

HEALTH TECHNOLOGY BRIEFING MAY 2020

Veverimer for metabolic acidosis associated with chronic kidney disease

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

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

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).¹⁻³

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.^{4,5} 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.⁵

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.¹⁻³

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.⁶

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.⁷

PATIENT GROUP

DISEASE BACKGROUND

Chronic kidney disease (CKD) is a long term condition where the kidneys do not work as well as they should.⁸ 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.⁹

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.^{10,11} 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.¹²

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/1.73m² (stage 4 and stage 5 CKD).^{13,14}

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.¹⁵

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.¹⁶

CURRENT TREATMENT OPTIONS

According to NICE clinical guidelines, sodium bicarbonate supplementation is considered for people with both a GFR less than 30ml/min/1.72m² (GFR category G4 or G5) and a serum bicarbonate concentration of less than 20mmol/lite.¹⁷

PLACE OF TECHNOLOGY

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

CLINICAL TRIAL INFORMATION

Trial	VALOR-CKD , NCT03710291 , EudraCT 2018-001303-36 ; 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 Phase III - ongoing Locations: 13 EU (incl UK), USA, Canada and other countries
Trial design	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 ² ; 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	NCT03317444 , EudraCT 2016-003825-41 ; 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 Phase III - completed Locations: 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 ² ; 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. ¹⁸
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). ¹⁸

Trial	NCT03390842 , TRCA-301E ; 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 Phase III - completed
-------	---

	Locations: 3 EU (not incl UK) USA and other countries
Trial design	Randomised, Parallel Assignment, Blinded, Placebo-Controlled, Extension
Population	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
Intervention(s)	6g veverimer (oral suspension) Administered once daily
Comparator(s)	Placebo (oral suspension) Administered once daily
Outcome(s)	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
Results (efficacy)	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. ¹⁹
Results (safety)	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. ¹⁹

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. 2019.²⁰
- Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012.²¹
- Scottish Intercollegiate Guidelines Network. SIGN 103: Diagnosis and management of chronic kidney disease. 2008.²²

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

- 1 Clinicaltrials.gov. *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*. Trial ID. 2017. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT03317444> [Accessed 09 April 2020].
- 2 Clinicaltrials.gov. *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*. Trial ID. 2018. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT03390842> [Accessed 09 April 2020].
- 3 Clinicaltrials.gov. *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*. Trial ID. 2018. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT03710291> [Accessed 09 April 2020].
- 4 Tricida. *Veverimer (also known as TRC101)*. 2020. Available from: <https://www.tricida.com/trc101/> [Accessed 10 April 2020].
- 5 Bushinsky, D., Vandana M., Wesson D. *Mechanism of Action and Onset of Effect of Veverimer, A Novel Acid Binder for the Treatment of Metabolic Acidosis Associated with Chronic Kidney Disease (CKD)*. American Journal of Kidney Diseases. 2020 2020/04/01/;75(4):552-3. Available from: <https://doi.org/10.1053/j.ajkd.2020.02.060>
<http://www.sciencedirect.com/science/article/pii/S0272638620301037>
- 6 Renal & Urology News. *Novel Acid Binder Veverimer Has Rapid Onset of Action*. 2020. Available from: <https://www.renalandurologynews.com/home/conference-highlights/national-kidney-foundation-annual-meeting/nkf-2020-spring-meeting/novel-acid-binder-veverimer-has-rapid-onset-of-action/> [Accessed 28 March 2020].
- 7 Clinicaltrials.gov. *Search for veverimer studies: Phase II and III*. 2020. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=veverime&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&

