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

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- 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. & PRINCETON, N.J.--(BUSINESS WIRE)-- 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 or hospitalization for heart failure, unstable angina or 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.

“Given the correlation between diabetes and cardiovascular complications, there is a need for thorough assessments of the cardiovascular risks among therapies that improve glycemic control,” said Deepak L. Bhatt, MD, MPH, Senior Investigator of the TIMI Study Group, Brigham and Women’s Hospital, and a Principal Investigator for the trial. “The results from SAVOR add important evidence to the overall body of data to further define the clinical profile of saxagliptin for the treatment of type 2 diabetes.”

“No other DPP-4 inhibitor and few other anti-hyperglycemic agents have been studied as extensively as Onglyza to address the question of cardiovascular safety,” said Brian Daniels, MD, senior vice president, Global Development and Medical Affairs, Research and Development, Bristol-Myers Squibb. “Bristol-Myers Squibb and AstraZeneca are dedicated to meeting needs of physicians and patients in diabetes care and helping to ensure a better understanding of the value of our medications.”
“SAVOR is an important contribution to our knowledge of the safety of Onglyza in type 2 diabetes patients at an increased risk for cardiovascular events similar to those found in a real-world population,” said Briggs Morrison, MD, executive vice president, Global Medicines Development, AstraZeneca. “In addition, the data on pancreatitis and pancreatic cancer in a study of more than 16,000 patients provide important and timely scientific information from a robust, randomized trial for the diabetes community.”

Study Results

In the study, 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 (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 three months (454 patients [5.5%] vs. 634 patients [7.8%], respectively; HR: 0.70; 95% CI: 0.62, 0.79; p-value < 0.001). 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 seven percent 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 (14.4%) 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 (saxagliptin) 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. nine patients (0.1%) (p-value = 0.17); and chronic pancreatitis in two patients (< 0.1%) vs. six 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 was 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.

**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 (e.g., 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 antidiabetic 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.
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 or 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.

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 or follow us on Twitter at 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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