

Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: First licensed paediatric treatment for children with adrenal insufficiency		
Period when the underpinning research was undertaken: 2000–2018		
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:
Richard Ross	Professor of Endocrinology	1995–present
Period when the claimed impact occurred: 2018–31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Adrenal insufficiency (AI), deficiency of the stress hormone cortisol affects ~10,000 children in Europe, and requires lifelong treatment to prevent death by adrenal crisis. Research and clinical trials at Sheffield led to: the development of Alkindi® hydrocortisone granules, the first paediatric licensed hydrocortisone treatment for AI, and its approval in Europe by the European Medicines Agency (EMA) and in the USA by the Food and Drug Administration (FDA). The research underpinned commercial impact, including £4.7M cumulative Alkindi® sales by Diurnal Ltd., a University of Sheffield spin-out company. Alkindi® has improved health outcomes for children with AI. There were no adrenal crises in over 2 years of Alkindi® clinical trials, whereas previously up to 10% of AI children had a crisis per year, evidence that Alkindi® provides life-saving treatment to this vulnerable patient group.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Note: Alkindi®, to which this impact case refers, was called Infacort during the development phase.</p> <p>AI results from failure of the adrenal gland to secrete the essential stress hormone cortisol, and untreated patients die from an adrenal crisis. Congenital adrenal hyperplasia (CAH) is the most common inherited endocrine condition and the most common cause of AI in children. The challenge for AI treatment in children was that only adult-dose tablets were licensed for treatment, resulting in inaccurate administration of crushed adult-dose tablets [R3] that caused under- and over-dosing during childhood and lifelong poor health outcomes, with increased morbidity and mortality in children and adults and the health outcomes in adults related to poor replacement therapy in childhood [R1].</p> <p>In 2000, Professor Richard Ross led a UK audit assessing the standard of care for patients with CAH which demonstrated a lack of consensus on patient care and inadequate treatment regimens. Between 2001 and 2010, the CAH Adult Study Executive (CaHASE, a study on the world's largest cohort of adult CAH patients at the time), chaired by Ross, investigated the health of 203 patients with CAH across 17 UK endocrine centres. The results demonstrated that the patients had poor health outcomes that were related to a lack of appropriate cortisol (hydrocortisone) replacement therapy in childhood and adulthood [R1].</p>		

Between 2010 and 2017, Professor Ross and Whitaker assembled the Treatment of Adrenal Insufficiency in Neonates (TAIN) Consortium to; investigate the unmet medical need for licensed preparations of hydrocortisone for children with CAH and AI, and develop such a formulation [G1]. A survey of European paediatricians revealed that children with CAH and AI received predominantly unlicensed compounded adult medication [R2], and further work examining over 1,000 capsules of compounded hydrocortisone collected from parents of children with CAH in Germany revealed that >20% were out of specification, placing children at risk of cortisol excess and deficiency [R3]. In addition, through public and patient involvement in collaboration with Genetic Alliance UK (a UK national charity), Ross and Whitaker demonstrated that parents experienced considerable anxiety and disruption of their lives associated with the intensive CAH treatment regimen [R4].

Based on this evidence and a detailed understanding of dose and formulation requirements for neonates, infants, and children [R2], the TAIN Consortium developed a new formulation of hydrocortisone granules (Infacort) with taste masking using multiparticulate technology since compounded hydrocortisone is bitter and often rejected by children. The Infacort hydrocortisone granules were then tested in phase 1 clinical trials in healthy adults in 2013 [R2]. At phase 1, the new formulation was demonstrated to be tasteless and bioequivalent to adult hydrocortisone tablets.

The consortium then built a pharmacokinetic model of hydrocortisone to understand how to dose the hydrocortisone granules in children [R5]. The Infacort hydrocortisone granules were then trialled in 2017 in 24 patients and found to be well tolerated by neonates, infants and children, and their parents reported satisfaction with the treatment regimen [R6]. A cohort of children taking Infacort hydrocortisone granules were followed from 2015-2018 for over two years, constituting the first prospective study of glucocorticoid treatment in children with AI and CAH. The trial results showed that accurate dosing and monitoring from birth resulted in hydrocortisone doses at the lower end of the recommended dose range, normal growth, and no occurrence of adrenal crises [S4].

In 2017, an application for a Paediatric Use Market Authorisation (PUMA) for Infacort under the marketing name Alkindi® was submitted based on the underpinning research including phase 1 to 3 clinical trials. The PUMA was granted by the European Commission in 2018, and it is one of only four PUMAs ever granted and the first developed from an EU grant.

