

FDA REVIEWS SAVOR OUTCOMES STUDY RESULTS

FDA ADVISORY COMMITTEE REVIEWS SAVOR OUTCOMES STUDY RESULTS FOR ONGLYZA® (SAXAGLIPTIN) AND KOMBIGLYZE® XR (SAXAGLIPTIN AND METFORMIN HCl EXTENDED-RELEASE)

AstraZeneca today announced that the US Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) voted 13 to 1 (1 abstained; 15 total votes) that the results of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) study demonstrated that the use of saxagliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile. In addition, 14 out of 15 Committee members recommended that the FDA supplement the products' labeling to add new safety information, with one vote to withdraw saxagliptin from the market.

AstraZeneca will also conduct further investigation to better understand the signal of hospitalisation for heart failure found in the SAVOR results.

The Advisory Committee was asked to consider data from SAVOR, a large, randomised, double-blind, placebo-controlled postmarketing study designed to evaluate the cardiovascular effects of ONGLYZA when added to current type 2 diabetes background therapy in adult patients with type 2 diabetes mellitus at risk for cardiovascular disease.

SAVOR met the primary safety objective, demonstrating that ONGLYZA did not increase the risk for cardiovascular death, nonfatal myocardial infarction and nonfatal ischemic stroke when added to a patient's current standard of care, with or without other antidiabetic therapies, as compared to placebo. The supplemental New Drug Applications (sNDAs) based on the SAVOR results, if approved, will provide prescribers and patients important additional information about the benefit-risk profile of ONGLYZA and KOMBIGLYZE XR.

The Advisory Committee was convened to discuss previously submitted sNDAs to the FDA for ONGLYZA and KOMBIGLYZE XR. The FDA is not bound by the Advisory Committee's recommendation but takes its advice into consideration when reviewing these sNDAs. AstraZeneca remains committed to working closely with the FDA to support further review of these sNDAs.

About SAVOR

The SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) clinical trial of ONGLYZA (saxagliptin) was a large, randomised, double-blind, placebo-controlled Phase IV study in patients with type 2 diabetes at high risk of cardiovascular disease, designed and conducted in accordance with the 2008 FDA guidance, "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." 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 to placebo.

SAVOR met the primary safety objective, demonstrating that ONGLYZA did not increase the risk for cardiovascular death, nonfatal MI and nonfatal ischaemic stroke when added to a patient's current standard of care (with or without other antidiabetic therapies), as compared to placebo (613 patients [3.7 per 100 person-years] in the ONGLYZA group compared with 609 patients [3.7 per 100 person-years] 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)). ONGLYZA did not meet the primary efficacy objective of superiority to placebo for the same composite endpoint. For the secondary endpoint of nonfatal MI, nonfatal stroke, cardiovascular death, hospitalisation for heart failure (hHF), hospitalisation for unstable angina, or hospitalisation for coronary revascularization, no statistically significant treatment differences were observed between ONGLYZA and placebo (HR 1.02 [95% CI 0.94, 1.11]; nominal p=0.66 for a difference between the 2 treatment groups). However, an increased risk for hHF, a component of the balanced secondary endpoint, was observed with ONGLYZA treatment. The analysis showed a numerical imbalance with more events on ONGLYZA (HR 1.11 [95% CI 0.96, 1.27]; nominal p=0.154). This finding was most relevant for patients at increased risk for heart failure (HF), such as those with a history of HF or renal impairment, and is manageable in the context of the routine care of patients at risk for HF. The other secondary endpoint of the SAVOR study was all-cause mortality. The analysis showed a numerical imbalance with more events on ONGLYZA (HR 1.11 [95% CI 0.96, 1.27]; nominal p=0.154). The results of the evaluation of all-cause mortality indicate that there was no excess mortality attributable to saxagliptin in the SAVOR study.

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 utilisation 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 US and more than 382 million people worldwide. 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 US. Type 2 diabetes is a chronic disease characterised by pathophysiologic defects leading to elevated glucose levels. Significant unmet needs still exist, as many patients remain inadequately controlled on their current glucose-lowering regimen. 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.

About AstraZeneca in Diabetes

AstraZeneca is pushing the boundaries of science to create life-changing medicines to reduce the burden and complications of diabetes. Our comprehensive diabetes portfolio provides treatment options to patients throughout the different stage of their disease, supporting them to reach treatment goals with a mono or combination therapies. 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, NASH, and chronic kidney disease. Our research efforts are also targeting the regeneration of pancreatic cells aiming to address the

underlying cause of the disease. In partnership with diabetes professional and patient societies and associations, AstraZeneca is contributing to solutions supporting prevention, awareness, diagnosis, professional education and advance care for diabetic patients.

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

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15 April 2015

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