

**NIHR Innovation Observatory  
Evidence Briefing: April 2018****Sodium thiosulfate for acute calciphylaxis-  
associated pain in chronic haemodialysis patients**

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**LAY SUMMARY**

Calciphylaxis is a severe and progressive disease mainly seen in patients with end-stage kidney disease (when the kidneys have stopped working) undergoing haemodialysis. It involves the build-up of calcium in very small arteries resulting in a restricted blood supply and small clots. The skin develops ulcers that do not heal and usually cause severe pain. Calciphylaxis is a long-term debilitating and life-threatening condition, particularly due to the deep, painful, non-healing ulcers and the risk of infection. Calciphylaxis is a life-threatening condition. Once ulcerations develop, up to 80% of people with the condition will die, and just less than half will die within one year. Patients who do not die of sepsis or organ failure frequently undergo amputation of the involved limb.

Sodium thiosulfate is an injectable solution that is being developed to treat calciphylaxis-associated pain in patients undergoing dialysis. It is thought that sodium thiosulfate works by attaching itself to the calcium to form a compound that is removed from the body in the urine, reducing the build-up of calcium in the arteries. If licensed, this product will provide a treatment option for patients with calciphylaxis, who currently have few effective treatments available.

*This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Chronic haemodialysis patients with acute calciphylaxis-associated pain

## TECHNOLOGY

### DESCRIPTION

Sodium thiosulfate has been used for many years in the EU for the treatment of cyanide poisoning. In patients with calciphylaxis sodium thiosulfate acts as a calcium chelator, attaching to calcium to form a compound which is easily eliminated in the urine, thereby reducing the build-up of calcium in the arteries.<sup>1</sup> Sodium thiosulfate also provides persistent and prompt relief of ischaemic pain, possibly because of its ability to generate both glutathione and hydrogen sulphide, making it a potent antioxidant and a vasodilator. Its antioxidant actions may also prevent the oxidation of tetrahydrobiopterin to its oxidised forms, which uncouple the endothelial nitric oxide (NO) synthase enzyme and allow the endothelium to become a net producer of superoxide while decreasing the amount of bioavailable endothelial derived NO. Sodium thiosulfate not only improves vascular endothelial function and vasodilation due to increased bioavailability of NO but also may improve overall vascular integrity, contributing to decreased vascular calcification.<sup>2</sup>

In the phase III clinical trial evaluating the efficacy and safety of sodium thiosulfate for treatment of acute calciphylaxis-associated pain in chronic haemodialysis patients (CALISTA; NCT03150420), sodium thiosulfate is administered as an intravenous injection at 25g at each haemodialysis session (3 times weekly) for 3 weeks.<sup>3</sup>

Sodium thiosulfate is licensed in the EU for poisoning with cyanides (used in conjunction with sodium nitrite).<sup>4</sup> For this indication there have been no controlled clinical trials to systematically assess the adverse events profile of sodium thiosulfate. Adverse events that have been reported in medical literature include hypotension, headache, disorientation, nausea and vomiting, prolonged bleeding time, salty taste in mouth and warm sensation over body. These adverse events were not reported in the context of controlled trials or with consistent monitoring and reporting methodologies for adverse events. The frequency of occurrence of these adverse events cannot be assessed.<sup>5</sup>

## INNOVATION and/or ADVANTAGES

A number of reports and case studies have suggested that sodium thiosulfate may be an effective therapy for calciphylaxis.<sup>6,7,8</sup> Current treatment options include balancing minerals in the body, wound care and pain relief, and there is no pharmacological cure available. If licensed, sodium thiosulfate will offer a treatment option for patients with calciphylaxis, who currently have no effective therapy available.

## DEVELOPER

Hope Pharmaceuticals Ltd

## REGULATORY INFORMATION/ MARKETING PLANS

Sodium thiosulfate was designated an orphan drug in the EU for calciphylaxis in March 2015.<sup>1</sup>

Sodium thiosulfate was designated an orphan drug in the USA for uraemic calciphylaxis in September 2011.<sup>9</sup>

## PATIENT GROUP

### BACKGROUND

Calciphylaxis, also known as calcific uraemic arteriopathy, is a severe and progressive disease mainly seen in patients with end-stage kidney disease on dialysis, or in those with known risk factors such as: protein C or S deficiency; hyperphosphataemia; hypercalcaemia; or hypoalbuminaemia. Cases have also been reported in patients taking warfarin; pre-existing renal disease was commonly reported in cases, but some reports noted normal renal function.<sup>10</sup> In addition to chronic kidney disease, other risk factors for calciphylaxis include female gender, Caucasian race, liver disease, and lower serum albumin.<sup>11</sup>

Calciphylaxis involves the build-up of calcium in very small arteries resulting in a restricted blood supply and small clots. The skin develops ulcers that do not heal and usually cause severe pain. Calciphylaxis is a long-term debilitating and life-threatening condition, particularly due to the deep, painful, non-healing ulcers and the risk of infection.<sup>1</sup> It commonly affects the legs and arms but can also affect the torso, back and breasts.<sup>12</sup>

The pathogenesis of calciphylaxis is poorly understood, but there is a hypothesis of a 2-stage process. The first stage involves vascular injury, characterised by mural calcification, intimal hyperplasia and endovascular fibrosis. In the second phase, additional vascular damage is triggered by clinical events such as local trauma, hypotension or thrombosis. This leads to the development of an ischaemic infarct, dystrophic calcification or ulceration.<sup>8</sup>

## CLINICAL NEED and BURDEN OF DISEASE

Calciphylaxis is a life-threatening condition. Once ulcerations develop, the mortality rate is as high as 80%,<sup>13</sup> and the 1- and 5-year survival rates are estimated to be 45% and 35% respectively.<sup>14</sup> Patients who do not die of sepsis or organ failure frequently undergo amputation of the involved limb. Vascular calcification is theoretically reversible with aggressive management, but many patients have numerous co-morbidities and intervention may be too late.<sup>14</sup>

The prevalence of calciphylaxis is estimated to be 5.0 per 100,000 population;<sup>15</sup> using the latest mid-year population estimates for England Wales this would equate to 2,919 persons.<sup>16</sup> The UK Calciphylaxis Study states that calciphylaxis occurs in about one case per year for every 600 dialysis patients in the UK; there are estimated to be around 30,000 people on dialysis in the UK,<sup>17</sup> which equates to 50 cases per year.

