Results of the SAVOR-TIMI53 clinical trial for Onglyza® will be presented at the European Society of Cardiology Congress and published in The New England Journal of Medicine

Tokyo, Japan, September 2, 2013 -- Kyowa Hakko Kirin Co., Ltd. (Tokyo:4151, President and CEO: Nobuo Hanai, "Kyowa Hakko Kirin") announced that Bristol-Myers Squibb Company (Princeton, N.J., USA, President and CEO: Lamberto Andreotti), who has licensed out Onglyza® (saxagliptin hydrate) to Kyowa Hakko Kirin for Japanese market, put out a press release with AstraZeneca starting that results of the clinical trial for Onglyza®, called SAVOR-TIMI53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) will be presented on the European Society of Cardiology and published in The New England Journal of Medicine.

~ The excerpt from the press release which Bristol Myers Squibb and AstraZeneca put out is following ~

Onglyza® (saxagliptin) Achieves Primary Safety Endpoint, Demonstrating No Increased Risk for Cardiovascular Death, Heart Attack or Stroke in SAVOR Cardiovascular Outcomes Trial

- *SAVOR provides information on cardiovascular safety for Onglyza in the wake of past questions about cardiovascular safety of type 2 diabetes treatments*
- *SAVOR is the largest cardiovascular outcomes trial to study a diverse population of type 2 diabetes patients at high risk for cardiovascular events*
- *Onglyza did not meet the primary efficacy endpoint of superiority to placebo*
- *In additional analyses, patients treated with Onglyza had improved glycemic control* over two years

(WILMINGTON, Del., and PRINCETON, N.J., September 2, 2013) – AstraZeneca (NYSE: AZN) and Bristol-Myers Squibb Company (NYSE: BMY) today announced the full results of the SAVOR clinical trial in 16,492 adult patients with type 2 diabetes at high risk for cardiovascular events. In this study, Onglyza® (saxagliptin) met the primary safety objective, demonstrating no increased risk for the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal ischemic stroke, when added to a patient's current standard of care (with or without other anti-diabetic therapies), as compared to placebo. Onglyza did not meet the primary efficacy endpoint of superiority to placebo for the same composite endpoint. Patients treated with Onglyza experienced improved glycemic control and reduced development and progression of microalbuminuria over two years as assessed in exploratory analyses.

The major secondary composite endpoint of cardiovascular death, non-fatal MI, non-fatal ischemic stroke and hospitalization for heart failure, unstable angina and coronary revascularization was balanced across the two arms. One component of the composite secondary endpoint, hospitalization for heart failure, occurred more in the Onglyza group compared to placebo. Rates of pancreatitis were low and balanced between Onglyza and placebo. Overall rates of malignancy were balanced, and the observed rates of pancreatic cancer were lower in the Onglyza group than in the placebo group. More patients in the Onglyza group reported at least one hypoglycemic event compared to placebo. Results were presented today during a Hot Line session at the ESC Congress 2013 in Amsterdam, Netherlands, and published in The New England Journal of Medicine.

In the past, questions have been raised about the safety of many diabetes treatments, in particular regarding their impact on the risk of cardiovascular death, heart attack or stroke. Led by the academic research organizations TIMI Study Group and Hadassah University Medical Center and conducted at more than 700 sites worldwide, SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) was a randomized, double-blind, placebo-controlled trial of 16,492 patients designed to evaluate the cardiovascular safety and efficacy of Onglyza(Saxagliptin) in adults with type 2 diabetes at risk for cardiovascular death, heart attack and stroke, compared to placebo.

Study Results

In the study, the primary composite safety endpoint of cardiovascular death, non-fatal MI or non-fatal ischemic stroke occurred in 613 patients (7.3%) in the Onglyza group vs. 609 patients (7.2%) in the placebo group (Hazard Ratio [HR]: 1.00; 95% Confidence Interval [CI]: 0.89, 1.12; non-inferiority p-value < 0.001; superiority p-value = 0.99). The major secondary endpoint, consisting of the primary composite endpoint and hospitalization for heart failure, unstable angina or coronary revascularization, occurred in 1,059 patients (12.8%) in the Onglyza(Saxagliptin) group vs. 1,034 patients (12.4%) in the placebo group (HR: 1.02; 95% CI: 0.94, 1.11; p-value = 0.66). Hospitalization for heart failure, a component of this secondary composite endpoint, occurred at a greater rate in the Onglyza group (3.5%) than in the placebo group (2.8%) (HR: 1.27; 95% CI: 1.07, 1.51; p-value = 0.007). The pre-specified secondary endpoint of all-cause mortality occurred in 420 patients (4.9%) in the Onglyza group compared to 378 patients (4.2%) in the placebo group (HR: 1.11; 95% CI: 0.96, 1.27; p-value = 0.15).

