

## HEALTH TECHNOLOGY BRIEFING MAY 2020

### Veverimer for metabolic acidosis associated with chronic kidney disease

<b>NIHRIO ID</b>	18330	<b>NICE ID</b>	9919
<b>Developer/Company</b>	Tricida Inc	<b>UKPS ID</b>	Not available

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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### SUMMARY

Veverimer is currently in clinical development for the treatment of metabolic acidosis associated with chronic kidney disease (CKD). One of the roles of the kidneys is to remove excess acid from the blood and excrete the acid in urine. In CKD, the kidneys do not function as well as they should so they cannot remove acid adequately. This results in a build-up of acid in the blood that can cause symptoms such as confusion, fast heartbeat, headache, loss of appetite, vomiting and feeling weak or tired. Metabolic acidosis in CKD can result in increased bone loss, progression of kidney disease, muscle loss and endocrine disorders such as diabetes.

Veverimer is given as an oral suspension and it works by binding to hydrochloric acid in the gastrointestinal tract and removing it from the body through excretion in the faeces. Preliminary results from early studies have demonstrated that veverimer is efficacious and safe. If licensed, veverimer could offer an additional treatment option for patients with metabolic acidosis associated with CKD.

## PROPOSED INDICATION

For the treatment of metabolic acidosis associated with chronic kidney disease (CKD).<sup>1-3</sup>

## TECHNOLOGY

### DESCRIPTION

Veverimer (TRC-101) is a novel, non-absorbed, counterion-free polymer that is administered orally as suspension in water. It is designed to treat metabolic acidosis by binding hydrochloric acid in the gastrointestinal tract and removing it from the body through excretion in the faeces, thereby decreasing the total amount of acid in the body and increasing serum bicarbonate.<sup>4,5</sup> When ingested, veverimer binds protons with high capacity. The resulting positively charged polymer selectively binds chloride, the smallest anion in the gastrointestinal tract. The high proton and chloride binding capacity of veverimer is a function of its high amine content. Extensive crosslinking imparts size exclusion properties and selectivity for binding chloride over larger competing anions such as phosphate, citrate, bile acids and fatty acids.<sup>5</sup>

Veverimer is currently in clinical development for the treatment of metabolic acidosis associated with CKD. In the phase III clinical trials NCT03390842, NCT03710291 and NCT03317444 participants are given 6g veverimer by oral administration once daily.<sup>1-3</sup>

### INNOVATION AND/OR ADVANTAGES

Veverimer, unlike alkali supplements, removes accumulated acid rather than neutralizing it and unlike exchange resin, does not deliver a counterion load such as sodium or potassium.<sup>6</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Veverimer is not currently in phase II or III development for any other indication.<sup>7</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

Chronic kidney disease (CKD) is a long term condition where the kidneys do not work as well as they should.<sup>8</sup> The kidneys play a central role in maintaining bicarbonate homeostasis by reabsorbing the filtered bicarbonate in the proximal tubule and synthesising enough to neutralize the net acid load. This allows renal excretion of hydrogen ions as either ammonium or titratable acidity. Therefore, the kidneys contribute to a normal acid-base homeostasis. When the functional renal mass is reduced as is the case in CKD, impairment of renal acid handling occurs resulting in acidosis and consumption of bicarbonate in order to buffer the retained acid.<sup>9</sup>

Metabolic acidosis is generally defined by the presence of a low serum bicarbonate concentration (normal range 22-28 mEq/L) and can result in symptoms such as confusion, fast heartbeat, headache, loss of appetite, vomiting and feeling weak or tired.<sup>10,11</sup> Metabolic acidosis in kidney disease can result in complications such as increased bone loss (osteoporosis), muscle loss and progression of kidney disease. If left untreated it can cause endocrine disorders such as diabetes.<sup>12</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

Metabolic acidosis is a common complication of advanced CKD, present in 30-50% of individuals with estimated glomerular filtration rate (eGFR), < 30 mL/min/1.73m<sup>2</sup> (stage 4 and stage 5 CKD).<sup>13,14</sup>

In England, in 2018-19, there were 58,850 finished consultant episodes (FCE) for chronic kidney disease (ICD-10 code N18) resulting in 41,479 admissions and 110,588 FCE bed days. There were 2,456 FCE for acidosis (ICD-10 code E87.2) resulting in 1,403 admissions and 7,563 FCE bed days.<sup>15</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

The goal of treatment of metabolic acidosis in patients with CKD is to achieve a venous plasma or venous blood bicarbonate concentration equal to or greater than 22mmol.<sup>16</sup>

### CURRENT TREATMENT OPTIONS

According to NICE clinical guidelines, sodium bicarbonate supplementation is considered for people with both a GFR less than 30ml/min/1.72m<sup>2</sup> (GFR category G4 or G5) and a serum bicarbonate concentration of less than 20mmol/lite.<sup>17</sup>

