Institution: Aston University

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: 1. Dapagliflozin: a new treatment for type 2 diabetes

Period when the underpinning research was undertaken: 2007-2012

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:
Clifford Bailey	Professor	1973-2019

Period when the claimed impact occurred: August 2013 to date

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Dapagliflozin is the first and the most-prescribed member of a new class of diabetes therapies, the SGLT-2 inhibitors. Dapagliflozin prevents renal glucose re-uptake so causing excretion of glucose via the urine and also leads to weight loss and blood pressure reduction. Approximately 5 million patients have been treated since launch (2012). Aston-led design, analysis and interpretation of clinical trials in collaboration with global pharma BristolMyersSquibb (BMS) plus Aston's major conference presentations and education programmes for healthcare professionals have contributed directly to this status.

Impacts on **Health & Wellbeing** and **Commerce & the Economy** are claimed.

2. Underpinning research

Background: Type 2 diabetes affects over 420 million people globally (>6% of the world population). It mostly develops in middle-to-later life, causes serious complications of the eyes, kidneys, nerves, heart and blood vessels and accounts for ~10% of healthcare costs in western society. The varied and progressive nature of type 2 diabetes requires use of a selection of differently-acting medicines for differing individuals and disease stages. Dapagliflozin was synthesised by BMS as a derivative of phlorizin (a chemical in apple peel) with selective potency to inhibit sodium/glucose co-transporter-2 (SGLT-2) in the apical membranes of epithelial cells in segment 1 of renal proximal convoluted tubules. The early development of dapagliflozin is summarised in regulatory documents and an early publication (**S3.1**). Dapagliflozin was subsequently purchased from BMS by AstraZeneca.

Research Insights/Findings: By inhibiting SGLT-2, dapagliflozin offers a novel mechanism to reduce excess blood glucose through decreased reabsorption of glucose filtered by the kidneys. This increases the elimination of glucose in the urine. This new mechanism of action has allowed combination therapies with other glucose-lowering therapies such as metformin, showing efficacy in large, multinational clinical trials (**S3.2**). Clinical trials also revealed that the caloric loss and osmotic effects associated with dapagliflozin improve control of body weight and blood pressure. Further, long-term post-approval studies have revealed an improved prognosis of renal patients and reduced cardiovascular risk (**S3.3**). Thus dapagliflozin fulfils a diversity of unmet therapeutic needs for type 2 diabetes, and this has been recognised by its incorporation into the standard treatment algorithms for type 2 diabetes (**S3.4**).

Underpinning Research: Bailey was the principal investigator (PI) in the design, conduct, analysis and communication of the Phase III pivotal clinical trials for dapagliflozin. He also led subsequent clinical studies exploring the mode of action and clinical opportunities for use of dapagliflozin as the initial glucose-lowering therapy for type 2 diabetes (**S3.5**, **S3.6**).

Key Researchers (Phase III clinical trials): Prof C. Bailey, Aston University, UK; Prof Jorge Gross, University of San Paulo, Brazil; Drs D Hennicken, N Iqbal, TA Mansfield and JF List, BMS, USA; Prof Vincent Woo, University of Manitoba, Canada.

Dates: All research described was conducted between 2007-2012.

Key contextual information: Drug development involves a series of detailed clinical research studies which are designed to assess efficacy, safety, side effects, mode of action and other credentials. Such design requires unique skills that are applied in a careful, thorough and exacting manner to ensure patient safety, establish the therapeutic profile and comply with the rigorous standards set by medicines regulation to determine suitability for approval in routine treatment. Appropriate planning of these studies is crucial: errors at this stage incur undue risk to patients and jeopardise future prospects for the medicine. Independent academic input to the design stages and for the interpretation of these studies customarily involves a small team of international experts. Prof Bailey was diabetes representative to the European Medicines Agency 2006-2012 and an FDA diabetes expert witness on multiple occasions. Hence his selection to guide initial clinical studies with dapagliflozin.

