Institution: University of Liverpool		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Development of the first effective therapy for the rare disease Alkaptonuria		
Period when the underpinning research was undertaken: 2008-2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
J A Gallagher	Professor	1986 – present
L R Ranganath	Honorary Professor	2012 – present
Period when the claimed impact occurred: 2013 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Alkaptonuria is a rare, hereditary, lifelong condition characterised by severe early-onset osteoarthritis. Liverpool has developed the first effective therapy for alkaptonuria, by repurposing nitisinone to arrest the metabolic dysfunction underlying the disease. The research led to off-license prescribing in England and Scotland, with near 100% uptake and provision of NHSE's Highly Specialised Service for alkaptonuria, at Royal Liverpool University Hospital. The European Medicines Agency has now licensed the therapy based on Liverpool's clinical trial.

Nitisinone therapy transforms physician management and patient experience of the disease. Young people with alkaptonuria can now look forward to life free of its debilitating symptoms. For existing older patients, symptoms are arrested, some reversed.

2. Underpinning research

Alkaptonuria is the oldest known genetic disease. It is a rare, hereditary metabolic disease that causes severe early-onset osteoarthritis. It occurs in 1 in every 250,000 to 1,000,000 people. Higher incidence occurs in some countries e.g., 1 in 19,000 in Slovakia. There was previously no effective treatment.

The alkaptonuria patient group and Professor Ranganath, a consultant at Royal Liverpool University Hospital, approached Professor Gallagher (expert in bone and cartilage), to explore how the bone and cartilage deterioration characteristic of alkaptonuria could be blocked.

Alkaptonuria is caused by deficiency of an enzyme (4-hydroxyphenylpyruvate) involved in tyrosine metabolism. This deficiency leads to failure to break down homogentisic acid (HGA). Deposited as pigment in tissues, including cartilage (a process known as ochronosis), HGA leads to severe, early-onset osteoarthritis. The drug nitisinone is a known inhibitor of the conversion of 4-hydroxyphenylpyruvate into HGA, which is used in another rare disease of tyrosine metabolism, hereditary tyrosinaemia 1 (HT1). The Liverpool team therefore undertook biological and clinical studies of nitisinone, proving its efficacy as a therapy for alkaptonuria, as follows:

We developed a mouse model of ochronosis (3.1). The model demonstrated that nitisonone completely blocks ochronosis (3.1). Urine (3.2) and serum (3.3) assays for HGA and other alkaptonuria biomarkers were developed. To enable clinical trialling in humans, we identified alkaptonuria patients in the general population in the UK, through survey of general practitioners, a website and medical conference targeting. Patients identified in the UK totalled 75; a further 549 patients were identified internationally. We developed an AKU severity score index (AKUSSI), to enable categorisation of patients. AKUSSI enables a composite scoring of the progression of the disease across its multiple symptoms: joint and spinal pains; ear and eye pigmentation; hearing impairment; renal and prostrate stones; osteopenia; aortic sclerosis and stenosis.

During a ten-year period (2009-2019) we completed an observational study and clinical trials of nitisinone therapy. The trial from which EMA licensing followed was the pan-European clinical trial 'SONIA (Suitability of Nitisinone In Alkaptonuria) 2', a phase 3 efficacy study (NCT01916382, EudraCT: 2012-005340-24) funded by an FP7 programme grant. The multicentre, randomised, evaluator-blind, no-treatment controlled, SONIA2 trial assessed 10mg once daily nitisinone in 140 patients with alkaptonuria after 12 months of treatment, followed by an additional 36-month treatment period. The study started November 2013 and completed January 2019.The primary outcome was 24-hour urine HGA at 1 year.

Findings of SONIA2 included (i) 24-hr urine HGA at 12 months was decreased by 99.7% compared with baseline in the nitisinone group ($p< 0.001$), (ii) Ochronosis of eyes and ears was decreased in the nitisinone group at 48 months compared with an untreated control group ($p< 0.001$ and $p< 0.05$ respectively); and (iii) AKUSSI was decreased in the nitisinone group compared with an untreated control group ($p< 0.05$). These results confirmed that 10mg nitisinone daily decreases HGA, partially reverses ochronosis, and decreases the damaging consequences of alkaptonuria (3.6).

