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HEALTH TECHNOLOGY BRIEFING
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Canagliflozin for chronic kidney disease in adult patients with type 2 diabetes mellitus

NIHRIO ID	9960	**NICE ID**	9556
Developer/Company	Napp Pharmaceuticals Ltd	**UKPS ID**	647297

Licensing and market availability plans	Currently in phase III/IV clinical trials.

SUMMARY

Canagliflozin is in clinical development for the treatment of chronic kidney disease in adults with type 2 diabetes mellitus. Diabetes is a condition that causes blood sugar level to become too high. The majority of diabetes cases are type 2 diabetes, where the pancreas does not produce enough insulin or when the cells in the body do not respond properly to insulin. Diabetes is the leading cause of chronic kidney disease and failure in adults. People affected by chronic kidney disease have a reduced life expectancy and lower quality of life, as well as substantially increased risk of cardiovascular disease and adverse health outcomes.

Canagliflozin belongs to a class of antidiabetic drugs called SGLT2 inhibitors that act by encouraging the body to filter out more glucose from the blood and excrete it via the urine. Canagliflozin is already licensed for use in type 2 diabetes mellitus but emerging evidence has also suggested that it offers substantial kidney protection, by slowing the progression of diabetic kidney disease. Canagliflozin will offer patients with type 2 diabetes mellitus who have chronic kidney disease a single treatment option to improve both kidney function alongside blood glucose control.

PROPOSED INDICATION

Chronic kidney disease (CKD; stage 2 or 3 defined by eGFR or presence of albuminuria) in adults with type 2 diabetes mellitus, as an adjunct to standard of care.[1]

TECHNOLOGY

DESCRIPTION

Canagliflozin (Invokana) is a selective sodium-glucose transporter-2 (SGLT2) inhibitor. SGLT2 is a glucose transport protein which is responsible for most of the glucose reabsorption by the kidney from the tubular lumen.[2] SGLT2 inhibitors represent a new class of recently developed antidiabetic agents that improve glycaemic control, decrease glycated haemoglobin (HbA1c), and reduce body weight, presenting also a low risk for hypoglycaemia.[3] In addition to blocking the reabsorption of glucose in the kidney, SGLT2 inhibitors such as canagliflozin are thought to confer kidney benefits through a direct renal mechanism (which is independent of glycemic control). This direct renal mechanism results in an increase in the delivery of glucose and sodium in the distal tubule and the juxtaglomerular apparatus, which is sensed as an increase in glomerular perfusion. This leads to a feedback signal that causes afferent arteriolar vasoconstriction, an acute fall in glomerular perfusion and pressure, as well as a diminished extracellular plasma volume and blood pressure. Additionally, these effects reduce atrial natriuretic peptide secretion that may also be important in reducing intraglomerular pressure. These effects are clinically manifested as acute reductions in albuminuria and estimated glomerular filtration rate (eGFR), followed by stabilization in eGFR in the longer term. Thus, SGLT2 inhibitors specifically alter renal haemodynamics and reduce intraglomerular pressure, which could be expected to translate into improved long-term kidney outcomes.[4]

Canagliflozin is in clinical development for the treatment of chronic kidney disease associated with type 2 diabetes. In the phase III (CREDENCE; NCT02065791) and phase IV trials (CANVAS-R; NCT01989754), participants received oral canagliflozin (or matching placebo) at a dose of 100 mg daily (which may be increased to 300 mg from week 13 for the CANVAS-R study if the participant requires additional glycaemic control and is tolerating the 100 mg dose). Treatment period is continued for up to 66 months for CREDENCE and between 78 and 156 weeks for CANVAS-R.[1,5] The proposed dosing regimen by the company is 100mg once daily if eGFR is below 60 ml/min or CKD-3. Canagliflozin should be discontinued when eGFR is persistently below 30 mL/min/1.73 m2 or creatinine clearance is persistently below 30 mL/min.[a]

INNOVATION AND/OR ADVANTAGES

Diabetic nephropathy is more common in people with diabetes and high blood pressure. Although canagliflozin is licensed for type 2 diabetes mellitus (T2DM), its effects on patients with kidney disease have not been formally examined, although previous trials suggested possible benefits.[6] It is thought that SGLT2 inhibition could reduce (single-nephron) hyperfiltration in diabetes by (1) restoring sodium-chloride concentration at the macula densa and subsequent TGF-mediated afferent arteriolar vasoconstriction and (2) increasing intraluminal volume thereby causing a retrograde increase in hydraulic pressure in Bowman's space, which constrains filtration pressure.

