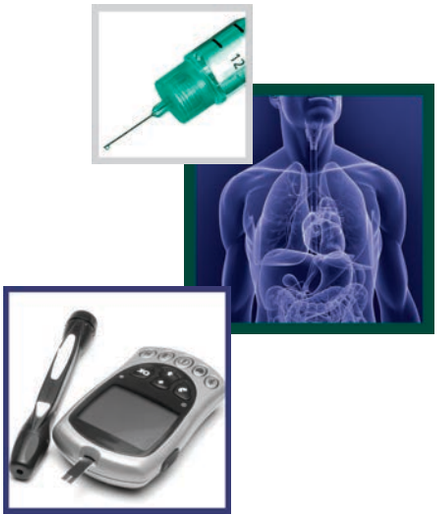
Primary safety end point achieved for Onglyza®



Drug demonstrates no increased risk of cardiovascular events in adults with Type 2 diabetes.

AstraZeneca and Bristol–Myers Squibb recently announced results from the SAVOR trial that patients with Type 2 diabetes who are at high risk of cardiovascular events had no increased risk of cardiovascular death, nonfatal myocardial infarction or nonfatal ischemic stroke when Onglyza® (saxagliptin) was added to their current treatment regimen.

There have been serious concerns raised in the past about the link between Type 2 diabetes treatments and cardiovascular events, such as stroke and heart attack. It is estimated that cardiovascular events could be the cause of death in as many as 80% of individuals with Type 2 diabetes. In this double-blind, placebo-controlled study, 16,492 patients with Type 2 diabetes with a high risk of cardiovascular events were randomized to received either Onglyza or placebo (n = 8280 and 8212, respectively). It was observed that cardiovascular death, nonfatal myocardial infarction or nonfatal ischemic stroke (i.e., the primary composite end point) occurred in 7.3% (n = 613) of individuals in the Onglyza group compared with 7.2% (n = 609) of individuals in the placebo group (hazard ratio: 1.00; 95% CI: 0.89–1.12; noninferiority $p < 0.001$; superiority $p = 0.99$). However, Onglyza did not meet the primary efficacy end point of superiority to placebo for the same composite end point. In addition, it was observed that there were greater reductions in blood sugar levels from baseline in the Onglyza group when compared with the placebo group. More individuals from the former group also achieved or maintained the goal HbA1c of less than 7% compared with the latter group at 2 years (40.0 vs 30.3%; $p < 0.001$).

Deepak Bhatt, from Brigham and Women's Hospital (MA, USA), a principal investigator for the trial, explained the importance of the research: "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. 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."

Onglyza is currently approved in 86 countries worldwide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. However, it is yet to be studied in patients with a history of pancreatitis.

Source: AstraZeneca press release: www.astrazeneca.com/Media/Press-releases/Article/20130902---onglyza-saxagliptin-achieves-primary-safety

Refined diabetes classification may be needed

A new study, published recently in *PLoS One*, reports that after comparing clinical and laboratory parameters in diabetic patients under the age of 20 years, patients with and without islet autoantibodies had different metabolic and genetic markers; however, an overlap of phenotypes was observed. The authors suggest that both immune and metabolic phenotyping may be needed for a refined diabetes classification.

Most diabetics under the age of 20 years have Type 1 diabetes, but the incidence of Type 2 diabetes in this population is increasing, resulting in more children and adolescents with diabetes worldwide. Previous work has indicated that some individuals exhibit phenotypes of both Type 1 and 2 diabetes and, therefore, insulin loss and insulin resistance must be considered when treating them.

Using the Diabetes Mellitus Incidence Cohort, the authors compared the clinical and laboratory parameters between islet autoantibody status in 630 individuals with diabetes (aged <20 years) in Bavaria (Germany). A total of 522 participants had two or more diabetes-specific antibodies, 64 had one antibody and 44 had no antibodies. Individuals within these three groups were significantly different in their BMI percentile, weight loss before diagnosis, fasting C-peptide ($p < 0.001$ for all) and IS Score ($p = 0.034$). It was observed that the phenotypic features could not be clearly assigned to a specific disease type.

> "In order to be able to introduce the right steps in treatment and to offer patients accurate information about their disease, it is essential to refine the criteria for differentiating and diagnosing the different forms of diabetes."

Anette-Gabriele Ziegler, one of the study authors, explained that although their study was limited by the low number of autoantibody-negative individuals, the results are exciting: "In order to be able to introduce the right steps in treatment and to offer patients accurate information about their disease, it is essential to refine the criteria for differentiating and diagnosing the different forms of diabetes. Further studies are now required to shed light on the long-term development of the phenotypes, the distribution of different types of diabetes and the way in which their features present themselves in adult patients."

Sources: Warncke K, Krasmann M, Puff R, Dunstheimer D, Ziegler AG, Beyerlein A. Does diabetes appear in distinct phenotypes in young people? Results of the Diabetes Mellitus Incidence Cohort Registry (DiMelli). *PLoS One* 8(9), e74339 (2013); Helmholtz Zentrum München press release: www.helmholtz-muenchen.de/en/news/latest-news/press-releases-2013/press-release/article/22313/index.html

Cognitive decline in diabetes may be predicted by urine test

A study, recently published in the *Clinical Journal of the American Society of Nephrology*, suggests that persistent and progressive albuminuria is linked with cognitive decline in individuals with diabetes.

