Therapeutic Safety of the New Oral Antidiabetic Agent Canagliflozin in Type 2 Diabetics with Reduced GFR

Type 2 diabetes is among the most common causes of chronic kidney disease and is associated with a high cardiovascular risk, in particular also microvascular risk (retinopathy-neuropathy-nephropathy). Adequate blood glucose control reduces the risk of mortality, as well as all frequencies related to complications. The release of insulin can be increased with oral antidiabetic agents in cases where the body's intrinsic insulin production has not yet fully ceased to function. These substances are not suitable with increasing failure of the pancreatic β cells and increasing resistance of the organism to insulin. Furthermore, some oral antidiabetic agents are associated with an increase in weight, thus further aggravating the type 2 diabetic metabolic syndrome and increasing cardiovascular risk. One compound, rosiglitazone, was even removed from the EU markets in 2010 because of the increase in the risk of myocardial infarction. Most of the oral antidiabetic agents used to date are also not without problems in patients with chronic impairment to renal function and require close medical monitoring (danger of lactacidosis, elevated risk of hypoglycaemia, potential nephrotoxicity).

Canagliflozin is a novel oral antidiabetic agent belonging to the gliflozin group, with a mechanism of action that is independent from insulin. Canagliflozin was the first SGLT2 inhibitor to be authorized in the US and EU in 2013 and in Switzerland in 2014. It is easy to use (once daily in the mornings).

Gliflozins are so-called SGLT2 inhibitors, i.e., they selectively inhibit the sodium glucose co-transporter (SGLT2) in the proximal renal tubule. This results in lower renal re-absorption of glucose and, instead, the excessive glucose is excreted in the urine and blood glucose drops. One highly desirable effect of this is the reduction in body weight and blood pressure. Due to their mechanism of action, gliflozins are ineffective in patients who produce no urine (terminal CKD, dialysis).

Potential side effects of canagliflozin are mainly associated with the increase in urinary glucose content (frequent urge to urinate, urinary tract infections, vaginal mycosis). In addition, a transient decrease in glomerular filtration rate (GFR) was observed in phase III studies, which was to be further investigated in the current study.
Efficacy And Safety Of Canagliflozin (Cana) In Patients With Type 2 Diabetes Mellitus (T2dm) Who Had Estimated Glomerular Filtration Rate (Egfr) Reduction During Treatment

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INTRODUCTION AND AIMS: CANA, a sodium glucose co-transporter 2, has provided reductions in HbA1c, body weight (BW), and systolic blood pressure (SBP) across Phase 3 studies in a broad range of patients with T2DM. In these studies, CANA was also associated with transient reductions in eGFR that stabilized or attenuated over the treatment period. This analysis evaluated the impact of decreases from baseline in eGFR on the efficacy and safety of CANA in patients with T2DM.

METHODS: Changes from baseline in HbA1c, BW, and SBP were assessed in the subset of patients with eGFR ≥60 mL/min/1.73 m² at baseline who had a reduction in eGFR to ≥45 and <60 mL/min/1.73 m² at the last post-baseline time point based on pooled data from 6 randomised, double-blind, placebo (PBO)-controlled studies over 18 or 26 weeks (N = 262/4,158; 6.3%). Safety analyses, including the incidence of adverse events (AEs), were conducted in those who had a reduction in eGFR from ≥60 mL/min/1.73 m² to ≥45 and <60 mL/min/1.73 m² at the last time post-baseline in a broader pooled population of patients with T2DM from 8 randomised, double-blind, PBO- and active-controlled studies over 26 or 52 weeks (N = 664/9,439; 7.0%).

RESULTS: Among patients who had a reduction in eGFR from ≥60 mL/min/1.73 m² to ≥45 and <60 mL/min/1.73 m² (mean baseline eGFR 67.3 mL/min/1.73 m²), mean eGFR at the last post-baseline time point was 54.6, 54.8, and 55.9 mL/min/1.73 m² with CANA 100 and 300 mg and PBO, respectively (mean change from baseline of −12.7, −12.6, and −11.5 mL/min/1.73 m², respectively). In these patients, CANA 100 and 300 mg provided PBO-subtracted reductions (95% confidence interval) in HbA1c (-0.56% [-0.84, -0.28] and -0.78% [-1.05, -0.51], respectively), BW (-2.1% [-3.2, -1.0] and -2.6% [-3.6, -1.5], respectively), and SBP (-6.2 mmHg [-11.1, -1.3] and -6.4 mmHg [-11.0, -1.9], respectively). Changes in HbA1c and BW in patients who had eGFR reductions were similar to those in the overall efficacy population; changes in SBP with CANA were greater in those with eGFR reductions compared with the overall population (Figure). eGFR reductions were reversible once patients discontinued CANA treatment. In the broad dataset used for safety analyses, the incidence of overall AEs in patients whose eGFR decreased to ≥45 and <60 mL/min/1.73 m² was 62.7%, 64.2%, and
58.6% with CANA 100 and 300 mg and non-CANA, respectively; rates of AE-related discontinuations were 6.0%, 8.1%, and 6.4%, respectively. CANA 100 and 300 mg were associated with a higher incidence of serious AEs versus non-CANA (12.4%, 10.0%, and 7.9%). The incidence of volume depletion-related AEs was low across groups but higher with CANA 100 and 300 mg than with non-CANA (4.5%, 4.6%, and 2.0%); discontinuations and serious AEs related to volume depletion were infrequent across groups.

CONCLUSIONS: In summary, among patients with T2DM with reductions from eGFR ≥60 mL/min/1.73 m² at baseline to eGFR ≥45 and <60 mL/min/1.73 m² during treatment, CANA 100 and 300 mg provided reductions in HbA1c, BW, and SBP, consistent with the overall population. Among patients that had reductions in eGFR during treatment, CANA was generally well tolerated, with a low incidence of volume depletion-related AEs across groups.

Figure. Changes in HbA₁c, BW, and SBP (A) in the overall population and (B) in patients with baseline eGFR ≥60 mL/min/1.73 m² and reduction to ≥45 and <60 mL/min/1.73 m² at the last post-baseline time point.*