3. References to the research

S3.1 European Medicines Agency, 18 September 2012, EMA/689976/2012. Committee for Medicinal Products for Human Use (CHMP), Assessment report, Forxiga, dapagliflozin, Procedure No.: EMEA/H/C/002322. https://www.ema.europa.eu/en/documents/assessment-report/forxiga-epar-public-assessment-report_en.pdf; FDA Center for Drug Evaluation and Research, Application number: 202293orig1s000, Medical Review, 22 Dec 2013. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000MedR.pdf; Bailey C.J. & Day C. SGLT2 inhibitors: glucuretic treatment for type 2 diabetes. *Brit J Diabetes* (2010) **10**:193–19. https://doi.org/10.1177/1474651410377832.

S3.2 Bailey C.J., Gross, J.L., Pieters, A., Bastien, A. & List, J.F. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* (2010) **375:**2223–33. https://doi.org/10.1016/S0140-6736(10)60407-2.

S3.3 Bailey C.J. & Marx N. Cardiovascular protection in type 2 diabetes: Insights from recent outcome trials. *Diabetes Obes. Metab.* (2019) **21**:3-14. https://doi.org/10.1111/dom.13492.

S3.4 Dapagliflozin (Forxiga) for type 2 diabetes. *Drug Ther. Bull.* (2013), **51**:105-7. https://learning.bmj.com/learning/returnHighwirePDF.html?doi=10.1136/dtb.2013.9.0205

S3.5 Bailey C.J., Iqbal N., T'joen C. & List J.F. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes Obes. Metab*. (2012) **14**, 951-9. https://doi.org/10.1111/j.1463-1326.2012.01659.x.

S3.6 Bailey C.J., Morales Villegas E.C., Woo V., Tang W., Ptaszynska A. & List J.F. Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. *Diabetic Med*. (2015) **32**, 531-41. https://doi.org/10.1111/dme.12624.

4. Details of the impact

Bailey was previously instrumental in the development of metformin as the most-prescribed drug worldwide for type 2 diabetes, both in terms of fundamental research and design/implementation of clinical trials (**S5.1**) and as a consequence, was selected by BMS as PI for the initial phase III clinical trials of dapagliflozin (**S5.2**). The resulting clinical research provided the primary evidence required to illustrate the efficacy and safety profile of

dapagliflozin as a suitable medicine for the treatment of type 2 diabetes, both as a monotherapy (**S3.5**) and as a combination therapy with metformin (**S3.2**). From those and subsequent phase III clinical trials, this clinical research into dapagliflozin has resulted in:

Impact on Health & Wellbeing 1: Alternative treatment for type 2 diabetes with worldwide reach

Following formal launch of the drug in the EU in 2012 as both a mono- and combined therapy, dapagliflozin has since been approved for routine clinical use in Europe, North America and most other regions of the world (**S5.3**). The National Institute for Health and Care Excellence (NICE), which assessed the clinical studies described above, concluded that the improved management of type 2 diabetes afforded by dapagliflozin (and its related compounds) will enhance patient quality of life, reduce complications and hospital admissions, and provide substantial cost-benefits to the NHS and other healthcare systems (**S5.4**). Consequently, dapagliflozin is now the most commonly-used agent in the class of SGLT-2 inhibitors, with more than with more than $1.54 billion sales in 2019, a rise of 11% from 2018 (**S5.5**).

Impact on Health & Wellbeing 2: Control of blood glucose levels in those with demonstrable poor control on other medications, leading to reduction in the use of injectable therapies

Owing to the unusual mechanism of action of dapagliflozin (it affects glucose excretion rather than glucose homeostasis via insulin-based control), dapagliflozin may be combined successfully with other drugs including metformin and insulins (**S5.3**). For those for whom monotherapy gives inadequate control, combination therapy with an SGLT-2 inhibitor such a dapagliflozin can prove effective and so delay the use of injectable therapies such as insulins. Conversely, those already on insulin are generally required to reduce their dose when used in combination with dapaglifozin (**S5.7**).

