Subanalyses of the SAVOR clinical trial for Onglyza® will be presented at the 49th Annual Meeting of the European Association for the Study of Diabetes

Tokyo, Japan, September 26, 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 from a subanalysis of the clinical trial for Onglyza®, called SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) will be presented at the 49th Annual meeting of the European Association for the Study of Diabetes.

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

New Hypoglycemia and Pancreatitis Subanalyses from the Onglyza® (saxagliptin) SAVOR Cardiovascular Outcomes Trial Presented at the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD)

- No increased rate of hypoglycemia when Onglyza was added to metformin monotherapy compared to placebo
- Higher rates of hypoglycemia compared to placebo only observed in patients receiving Onglyza in combination with sulfonylureas, agents known to cause hypoglycemia
- More patients taking Onglyza vs. placebo achieved target HbA1c without hypoglycemia, except those who had received sulfonylureas alone at baseline
- Rates of pancreatitis were balanced between the Onglyza and placebo groups and majority of cases resolved without study treatment being withdrawn
- Overall incidence of adverse events similar between Onglyza and placebo

(WILMINGTON, Del., and PRINCETON, N.J., September 26, 2013) – AstraZeneca (NYSE: AZN) and Bristol-Myers Squibb Company (NYSE: BMY) today announced additional results from the SAVOR cardiovascular outcomes trial, which found no increased rate of hypoglycemia among patients treated with Onglyza® (saxagliptin) compared to placebo when added to metformin monotherapy and higher rates of hypoglycemia only in the Onglyza group compared to the placebo group among patients taking sulfonylureas, agents known to cause hypoglycemia, at baseline. Additionally, a greater percentage of patients taking Onglyza reached their target HbA1c without

hypoglycemia, except patients who were treated with sulfonylureas alone at baseline. These findings are consistent with previous studies of Onglyza. Results were presented today at the 49th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Barcelona, Spain.

"Treating diabetes often requires the use of multiple therapies to help lower blood glucose levels without increasing the risk of hypoglycemia," said Itamar Raz, MD, Co-Primary Study Investigator and Head of the Diabetes Unit, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel. "In a post-hoc analysis from SAVOR, the data reflected that when saxagliptin was used in combination with metformin, there was a lowering of blood sugar and no increase in the risk of hypoglycemia."

Additionally, results from SAVOR found rates of any events of adjudication-confirmed pancreatitis were balanced between the Onglyza and placebo treatment groups (24 patients in the Onglyza arm versus 21 patients in the placebo arm). Moreover, in patients who experienced pancreatitis, the duration of the event, study drug actions and outcome of the adverse event were balanced across the two treatment arms. Observed rates of pancreatic cancer were also low (five patients in the Onglyza arm versus 12 patients in the placebo arm).

"Recent discussions regarding the pancreatic safety of some type 2 diabetes medicines, including incretin-based therapies such as DPP-4 inhibitors, have been largely based on non-randomized studies with significant limitations," said Prof. Raz. "SAVOR is the first large-scale, randomized, blinded study of a type 2 diabetes treatment to report an adjudicated review of pancreatitis events, and results from this trial showed no overall increased risk of pancreatitis or pancreatic cancer in patients taking saxagliptin."

Study Results

SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus), a randomized, double-blind, placebo-controlled trial of 16,492 adult patients with type 2 diabetes, was designed to minimize glycemic control differences between Onglyza and placebo by allowing study physicians to actively manage blood glucose through use of additional antidiabetic drugs or dose titration.

In this assessment of hypoglycemia, patients were analyzed by antidiabetic medication at baseline (not treated with antidiabetic drugs, treated with metformin alone, treated with sulfonylurea, treated with insulin alone or treated with insulin in combination with other antidiabetic drugs) and HbA1c at baseline (entire study population, HbA1c < 7% or HbA1c ≥ 7%). Results showed there was no significant increase in the incidence of hypoglycemia with Onglyza compared to placebo when added to patients who were treated with metformin alone (2.4 events per 100 patient years for Onglyza versus 2.6