Prior to the above trial, we had conducted an observational study in 39 patients attending the National Alkaptonuria Centre in Liverpool. This involved serial assessments over 4 years, whilst the patients were receiving 2mg of oral nitisinone daily. This demonstrated that nitisinone arrests ochronosis and decreases clinical progression of joint disease. Combined ocular and ear ochronosis progression was arrested. Our European Commission Seventh Framework Programme (FP7) grant for SONIA2 followed the promising results of the observational study, enabled SOFIA and SONIA1. SOFIA was a cross-sectional study, to identify optimal age of commencement (age 18 years); SONIA1 was a phase 2 dose-ranging study, which concluded that 10mg was the optimal dose.

The above findings addressed an earlier trial result, funded by NIH 2005. The NIH trial (40 patients, spanning 3 years) failed to demonstrate the efficacy of nitisinone therapy in alkaptonuria. However, the Liverpool trial included a larger population and with a full range of alkaptonuria symptoms considered. We convincingly demonstrated that nitisinone administered at 10mg daily offers a highly effective therapy.

3. References to the research

3.1. Preston AJ, Keenan CM, Sutherland H, Wilson PJ, Wlodarski B, Taylor AM, Williams DP, **Ranganath LR**, **Gallagher JA**, Jarvis JC. Ochronotic osteoarthropathy in a mouse model of alkaptonuria, and its inhibition by nitisinone. Annals of Rheumatic Diseases. 2014 Jan;73(1):284-9. http://dx.doi.org/10.1136/annrheumdis-2012-202878. Epub 2013 Mar 19. PMID: 23511227.

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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. Ann Rheum Dis. 2016 Feb;75(2):362-7. http://dx.doi.org/10.1136/annrheumdis-2014-206033. Epub 2014 Dec 4. PMID: 25475116

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4. Details of the impact

Context

Liverpool has developed the first effective pharmacological treatment for the rare disease alkaptonuria (AKU). AKU is a metabolic disease causing severe early-onset osteoarthritis. Bones and cartilage become black and brittle. Presenting from mid to late 20s it is progressive and debilitating. Multiple joint replacements and medication for chronic pain are typically required. High-risk surgery may be needed e.g., for associated heart valve disease. Scope and quality of life gradually reduce, with mobility loss and dependence on carers (**5.1**).

An EMA licensed therapy

On the strength of Liverpool's FP7-funded trial results, pharmaceutical company Swedish Orphan Biovitrum AB (publ) (SOBI) applied to the European Medicine Agency (EMA) to license the treatment as Orfadin (February 2020) (**5.2**). This was the culmination of a decade long collaboration with the Liverpool research team (**5.2**). EMA granted the license (September 2020) basing that decision wholly on the Liverpool phase 3 trial: "*the opinion of EMA's human medicines committee (CHMP) is based on data from a randomised clinical study*" (**5.3, 3.6**).

The licencing received international media coverage (**5.3**). Estimated EU market size is 2,275 patients, with new patients identified annually (**5.4**); the treatment will help prevent thousands of people suffering from AKU. NICE had planned a Single Technology Appraisal of nitisinone for alkaptonuria (from June 2020). Following EMA's licensing decision, the need for that appraisal was removed (**5.5**).

Off-label prescribing

Prior to EMA approval, Liverpool had already provided research evidence sufficient for NHS England and NHS Scotland to offer off-label prescribing to patients (**5.6, 3.1, 3.4**). Between 2016 and 2019 approximately 60 England and Scotland patients per year (most of the known AKU population in those countries) received the treatment at the AKU Centre. Several patients from Wales, Northern Ireland, and internationally self-fund for the treatment via the Centre (**5.6**).

