

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CRENCE)

Introduction

There are more than 3 million people with chronic kidney disease (CKD) requiring renal replacement therapy globally, and this number is likely to increase to more than 5 million by 2030.¹ People affected by CKD have a reduced life expectancy and lower quality of life, as well as a substantially increased risk of cardiovascular disease and other adverse health outcomes.^{2,3} The high cost of dialysis challenges health service budgets in the European Union.⁴ There is, therefore, an urgent need to develop newer therapies to address CKD in diabetes.

The CRENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) trial was the first dedicated renal outcome trial evaluating renal and cardiovascular outcomes in people with type 2 diabetes mellitus (T2DM) at high risk of progression of CKD with a sodium glucose co-transporter 2 (SGLT2) inhibitor.⁵

Study Summary⁵

The CRENCE study is the first dedicated renal outcome trial evaluating renal and cardiovascular outcomes in people with type 2 diabetes mellitus (T2DM) and kidney disease with a sodium glucose co-transporter 2 (SGLT2) inhibitor.

It is a phase 3 randomised, double-blind, placebo-controlled, parallel-group, multi-centre, event-driven clinical trial of the effects of canagliflozin on renal and cardiovascular (CV) outcomes in subjects with T2DM and chronic kidney disease (CKD).

In particular, it evaluated the efficacy and safety of canagliflozin versus placebo at preventing clinically important kidney and cardiovascular (CV) outcomes when used in addition to standard of care for patients with T2DM and CKD.

Primary Objective⁵

The primary objective was to demonstrate the superiority of canagliflozin relative to placebo in reducing the primary composite endpoint of time to the first occurrence of doubling of serum creatinine, end-stage kidney disease (ESKD), and renal or CV adjudicated death.

Safety Objective⁵

The safety objective was to assess the overall safety and tolerability of canagliflozin.

Primary Composite Endpoint⁵

- Time to the first occurrence of doubling of serum creatinine, end-stage kidney disease (ESKD) and renal or CV adjudicated death

Secondary Endpoints⁵

- Composite endpoint of CV death and hospitalized congestive heart failure
- Composite endpoint of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (i.e., 3-point major adverse cardiovascular events (MACE))
- Composite of doubling of serum creatinine, ESKD and renal death
- Hospitalized congestive heart failure
- CV death
- All-cause death
- Composite of CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure and hospitalized unstable angina

Recruitment and Timings⁶

The study commenced on February 17, 2014 and was completed on October 30, 2018. The trial was halted early in July 2018 due to a signal of overwhelming efficacy in the prevention of the primary endpoint. The trial randomised 4,401 adults with T2DM at 690 sites in 34 countries across six continents. The enrolment criteria stipulated that participants must be:

- T2DM patients with a hemoglobin A1c (HbA1c) \geq 6.5% and \geq 12.0%, with an estimated glomerular filtration rate (eGFR) of \geq 30 to $<$ 90 mL/min/1.73 m²
- On a stable maximum tolerated labeled daily dose

of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomisation

- Have a urine albumin to creatinine ratio (UACR) >300 to ≤5,000 mg/g

Results⁵

The study met its primary endpoint showing that canagliflozin reduced the risk of ESKD and renal or CV death by 30% [HR: 0.70; 95% CI: 0.59 to 0.82; p=0.00001]. These findings were consistent across the individual components of the primary composite endpoint, as well as across all 15 subgroups tested.

The study also demonstrated that canagliflozin reduced the risk of:

- The secondary renal endpoint (composite of doubling of serum creatinine, ESKD, and renal death) by 34% [HR: 0.66; 95% CI: 0.53 to 0.81; p<0.001]
- The secondary endpoint of major adverse cardiac events (composite of non-fatal myocardial infarction, non-fatal stroke and CV death) by 20% [HR: 0.80; 95% CI: 0.67 to 0.95; p=0.01]
- CV death and hospitalization for heart failure by 31% [HR: 0.69; 95% CI: 0.57 to 0.83; p<0.001]
- Hospitalization for heart failure alone by 39% [HR: 0.61; 95% CI: 0.47 to 0.80; p<0.001]

Safety⁵

The incidence rates of adverse events and serious adverse events were numerically lower for patients treated with canagliflozin as compared to placebo. There were no observed differences in the incidence of lower limb amputations (HR: 1.11; 95% CI: 0.79 to 1.56) or adjudicated fractures (HR: 0.98; 95% CI: 0.70 to 1.37).

Subgroup analysis results⁷

Two subgroups were analysed to further determine the CV and renal protection of canagliflozin on this patient population. The primary prevention group included participants with CV risk factors but no history of CV disease (n=2,181; 49.6%) and a secondary prevention group included patients defined as having a history of coronary, cerebrovascular or peripheral vascular disease (n=2,220; 50.4%).

The CV and renal results observed in the overall study population were consistent across both of these subgroups:

- Canagliflozin reduced the risk of the composite of CV death, heart attack and stroke by 32% in the primary prevention group (HR: 0.68; 95% CI: 0.49 to 0.94) and 15% in the secondary prevention group (HR: 0.85; 95% CI: 0.69 to 1.06)
- Canagliflozin reduced the risk of ESKD by 31% (HR: 0.69; 95% CI: 0.51 to 0.95; P-interaction: 0.89) and 33% (HR: 0.67; 95% CI: 0.47 to 0.96; P-interaction: 0.89) in the primary and secondary prevention groups, respectively

About canagliflozin

Canagliflozin is an oral, once-daily medication which belongs to a new class of medications called SGLT2 inhibitors. SGLT2 inhibitors work by inhibiting SGLT2, which promotes the loss of glucose via the urine, lowering blood glucose levels in adults with type 2 diabetes. Canagliflozin was approved in the European Union by the European Commission in November 2013. It is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications and in addition to other medicinal products for the treatment of diabetes.⁸

The initiation dose is 100mg once daily in adults with an eGFR of ≥ 60 mL/min/1.73 m² and can be increased to 300mg once daily orally if tighter glycaemic control is needed. Canagliflozin should **not** be initiated if eGFR is < 60 mL/min/1.73 m². In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² the dose should be adjusted to or maintained at 100mg once daily. Canagliflozin should be stopped if eGFR falls persistently below 45 mL/min/1.73 m².⁸

Last year, the European Medicines Agency (EMA) approved label updates for canagliflozin to include data on the reduction in major adverse CV events in patients with T2DM who had either a history of CV disease or at least two CV risk factors.⁸ The label update was supported by the results from the CANVAS clinical trial.⁹

References

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