for placebo; Hazard Ratio [HR]: 0.92), insulin alone (17.4 events per 100 patient years for both the Onglyza and placebo groups; HR: 1.00), or patients not treated with other antidiabetic medications at baseline (3.0 events per 100 patient years for Onglyza versus 2.1 for placebo; HR: 1.44), regardless of baseline HbA1c. There was an increased incidence of hypoglycemia with Onglyza compared to placebo in patients who were taking a sulfonylurea (a class of agents known to cause hypoglycemia) at baseline, regardless of HbA1c (9.7 events per 100 patient years for Onglyza versus 6.8 for placebo; HR: 1.42) and in patients who were treated with insulin in combination with other antidiabetic drugs, but only those with a baseline HbA1c < 7% (HR: 1.42). There was no increase in rates of major hypoglycemia between Onglyza and placebo, in any subgroup, other than patients taking sulfonylurea with baseline HbA1c < 7% (HR: 2.24). At two years, the percentage of patients achieving HbA1c < 7% without hypoglycemic events was greater among patients who were treated with Onglyza and metformin alone (36.1% vs. 23.6%), insulin alone (12.1% vs. 7.6%) or other antidiabetic medications (16.1% vs. 11.4%), compared to placebo. Among patients treated with Onglyza and sulfonylurea alone, fewer patients (20.6% vs. 22.4%) achieved their target HbA1c without hypoglycemia compared to placebo.

The SAVOR trial also included evaluation of possible events of pancreatitis and pancreatic cancer, which were reported by investigators. All reports of pancreatitis were, in addition, adjudicated without knowledge of treatment assignment by an independent external expert committee, which included two pancreatic disease experts. Reported cases of pancreatitis were classified into four categories: definite acute pancreatitis, possible acute pancreatitis, chronic pancreatitis or unlikely to be pancreatitis.

Overall, a total of 33 patients treated with Onglyza and 30 patients who received placebo were reported by investigators to have pancreatitis, with 35 cases in each group. By adjudication, pancreatitis was confirmed in 24 patients (26 cases) in the Onglyza arm versus 21 patients (25 cases) in the placebo arm. Additional results from the adjudicated analysis on pancreatitis found that:

- Definite or possible acute pancreatitis was observed in 38 patients, 22 patients in the Onglyza arm versus 16 patients in the placebo arm. Out of these patients, 17 (0.2%) in the Onglyza arm and nine (0.1%) in the placebo arm were classified as having definite acute pancreatitis.
- Recovery rates from pancreatitis were similar between the two treatment groups (21 patients [80.8%] in the Onglyza arm versus 21 patients [84.0%] in the placebo arm were resolved, three patients [11.5%] versus one patient [4.0%] was recovering, two patients [7.7%] versus one patient [4.0%] was not resolved, zero patients versus one patient [4.0%] was resolved with sequelae and zero

patients vs. one patient [4.0%] died in the Onglyza and placebo groups, respectively).

- Chronic pancreatitis was reported in two patients (0.02%) in the Onglyza arm versus six patients (0.07%) in the placebo arm.
- Among patients with pancreatitis, the majority remained on treatment, with four patients (15.4%) discontinuing study medication and two patients (7.7%) interrupting study medication in the Onglyza arm versus six patients (24.0%) discontinuing study medication and one patient (4.0%) interrupting study medication in the placebo arm.
- Pancreatic cancer was reported in five patients in the Onglyza arm versus 12 patients in the placebo arm (p-value = 0.095).

Primary Study Results and Study Design

The primary study results from the SAVOR trial were presented at the 2013 European Society of Cardiology (ESC) Congress in Amsterdam, Netherlands and published in The New England Journal of Medicine.

Led by the academic research organizations TIMI Study Group and Hadassah University Medical Center and conducted at more than 700 sites worldwide, SAVOR was a randomized, double-blind, placebo-controlled trial designed to evaluate the cardiovascular safety and efficacy of Onglyza in adults with type 2 diabetes at risk for cardiovascular death, heart attack and stroke, compared to placebo.

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% and < 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 myocardial infarction [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.

Results from the primary analysis of SAVOR found that the primary composite 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 (HR: 1.00; 95% Confidence Interval [CI]: 0.89, 1.12; non-inferiority p-value < 0.001). Onglyza did not meet the primary efficacy endpoint of superiority to placebo for the same composite endpoint (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 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).

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