Alkaptonuria (AKU), also known as black bone disease, is so rare that currently there are only roughly 65 patients in the UK that are known to have it. It is a genetic disease caused when both parents pass the AKU gene to their children. AKU is caused by the lack of an enzyme called homogentisic acid dioxygenase. This leads to a condition in which patients cannot fully break down a toxic acid called homogentisic acid (HGA). The accumulation of HGA causes discolouration to bone and cartilage. Black and brittle cartilage is more susceptible to the normal wear and tear that occurs in the body, quickly leading to disability and painful movements of the joints. AKU affects all the major joints including the spine once the symptoms start to show, this is usually when patients reach their 20s. Eventually this leads to early-onset osteoarthritis and often becoming wheelchair bound.

Until recently, little has been known about the best way to treat AKU for patients and so thanks to a €6m European Commission funding grant, clinical research into this has begun. The NIHR Clinical Research Network (CRN) is supporting this research in the NHS through two studies, SONIA 1 and SONIA 2. Both studies are utilising the drug Nitisinone to investigate how best to treat AKU.

Nitisinone is not licensed for the treatment of AKU, but it is licensed for use in babies to treat tyrosinaemia type 1 (HT-1), an amino acid disorder which can cause serious liver damage if left untreated.

SONIA 1 was investigating the correct dosage of Nitisinone to patients and SONIA 2 is looking at how effective and safe the drug is for use in AKU patients.
Outcomes and findings

During SONIA 1 the main way the study team could establish whether the drug was working was by examining the urine from patients. As patients with AKU typically have black urine which is one of the main symptoms.

Over a period of a few weeks the participants’ urine became clearer, which showed a reduction of HGA build up. The reduction was dependent on the dose of Nitisinone. This means a larger dose of Nitisinone results in a greater reduction of HGA. The results show the correct dosage of Nitisinone to be 10mg daily. This dosage is now being administered to participants in the SONIA 2 study.

The study did not look especially at safety, there were no safety concerns during SONIA 1. SONIA 2 closed to recruitment in late February 2015 and will run for four years until 2019. It is investigating how effective and safe Nitisinone is for use in AKU patients.

The participants are split into two groups; one group which receives Nitisinone and one group that does not.

This enables a thorough analysis between the two groups to illustrate improvements in patients.

Patients recruited to the study were given a thorough assessment of their physical health through blood tests, MRI scans, X-rays and ear biopsies to provide baseline measurements. They were followed up three months later and then just once a year until the end of the trial.

Value to the NHS

SONIA 1 has improved the knowledge of AKU for patients and clinicians through a short four week study. The international clinical trial, across multiple centres has provided evidence to support the treatment of AKU with Nitisinone. The study was also able to identify the correct dosage required to effectively reduce the build up of HGA (10mg daily).

While SONIA 1 did not look specifically at safety, there were no safety concerns during SONIA 1. SONIA 2 is due to finish by March 2019 and the full data analysis and study report will be complete by end of December 2019. This will provide further understanding of the effectiveness of Nitisinone in treating people with AKU.

"These studies are absolutely vital in understanding more about how best to treat patients living with Alkaptonuria."

Professor Lakshminarayan Ranganath, Chief Investigator and Consultant in Clinical Biochemistry and Metabolic Medicine at the National Alkaptonuria Centre, Liverpool