Furthermore, SGLT2 inhibitors consistently reduce bodyweight and blood pressure, and therefore may influence several vascular mediators of renal hemodynamics in both the fasting and postprandial state (e.g., a decrease in atrial natriuretic peptide and insulin, and an increase in glucagon, RAS components, and glucagon-like peptide).[a]

[a] Information provided by Napp Pharmaceuticals Ltd. on UK PharmaScan.

These effects are not observed with other classes of glucose-lowering agents. In a pre-specified exploratory analysis, canagliflozin treatment was associated with a reduced risk of sustained loss of kidney function, end stage kidney disease, death from renal causes, attenuated eGFR decline, and a reduction in albuminuria, which supports a possible renoprotective effect of this drug in people with type 2 diabetes.[7] If licensed, canagliflozin could have an important role in slowing the progression of diabetic kidney disease.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Canagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:[2]

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

Canagliflozin is in phase III/II clinical development for the treatment of T2DM in children and adolescents.[8]

PATIENT GROUP

DISEASE BACKGROUND

T2DM is a lifelong condition which constitutes 90% of all diabetes cases and is caused by a combination of insulin resistance (where the body is unable to respond to normal levels of insulin) and insulin deficiency (where the pancreas is unable to secrete enough insulin to compensate for this resistance).[9]

Kidney disease (nephropathy) is more common in people with diabetes, high blood pressure, and in people who have had diabetes for over 20 years.[10] In the early stages of kidney disease, there are usually no symptoms and patients may not feel unwell, however swelling in the feet and ankles may be indicative. As the disease progresses, the kidneys become less efficient as small blood vessels become leaky, or in some cases stop working. The resulting build-up of waste products in the blood causes the patient to become very ill.[10] If the disease progresses, symptoms such as vomiting, nausea, weight loss, itching, bone damage, etc. become noticeable.[11]

A blood test measures the levels of a waste product called creatinine in the blood. Using this result, a calculation that takes into account age, gender and ethnic group is then done to work out how many milliliters of waste the kidneys are able to filter out in a minute. This measurement is known as eGFR. Healthy kidneys filter more than 90ml/min and a lower result may indicate a kidney disease, and the result is given as a stage from 1 to 5.[12]

- **stage 1 (G1)** – a normal eGFR (above 90ml/min), but other tests have detected signs of kidney damage
- **stage 2 (G2)** – a slightly reduced eGFR (60-89ml/min), with other signs of kidney damage
- **stage 3a (G3a)** – an eGFR of 45-59ml/min
- **stage 3b (G3b)** – an eGFR of 30-44ml/min
- **stage 4 (G4)** – an eGFR of 15-29ml/min
- **stage 5 (G5)** – an eGFR below 15ml/min, meaning the kidneys have lost almost all of their function

Urine tests are also carried out to check the albumin to creatinine ratio (ACR). The ACR result is given as a stage from 1 (ACR level less than 3mg/mmol) to 3 (an ACR of more than 30mg/mmol). A higher stage for both ACR and eGFR indicates more severe kidney disease.[12]

Diabetic nephropathy is the most common cause or in combination with hypertensive nephropathy, the most common causes of end-stage renal disease (ESRD).[13] At stage 5, maintenance renal replacement therapy is required.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-2018 the prevalence of diagnosed cases of diabetes was 3,222,559.[15] If 90% of these cases are T2DM, the prevalence of T2DM in England in 2017-2018 was 2,900,303. However these numbers are considered to underestimate the true prevalence, as there are an estimated 1 million people (in the UK) with T2DM who are undiagnosed.[15] Furthermore, by 2030, people living with T2DM in the UK is predicted to rise to 5.5 million.[16] About one in four people with diabetes will develop some stage of kidney disease during their lifetime, with nearly one in five developing overt kidney disease which may need treatment.[17]

Using data from 2015/16, there are approximately 590,652 people with T2DM with CKD stage 2 (eGFR), 156,829 with CKD stage 3a and 73,151 people with T2DM with CKD stage 3b.[18] Diabetes is the single most common cause of end stage renal disease requiring dialysis or transplant (renal replacement therapies – RRT) with nearly a quarter of all patients having diabetes recorded as the primary cause of their kidney failure[19] and a third of all patients starting RRT having diabetes.[20] For those undergoing RRT, survival rates are lower than for people without the condition (3.4 years vs 6.5 years).[21] People with diabetes are nearly three times as likely to need RRT as the general population.[17] Kidney disease accounts for 11% of deaths in T2DM.[22,23]

Hospital admissions data for England in 2017-2018 recorded 553 finished consultant episodes (FCE) for non-insulin-dependent diabetes mellitus with renal complications (ICD 10: E11.2), 374 hospital admissions, 118 day cases and 1480 FCE bed days.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

