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)

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• 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were balanced between the Onglyza and placebo groups and majority of cases resolved without study treatment being withdrawn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. & PRINCETON, N.J. --(BUSINESS WIRE)-- 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 (2.6 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).

About Onglyza (saxagliptin)

As of September 2013, Onglyza is approved in 86 countries including those in the European Union, the United States, Canada, Mexico, India, Brazil and China.

Indication and Limitations of Use for Onglyza

Onglyza is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

Onglyza should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Onglyza has not been studied in patients with a history of pancreatitis.

Important Safety Information for Onglyza

Contraindications

- History of a serious hypersensitivity reaction to Onglyza (e.g., anaphylaxis, angioedema, or exfoliative skin conditions)

Warnings and Precautions

- Pancreatitis: There have been post-marketing reports of acute pancreatitis in patients taking Onglyza. After initiating Onglyza, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue Onglyza and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using Onglyza.

- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin: When Onglyza was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with Onglyza.

- Hypersensitivity Reactions: There have been post-marketing reports of serious hypersensitivity reactions in patients treated with Onglyza, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with Onglyza, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue Onglyza, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in patients with a history of angioedema to another DPP-4 inhibitor as it is unknown whether they will be predisposed to angioedema with Onglyza.

- Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Onglyza or any other antidiabetic drug.

Most Common Adverse Reactions

- Most common adverse reactions reported in ≥5% of patients treated with Onglyza and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).

- When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for Onglyza 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

- Confirmed hypoglycemia was reported more commonly in patients treated with Onglyza 2.5 mg and Onglyza 5 mg compared to placebo in the add-on to glyburide trial (2.4%, 0.8% and 0.7%, respectively), with Onglyza 5 mg compared to placebo in the add-on to insulin (with or without metformin) trial (5.3% and 3.3%, respectively), with Onglyza 2.5 mg compared to placebo in the renal impairment trial (4.7% and 3.5%, respectively), and with Onglyza 5 mg compared to placebo in the add-on to metformin plus sulfonylurea trial (1.6% and 0.0%, respectively).
Drug Interactions

Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of Onglyza should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Patients with Renal Impairment**: The dose of Onglyza is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min). Onglyza should be administered following hemodialysis. Onglyza has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of Onglyza and periodically thereafter.

- **Pregnant and Nursing Women**: There are no adequate and well-controlled studies in pregnant women. Onglyza, like other anti diabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when Onglyza is administered to a nursing woman.

- **Pediatric Patients**: Safety and effectiveness of Onglyza in pediatric patients have not been established.

*Please click here for full U.S. Prescribing Information and Medication Guide for Onglyza (saxagliptin).*

About Diabetes

In 2012, diabetes was estimated to affect more than 370 million people worldwide. The prevalence of diabetes is projected to reach more than 550 million by 2030. Type 2 diabetes accounts for approximately 90% to 95% of all cases of diagnosed diabetes in adults. Type 2 diabetes is a chronic disease characterized by insulin resistance and dysfunction of beta cells in the pancreas, leading to elevated glucose levels. Over time, this sustained hyperglycemia contributes to further progression of the disease. Significant unmet needs still exist, as many patients remain inadequately controlled on their current glucose-lowering regimen.

The major cause of death and complications in patients with type 2 diabetes is cardiovascular disease. As many as 80% of patients with type 2 diabetes will develop and possibly die from a cardiovascular event.

About the AstraZeneca / Bristol-Myers Squibb Diabetes Alliance

Dedicated to addressing the global burden of diabetes by advancing individualized patient care, AstraZeneca and Bristol-Myers Squibb are working in collaboration to research, develop and commercialize a versatile portfolio of innovative treatment options for diabetes and related metabolic disorders that aim to provide treatment effects beyond glucose control. Find out more about the Alliance and our commitment to meeting the needs of health care professionals and people with diabetes at [www.astrazeneca.com](http://www.astrazeneca.com) or [www.bms.com](http://www.bms.com).

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business with a primary focus on the discovery, development and commercialization of prescription medicines for gastrointestinal, cardiovascular, neuroscience, respiratory and inflammation, oncology and infectious disease. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: [www.astrazeneca.com](http://www.astrazeneca.com).

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [http://www.bms.com](http://www.bms.com) or follow us on Twitter at [http://twitter.com/bmsnews](http://twitter.com/bmsnews).

AstraZeneca Cautionary Statement Regarding Forward-Looking Statement

*In order, among other things, to utilise the 'safe harbour' provisions of the US Private Securities Litigation Reform Act 1995, we are providing the following cautionary statement: This press release contains certain forward-looking statements with respect to the operations, performance and financial condition of the Group. Although we believe our expectations are based on reasonable assumptions, any forward-looking statements, by their very nature, involve risks and uncertainties and may be influenced by factors that could cause actual outcomes and results to be materially different from those predicted. The forward looking statements reflect knowledge and information available at the date of preparation of this press release and AstraZeneca undertakes no obligation to update these forward-looking statements. We identify the forward-looking statements by using the words 'anticipates', 'believes', 'expects', 'intends' and similar expressions in such statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things: the loss or expiration of patents; marketing exclusivity or trade marks, or the risk of failure to obtain patent protection; the risk of substantial adverse litigation/government investigation claims and insufficient insurance coverage; exchange rate fluctuations; the risk that R&D will not yield new products that achieve commercial success; the risk that strategic alliances and acquisitions will be unsuccessful; the impact of competition, price controls and price reductions; taxation risks; the risk of substantial product liability claims; the impact of any failure by third parties to supply materials or services; the risk of failure to manage a crisis; the risk of delay to new product launches; the difficulties of obtaining and maintaining regulatory approvals for products; the risk of failure to observe ongoing regulatory oversight; the risk that new products do not perform as we expect; the risk of environmental liabilities; the risks associated with conducting business in emerging markets; the risk of reputational damage; the risk of product counterfeiting; the risk of failure to successfully implement planned cost reduction measures through productivity initiatives and restructuring programmes; the risk that regulatory approval processes for biosimilars could have an adverse effect on future commercial prospects; and the impact of increasing implementation and enforcement of more stringent anti-bribery and anti-corruption legislation. Nothing in this press release should be construed as a profit forecast.*
Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2012, in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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