NEW REAL-WORLD DATA ANALYSIS FINDS NO EVIDENCE OF INCREASED RISK OF HOSPITALISATION FOR HEART FAILURE WITH SAXAGLIPTIN COMPARED WITH SITAGLIPTIN

Study also found no evidence of increased risk of hospitalisation for heart failure for DPP-4 inhibitors compared with sulfonylureas

8 June, 2015
AstraZeneca today presented results from an observational, retrospective claims database study, which found no evidence of increased risk of hospitalisation for heart failure (hHF) with saxagliptin, compared with sitagliptin, both of which are dipeptidyl peptidase-4 (DPP-4) inhibitors, in patients with type 2 diabetes.1
A similar finding was obtained when comparing the overall DPP-4 class to sulfonylureas. However, among patients without prior cardiovascular disease (CVD), DPP-4 treatment was associated with statistically significant lower risk for hHF compared to treatment with sulfonylureas. These data were presented this week during a late-breaker poster session at the 75th Scientific Sessions of the American Diabetes Association (ADA) in Boston, 5-9 June 2015.1

"These new data provide valuable real-world information regarding the cardiovascular safety of the DPP-4 inhibitor class in patients with type 2 diabetes," said Alex Fu, PhD, Principal Investigator for this study and Associate Professor, Georgetown University Medical Center, Washington, D.C. "In particular, the study findings provide new information on the risk of hospitalisation for heart failure for DPP-4 inhibitors, and specifically for saxagliptin relative to sitagliptin, within this class."

This real-world evidence study used a retrospective, observational, new-user cohort design comprised of US inpatient medical, outpatient medical, and outpatient pharmacy claims data for patients with type 2 diabetes from August 2010 to August 2013. Both commercial and Medicare databases were part of the analysis. Analyses of the claims were stratified by the presence or absence of baseline CVD, which was defined as patients having at least one medical claim with any CVD code, and those without CVD. Patients in the comparator groups were matched for demographic, clinical and hHF risk factors using propensity score matching.1

For the comparison of saxagliptin versus sitagliptin for the risk of hHF, more than 100,000 patients were included. For patients with baseline CVD, the hazard ratio (HR) was 0.95: 95% confidence interval (CI): 0.70, 1.28. For patients with no baseline CVD, the HR was 0.99: 95% CI: 0.56, 1.75.1
For the comparison of DPP-4 inhibitors versus sulfonylureas, more than 200,000 patients were included. For patients with CVD at baseline, the HR was 0.95: 95% CI: 0.78, 1.15. For patients with no baseline CVD, the HR was 0.59: 95% CI: 0.38, 0.89.1

Secondary outcomes of this retrospective, observational analysis, including hospitalisation for acute myocardial infarction, stroke, unstable angina; coronary revascularisation; and a composite of all outcomes together, including hHF, were consistent with the primary findings of this study.1 While the study observations provide important information, all retrospective claims database studies have inherent limitations that include the potential for bias due to their retrospective non-randomised design and the potential for incomplete or inaccurate claims data.1

In October 2013, the New England Journal of Medicine published results from the SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) study, a large, randomised, double-blind, placebo-controlled Phase IV clinical trial in patients with type 2 diabetes at high risk of CVD, designed and conducted in accordance with the 2008 FDA guidance, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." Patients who participated in SAVOR were to have either a history of established CVD or multiple risk factors for vascular disease, including renal impairment. The primary objective of this trial was to determine that the addition of saxagliptin to standard of care in this patient population did not significantly increase the incidence of major

cardiovascular events as compared with placebo.2

SAVOR met the primary safety objective, demonstrating that saxagliptin did not increase the risk for cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal ischaemic stroke when added to a patient's current standard of care (with or without other antidiabetic therapies), as compared with placebo (613 patients [3.7 per 100 person-years] in the saxagliptin group compared with 609 patients [3.7 per 100 person-years] in the placebo group (HR: 1.00; [95% CI: 0.89, 1.12]; non-inferiority p-value < 0.001; superiority p-value = 0.99).2