In August 2020, Professor Ross was recognised internationally for his research and contribution to the field with the 2021 Outstanding Innovation Laureate Award from the Endocrine Society – one of the top honours in the field.

3. References to the research (indicative maximum of six references)

Sheffield staff in bold.

- R1.** Arlt, W., Willis, D. S., Wild, S. H., Krone, N., Doherty, E. J., ... **Ross, R. J.** (2010). Health Status of Adults with Congenital Adrenal Hyperplasia: A Cohort Study of 203 Patients. *The Journal of Clinical Endocrinology & Metabolism*, 95(11), 5110–5121.
<https://doi.org/10.1210/jc.2010-0917>
- R2.** **Whitaker, M. J.**, Spielmann, S., Digweed, D., Huatan, H., Eckland, D., Johnson, T. N., Tucker, G., Krude, H., Blankenstein, O., & **Ross, R. J.** (2015). Development and Testing in Healthy Adults of Oral Hydrocortisone Granules With Taste Masking for the Treatment of

Impact case study (REF3)

Neonates and Infants With Adrenal Insufficiency. *The Journal of Clinical Endocrinology & Metabolism*, 100(4), 1681–1688. <https://doi.org/10.1210/jc.2014-4060>

- R3.** Neumann, U., Burau, D., Spielmann, S., **Whitaker, M. J., Ross, R. J.**, Kloft, C., & Blankenstein, O. (2017). Quality of compounded hydrocortisone capsules used in the treatment of children. *European Journal of Endocrinology*, 177(2), 239–242. <https://doi.org/10.1530/eje-17-0248>
- R4.** Simpson, A., **Ross, R.**, Porter, J., Dixon, S., **Whitaker, M. J.**, & Hunter, A. (2018). Adrenal Insufficiency in Young Children: a Mixed Methods Study of Parents' Experiences. *Journal of Genetic Counseling*, 27(6), 1447–1458. <https://doi.org/10.1007/s10897-018-0278-9>
- R5.** Melin, J., Parra-Guillen, Z. P., Hartung, N., Huisinga, W., **Ross, R. J., Whitaker, M. J.**, & Kloft, C. (2017). Predicting Cortisol Exposure from Paediatric Hydrocortisone Formulation Using a Semi-Mechanistic Pharmacokinetic Model Established in Healthy Adults. *Clinical Pharmacokinetics*, 57(4), 515–527. <https://doi.org/10.1007/s40262-017-0575-8>
- R6.** Neumann, U., **Whitaker, M. J.**, Wiegand, S., Krude, H., Porter, J., Davies, M., Digweed, D., Voet, B., Ross, R. J., & Blankenstein, O. (2017). Absorption and tolerability of taste-masked hydrocortisone granules in neonates, infants and children under 6 years of age with adrenal insufficiency. *Clinical Endocrinology*, 88(1), 21–29. <https://doi.org/10.1111/cen.13447>

Patents

Two patent families: “Treatment of Adrenal Insufficiency in Children” and “Paediatric Formulation”, both granted in EP (12806617.2 & 14727028.4) and US (9675559 & 9649280), with 31 filed or grant patents in different territories.

Grants

[G1] Richard Ross (PI) and Martin Whitaker (Project Coordinator). Treatment of Adrenal Insufficiency in Neonates - Development of a Hydrocortisone Preparation for the Treatment of Adrenal Insufficiency in Neonates and Infants. European Commission, FP7 – Health; TAIN Grant agreement ID: 281654. €4.2M

4. Details of the impact (indicative maximum 750 words)

Approximately 10,000 children suffer from paediatric AI (including CAH) in Europe and prior to research at the University of Sheffield, there were no licensed preparations of hydrocortisone specifically for neonates and infants with CAH and the related disease paediatric AI. Sheffield research led to the formulation of the first licensed and marketed treatment for paediatric AI, Alkindi® hydrocortisone granules. The phase 3 clinical trial results [R6] confirming the efficacy of the drug led to EC authorisation for Alkindi® as a replacement therapy for children from birth to <18 years old across Europe [S1, S3]. Throughout the impact period, Diurnal Ltd., a Sheffield spin-out company, has worked closely in research and development with Sheffield and invested over £528K in the university to progress Alkindi® through regulatory approval and to market [S2].

