News Release

AstraZeneca

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 glycaemic control over two years

AstraZeneca and Bristol-Myers Squibb 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 ischaemic 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 glycaemic 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 ischaemic stroke or hospitalisation for heart failure, unstable angina or coronary revascularization was balanced across the two arms. One component of the composite secondary endpoint, hospitalisation 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 hypoglycaemic 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 randomised, double-blind, placebo-controlled trial of 16,492 patients 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.

"Given the correlation between diabetes and cardiovascular complications, there is a need for thorough assessments of the cardiovascular risks among therapies that improve glycaemic 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-hyperglycaemic 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, randomised trial for the diabetes community."

Study Results

In the study, the primary composite endpoint of cardiovascular death, non-fatal MI or non-fatal ischaemic 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 hospitalisation 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). Hospitalisation 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 hypoglycaemic 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. Hospitalisation for hypoglycaemia 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 hypoglycaemia).

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. 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 randomised to receive *Onglyza* and 8,212 of whom were randomised 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 ischaemic heart disease, peripheral vascular disease or ischaemic 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 ischaemic 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 ischaemic stroke in patients with type 2 diabetes. Secondary efficacy objectives included a reduction in the primary composite endpoint together with hospitalisation 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 randomised between May 2010 and December 2011. The median follow-up was 2.1 years and maximum follow-up was 2.9 years.

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NOTES TO EDITORS

About *Onglyza*® (saxagliptin)
Onglyza is indicated as an adjunct to diet and exercise to improve glycemic (blood sugar) control in adults with type 2 diabetes mellitus in multiple clinical settings. *Onglyza* should not be used for the treatment of patients with type 1 diabetes mellitus or diabetic ketoacidosis (increased levels of ketones in the blood or urine), as it would not be effective in these settings. *Onglyza* has not been studied in patients with a history of pancreatitis.

Onglyza is contraindicated in patients with a history of a serious hypersensitivity reaction to *Onglyza* (e.g., anaphylaxis, angioedema or exfoliative skin conditions). There have been post-marketing reports of acute pancreatitis and serious hypersensitivity reactions in patients taking *Onglyza*. If pancreatitis or a serious hypersensitivity reaction is suspected, promptly discontinue *Onglyza* and institute appropriate medical treatment. It is unknown whether patients with a history of pancreatitis are at an increased risk for development of pancreatitis while using *Onglyza*.

When *Onglyza* was used in combination with a sulfonylurea or with insulin (two 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*.

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.

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 characterised by insulin resistance and dysfunction of beta cells in the pancreas, leading to elevated glucose levels. Over time, this sustained hyperglycaemia 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 individualised patient care, AstraZeneca and Bristol-Myers Squibb are working in collaboration to research, develop and commercialise 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 that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. 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.

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