NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
AUGUST 2019

Nitisinone for Alkaptonuria

NIHRIO ID	13330	**NICE ID**	9967
Developer/Company	Swedish Orphan Biovitrum AB	**UKPS ID**	NA

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

SUMMARY

Nitisinone is in clinical development for the treatment of alkaptonuria. Alkaptonuria is a rare metabolic disorder, in which patients lack a functional enzyme that prevents the body fully breaking down two amino acids called tyrosine and phenylalanine. This results in a build-up of a chemical called homogentisic acid (HGA) in the body, which is deposited as black pigment in tissues, in a process called ochronosis. This results in dark colouration of urine, joint problems, breathing difficulties and heart, kidney and prostate problems. In the later stage, patients may experience physical disability and inability to perform daily activities. Early recognition and management of alkaptonuria is desirable to slow the progression of this disease.

Nitisinone, which is administered orally, works by blocking the production of the HGA molecule, and early trial evidence confirms a reduction in HGA levels and suggests the nitisinone could slow down or stop the disease and may partially reverse ochronosis. If licensed, nitisinone may provide the first pharmacological treatment option for patients with alkaptonuria who do not have any approved treatment.

PROPOSED INDICATION

Adults who have alkaptonuria (AKU).[1]

TECHNOLOGY

DESCRIPTION

Nitisinone (Orfadin) is an inhibitor of para-hydroxyphenylpyruvic acid oxygenase, the second enzyme in the tyrosine catabolic pathway. By blocking production of the offending homogentisic acid (HGA) molecule, nitisinone can reduce urinary excretion of HGA in individuals with AKU.[2] Nitisinone is being developed for the treatment of AKU[1] which is a rare autosomal recessive disorder mapped to chromosome 3 between regions 3q21-q23, the site of the homogentisate 1,2 dioxygenenase (HGD) gene. HGD is a vital enzyme in tyrosine metabolism. With a malfunctioning or inactive HGD enzyme, AKU patients are unable to convert HGA into maleylacetoacetic acid. In AKU, excess tyrosine is not eliminated from the body, but instead is converted into HGA,[3] and cannot be broken down any further.[3]

It is hypothesised that if HGA levels are reduced, through treatment with nitisinone before the onset of overt ochronosis, this might prevent the development of the debilitating features of AKU.[4]

Nitisinone is in clinical development for the treatment of AKU. In the most recent phase III clinical trial (NCT01916382, EudraCT: 2012-005340-24) nitisinone is administered as 10 mg daily dose as capsule formulation.[a]

INNOVATION AND/OR ADVANTAGES

Currently, no approved therapeutics exist for the treatment of AKU. Current options centre on analgesics, joint replacement when required, dietary protein restriction and large doses of vitamin C, all of which have varying degrees of efficacy.[4,5] Therefore there is significant unmet need for a treatment option to reduce the levels of HGA and prevent disease progression.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nitisinone is licensed in the EU/UK for treating hereditary tyrosinaemia type 1 (in combination with dietary restriction of tyrosine and phenylalanine) (specialist use only).[7] Recognised adverse effects include ocular toxicity and transient neutropenia or thrombocytopenia.[8]

Nitisinone was granted orphan drug designation in the EU in March 2002 for the treatment of AKU.[9]

Nitisinone has been tested in a phase I/II clinical trial for Oculocutaneous albinism, type 1B.[10]

PATIENT GROUP

DISEASE BACKGROUND

AKU, or 'Black Bone Disease' is a very rare inherited condition which can cause significant damage to the bones, cartilage and tissues of those affected. AKU is a recessive condition that is caused by a mutation of one chromosome that stops patients' bodies from breaking down HGA.[11] A proportion of the HGA circulating in AKU patients is deposited in connective tissue as a pigmented polymer, during a process termed ochronosis.[12,13] The effects of ochronosis include premature arthritis, lithiasis, cardiac valve disease, fractures, muscle and tendon ruptures and osteopenia.[14,15]

[a] Information provided by Swedish Orphan Biovitrum AB

Although AKU is a genetic condition that is present at birth, overt ochronotic manifestations of the disease are delayed, typically beginning after 30 years.[16] A natural history evaluation of 58 AKU patients found joint replacement was performed at a mean age of 55 years and that renal stones developed at 64 years, cardiac-valve involvement at 54 years, and coronary-artery calcification at 59 years.[17]