Alkindi® received a PUMA in 2018 [S1]. Since 2019, it has been prescribed in the NHS [S2] and been made available to over 50% of paediatric patients with AI across Europe, including Germany, Austria, Italy, the UK, the Netherlands, Sweden, Norway, Denmark, and Iceland [S2].

Three new agreements cover the distribution and marketing of Alkindi® in the Benelux Union (consisting of Belgium, the Netherlands, and Luxemburg) [S2], Switzerland [S2], and the US [S1, S2]. In August 2020, Diurnal announced that Alkindi® had also been approved by the Australian Therapeutic Goods Administration (TGA) and the Israeli Ministry of Health [S1, S2], with anticipated launches in these countries in 2021. These approvals make Alkindi® a truly global pharmaceutical product with wide-ranging impact across the world. Thus, through the commercialisation of Alkindi®, the Sheffield research has underpinned commercial impact (measured in sales of pharmaceutical product), health impact (measured by the provision of licensed drug to thousands of patients across Europe and worldwide), and impact on patient and public understanding.

Commercial impact

The research and subsequent development of Alkindi® has had commercial impact for Diurnal Ltd., which floated on the London Stock Exchange (Alternative Investment Market - AIM) in 2015 to commercialise Alkindi® and other endocrine treatments [S2]. It is extremely rare for a UK university spin-out company to take a drug through regulatory approval and to market, and Diurnal is one of only three AIM-listed companies to get a drug approved in the US. Since the launch of Alkindi® (based on strong sales), Diurnal's revenue streams were reported as £4.7M cumulative at the end of June 2020 [S2]. Diurnal has successfully raised over £55M in investments and generated major industrial contracts with pharmaceutical companies [S2]. Diurnal's share price has been increasing with the success of Alkindi®. In addition, the company continues to expand; it has created 30 new highly skilled jobs, and the number of staff has increased from five in 2013 to 38 in 2020 [S2].

Health impact

The TAIN project offered unique insights into the realities and challenges of managing paediatric AI from the family perspective. Public and patient awareness of paediatric AI was supported by the collaboration with Genetic Alliance UK, who enabled family participation in the research and shared findings with patient organisations, including Living with CAH, the Addison's Disease Self-Help Group and the Dutch Adrenal Society (NVACP). Presentations to European and US patient support groups, including to the American CAH patient group CARES (5,000 community members) in 2009, the UK CAH patient group in 2011, and the UK Addison's Disease Self-Help Group (1,400 members) in 2012 (<http://www.tain-project.org/>) raised awareness of the impact of the rare condition amongst clinicians and other stakeholders in the UK and in Europe.

This awareness raising was key to Alkindi®, being prescribed to children and administered by parents across mainland Europe since 2018 [S2] and in the UK since 2019 [S2]. The most significant impact to date is that during the clinical trials there were no reported adrenal crises in young patients receiving the drug compared to the up to 10% of AI children that had a crisis each year, demonstrating that Alkindi® provides live-saving treatment to this vulnerable patient group [S4]

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. International approvals for Alkindi® in Europe (EMA), the US (FDA), Australia and Israel:

EMA market authorisation: <https://www.ema.europa.eu/en/medicines/human/EPAR/alkindi>

EMA press release, 'First paediatric medicine to treat rare hormonal disorder':

<https://www.ema.europa.eu/en/news/first-paediatric-medicine-treat-rare-hormonal-disorder>

FDA Market Authorisation:

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppI No=213876>

Australian Therapeutic Goods Administration approval: [https://tga-](https://tga-search.clients.funnelback.com/s/search.html?query=Alkindi&collection=tga-artg)

[search.clients.funnelback.com/s/search.html?query=Alkindi&collection=tga-artg](https://tga-search.clients.funnelback.com/s/search.html?query=Alkindi&collection=tga-artg)

Israeli Ministry of Health approval

- S2.** Supporting statement from Diurnal Ltd. to University of Sheffield confirming their investment and sales since August 2013.
- S3.** FP7 TAIN Consortium Final Report.
- S4.** Publication of Alkindi® results – Neumann, U., Braune, K., Whitaker, M. J., Wiegand, S., Krude, H., Porter, J., Digweed, D., Voet, B., Ross, R. J. M., & Blankenstein, O. (2020). A Prospective Study of Children Aged 0–8 Years with CAH and Adrenal Insufficiency Treated with Hydrocortisone Granules. *The Journal of Clinical Endocrinology & Metabolism*, 106(3), e1433–e1440. <https://doi.org/10.1210/clinem/dgaa626>