Study physicians were allowed to actively manage patients' glucose through concomitant use of other anti-diabetic drugs and dose titration. Fewer patients in the

Onglyza group required the addition or increase of any new anti-diabetic medication compared to placebo (1,938 patients [23.7%] vs. 2,385 patients [29.3%], respectively; HR: 0.77; 95% CI: 0.73, 0.82; p-value < 0.001) or the initiation of insulin therapy for more than 3 months (454 patients [5.5%] vs. 634 patients [7.8%], respectively; HR: 0.70; 95% CI: 0.62, 0.79; p-value < 0.001).1 Patients in the Onglyza group had greater reductions in blood sugar levels both from baseline and compared to those in the placebo group, with mean reductions in glycosylated hemoglobin (HbA1c) levels of 0.5% at two years of treatment in the Onglyza group vs. 0.2% in the placebo group (p-value < 0.001).

More patients in the Onglyza group achieved or maintained goal HbA1c of less than 7% compared to those in the placebo group at two years (40.0% vs. 30.3%; p-value < 0.001).

A total of 1,264 patients (15.3%) in the Onglyza group reported at least one hypoglycemic event compared to 1,104 (13.4%) in the placebo group (p-value < 0.001), which included patients with both major (177 patients [2.1%] vs. 140 patients [1.7%]; p-value = 0.047) and minor (1,172 patients [14.2%] vs. 1,028 patients [12.5%]; p-value = 0.002) events for the Onglyza and placebo groups, respectively. Hospitalization for hypoglycemia was infrequent and similar between groups (0.6% vs. 0.5%; p-value = 0.33).

Patients in the Onglyza group experienced reduced development and progression of microalbuminuria, and were more likely to have an improved albumin:creatinine ratio at two years (372 patients [11.1%] in the Onglyza group vs. 295 patients [9.2%] in the placebo group), and less likely to have a worsening ratio (414 patients [12.4%] in the Onglyza group vs. 457 patients [14.2%] in the placebo group), compared to placebo.

A number of pre-specified safety endpoints for diabetes treatments were evaluated (pancreatitis, cancer, liver abnormalities, renal abnormalities, thrombocytopenia, lymphocytopenia, infections, hypersensitivity or skin reactions, bone fractures and hypoglycemia).

All suspected cases of pancreatitis were independently reviewed and adjudicated by a committee of medical experts external to the sponsors and investigators. Pancreatitis occurred infrequently and the number of patients with acute or chronic pancreatitis was similar between the treatment groups (24 [0.3%] in the Onglyza group vs. 21 [0.3%], in the placebo group; p-value = 0.77). Definite/possible acute pancreatitis occurred in 22 patients (0.3%) in the Onglyza group vs. 16 patients (0.2%) in the placebo group (p-value = 0.42); definite acute pancreatitis in 17 patients (0.2%) vs. 9 patients (0.1%) (p-value = 0.17); and chronic pancreatitis in two patients (< 0.1%) vs. 6 patients (0.1%) (p-value = 0.18), respectively. There were five cases of pancreatic cancer in the Onglyza group and 12 cases in the placebo group (p-value = 0.095). Renal

abnormalities were observed more frequently in the Onglyza group compared to the placebo group (5.8% vs. 5.1%, respectively; p-value = 0.04). The incidence of the other pre-specified safety endpoints were balanced between the two groups.

Study Design

The study included 16,492 adult patients with type 2 diabetes, 8,280 of whom were randomized to receive Onglyza and 8,212 of whom were randomized to receive placebo.

Recruitment included patients with type 2 diabetes and baseline HbA1c levels of 6.5% to 12% on any diabetes treatment including diet, insulin and/or oral therapy (excluding GLP-1 agonists and DPP-4 inhibitors) who were at elevated risk for cardiovascular events according to two categories:

- Patients ≥ 40 years of age with established cardiovascular disease, defined as ischemic heart disease, peripheral vascular disease or ischemic stroke.
- Males ≥ 55 years of age and females ≥ 60 years of age with at least one of the following risk factors: dyslipidemia, hypertension or current smoking, but without established cardiovascular disease.

Further grouping was based on renal function, including patients with normal/mild (eGFR > 50 mL/min), moderate (30 - 50 mL/min) or severe (eGFR < 30 mL/min) renal impairment.

The primary safety objective was to establish that the upper bound of the 95% confidence interval for the estimated risk ratio comparing the incidence of the composite endpoint (cardiovascular death, non-fatal MI or non-fatal ischemic stroke) observed with Onglyza to that observed in the placebo group was less than 1.3. The primary efficacy objective was to determine, as a superiority assessment, whether treatment with Onglyza compared to placebo when added to current background therapy would result in a reduction in the composite endpoint of cardiovascular death, non-fatal MI or non-fatal ischemic stroke in patients with type 2 diabetes. Secondary efficacy objectives included a reduction in the primary composite endpoint together with hospitalization for heart failure, coronary revascularization or unstable angina pectoris and reduction of all-cause mortality. Secondary safety objectives included the evaluation of safety and tolerability by assessment of overall adverse events and adverse events of special interest.

Patients were randomized between May 2010 and December 2011. The median follow-up was 2.1 years and maximum follow-up was 2.9 years.