The researchers from Kaiser Permanente (GA, USA), Emory School of Medicine (GA, USA) and the National Institute on Aging (MD, USA) recruited 2977 participants from the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes study (mean age: 62.5 ± 5.8 years) to undergo three neuropsychologic tests at baseline, 20 and 40 months. It was observed that individuals with persistent albuminuria (-5.8%; 95% CI: -7.3 to -4.2) and progressive albuminuria (-4.1%; 95% CI: -5.6 to -2.7) had greater percentage declines on information processing speed when compared with individuals with no albuminuria (-2.6%; 95% CI: -3.4 to -1.9; $p = 0.001$ and $p = 0.10$, respectively).

Joshua Barzilay, Kaiser Permanente of Georgia and Emory School of Medicine, explained: "Our finding was a subtle change in cognition. However, were this decline to continue over 10 to 15 years it could translate into noticeable cognitive decline by the age of 75 to 80 years, when cognitive impairment generally becomes clinically evident."

Although the results suggest that persistent and progressive albuminuria is linked with cognitive decline in individuals with diabetes, the study was unable to exclude other processes that could have caused cognitive decline; therefore, further studies are needed.

Source: Barzilay JI, Lovato JF, Murray AM *et al.* Albuminuria and cognitive decline in people with diabetes and normal renal function. *J. Am. Soc. Nephrol.* doi:10.2215/CJN.11321112 (2013) (Epub ahead of print).

About the News

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Study shows that alogliptin does not increase the rates of major adverse cardiovascular events in Type 2 diabetics

Takeda Pharmaceutical Company Limited recently announced that the primary end point of the EXAMINE trial has been reached. The primary end point of noninferiority of cardiovascular risk when alogliptin (a dipeptidyl peptidase-4 inhibitor) was compared with placebo was met with no increase in cardiovascular risk in Type 2 diabetes patients who are at high risk for cardiovascular events. It is hoped that these data will be of benefit for clinicians treating individuals with Type 2 diabetes and a high cardiovascular risk.

Previous studies have demonstrated the adverse link between glycemic control and macrovascular events in individuals with Type 2 diabetes, highlighting the need for specific requirements regarding cardiovascular safety assessment before and after the approval of new antidiabetic therapies.

In this multicenter, randomized, double-blind trial, 5380 individuals with Type 2 diabetes and a recent acute coronary syndrome, from 898 centers in 49 countries, were randomly assigned to receive either alogliptin or placebo and were followed for up to 40 months.

> "Given the EXAMINE study design and high-risk patient population evaluated, these results provide key insights to clinicians treating diabetes patients with coronary disease."

A primary end point event occurred in 11.3% (n = 305) of individuals in the alogliptin group and in 11.8% (n = 316) of individuals in the placebo group (hazard ratio: 0.96; upper boundary of the one-sided repeated confidence interval: 1.16; $p < 0.001$ for noninferiority). It was also observed the HbA1c levels were lower in the alogliptin group when compared with the placebo group (mean difference: -0.36 percentage points; $p < 0.001$).

William White, principal investigator of the EXAMINE trial explained: "There is a need for safer glucose lowering therapies in patients with diabetes who are at an elevated risk for cardiovascular disease. Given the EXAMINE study design and high-risk patient population evaluated, these results provide key insights to clinicians treating diabetes patients with coronary disease."

Alogliptin is not currently licensed or available in Europe.

Sources: White WB, Cannon CP, Heller SR *et al.*; the EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with Type 2 diabetes. *N. Engl. J. Med.* doi:10.1056/NEJMoa1305889 (2013) (Epub ahead of print); Takeda press release: www.takeda.com/news/2013/20130902_5975.html

Lower risk of diabetes linked with fruit consumption

Researchers from Harvard University (MA, USA) and University of Cambridge (UK), have recently reported in *BMJ* that increased consumption of certain fruits could reduce an individual's risk of developing Type 2 diabetes, but consuming a greater amount of fruit juice can increase the risk.

Fruits have many health benefits owing to their abundance of antioxidants, fiber and phytochemicals; however, their link with prevention of Type 2 diabetes has been inconclusive. In three prospective cohorts of US men and women, using data from the Nurse's Health Study, it was found that 12,198 individuals developed Type 2 diabetes. Following mutual adjustment of individual fruits, the pooled hazard ratios of Type 2 diabetes for every three servings per week were 0.74 (0.66–0.83) for blueberries and 0.88 (0.83–0.93) for grapes and raisins.

> "Fruits have many health benefits owing to their abundance of antioxidants, fiber and phytochemicals; however, their link with prevention of Type 2 diabetes has been inconclusive."

Although the results add to the literature regarding primary prevention of chronic disease, the authors did acknowledge that as the study was based on food frequency questionnaires recall bias was possible. In addition, the findings may not be generalized to other populations because the study population mainly consisted of health professionals of European heritage.

Source: Muraki I, Imamura F, Manson JE *et al.* Fruit consumption and risk of Type 2 diabetes: results from three prospective longitudinal cohort studies. *BMJ* 28, 347 (2013).

– All stories written by Natasha Leeson