The AKU Centre, Liverpool

Liverpool's research has been fundamental to sustained provision of the Liverpool-based National Alkaptonuria Centre, an NHS England Highly Specialised Service for alkaptonuria patients, at Royal Liverpool University Hospital (**5.7**). An objective of the Service was "*commencement and utility of new treatments*", and to "*deliver opportunities to enhance research*" (**5.7**). The partnership with University of Liverpool researchers to run clinical trials and deliver nitisinone treatment was central, ensuring sustained funding from the Department of Health to the value of GBP500,000 – GBP1,000,000 per year (**5.7**). Also, Liverpool's Alkaptonuria Severity Score Index provided NHS England with a tool for monitoring and evaluating the Service (**5.7**).

The Service is the only highly specialised provision for alkaptonuria in the UK (**5.1**). All UK alkaptonuria patients are referred (**5.7**). They receive annual review and specialist coordinated care for the disease's multiple symptoms.

Patient experience

Arrest in the progression of the disease can transform the patient experience, for example, "*as a patient who has suffered from the degenerative effects of alkaptonuria for nearly 30 years…I am at the age when heart complications should start, but thanks to nitisinone there is no evidence of any issues*." (**5.8**) and "*being on nitisinone has meant...my body is ageing at a more normal pace*." (**5.8**). Annual NHS evaluations of AKU patients, via the AKU Centre, confirm broad improvement in patient quality of life. For example, the 2017 evaluation states: "Of 21 patients who had been seen for more than a year, improvements were seen in all domains of the SF36 quality of life scale except 'energy/fatigue' (**5.7**).

The research team has received over one hundred unsolicited emails from patients, praising their work. For example, *"what you have done for alkaptonuria patients and your contribution is wonderful*" (from Jordan) (**5.8**). The researchers are trustees of the AKU Society and attend the Society's annual international workshop to disseminate their research (**5.6**). An AKU Society patient survey found 98% of patients rate their knowledge of AKU 'good or excellent' (2016) (**5.6**).

Patients from the UK and abroad have been inspired to support the research by taking part in the trials (3.4-3.6), some committing to eventual body donation for furthering research.

Savings

Tangible direct costs of alkaptonuria can amount to GBP94,000 per year per patient (estimate from 2010, for disease at advanced stage): from joint replacement and other surgery; testing and consultation; hospital stays; home care; GP visits and physiotherapy. Additional socio-economic costs are incurred e.g., reduced capacity for work. Cost to the NHS of a year's prescribing of nitisinone is GBP4,000 per year (**5.9**). Treatment by nitisinone is therefore considered a cost-effective approach to managing the condition over the life course.

Findacure

Findacure is a social enterprise supporting and training rare disease charities in lobbying for research and drug repurposing. Operating since 2013, Findacure is rooted in the successful alkaptonuria therapy development by Liverpool. The Chair of the AKU Society co-founded the organisation: "[*He] quickly realised that he could use his AKU experience to find cures for other diseases… "With our experience of alkaptonuria, we believe we can develop trials for the most neglected fundamental diseases at an affordable cost.'*" (**5.10**).

5. Sources to corroborate the impact

5.1. AKU and its symptoms: NIHR Innovation Observatory, 'Health Technology Briefing, Nitisinone for Alkaptonuria, August 2019', (p2-p3 'Patient Group' and 'Patient Treatment Pathway' for description of ailments and incidence). http://www.io.nihr.ac.uk/wp-content/uploads/2019/08/13330-Nitisinone-for-Alkaptonuria-V1.0-AUG2019-NON-CONF.pdf

5.2. SOBI commercialisation/ application to EMA, Liverpool research as driver: SOBI Annual Report 2019. 'Focus on Rare Diseases, Annual and Sustainability Report 2019' (proof of application p.21, 'Our innovation pipeline as per 25.03.2020'); and SOBI Annual

Report 2013. 'Pioneer in Rare Diseases' (proof of Liverpool role p.3., re. DevelopAKUre and SONIA1). https://www.sobi.com/en/reports-presentations. For expanded discussion of EMA application progression, Liverpool results as driver, Cordis article, 29 January 2020: 'Catching up with DevelopAKUre' https://cordis.europa.eu/project/id/304985/news