CLINICAL NEED AND BURDEN OF DISEASE

AKU has an global incidence of 1:250,000 to 1:1,000,000.[18] In 2016/17, the Royal Liverpool and Broadgreen University Hospitals NHS Trust (the only highly specialised service provider for patients in England and Scotland) had a caseload of 50 AKU patients.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

AKU may be picked up in infancy, as one of the earliest signs of the condition is dark-stained nappies arising from the HGA causing urine to turn black when exposed to air for a few hours. However, if this sign is missed or overlooked, the condition may go unnoticed until adulthood, as there are usually no other noticeable symptoms until the person reaches their late 20s to early 30s.[20]

Alkaptonuria is a lifelong condition, and currently there is no specific treatment or cure.[20] In addition to nitisinone which is being offered 'off label' at the National Alkaptonuria Centre (based at Royal Liverpool University Hospital), there are various painkillers and lifestyle changes which may help cope with the symptoms:[20]

- Diet: Restricting protein can slow disease progression if diagnosed in childhood.
- Exercise: Regular exercise can help build muscle, strengthen joints, relieving stress, losing weight and improving posture.
- Pain relief: Painkillers can be used to manage pain.
- Emotional support
- Surgery: Surgery may be necessary if joints are damaged and need replacing, or if heart valves or vessels have hardened.

No single treatment seems appropriate over the lifecourse however a sequential therapeutic strategy may be most beneficial:[21]

- During childhood: a vegetarian diet might limit/delay bone disease progression and pigment deposition on cartilage and kidneys.
- During adulthood: nitisinone associated with mild protein restriction in order to contain the rise of plasma tyrosine (it is recommended that this treatment regime should be stop before and during pregnancy).

CURRENT TREATMENT OPTIONS

Currently no pharmacological treatment options available for this population group apart from painkillers to help coping with the condition.[20]

PLACE OF TECHNOLOGY

If licensed, nitisinone may provide the first pharmacological treatment option for patients with AKU who do not currently have any approved treatments available.

CLINICAL TRIAL INFORMATION

Trial	**SONIA 2; NCT01916382, EudraCT: 2013-001633-41; adults and older adults; nitisinone; phase III**
Sponsor	University of Liverpool
Status[b]	Completed
Source of Information	Trial registry[1,22], manufacturer
Location[1,b]	Three EU countries, incl UK
Design	Randomised (open label)
Participants	n=140 (planned); diagnosis of AKU (any clinical manifestations of AKU, such as clinical ochronosis or chronic back/joint pain; age ≥25 years); willing and able to visit the investigational site for study visits; signed written informed consent given.
Schedule[b]	Orfadin capsules containing 10 mg nitisinone, administered orally once daily (treatment group) or no treatment (control group). Duration of treatment: 48 months.
Follow-up[b]	Visits at 0, 3, 12, 24, 36, 48, 49 months.
Primary Outcomes	24 hr urine HGA [time frame: yr 1]
Secondary Outcomes[22,b]	• 24 hr urine HGA at 3, 24, 36 and 48 months • Clinical AKUSSI scores at 12, 24, 36 and 48 months compared with baseline. • Modified AKUSSI scores at 12, 24, 36 and 48 months compared with baseline. • Individual cAKUSSI items at 12, 24, 36 and 48 months compared with baseline. • Ear cartilage pigmentation at 48 months compared with baseline. • Pre-defined rheumatology assessments at 12, 24, 36 and 48 months compared with baseline • Pain scores measured by visual analogue scale (VAS) at 12, 24, 36 and 48 months compared with baseline. • Quality of life (QoL) measured by SF36 at 12, 24, 36 and 48 months compared with baseline. • Health assessment measured by HAQ at 12, 24, 36 and 48 months compared with baseline. • Physical function as measured by KOOS index at 12, 24, 36 and 48 months compared with baseline. • Range of joint and spine motion at 12, 24, 36 and 48 months compared with baseline. • Predose s-HGA at 3, 12, 24, 36 and 48 months. • Predose s-Tyr at 3, 12, 24, 36 and 48 months. • Pre-dose serum nitisinone at 3, 12, 24, 36 and 48 months.