All diabetic patients, including those suffering from CKD will benefit from keeping glucose levels under control. NICE guidelines recommend that clinicians should adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with T2DM, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.[25] Improved glycaemic control has been shown to reduce the occurrence of early diabetic nephropathy.[26-30]

All adults with T2DM (with and without detected nephropathy) should receive annual screening for diabetic nephropathy. People who are suspected to have diabetic nephropathy will be offered further testing. CKD is diagnosed when tests have persistently (for at least three months or more) shown a reduction in kidney function or the presence of proteinuria.[31]

After formal diagnosis and assessment of the stage of the disease, it may be possible for routine follow-up at a patients GP surgery, or alternatively by a consultant nephrologist who will discuss treatment options.[32]

Depending on the severity of the condition, a range of management options may be considered:[32]

- Information and education;
- Lifestyle and diet advice (regarding potassium, phosphate, calorie and salt intake);
- Self-management;
- Blood pressure control and antihypertensive treatment;

- Preventing and treating cardiovascular disease.

CURRENT TREATMENT OPTIONS

There are various treatments for CKD, the choice is dependent on the individual, the type of diabetes and other factors such as blood pressure.[10] Once diagnosis of chronic kidney disease has been confirmed, treatment centres on;

- controlling blood pressure (with an antihypertensive agent),
- using statins for lipid modification and
- the use of oral antiplatelet drugs for the secondary prevention of cardiovascular disease.[32]

PLACE OF TECHNOLOGY

If licensed, canagliflozin will offer patients with T2DM who have renal disease (stage 2 and 3) a treatment both to improve kidney function alongside glycaemic control and reduce the risk of major adverse cardiovascular events.

CLINICAL TRIAL INFORMATION

Trial	**The CANVAS programme: CANVAS, NCT01032629; canagliflozin + standard of care vs placebo + standard of care; phase III and CANVAS-R, NCT01989754; canagliflozin + standard of care vs placebo + standard of care; phase IV**
Sponsor	Janssen Research & Development, LLC
Status	Completed
Source of Information	Trial registry[5,33], publication[7,34], manufacturer[b]
Location	10 EU (including UK), USA, Canada and other countries
Design	Randomised, parallel assignment, quadruple blinded
Participants (CANVAS-R)	N=5,812; males and females aged ≥30 years of age; must have a diagnosis of type 2 diabetes mellitus; must have inadequate diabetes control (as defined by glycosylated hemoglobin level >=7.0% to <=10.5% at screening); greater than or equal to (>=) 30 years old with history of cardiovascular (CV) event, or >= 50 years old with high risk of CV events; must be either not on antihyperglycemic agents (AHA) therapy, or on AHA monotherapy, or combination AHA therapy with any approved agent for the control of blood glucose levels.
Schedule (CANVAS-R)	Patients are randomised to receive either: • 100mg tablet once daily during the first 13 weeks, then the dose may be increased to 300 mg once daily • One matching placebo tablet once daily Duration is approximately 156 weeks
Follow-up (CANVAS and CANVAS-R)	Three visits during the first year ad at 6 month intervals thereafter, with telephone follow-up between face-to-face assessments[34]
Primary Outcomes (CANVAS-R)	Progression of albuminuria [Time frame: up to 3 years]
Secondary Outcomes	• Composite of cardiovascular (CV) death events or hospitalization for heart failure [Time frame: approximately 3 years

[b] Information provided by Napp Pharmaceuticals Ltd.

(CANVAS-R)	• Cardiovascular (CV) death [Time frame: approximately 3 years]
Key Results	Results for CANVAS and CANVAS-R are presented together for increased power. Canagliflozin treatment was associated with:[7,34] • **A reduced risk of sustained loss of kidney function:** The composite outcome of sustained doubling of serum creatinine, end-stage kidney disease, and death from renal causes occurred less frequently in the canagliflozin group compared with the placebo group (1·5 per 1000 patient-years in the canagliflozin group vs 2·8 per 1000 patient-years in the placebo group; hazard ratio 0·53), with consistent findings across prespecified patient subgroups • **Attenuated eGFR decline**: Annual eGFR decline was slower (slope difference between groups 1·2 mL/min per 1·73 m^2 per year) and mean UACR was 18% lower in participants treated with canagliflozin than in those treated with placebo • **A reduction in albuminuria** (hazard ratio, 0.73): An increase in albuminuria regression (hazard ratio of 1.70 (95% CI: 1.51, 1.91)[c]
Adverse effects (AEs)	Total serious renal-related adverse events were similar between the canagliflozin and placebo groups (2·5 vs 3·3 per 1000 patient-years; HR 0·76).[7] An increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio 1.97). Amputations were primarily at the level of the toe or metatarsal.[34]
Expected reporting date	-

