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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Finerenone for chronic kidney disease in patients with type 2 diabetes mellitus

NIHRIO ID	9339	**NICE ID**	10049
Developer/Company	Bayer AG	**UKPS ID**	622563

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

SUMMARY

Finerenone is in clinical development for the treatment of chronic kidney disease in adults with type 2 diabetes mellitus. Diabetes is a condition that causes the 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 heart disease and adverse health outcomes.

Finerenone is selective inhibitor of a specific protein, which blocks the damaging effects of hormones (such as aldosterone and cortisol) which can cause damage to the heart and kidneys in diabetic patients. Finerenone is administered orally in tablet form, and evidence suggests it may offer organ protection compared to similar inhibitors which are currently used. If licensed, finerenone will offer patients with type 2 diabetes mellitus who have chronic kidney disease an add-on therapy to slow down long-term kidney damage and reduce the adverse impact on the structure and function of the heart and vessels.

PROPOSED INDICATION

An add-on therapy to the standard of care for the treatment of chronic kidney disease (CKD) in patients with type 2 diabetes (T2DM).[1-3]

TECHNOLOGY

DESCRIPTION

Finerenone (BAY 94-8862) is a potent non-steroidal, selective mineralocorticoid receptor (MR) antagonist (MRAs) being developed for the treatment of patients with T2DM and CKD.[4] Finerenone induces a conformational change within the MR complex, thereby ultimately changing the stability and nuclear translocation of the receptor.[5] As such, finerenone treatment blocks the detrimental effects due to over-activation of the receptor by aldosterone and cortisol, which increases blood pressure and has been implicated in a number of other damaging effects in the kidney, vasculature, and heart.[6]

Finerenone is in phase II/III clinical development for the treatment of CKD on top of standard care (FIDELIO-DKD[1], FIGARO-DKD[2], ARTS-DN[3]). Finerenone dosing is a 10 mg or 20 mg tablet to be given orally, once daily.[2,3]

INNOVATION AND/OR ADVANTAGES

There are a number of advantages of finerenone over other MRAs which are currently used to treat CKD.[7] Compared with currently available steroid-based MRAs, preclinical studies demonstrated that finerenone treatment prevented the development of functional and structural heart and kidney damage more efficiently than the steroidal MRA eplerenone, when comparing equinatriuretic doses.[8]

Furthermore, compared to eplerenone, finerenone distributes equally to the heart and kidney.[9] Finerenone combines spironolactone's potency with eplerenone's selectivity and, based on its non-steroidal chemical structure,[10] it may have an improved cardiac vs. renal activity ratio (relative renal sparing) because of a combination of physicochemical properties that influence plasma transport and tissue penetration and differential affinity of the MR - drug complex for tissue-specific cofactors. Therefore, finerenone may offer end-organ protection with a reduced risk of electrolyte disturbances (and therefore hyperkalaemia) compared with steroidal MRAs.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Finerenone does not currently have a Marketing Authorisation in the EU/UK for any indication.

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).[11]

Kidney disease (nephropathy) is more common in people with diabetes and high blood pressure.[12] 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.[12] If the disease progresses, symptoms such as vomiting, nausea, weight loss, itching, bone damage, etc. become noticeable.[13]

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 estimated glomerular filtration rate (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.[14]

- **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.[14]

Diabetic nephropathy is the most common cause or in combination with hypertensive nephropathy, the most common causes of end-stage renal disease (ESRD).[15] At stage 5, maintenance renal replacement therapy is required.[16]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-2018 the prevalence of diagnosed cases of diabetes was 3,222,559.[17] 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.[17] Furthermore, by 2030, people living with T2DM in the UK is predicted to rise to 5.5 million.[18] Almost one in five people with diabetes will need treatment for kidney disease in their lifetime.[12]

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.[19] 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.[20] For those undergoing RRT, survival rates are lower than for people without the condition (3.4 years vs 6.5 years).[21] Kidney disease accounts for 11% of deaths in T2DM.[22]

Hospital admissions data for England in 2018-2019 recorded 627 finished consultant episodes (FCE) for non-insulin-dependent diabetes mellitus with renal complications (ICD 10: E11.2), 366 hospital admissions, 108 day cases and 1,891 FCE bed days.[23]

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.[24] Improved glycaemic control has been shown to reduce the occurrence of early diabetic nephropathy.[25-29]

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.[30]

After formal diagnosis and assessment of the stage of the disease, it may be possible for routine follow-up at the patient's GP surgery, or alternatively by a consultant nephrologist who will discuss treatment options.[31]

Depending on the severity of the condition, a range of management options may be considered:[31]

- 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

Pharmacological management is focused on reducing risk factors for kidney disease progression. There are no treatments that are specifically approved to prevent kidney damage.