[b] Information provided by Swedish Orphan Biovitrum AB

	• Adverse events, clinical chemistry and haematology, vital signs, ECG and slit-lamp eye assessments.
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Study completion date 2nd February 2020

Trial	**SONIA 1; NCT01828463; EudraCT: 2012-005340-24; adults 18 yrs and older; nitisinone vs no treatment; phase II**
Sponsor	University of Liverpool
Status	Published[4]
Source of Information	Trial registry[23,24], publication[4], manufacturer
Location[23,c]	Two EU countries, incl UK
Design	Randomised, open label, parallel-group
Participants	n=40; diagnosis of alkaptonuria verified by documented elevated urinary HGA excretion; age ≥18 years; willing and able to visit the investigational site for study visits; signed written informed consent obtained.
Schedule[23]	**No intervention arm**: no treatment comparator **Experimental arm 1**: Nitisinone 1 mg **Experimental arm 2**: Nitisinone 2 mg **Experimental arm 3**: Nitisinone 4 mg **Experimental arm 4**: Nitisinone 8 mg
Follow-up[c]	Visits at 0, 2, 4 and 6 weeks (6 weeks' visit: telephone follow-up call)
Primary Outcomes[c]	To investigate the effect of different doses of once daily nitisinone on 24-hour urinary HGA (u-HGA24) excretion [time frame: 4 weeks]
Secondary Outcomes[24]	• To investigate the effect of different doses of once daily nitisinone on serum HGA concentration (s-HGA) and serum tyrosine concentration (s-Tyr) in patients with alkaptonuria. • To determine the pharmacokinetics (PK) of nitisinone at steady state and to test for PK dose-proportionality. • To describe the relationship between PK variables of nitisinone, u-HGA24, s-HGA and s-Tyr. • To assess the safety of nitisinone at doses relevant for the treatment of alkaptonuria.
Key Results[4]	A clear dose-response relationship was observed between nitisinone and the urinary excretion of HGA: At 4 weeks, the adjusted geometric mean u-HGA was 31.53 mmol, 3.26 mmol, 1.44 mmol, 0.57 mmol and 0.15 mmol for the no treatment or 1 mg, 2 mg, 4 mg and 8 mg doses, respectively. For the most efficacious dose, 8 mg daily, this corresponds to a mean reduction of u-HGA of 98.8% compared with baseline. An increase in tyrosine levels was seen at all doses but the dose-response relationship was less clear than the effect on HGA.

[c] Information provided by Swedish Orphan Biovitrum AB

Adverse effects (AEs)[4]	Despite the presence of tyrosinaemia, there were no safety concerns and no serious adverse events were reported over the 4 weeks of nitisinone therapy.
Expected reporting date	-

ESTIMATED COST

Nitisinone is already marketed in the UK. A pack of 60 x 2 mg Nitisinone (Orfadin) capsules from Swedish Orphan Biovitrum Ltd. costs £564.00.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

No relevant guidance identified.

ADDITIONAL INFORMATION

Swedish Orphan Biovitrum AB 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. *Suitability of Nitisinone in Alkaptonuria 2 (SONIA 2). Trial ID: NCT01916382*. 2013. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT01916382 [Accessed 20th June 2019].

2 Introne WJ, Perry MB, Troendle J, Tsilou E, Kayser MA, Suwannarat P, et al. A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. *Molecular genetics and metabolism*. 2011;103(4):307-14. Available from: http://doi.org/10.1016/j.ymgme.2011.04.016.

3 Alkaptonuria Society. *For Healthcare Professionals.* 2019. Available from: https://www.akusociety.org/aku-for-healthcare-professionals.html [Accessed 27th June 2019].

4 Ranganath LR, Milan AM, Hughes AT, Dutton JJ, Fitzgerald R, Briggs MC, et al. Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment. *Annals of*

the Rheumatic Diseases. 2016 Feb;75(2):362-7. Available from: http://doi.org/10.1136/annrheumdis-2014-206033.

5 Ranganath L, Jarvis J, Gallagher J. Recent advances in management of alkaptonuria. *Journal of Clinical Pathology*. 2013;66 367-73. Available from: http://dx.doi.org/10.1136/jclinpath-2012-200877.

6 Alkaptonuria Society. *Nitisinone.* 2016. Available from: https://www.akusociety.org/national-aku-centre/nitisinone [Accessed 12th August 2019].

7 National Institute for Health and Care Excellence. *Nitisinone.* 2019. Available from: https://bnf.nice.org.uk/drug/nitisinone.html [Accessed 25th June 2019].

8 McKiernan PJ. Nitisinone in the Treatment of Hereditary Tyrosinaemia Type 1. *Drugs*. 2006 April 01;66(6):743-50. Available from: https://doi.org/10.2165/00003495-200666060-00002.