Impact on Health & Wellbeing 3: A treatment for type 2 diabetes that has demonstrable health benefits beyond control of blood glucose levels

Unlike several other treatments for type 2 diabetes such as sulphonylureas and insulins, dapagliflozin assists control of body weight and blood pressure, and has recently received approval for use as an adjunct to insulin in the treatment of type 1 diabetes (**S5.7**). Dapagliflozin has also been shown to reduce rates of cardiovascular death and hospitalization for heart failure, and is now approved by FDA to assist treatment of type 2 diabetes patients with cardiovascular conditions (**S5.8**).

Additionally, dapagliflozin has been shown to protect against deteriorating renal function, promote secretion of beneficial adipocyte hormones (adiponectin and leptin), and increase uric acid excretion, raising the possibility of therapeutic uses to treat hyperuricaemia (**S5.9**, **S3.5**). Accordingly, dapagliflozin has recently been granted Breakthrough Therapy Designation in the US for patients with chronic kidney disease, with and without type-2 diabetes. Finally, it is noted that the successful early clinical studies with dapagliflozin encouraged development of related compounds including canagliflozin and empagliflozin.

Impact on Commerce and the Economy: Royalty revenue stream for BMS

BMS and AZ entered into a "*Diabetes alliance*" in 2007 (**S5.3**) in which BMS developed dapagliflozin. In February 2014, AZ subsequently completed *"acquisition of the entirety of Bristol-Myers Squibb's interests in the companies' diabetes alliance"*, for a total of $2.7 billion, of which $0.6 billion related to royalty payments up to 2025 for Farxiga (dapagliflozin) in the USA (**S5.10**).

5. Sources to corroborate the impact

S5.1 REF 2014 Impact Case Study: METFORMIN: CHANGING THE TREATMENT ALGORITHM FOR TYPE 2 DIABETES.

S5.2 Letter from Astra/Zeneca outlining the reason for Prof Bailey's selection and his essential contribution to the development of dapagliflozin.

S5.3 Dapaglifoxin approval/launch dates worldwide. EU: https://news.bms.com/news/r-and-d/2012/Forxiga-dapagliflozin-First-In-Class-SGLT2-That-Works-Independently-of-Insulin-Now-Approved-in-European-Union-for-Treatment-of-Type-2-Diabetes/default.aspx USA, https://news.bms.com/news/r-and-d/2014/US-FDA-Approves-Farxiga-Dapagliflozin-Tablets-for-the-Treatment-of-Adult-Patients-with-Type-2-Diabetes/default.aspx

S5.4 NICE Technical Appraisal TA288. Dapagliflozin in combination therapy for treating type 2 diabetes. Technology appraisal guidance [TA288] Published 26 June 2013. Last updated: 23 November 2016.

S5.5 Dapagliflozin (Farxiga) sales, 2019 https://www.astrazeneca.com/content/dam/az/PDF/2019/full-year/Full-year_and_Q4_2019_results_announcement.pdf, See p 16.

S5.6 Wilding J., Bailey C., Rigney U., Blak B., Kok M. & Emmas C. Dapagliflozin therapy for type 2 diabetes in primary care: changes in HbA1c, weight and blood pressure over 2 years follow-up. *Prim. Care Diabetes* (2017) **11**:437-444. https://doi.org/10.1016/j.pcd.2017.04.004

S5.7 European Medicines Agency. Dapagliflozin. Summary of Product Characteristics. 19 November 2019. https://www.medicines.org.uk/emc/product/2865/smpc

S5.8 FDA approves dapagliflozin to reduce heart failure. 21 October 2019. https://www.astrazeneca.com/media-centre/press-releases/2019/farxiga-approved-in-the-us-to-reduce-the-risk-of-hospitalisation-for-heart-failure-in-patients-with-type-2-diabetes-21102019.html

S5.9 Bailey CJ. Uric acid and SGLT2 inhibition. *Diabetes Obes Metab.* (2019), **21**: 1291-1298. doi: 10.1111/dom.13670 and https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-granted-breakthrough-therapy-designation-in-us-for-chronic-kidney-disease.html

S5.10 https://www.astrazeneca.com/media-centre/press-releases/2014/astrazeneca-aquisition-bristol-myers-squibb-global-diabetes-alliance-03022014.html#