5.3. European Medicines Agency licensing: EMA approval of nitisinone for alkaptonuria, 18 September 2020 and associated press coverage (incl. SOBI pharmaceutical company press release and reporting of by Sky News screen and press 5.12.20): https://www.ema.europa.eu/en/news/first-treatment-rare-metabolic-disorder-alkaptonuria https://www.sobi.com/en/press-releases/orfadinr-nitisinone-receives-positive-opinion-chmp-treatment-alkaptonuria-1844542; https://www.youtube.com/watch?v=7PWJUJfNVqg (2.37 min; 9,881 views, incl. interview with Professor Gallagher) https://news.sky.com/story/drug-used-in-weedkiller-could-help-thousands-suffering-from-black-bone-disease-12151578

5.4. EU market size: FP7 'Final Report Summary - DevelopAKUre (Clinical Development of Nitisinone for Alkaptonuria)'. The market size figure is in the public domain, cited in this report (p.13, highlighted). https://cordis.europa.eu/project/id/304985/reporting

5.5. NICE Technology Appraisal/ cessation following EMA license: 'Nitisinone for treating alkaptonuria ID2691'. NICE Technology Appraisal project overview page https://www.nice.org.uk/guidance/indevelopment/gid-ta10659. Communication from NICE to stakeholders announcing cessation of above (23.10.20).

5.6. Off-label prescribing: NHS website. 'Alkaptonuria. 2019' (see p3-4 'Nitisinone'). https://www.nhs.uk/conditions/alkaptonuria/. AKU Centre data on patient numbers from AKU Society Impact Reports 2016-2019 (patients at the Centre receive nitisinone as part of their care). https://akusociety.org/about-us/impact-report-2019/. Self-funding information from the AKU Centre e.g. of 2019, summary data table supplied in Excel.

5.7. National Alkaptonuria Centre/Service: Contact for NHS lead for this Service supplied. 2013/14 NHS Standard Contract for Alkaptonuria Service (Adults) E06/S(HSS)/a (see p.5 'Key Service Outcomes', re. expectation of reduction in joint replacement surgery; see p.7, Appendix 2, for use of AKUSSI) https://www.england.nhs.uk/publication/201314-nhs-standard-contract-for-alkaptonuria-service-adults-november-2016/ and National Health Service England Highly Specialised Services 2017 and 2018 reports; sections on Alkaptonuria Centre (p.11, 2017; p.11, 2018): https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/ https://www.england.nhs.uk/wp-content/uploads/2018/03/highly-specialised-services-17.pdf

5.8. Patient perspectives: Patient comment cited in an independently produced media article - Science Daily, August 1, 2018. 'New treatment for ultra-rare disease, alkaptonuria' (see yellow highlight, p. 2); second quotation see 5.7., AKU Society Impact report 2016 p.10; https://www.sciencedaily.com/releases/2018/08/180801102554.htm; example of unsolicited positive feedback from patient community (patient correspondence); Professor engagement with patients evidenced in AKU Society Impact reports (5.7.) e.g. 2019 report discusses presentation by research team to the 2019 patient workshop; 98% figure from 2016 report; https://akusociety.org/about-us/our-staff-and-trustees/.

5.9. Chartered Accountant assessment of the costs of AKU: for the AKU Society, 2011. Source for the GBP amount cited (p.4, highlight, first bullet). This assessment considered sufficiently robust for citation in FP7 final report for the phase 3 clinical trial: https://www.rareconnect.org/uploads/documents/alkaptonuria-study-compilation-of-sample-patient-costs.pdf

5.10. Findacure/ spinout social enterprise: Guardian article, Aug 2013 – spotlights the social enterprise work inspired by successful drug development for AKU. Evidence of that as stimulus for Findacure highlighted. Confirms founder's role in AKU Society. Contact details supplied. https://www.theguardian.com/social-enterprise-network/2013/aug/29/findacure-and-rare-diseases