### PLACE OF TECHNOLOGY

If licensed, veverimer will offer an additional treatment option for patients with metabolic acidosis associated with CKD.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>VALOR-CKD</b> , <a href="#">NCT03710291</a> , <a href="#">EudraCT 2018-001303-36</a> ; A Phase 3b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of TRC101 in Delaying Chronic Kidney Disease Progression in Subjects With Metabolic Acidosis <b>Phase III - ongoing</b> <b>Locations:</b> 13 EU (incl UK), USA, Canada and other countries
<b>Trial design</b>	Randomised, Double-blind, Placebo-controlled

Population	N=1600 (estimated); adults aged 18 to 85 years old; estimated glomerular filtration rate (eGFR) 20-40 mL/min/1.73m <sup>2</sup> ; serum bicarbonate 12 - 20 mEq/L; on maximum tolerated dose of ACE inhibitor and/or ARB.
Intervention(s)	Veverimer (oral administration) once daily
Comparator(s)	Placebo
Outcome(s)	Progression of CKD [ Time Frame: Through study completion, on average 3.5 years ]  See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	<a href="#">NCT03317444</a> , <a href="#">EudraCT 2016-003825-41</a> ; A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TRC101 in Subjects With Chronic Kidney Disease and Metabolic Acidosis <b>Phase III - completed</b> <b>Locations:</b> 4 EU (not incl UK), USA and other countries.
Trial design	Randomised, Double-blind, Placebo-controlled
Population	N=217; adults aged between 18 and 85 years; blood bicarbonate level of 12 to 20 mEq/L; estimated glomerular filtration rate (eGFR) of 20 to 40mL/min/1.73m <sup>2</sup> ; stable kidney function defined as <= 20% variability in eGFR during screening period
Intervention(s)	6g veverimer (oral suspension) administered once daily
Comparator(s)	Placebo (oral suspension) administered once daily
Outcome(s)	Change from baseline in blood bicarbonate [ Time Frame: Week 12 ]  See trial record for full list of other outcomes
Results (efficacy)	The primary endpoint was met by 71 (59%) of 120 patients in the veverimer group versus 20 (22%) of 89 patients in the placebo group. <sup>18</sup>
Results (safety)	The most common body system in which adverse events in the veverimer group occurred was gastrointestinal; of these, non-treatment limiting diarrhoea was the most common event (11 [9%] vs three [3%] in the veverimer and placebo groups, respectively). The most common treatment-related adverse events were gastrointestinal (diarrhoea, flatulence, nausea and constipation) occurring in 16 (13%) patients with veverimer and five (5%) patients with placebo. Two deaths occurred during the study, both in the placebo group (unstable angina and pneumonia). <sup>18</sup>

Trial	<a href="#">NCT03390842</a> , <b>TRCA-301E</b> ; A Blinded, Placebo-Controlled Extension to Study TRCA-301 to Evaluate the Long-term Safety and Durability of Effect of TRC101 in Subjects With Chronic Kidney Disease and Metabolic Acidosis <b>Phase III - completed</b>
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	<b>Locations:</b> 3 EU (not incl UK) USA and other countries
<b>Trial design</b>	Randomised, Parallel Assignment, Blinded, Placebo-Controlled, Extension
<b>Population</b>	N=196 participants; adults aged 18 to 85 years; completed the 12 week treatment period and attended the week 12 parent study TRCA-301; blood bicarbonate level $\geq$ 12 mEq/L at the week 12 visit in the parent study TRCA-301
<b>Intervention(s)</b>	6g veverimer (oral suspension) Administered once daily
<b>Comparator(s)</b>	Placebo (oral suspension) Administered once daily
<b>Outcome(s)</b>	Incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal. [ Time Frame: From Week 12 (enrolment) to Week 54 (last follow-up visit) ]  See trial record for full list of other outcomes
<b>Results (efficacy)</b>	More patients on veverimer than placebo had an increase in bicarbonate ( $>4$ mmol/L or normalisation) at week 52 (63% vs 38%) and higher bicarbonate concentrations were observed with veverimer than placebo at all timepoints. Veverimer resulted in improved patient-reported physical functioning (Kidney Disease and Quality of Life-Physical Function Domain) versus placebo with a mean placebo-subtracted change at end of treatment 12.1 points. Time to do the repeat chair stand test improved by 4.3 seconds on veverimer versus 1.4 seconds on placebo. <sup>19</sup>
<b>Results (safety)</b>	Compared with placebo, fewer patients on veverimer discontinued treatment prematurely (3% vs 10% respectively) and no patients on veverimer discontinued treatment because of an adverse event. Serious adverse events occurred in 2% of veverimer-treated patients and in 5% of placebo patients (two of whom died). Renal system adverse events were reported in 8% and 15% in the veverimer and placebo groups respectively. <sup>19</sup>

## ESTIMATED COST

The estimated cost of veverimer is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE quality standard. Chronic kidney disease in adults (QS5). March 2011. Last updated July 2017.
- NICE clinical guideline. Chronic kidney disease in adults: assessment and management (CG182). 2015.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance

## OTHER GUIDANCE

- Boris Jung et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. 2019.<sup>20</sup>
- Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012.<sup>21</sup>
- Scottish Intercollegiate Guidelines Network. SIGN 103: Diagnosis and management of chronic kidney disease. 2008.<sup>22</sup>

## ADDITIONAL INFORMATION

Tricida Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## REFERENCES

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