MEDIA BACKGROUNDER:

Canagliflozin Outcome Trials CANVAS and CREDENCE

Cardiovascular and kidney disease in diabetes

More than 60 million people in Europe have diabetes mellitus, of which there are two main types called type 1 (affecting ~10% people) and type 2 (affecting ~90% people).[1] If left untreated, people with diabetes are at an increased risk of developing serious complications, including cardiovascular (CV) disease and renal disease. In fact, diabetes is a leading cause of both CV disease and kidney failure.[2]

Maintaining normal blood glucose levels in patients with diabetes can help reduce these long term complications.[2] Sodium glucose co-transporter 2 (SGLT2) inhibitors in the kidneys help to lower blood glucose levels through excretion of glucose into the urine, and have, in addition, shown to reduce the risk of major adverse cardiovascular events and worsening of diabetic kidney disease in patients with type 2 diabetes mellitus (T2DM).

Several clinical trials have been initiated to investigate the potential of SGLT2 inhibitors in improving cardiovascular and renal outcomes in patients with T2DM. These include CANVAS and CREDENCE, two clinical trial programmes which examined the potential of canagliflozin, an SGLT2 inhibitor, in patients with T2DM with either a prior history of CV disease or at least two CV risk factors, or reduced kidney function.

INVOKANA®(canagliflozin) is approved in the European Union for the treatment of adults with type 2 diabetes mellitus, to improve glycaemic control.[3]

What is CANVAS?

The CANVAS Program consisted of two large outcomes study analyses called CANVAS and CANVAS-R.

The Program included a pre-specified integrated analysis of these two studies to evaluate the potential for CV protection of canagliflozin in 10,142 patients with T2DM who had either a prior history of CV disease or at least two CV risk factors, including, but not limited, to having diabetes for 10 years or more, high systolic blood pressure, or a current smoker.[4]

- CANVAS (CANagliflozin cardioVascular Assessment Study, Trial 28431754DIA3008) was a double-blind, randomized, placebo-controlled, three parallel-group, global, multi-centre trial to evaluate the effects of canagliflozin on CV outcomes in adults with T2DM that have a history of CV events or at high risk for CV events.[5]

- CANVAS-R (CANagliflozin cardioVascular Assessment Study – Renal), which recruited a similar, high-risk patient population, is a double-blind, randomized, placebo-controlled, parallel-group, multi-centre trial to assess the effects of canagliflozin on renal and cardiovascular endpoints in adult patients with T2DM receiving standard care, but with inadequate glycaemic control and at an elevated risk of cardiovascular events.[5]

The CANVAS Program met its composite primary endpoint, reducing by 14% the combined risk of CV death, nonfatal myocardial infarction (MI) and nonfatal stroke, (known as Major Adverse Cardiovascular events, or 3-point MACE) and demonstrating an improved CV safety profile compared to placebo ($p<0.0001$ for non-inferiority) and superiority compared to placebo ($p=0.0158$). Canagliflozin was also associated with protection against hospitalization for heart failure and a reduction in doubling of serum creatinine, need for renal replacement therapy and renal death as well as a reduction in the progression of albuminuria.[4]

In the CANVAS program specifically, canagliflozin was associated with an increased risk in lower limb amputation (primarily of the toe and midfoot). However, this is a very low risk (0.6 subjects per 100 patients treated per year, compared with 0.3 subjects per 100 patients per year in the placebo group). An underlying mechanism has not been established.[4]

Full results from the CANVAS trial were presented at the American Diabetes Association (ADA) 77th Scientific Sessions 2017 and were published in the New England Journal of Medicine (NEJM) in 2017.

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What is CREDENCE?

The existing evidence base for canagliflozin and other SGLT2 inhibitors in patients with normal or mildly impaired renal function supports a potential benefit for these therapies on renal outcomes in patients with impaired kidney function.[6]

CREDENCE, a landmark study and the largest randomized controlled trial to examine the effect of an SGLT2i on renal endpoints, was a randomized, double-blind, placebo-controlled, parallel-group, multicentre clinical trial, evaluating the efficacy and safety of canagliflozin versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and T2DM.[6] It was specifically designed to provide definitive evidence for the effect of canagliflozin, and more broadly SGLT2 inhibitors, in this population.[6]

The primary composite endpoint was any of the following: end stage kidney disease (ESKD), doubling of serum creatinine, and renal or CV death. Secondary endpoints included composite of CV death and hospitalisation for congestive heart failure.[6]

In contrast to other cardiovascular outcomes trials, CREDENCE has been designed to specifically assess effects on clinically important outcomes in individuals with diabetes at high risk of kidney disease progression.[6]

The CREDENCE trial was stopped in July 2018 – one year early – based on the achievement of pre-specified efficacy criteria.

References

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