- [sub=&strd s=&strd e=&prcd s=&prcd e=&sfpd s=&sfpd e=&rfpd s=&rfpd e=&lupd s=&lupd e=&sort=](#) [Accessed 26 April 2020].
- 8 National health Service (NHS). *Chronic Kidney Disease: Overview*. 2019. Available from: <https://www.nhs.uk/conditions/kidney-disease/> [Accessed 09 April 2020].
- 9 Stancu, S., Mircescu G., Mocanu A., Capusa C., Stefan G. *Metabolic Acidosis of Chronic Kidney Disease and Cardiovascular Disorders*. *Maedica*. 2018;13(4):267-72. Available from: 10.26574/maedica.2018.13.4.267 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6362877/>
- 10 Renal & Urology News. *Nephrology Hypertension Acid/Base Disorders: Metabolic Acidosis*. 2020. Available from: <https://www.renalandurologynews.com/home/decision-support-in-medicine/nephrology-hypertension/acid-base-disorders-metabolic-acidosis/> [Accessed 26 April 2020].
- 11 National Kidney Foundation. *Metabolic Acidosis*. 2020. Available from: <https://www.kidney.org/atoz/content/metabolic-acidosis> [Accessed 09 April 2020].
- 12 American Kidney Fund. *Metabolic Acidosis - symptoms, complications and treatment*. 2020. Available from: <https://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/complications/metabolic-acidosis/#what-are-the-symptoms-of-metabolic-acidosis> [Accessed 09 April 2020].
- 13 Chen, W., Abramowitz M. K. *Treatment of metabolic acidosis in patients with CKD*. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2014;63(2):311-7. Available from: 10.1053/j.ajkd.2013.06.017 <https://doi.org/10.1053/j.ajkd.2013.06.017>
- 14 American Kidney Fund. *Stages of Chronic Kidney Disease (CKD)*. 2020. Available from: <https://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/stages-of-chronic-kidney-disease/> [Accessed 26 April 2020].
- 15 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19: Diagnosis*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19> [Downloaded 19 September 2019].
- 16 Adamczak, M., Masajtis-Zagajewska A., Mazanowska O., Madziarska K., Stompor T., Wiecek A. *Diagnosis and Treatment of Metabolic Acidosis in Patients with Chronic Kidney Disease - Position Statement of the Working Group of the Polish Society of Nephrology*. *Kidney Blood Press Res*. 2018;43(3):959-69. Available from: 10.1159/000490475 <https://doi.org/10.1159/000490475>
- 17 National Institute for Health and Care Excellence (NICE). *Chronic kidney disease in adults: assessment and management (CG182)*. Last Update Date: 16 January 2015. Available from: <https://www.nice.org.uk/guidance/cg182> [Accessed 26 May 2020].
- 18 Wesson, D. E., Mathur V., Tangri N., Stasiv Y., Parsell D., Li E., et al. *Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial*. *Lancet*. 2019 Apr 6;393(10179):1417-27. Available from: 10.1016/s0140-6736(18)32562-5 [https://doi.org/10.1016/s0140-6736\(18\)32562-5](https://doi.org/10.1016/s0140-6736(18)32562-5)
- 19 Wesson, D. E., Mathur V., Tangri N., Stasiv Y., Parsell D., Li E., et al. *Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension*. *Lancet*. 2019 Aug 3;394(10196):396-406. Available from: 10.1016/s0140-6736(19)31388-1 [https://doi.org/10.1016/s0140-6736\(19\)31388-1](https://doi.org/10.1016/s0140-6736(19)31388-1)
- 20 Jung, B., Martinez M., Claessens Y.-E., Darmon M., Klouche K., Lautrette A., et al. *Diagnosis and management of metabolic acidosis: guidelines from a French expert panel*. *Annals of Intensive Care*. 2019 2019/08/15;9(1):92. Available from: 10.1186/s13613-019-0563-2 <https://doi.org/10.1186/s13613-019-0563-2>
- 21 Kidney Disease Improving Global Outcomes (KDIGO). *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. 2012. Available from: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf [Accessed 26 April 2020].
- 22 Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and management of chronic kidney disease (103)*. Last Update Date: 2008. Available from: http://www.seqg.es/download/gpc/62/3729/1043258133/1073968/cms/sign-diagnosis-and-management-of-chronic-kidney-disease_guideline.pdf/ [Accessed 26 April 2020].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.