For the secondary endpoint of nonfatal MI, nonfatal stroke, cardiovascular death, hospitalisation for heart failure, hospitalisation for unstable angina, or hospitalisation for coronary revascularisation, no treatment differences were observed between saxagliptin and placebo (HR 1.02 [95% CI 0.94, 1.11]; nominal p=0.66 for a difference between the two treatment groups). However, an increased risk for hHF, a component of the balanced secondary endpoint, was observed with saxagliptin treatment. The analysis showed a numerical imbalance with more events on saxagliptin [289 (3.5% and 228 (2.8%) (HR 1.27 [95% CI 1.07, 1.51]; nominal p=0.007), although a causal relationship has not been established. Caution is warranted if saxagliptin is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms. AstraZeneca is committed to patient safety and continues to work with regulatory agencies to ensure further the SAVOR findings are appropriately communicated in prescribing information.

NOTES TO EDITORS

About ONGLYZA (saxagliptin)
As of March 2015, ONGLYZA is approved in more than 90 countries, including those in the European Union, the United States, Canada, Mexico, India, Brazil and China.

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.

About DPP-4 Inhibitors
Saxagliptin belongs to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors. Incretin hormones decrease elevated blood sugar levels (glucose) by increasing the body's utilization of sugar, mainly through increasing insulin production in the pancreas, and by reducing the liver's production of glucose. DPP-4 inhibitors work by increasing the activity of the incretin hormones, increasing the release of insulin when glucose levels are elevated and reducing the levels of sugar produced by the liver.

About Type 2 Diabetes
Diabetes is estimated to affect 29.1 million people in the U.S.3 and more than 382 million people worldwide.4 The prevalence of diabetes is projected to reach more than 592 million people worldwide by 2035. Type 2 diabetes accounts for approximately 90-95 percent of all cases of diagnosed diabetes in the U.S.1 Type 2 diabetes is a chronic disease5 characterised by pathophysiologic defects leading to elevated glucose levels.6 Significant unmet needs still exist, as many patients remain inadequately controlled on their current glucose-lowering regimen.7 It is estimated that more than half of people living with type 2 diabetes are not achieving recommended HbA1c goals based on guidelines established by professional societies and advocacy organisations for diabetes management.8

About AstraZeneca in Diabetes
AstraZeneca is pushing the boundaries of science to create life-changing medicines that aim to reduce the global burden and complications of diabetes. Driven to redefine outcomes for diabetes patients, our current portfolio consists of the three newest classes of non-insulin, anti-diabetic treatments that support individualized treatment approaches: SGLT-2 inhibitors, GLP-1 receptor agonists and DPP-4 inhibitors. Our commitment to diabetes is exemplified by the depth and breadth of our global clinical research programme. This commitment is advancing understanding of the treatment effects of our diabetes medicines in broad patient populations, as well as exploring combination treatment approaches resulting in more patients achieving treatment success earlier in their disease progression. Our ambition is to reduce the long-term impact of diabetes. As a core strategic area for the company, we are focusing our research and development efforts in diverse populations and patients with significant co-morbidities, such as cardiovascular disease, heart failure, obesity, non-alcoholic steatohepatitis (NASH), and chronic kidney disease.

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.

1 Fu, A., et al. "Observational Study Comparing the Risk of Hospitalization for Heart Failure between Dipeptidyl Peptidase inhibtors vs. Sulfonlyureas and Saxaglitpin vs Sitagliptin." American Diabetes Association Scientific Sessions 2015. Abstract #164-LB
2 Scirica BM, et al. New England Journal of Medicine, 2013.10.1056/NEJMoa1307684; 2.
3 Center for Disease Control and Prevention. National Diabetes Statistics Report, 2014.Retrieved May 2015 from http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
4 International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Poster Update 2014. Available at: http://www.idf.org/diabetesatlas/update-2014. Accessed May 2015.
5 World Health Organization. Diabetes, Fact Sheet 312. Retrieved May 2015 from http://www.who.int/mediacentre/factsheets/fs312/en/
6 Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia. 2003;46:3-19.
7 Cheung B, Lond, Edin et al. Diabetes Prevalence and Therapeutic Target Achievement in the United States, 1999-2006. American Journal of Medicine. 2009;122:443-453.
8 Cook M.N., et al. "Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care." Diabetic Med 2007: 24; 350-358