The main treatments to relieve the symptoms of kidney disease are:[32]

- lifestyle changes – to help you stay as healthy as possible
- medicine – to control associated problems, such as high blood pressure and high cholesterol
- dialysis – treatment to replicate some of the kidney's functions, which may be necessary in advanced (stage 5) CKD
- kidney transplant – this may also be necessary in advanced (stage 5) CKD

PLACE OF TECHNOLOGY

If licensed, finerenone will be offered as an add-on therapy for adult patients with T2DM who have CKD and are currently treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

CLINICAL TRIAL INFORMATION

Trial	**FIDELIO-DKD**, NCT02540993; EudraCT: 2015-000990-11; **adults 18 yrs and older; finerenone vs placebo; phase III**
Sponsor	Bayer
Status	Ongoing
Source of Information	Trials registry[1,33] and company
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled, parallel assignment, quadruple masking.
Participants	n=5734; adults aged 18 years and older with T2DM as defined by the American Diabetes Association; diagnosis of diabetic kidney disease (DKD) with persistent high albuminuria or persistent very high albuminuria at the run-in and screening visits; pretreated with either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) at maximal tolerated labelled dose without adjustments; serum potassium <=4.8 mmol/L.
Schedule	Participants were randomised to: Experimental arm: 10 mg or 20 mg finerenone tablet to be given orally, once daily Placebo comparator arm: matching placebo to be taken orally, once daily
Follow-up	Follow-up visits were scheduled for 4 weeks ± 5 days after the last dose of study drug.
Primary Outcomes	Time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of estimated glomerular filtration rate (eGFR) ≥ 40% from baseline over at least 4 weeks or renal death. [Time frame: time to total follow up (up to 48 mths)]
Secondary Outcomes	• Time to first occurrence of the composite endpoint: cardiovascular death or non-fatal cardiovascular events (myocardial infarction, stroke, hospitalization for heart failure) [Time frame: time to total follow up (up to 48 mths)] • Time to all-cause mortality [Time frame: time to total follow up (up to 48 mths)] • Time to all-cause hospitalisations [Time frame: time to total follow up (up to 48 months)] • Time to first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease in estimated glomerular filtration rate (eGFR) of ≥ 57% from baseline over at least 4 weeks or renal death. [Time frame: time to total follow up (up to 48 mths)] • Change in urinary albumin-to-creatinine ratio (UACR) from baseline to month 4 [Time frame: baseline to mth 4]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as April 2020. Estimated study completion date reported as May 2020.

Trial	**FIGARO-DKD,** NCT02545049; EudraCT: 2015-000950-39**; adults 18 yrs and older; finerenone vs placebo; phase III**
Sponsor	Bayer
Status	Ongoing
Source of Information	Trials registry[2,34], publication[35] and company
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled, parallel assignment, quadruple masking
Participants	n= 7437; adults aged 18 years and older with T2DM as defined by the American Diabetes Association; diagnosis of diabetic kidney disease (DKD) with persistent high albuminuria or persistent very high albuminuria at the run-in and screening visits; pretreated with either angiotensin-converting enzyme inhibitor(ACEI) or angiotensin receptor blocker (ARB) at maximal tolerated labelled dose without adjustments; serum potassium <=4.8 mmol/L.
Schedule	Participants were randomised to: Experimental arm: 10 mg or 20 mg finerenone tablet to be given orally, once daily Placebo comparator arm: Matching placebo to be taken orally, once daily
Follow-up	Follow-up visits were scheduled for 4 weeks ± 5 days after the last dose of study drug.
Primary Outcomes	Time to the first occurrence of the composite endpoint of cardiovascular death and non-fatal cardiovascular events (myocardial infarction, stroke, or hospitalisation for heart failure) [Time frame: time to total follow up (up to 53 mths)]
Secondary Outcomes	• Time to first occurrence of the following composite endpoints: onset of kidney failure, a sustained decrease in estimated glomerular filtration rate (eGFR)of ≥40% from baseline over at least 4 weeks and renal death [Time frame: time to total follow up (up to 53 mths)] • Time to all-cause mortality [Time frame: time to total follow up (up to 53 mths)] • Time to all-cause hospitalisation [Time frame: time to total follow up (up to 53 mths)] • Change in urinary albumin-to-creatine ratio (UCAR) from baseline to month 4 [Time frame: baseline to mth 4] • Time to first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease in estimated glomerular filtration rate (eGFR) of ≥ 57% from baseline over at least 4 weeks or renal death. [Time frame: time to total follow up (up to 53 mths)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as June 2021 and estimated study completion date reported as July 2021.

