation to revise or update any forward-looking statements to reflect new information, future events or circumstances after the date of the forward-looking statement. If Takeda does update or correct one or more of these statements, investors and others should not conclude that Takeda will make additional updates or corrections.

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Contacts:
Elissa J. Johnsen
Takeda Pharmaceuticals International, Inc.
+1-224-554-3185
elissa.johnsen@takeda.com

Corporate Communications Department
Takeda Pharmaceutical Company Limited
+81-3-3278-2037

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[i] International Diabetes Federation (IDF). Diabetes Atlas Update 2012. http://www.idf.org/diabetesatlas/5e/Update2012. Accessed August 15, 2013.

[ii] International Diabetes Federation (IDF). Diabetes Atlas, 5th ed., 2012 Global Healthcare Expenditures. Available at: http://www.idf.org/diabetesatlas/5e/healthcare-expenditures. Accessed August 15, 2013.