Invokana® (canagliflozin) Significantly Reduced Major Cardiovascular Events and Kidney Failure in Patients with Type 2 Diabetes and Chronic Kidney Disease in New CREDENCE Analysis

- Invokana (canagliflozin) is the first type 2 diabetes mellitus (T2DM) treatment to offer cardiovascular (CV) and renal protection to this patient group,[1] building on the primary CREDENCE results which were recently added to the American Diabetes Association's Standards of Medical Care in Diabetes
- Approximately 40%[2] of the 58 million type 2 diabetes mellitus (T2DM) patients in Europe[3] will develop diabetic kidney disease (DKD), which is associated with a high risk of CV disease (heart attack, heart failure and stroke)[4,5]
- Mundipharma has a partnership with Janssen to be the exclusive distributor for canagliflozin across 18 countries in the European Economic Area (EEA) and Switzerland where the products currently have Pricing and Reimbursement status. This is with the exception of Spain, where the product is co-promoted by both Janssen and Mundipharma

CAMBRIDGE, UK: 11.06.19 – Mundipharma welcomes the results of a new subgroup analysis from the landmark Phase III CREDENCE study which shows Invokana® (canagliflozin) significantly reduced the risk of major cardiovascular (CV) events and kidney failure in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) in patients with and without known cardiovascular (CV) disease.[1] These results were presented today at the American Diabetes Association's 79th Scientific Sessions in San Francisco, USA.

"Cardiovascular disease and kidney disease are two serious complications of type 2 diabetes that may shorten life expectancy by several years. This latest analysis of the CREDENCE study demonstrates that for patients with type 2 diabetes and chronic kidney disease, canagliflozin reduced the risk of a cardiovascular event, whether or not patients had already experienced one. Thus, early treatment may help to prevent clinical manifestations of cardiovascular disease - an important message for healthcare professionals managing these patients." said David Wheeler, Professor of Kidney Medicine at University College London, UK and Honorary Consultant Nephrologist at the Royal Free London NHS Foundation Trust.

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The Phase III CREDENCE study evaluated CV and renal outcomes in patients with T2DM and CKD taking either canagliflozin or placebo, in addition to standard of care. The primary results were recently added to the American Diabetes Association's *Standards of Medical Care in Diabetes* and published in *The New England Journal of Medicine* in April this year.

In the new subgroup analysis of the clinical trial results, researchers specifically examined CV and renal outcomes in a primary prevention group, which included participants with CV risk factors but no history of CV disease (n=2,181; 49.6%) and a secondary prevention group, including patients defined as having a history of coronary, cerebrovascular or peripheral vascular disease (n=2,220; 50.4%).[1]

Building on the initial CREDENCE results presented at the World Congress of Nephrology in Melbourne in April 2019, this subgroup analysis showed that the CV results observed in the overall study population were consistent across the primary and secondary prevention groups, including all clinical subgroups and across groups defined by renal function. For CV death, heart attack and stroke, there was no evidence of heterogeneity between the primary and secondary prevention groups (p=0.25). Specifically, 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).[1]

Furthermore, the renal results observed in the overall study population were consistent across the primary and secondary prevention groups. Specifically, 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.[1]

The full results showed that the CREDENCE study met its primary endpoint by demonstrating that canagliflozin reduced the risk of composite doubling of serum creatinine, end-stage kidney disease (ESKD) and renal or CV death by 30% [HR: 0.70; 95% CI: 0.59 to 0.82; p=0.00001].[6] Furthermore, the CV results from CREDENCE found canagliflozin significantly reduced major CV events in the overall study population, including reducing the risk of CV death, heart attack or stroke by 20% (HR: 0.80; 95% CI: 0.67 to 0.95; p=0.01) and risk of CV death or hospitalization for heart failure by 31% (HR: 0.69; 95% CI: 0.57 to 0.83; p<0.001) and hospitalization for heart failure alone by 39% (HR: 0.61; 95% CI: 0.47 to 0.80; p<0.001).[6]

In addition, CREDENCE found the incidence rates of adverse events and serious adverse events were numerically lower for patients treated with canagliflozin as compared to placebo.[6] For the subgroup analysis, safety outcomes were similar in both primary and secondary prevention groups. Of note,

there was no difference in fracture risk or incidence of amputations in the primary and secondary prevention groups.[1]

"We are delighted the results from this subgroup analysis show canagliflozin can offer clinicians and their T2DM patients with chronic kidney disease protection from both CV and kidney disease, which are both high risk for this patient population" said Dr Vinicius Gomes de Lima, European Medical Affairs Lead. *"As the first type 2 diabetes medicine to show this benefit to patients with or without known CV disease, there is a potential to positively improve the outcomes for patients living with type 2 diabetes."*

In Europe, canagliflozin is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise. The initiation dose is 100mg once daily in adults with an eGFR of ≥ 60 mL/min/1.73 m^2 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 m^2. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 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 m^2.[7]

Currently, 58 million people in Europe currently live with T2DM, which is set to rise to 67 million by 2045.[3] Approximately 40% of these patients will develop diabetic kidney disease (DKD),[2] which is associated with a high risk of CV disease (heart attack, heart failure and stroke) and also amplifies the risk of other diabetes complications including; a reduced quality of life, infections, fatigue, depression, adverse drug reactions and premature death.[4,5]

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Notes to the editors:

About the CREDENCE Clinical Trial[6]

The CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) study was the first dedicated and full recruited renal outcome trial evaluating renal and cardiovascular outcomes in people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) with a sodium glucose co-transporter 2 (SGLT2) inhibitor. It was a Phase III randomised, double-blind, event-driven, placebo-controlled, parallel-group, 2 arm multi-centre study of the effects of canagliflozin on renal and cardiovascular outcomes in subjects with T2DM and CKD. In particular, it compared the efficacy and safety of canagliflozin versus placebo at preventing clinically important

kidney and cardiovascular outcomes in patients with T2DM and CKD when used in addition to standard of care, including a maximum tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

About Canagliflozin[7]

Canagliflozin is an oral, once-daily medication which belongs to a class of medications called sodium glucose co-transporter 2 (SGLT2) inhibitors. SGLT2 inhibitors work by inhibiting SGLT2, which promotes the loss of glucose via the urine, lowering blood glucose levels in adults with T2DM. 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. Approval was based on a comprehensive global Phase III clinical trial programme.

About the Mundipharma network

Mundipharma is a global network of privately-owned independent associated companies whose purpose is to move medicine forward. With a high performing and learning organization that strives for innovation and commercial excellence through partnerships, we successfully transformed and diversified our European portfolio of medicines to create value for patients, payers and wider healthcare systems across important therapeutic areas such as Diabetes, Respiratory, Oncology, Pain and Biosimilars.

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