9 European Medicines Agency. *EU/3/02/096.* 2002. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302096 [Accessed 27th June 2019].

10 Clinical Trials. *Search: Nitisinone.* 2019. Available from: https://clinicaltrials.gov/ct2/results?term=Nitisinone&age_v=&gndr=&type=&rslt=&phase=1&phase=2&phase=3&Search=Apply [Accessed 25th June 2019].

11 Alkaptonuria Society. *Alkaptonuria Explained.* 2019. Available from: https://www.akusociety.org/aku-explained.html [Accessed 27th June 2019].

12 O'Brien WM, La Du BN, Bunim JJ. Biochemical, pathologic and clinical aspects of alcaptonuria, ochronosis and ochronotic arthropathy: Review of world literature (1584–1962). *The American Journal of Medicine*. 1963;34(6):813-38. Available from: https://doi.org/10.1016/0002-9343(63)90089-5.

13 Zannoni VG, Lomtevas N, Goldfinger S. Oxidation of homogentisic acid to ochronotic pigment in connective tissue. *Biochimica et Biophysica Acta (BBA) - General Subjects*. 1969;177(1):94-105. Available from: https://doi.org/10.1016/0304-4165(69)90068-3.

14 La Du BN, Zannoni VG, Laster L, Seegmiller JE. The nature of the defect in tyrosine metabolism in alcaptonuria. *The Journal of biological chemistry*. 1958;230(1):251-60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/13502394.

15 Helliwell TR, Gallagher JA, Ranganath L. Alkaptonuria - A review of surgical and autopsy pathology. *Histopathology*. 2008;53(5):503-12. Available from: http://doi.org/10.1111/j.1365-2559.2008.03000.x.

16 Pettit SJ, Fisher M, Gallagher JA, Ranganath LR. Cardiovascular manifestations of Alkaptonuria. *Journal of Inherited Metabolic Disease*. 2011;34(6):1177-81. Available from: http://doi.org/10.1007/s10545-011-9339-z.

17 Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, et al. Natural history of alkaptonuria. *New England Journal of Medicine*. 2002 Dec;347(26):2111-21. Available from: http://doi.org/10.1056/NEJMoa021736.

18 Sakthivel S, Zatkova A, Nemethova M, Surovy M, Kadasi L, Saravanan MP. Mutation Screening of the HGD Gene Identifies a Novel Alkaptonuria Mutation with Significant Founder Effect and High Prevalence. *Annals of Human Genetics*. 2014;78(3):155-64. Available from: http://doi.org/10.1111/ahg.12055.

19 National Health Service England. *Highly Specialised Services 2017.* 2018. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/03/highly-specialised-services-17.pdf [Accessed 27th June 2019].

20 National Health Service. *Alkaptonuria.* 2019. Available from: https://www.nhs.uk/conditions/alkaptonuria/ [Accessed 25th June 2019].

21 Arnoux J-B, Le Quan Sang K-H, Brassier A, Grisel C, Servais A, Wippf J, et al. Old treatments for new insights and strategies: proposed management in adults and children with alkaptonuria. *Journal of Inherited Metabolic Disease*. 2015;38(5):791-6. Available from: http://doi.org/10.1007/s10545-015-9844-6.

22 EU Clinical Trials Register. *An international, multicenter, randomized, evaluator-blinded, no-treatment controlled, parallel-group study to assess the efficacy and safety of once daily nitisinone in patients with alkaptonuria after 12 months of treatment, followed by an additional 36-month treatment period*. *Trial ID: 2013-001633-41*. 2013. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001633-41/GB [Accessed 27th June 2019].

23 ClinicalTrials. *Dose Response Study of Nitisinone in Alkaptonuria (SONIA1)*. *Trial ID: NCT01828463*. 2013. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01828463 [Accessed 25th June 2019].

24 EU Clinical Trials Register. *An international, multicentre, randomised, open-label, no-treatment controlled, parallel group, dose-response study to investigate the effect of once daily nitisinone on 24-hour urinary homogentisic acid excretion in patients with alkaptonuria after 4-weeks treatment. Trial ID:*

2012-005340-24. 2013. Status: Completed. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-005340-24/GB [Accessed 27th June 2019].

25 National Institute for Health and Care Excellence (BNF). *Nitisinone.* 2019. Available from: https://bnf.nice.org.uk/medicinal-forms/nitisinone.html [Accessed 25th June 2019].

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.