Trial	**CREDENCE,** NCT02065791; EudraCT 2013-004494-28; **Canagliflozin vs placebo; phase III**
Sponsor	Janssen Research & Development, LLC
Status	Completed
Source of Information	Trial registry[1], publication[35], manufacturer[d]
Location	10 EU countries (including UK), United States, Canada and other countries
Design	Randomised, parallel assignment, double blinded
Participants[e]	The trial was designed to be event-driven, with the enrolment of at least 4200 patients (844 events); males and females aged ≥30 years of age; type 2 diabetes mellitus with a hemoglobin A1c (HbA1c) greater than or equal to (>=) 6.5 percent (%) and less than or equal to (<=) 12.0%, with an estimated glomerular filtration rate (eGFR) of >= 30 milliliter (mL)/minute (min)/1.73meter (m)^2 and less than (<) 90 mL/min/1.73 m^2; There was a prespecified plan to include approximately 60% of patients with an estimated GFR of 30 to <60 ml per minute per 1.73 m2. Participants need to be on a stable maximum tolerated labelled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) for at least 4 weeks prior to randomization; participants must have a urine albumin to creatinine ratio (UACR) of greater than (>) 300 milligram (mg)/gram (g) and <= 5000 mg/g
Schedule	Patients are randomised to receive either: • 100 mg over-capsulated tablet orally once daily or,

[c] Information provided by Napp Pharmaceuticals Ltd.
[d] Information provided by Napp Pharmaceuticals Ltd.
[e] Information provided by Napp Pharmaceuticals Ltd.

	• One matching placebo capsule orally once daily Duration is approximately 66 months
Follow-up	Total duration of the study is estimated to be about 5 to 5.5 years
Primary Outcomes	Time to the first occurrence of an event in the primary composite endpoint [Time frame: baseline, up to approximately 66 months]
Secondary Outcomes	• Time to the first occurrence of an event in the composite endpoint of cv death and hospitalized congestive heart failure [Time frame: baseline, up to approximately month 66] • Time to the first occurrence of an event in the composite endpoint of CV death, non-fatal MI, and non-fatal stroke (that is, 3-point major adverse cardiac event [mace]) [Time frame: baseline, up to approximately month 66] • Time to the first occurrence of hospitalized congestive heart failure [Time frame: baseline, up to approximately month 66] • Time to the first occurrence of an event in the renal composite endpoint [Time frame: baseline, up to approximately month 66] • Time to CV death [Time frame: baseline, up to approximately month 66] • Time to all-cause death [Time frame: baseline, up to approximately month 66] • Time to the first occurrence of an event in the CV composite endpoint [Time frame: baseline, up to approximately month 66]
Key Results[f]	The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome (composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 sustained for at least 30 days according to central laboratory assessment), doubling of the serum creatinine level from baseline (average of randomization and prerandomization value) sustained for at least 30 days according to central laboratory assessment, or death from renal or cardiovascular disease) was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.
Adverse effects (AEs)[g]	Rates of adverse events and serious adverse events were similar overall in the canagliflozin group and the placebo group. There was no significant difference in the risk of lowerlimb amputation, with rates of 1.23 versus 1.12 per 100 patient-years in the canagliflozin group and the placebo group, respectively (hazard ratio, 1.11; 95% CI, 0.79 to 1.56). Rates of fracture were also similar in the two groups (hazard ratio, 0.98; 95% CI, 0.70 to 1.37). Rates of diabetic ketoacidosis

[f] Information provided by Napp Pharmaceuticals Ltd.
[g] Information provided by Napp Pharmaceuticals Ltd.

	were low but higher in the canagliflozin group than in the placebo group (2.2 vs. 0.2 per 1000 patient-years).
Expected reporting date	-

ESTIMATED COST

Canagliflozin is already marketed in the UK for T2DM; 100mg and 300mg are priced the same at £39.20 per pack of 30 tablets, cost per patient per annum is £476.93 (£39.20/30 X 365 days).[36]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (TA390). May 2016.
- NICE technology appraisal. Canagliflozin in combination therapy for treating type 2 diabetes (TA315). June 2014.
- NICE guidance in development. Chronic kidney disease: assessment and management (GID-NG10118). Expected publication date July 2020.
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- NICE quality standard. Chronic kidney disease in adults (QS5). July 2017.
- NICE quality standard. Diabetes in adults (QS6). August 2016.
- NICE public health guidance. Type 2 diabetes: prevention in people at high risk (PH38). September 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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