It is not possible to state the number of hospital admissions with primary diagnosis of calciphylaxis. The most specific ICD-10 code for this condition is E83.59 - Other disorders of calcium metabolism,

but ICD-10 hospital data is only available to 4 characters (E83.5 - Disorders of calcium metabolism).<sup>18</sup> Similarly, it is not possible to state the number of deaths with calciphylaxis recorded as the primary cause of death.

## **PATIENT PATHWAY**

### **RELEVANT GUIDANCE**

#### **NICE GUIDANCE**

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

### **NHS ENGLAND and POLICY GUIDANCE**

- NHS England. Clinical Commissioning Policy: Hyperbaric Oxygen Therapy NHSCB/D11/P/a. April 2013.

### **OTHER GUIDANCE**

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). August 2009.<sup>19</sup>

### **CURRENT TREATMENT OPTIONS**

There is currently no specific pharmacological treatment for calciphylaxis, although a multi-interventional strategy is considered to be more effective than traditional therapeutic modalities.<sup>20</sup> Doctors often concentrate on getting the balance of minerals in the body right i.e. calcium and phosphate control. This may require changing dialysis regimes, changing medications, or considering surgery for overactive parathyroid glands which release a hormone which causes mineral to leech out of the bones. In addition, health-care teams focus on pain control, good nutrition and excellent ulcer care if the skin has broken down.<sup>12</sup>

The NHS Clinical Commissioning Policy on hyperbaric oxygen therapy (HBOT), published in April 2013, stated that there was insufficient evidence to support the routine use of HBOT as an adjunct to standard care.<sup>21</sup>

In July 2016 the Medicines and Healthcare products Regulatory Agency (MHRA) advised that consideration should be given to stopping treatment with warfarin if a patient developed calciphylaxis.<sup>10</sup> This may have an impact on the co-morbidities for which the patient was prescribed warfarin.

## EFFICACY and SAFETY

<b>Trial</b>	CALISTA, NCT03150420, ST-001; sodium thiosulfate vs placebo; phase III	OF-CALISTA, NCT03319914, ST-003; sodium thiosulfate; phase III extension
<b>Sponsor</b>	Hope Pharmaceuticals Ltd	Hope Pharmaceuticals Ltd
<b>Status</b>	Ongoing	Ongoing
<b>Source of Information</b>	Trial registry <sup>3</sup>	Trial registry <sup>22</sup>
<b>Location</b>	USA and Canada	USA and Canada
<b>Design</b>	Randomised, placebo-controlled	Observational follow-up study
<b>Participants</b>	N=111 (planned); aged 18 years and older; end-stage renal disease on chronic haemodialysis; calciphylaxis with active skin lesions and acute pain associated with calciphylaxis	Patients who participated in CALISTA trial
<b>Schedule</b>	Randomised to sodium thiosulfate 25g intravenous (IV) injection administered at each haemodialysis session (3 times weekly) for 3 weeks; or placebo IV injection administered at each haemodialysis session (3 times weekly) for 3 weeks.	8-week observation period following patients who participated in CALISTA trial
<b>Follow-up</b>	Active treatment for 3 wks, follow-up for 8 wks	Active treatment for 8 wks
<b>Primary Outcomes</b>	No. of pts with 30% improvement in pain severity based on pain intensity score (modified BPI/SF) [Time Frame: randomisation to 3 wks]	<p>Observation and recording of:</p> <ul style="list-style-type: none"> <li>• delayed adverse events</li> <li>• standard of care treatments for calciphylaxis (medications (including sodium thiosulfate injection and pain medication), wound debridement, amputation, hyperbaric oxygen therapy and surgical parathyroidectomy)</li> <li>• calciphylaxis-related complications (new or worsening skin lesions, ulceration, infection, sepsis and hospitalisations)</li> </ul> <p>following participation in CALISTA trial</p>

<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>No. of pts with stabilisation or improvement in calciphylaxis skin lesions [Time Frame: randomisation to 3 wks]</li> <li>Occurrence of surgical debridement of skin lesions and/or amputation [Time Frame: during Wk 3]</li> <li>Occurrence of surgical debridement of skin lesions and/or amputation [Time Frame: randomisation to 3 wks]</li> <li>Time to achieve <math>\geq 30\%</math> improvement in pain severity [Time Frame: randomisation to 3 wks]</li> </ul>	None
<b>Key Results</b>	-	
<b>Adverse effects (AEs)</b>	-	
<b>Expected reporting date</b>	Study completion date reported as May 2019	Study completion date reported as July 2019

### IMPACT - SPECULATIVE

#### IMPACT ON PATIENTS AND CARERS

- Reduced mortality/increased length of survival
  Reduced symptoms or disability
- Other
  No impact identified

#### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services
  Decreased use of existing services
- Re-organisation of existing services
  Need for new services
- Other
  None identified

## IMPACT ON COSTS and OTHER RESOURCE USE

- |   |   |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs        | <input type="checkbox"/> Other reduction in costs     |
| <input type="checkbox"/> Other                          | <input checked="" type="checkbox"/> None identified   |

## OTHER ISSUES

- |   |   |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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