Trial	**ARTS-DN,** NCT01874431; EudraCT: 2012-004179-38**; adults 18 yrs and older; finerenone vs placebo; phase IIb**
Sponsor	Bayer
Status	Completed

Source of Information	Trials registry[3,36], publication[35,37] and company
Location	EU (not UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled, parallel assignment, quadruple masking
Participants	n=823; adults aged 18 years and older with T2DM and a clinical diagnosis of diabetic nephropathy; subjects treated with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) for at least 3 months without any adjustments to this therapy for at least 4 weeks prior to the screening visit; serum potassium </= 4.8 mmol/L at both the run-in visit and the screening visit
Schedule	Participants were randomised to: – Experimental: Finerenone (1.25 mg) 1.25 mg dose oral once daily for 90 days – Experimental: Finerenone (2.5 mg) 2.5 mg dose oral once daily for 90 days – Experimental: Finerenone (5 mg) 5 mg dose oral once daily for 90 days – Experimental: Finerenone (7.5 mg) 7.5 mg dose oral once daily for 90 days – Experimental: Finerenone (10 mg) 10 mg dose oral once daily for 90 days – Experimental: Finerenone (15 mg) 15 mg dose oral once daily for 90 days – Experimental: Finerenone (20 mg) 20 mg dose oral once daily for 90 days – Placebo Comparator: Placebo Placebo oral dose once daily for 90 days
Follow-up	Follow-up visits were scheduled for 30 ± 5 days after the last intake of study medication.
Primary Outcomes	Change of Urinary Albumin-to-Creatinine Ratio (UACR) at visit 90 [Time Frame: from baseline to 90 days]
Secondary Outcomes	• Change From Baseline to Day 90 in Serum Potassium [Time frame: from baseline to day 90] • Change From Baseline to Day 90 in Renal Function [Time frame: from baseline to day 90] • Change in Health-Related Quality of Life (HRQoL) (Kidney Disease QOL [KDQOL]-36 Questionnaire) [Time frame: from baseline to day 90] • Change in Health-Related Quality of Life (EuroQol Group 5-Dimension, 3-Level [EQ-5D-3L] Questionnaire) [Time frame: from baseline to day 90]
Key Results	• Finerenone demonstrated a dose-dependent reduction in UACR. The primary outcome, the placebo-corrected mean ratio of the UACR at day 90 relative to baseline, was reduced in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups (for 7.5 mg/d, 0.79 [90% CI, 0.68-0.91; P = .004]; for 10 mg/d, 0.76 [90% CI, 0.65-0.88; P = .001]; for 15 mg/d, 0.67 [90% CI, 0.58-0.77; P<.001]; for 20 mg/d, 0.62 [90% CI, 0.54-0.72; P < .001]). • Hyperkalemia leading to discontinuation was not observed in the placebo and finerenone 10-mg/d groups; incidences in the finerenone 7.5-, 15-, and 20-mg/d groups were 2.1%, 3.2%, and 1.7%, respectively. • There were no differences in the incidence of the prespecified secondary outcome of an estimated glomerular filtration rate decrease

	of 30% or more or in incidences of adverse events and serious adverse events between the placebo and finerenone groups.
Adverse effects (AEs)	• No difference in the overall incidence of adverse events and serious adverse events between the finerenone groups and the placebo group. • No relevant increase in adverse events across finerenone dosages. • Drug-related serious adverse events occurred in 1.5% of patients receiving finerenone.
Expected reporting date	Study completion date previously reported as August 2014

ESTIMATED COST

The cost of finerenone is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Canagliflozin for treating chronic kidney disease in people with type 2 diabetes [ID1653]. Expected publication date: TBC
- NICE guidance in development. Chronic kidney disease: assessment and management (GID-NG10118). Expected publication date July 2020.
- NICE guideline. Type 2 diabetes in adults: management (NG28). December 2015, updated August 2019.
- NICE guideline. Chronic kidney disease: managing anaemia (NG8). June 2015.
- NICE quality standard. Chronic kidney disease in adults (QS5). July 2017.
- NICE quality standard. Diabetes in adults (QS6). August 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

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- Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes (SIGN 116). March 2010, updated November 2017.[39]
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ADDITIONAL INFORMATION

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