**Institution:** University of Surrey

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

**Title of case study:** Improving diabetes patients' well-being with insulin analogues

**Period when the underpinning research was undertaken:** 2005 – 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: |
|---|---|---|
| Professor David Russell-Jones | Honorary Professor of Diabetes & Endocrinology | 1/4/2005 - 31/3/19 |
| | Professor of Diabetes & Endocrinology and Vice-Chancellor's Fellow (0.2FTE) | 1/4/2019 - 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** (indicative maximum 100 words)

Diabetes affects over 450 million people worldwide, of whom ~30 million have Type 1 diabetes and are wholly dependent on insulin replacement therapy. Most other diabetes patients have Type 2 diabetes, and about 25% of these will also require insulin treatment for part of their lives. Ground-breaking University of Surrey research led to a new understanding of a hepato-selective long-acting insulin analogue (detemir) which informed the development of a further long-acting insulin analogue degludec (sold in 86 countries), and of a complementary rapid-acting analogue, Fiasp (sold in 33 countries). Substantial benefits have resulted for diabetes patients and for healthcare policy, and considerable commercial impact has occurred through sales of the new insulin analogues (>£1.6 bn).

**2. Underpinning research** (indicative maximum 500 words)

Effective management of both Type 1 and Type 2 diabetes mellitus with insulin therapy is essential to prevent potentially life-threatening diabetic ketoacidosis and minimise associated long-term complications by maintaining close to normal, healthy levels of blood sugar. Poor glycaemic control can lead to early-onset and increased severity of long-term complications affecting eyes, kidneys, nerves and blood vessels of diabetes patients.

In 2004, Professor David L. Russell-Jones led a collaboration between The University of Surrey and King's College London which established that because Novo Nordisk's insulin analogue detemir (trade name Levemir®) bound albumin, it would have relatively less access across the tight endothelium in peripheral tissues and relatively more access across the open sinusoidal lining in the liver **[3.1]**.

These features restore the physiological gradient of greater insulin exposure to the liver than to peripheral tissues. The result is better glycaemic control in diabetes patients than by traditional insulin replacement therapies which create a different ('unphysiological') distribution of insulin throughout the body when compared to the natural situation, in which the majority of insulin produced by the pancreas is delivered to the liver, and relatively less reaches peripheral tissues.

This new knowledge on the value of liver-selective insulin analogues prompted a step-change in insulin research by Novo Nordisk, the major provider of global diabetes pharmaceuticals.

In collaboration with Novo Nordisk, Prof Russell-Jones joined an international consortium of academics and clinicians which went on to research and optimise insulin analogues. Modifying the structure of insulin and the way in which it is carried within the circulation makes it possible to alter both the distribution and the biological effects of the resulting 'insulin analogues'. Such insulin analogues can be longer acting and can offer better glycaemic control for diabetes patients: (i) by providing a continuous low level of insulin in the circulation throughout the day, rather than a peak activity at administration that can compromise glycaemic control; and in so doing, (ii) reducing the risk of night-time variations in blood glucose levels. This crucial collaborative research resulted in the development of the detemir follow-on, degludec (Novo Nordisk, trade name Tresiba®), a long-acting insulin analogue for the treatment of Type 1 diabetes **[3.2, 3.3]**.

Whist long-acting insulin analogues greatly improve chronic glycaemic control over previous insulin treatments; a number of diabetes patients receiving them may still struggle to achieve control of their blood glucose levels around mealtimes. To further improve glycaemic control in these patients, Prof Russell-Jones led trials that established an enhanced clinical value for Type 1 patients of the rapid-acting insulin aspart (Novo Nordisk, trade name Fiasp®). Fiasp® more closely matches the healthy body's physiological response to improve glycaemic control after mealtimes by working more quickly in the bloodstream following injection than existing treatments **[3.4, 3.5]**. This Surrey led research identified that the combination of the long-acting degludec (Tresiba®) and fast-acting insulin aspart (Fiasp®) improved night-time glycaemic control, compared with the combination of Fiasp® and the previous conventional treatment of glargine **[3.2, 3.6]**.

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

**[3.1]** Hordern SV, Wright JE, Umpleby AM, Shojaee-Moradie F, Amiss J, **Russell-Jones DL**. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. Diabetologia 2005; 48: 420-426. doi: 10.1007/s00125-005-1670-1

**[3.2]** Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, **Russell-Jones D**, Philotheou A, Francisco AM, Pei H, Bode B; BEGIN Basal-Bolus Type 1 Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379:1489-97. doi: 10.1016/S0140-6736(12)60204-9

**[3.3]** Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, **Russell-Jones D**, Larsen J, Tamer SC, Bain SC; NN1250-3770 (BEGIN: Flex T1) Trial Investigators. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013; 98:1154-62. doi: 10.1210/jc.2012-3249

**[3.4] Russell-Jones D**, Bode BW, De Block C, Franek E, Heller SR, Mathieu C, Philis-Tsimikas A, Rose L, Woo VC, Østerskov AB, Graungaard T, Bergenstal RM. Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1). Diabetes Care 2017; 40: 943-950. doi:10.2337/dc16-1771

**[3.5]** Mathieu C, Bode BW, Franek E, Philis-Tsimikas A, Rose L, Graungaard T, Birk Østerskov A, **Russell-Jones D**. Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (Onset 1): A 52-week, randomized, treat-to-target, phase III trial. Diabetes Obes Metab 2018; 20: 1148-1155. doi: 10.1111/dom.13205

**[3.6]** Bode BW, Buse JB, Fisher M, Garg, SK, Marre, M, Merker, L, Renard, E, **Russell-Jones, DL**, Hansen CT, Rana A, Heller, SR. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial. Diabetic Medicine 2013, doi: 10.1111/dme.12243

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

Research at the University of Surrey led by Professor David L. Russell-Jones prompted a new vision for the design of insulin analogue therapies for diabetes patients. By exposing the liver-selective properties of the long-acting detemir, his work underpinned the development, clinical testing and approval to market of the improved insulin analogue, degludec. To complement this long-acting treatment for diabetes, a rapid-acting analogue, Fiasp®, was also developed and approved. These new insulin products have impacted on national and international healthcare policy and significantly benefitted diabetes patients worldwide **[5.1]**. The commercial impact has been considerable.

**1. Impact on national and international healthcare policy**

**Degludec**
In the UK, degludec was accepted for use in September 2013 when it was featured in the National Institute for Health and Care Excellence (NICE) Type I diabetes Evidence Summary **[5.2]**; Prof Russell-Jones co-authored all three clinical studies on which this evidence summary was based **[3.2, 3.6]**. On the basis of this evidence summary, degludec was recognised by the NICE diabetes guidelines for the treatment of Type 1 and Type 2 diabetes, in children, young people and adults, including those with diabetic co-morbidities such as eye disease **[5.3]**. Following UK approval, degludec was then authorised by the European Medicines Agency (EMA) for the treatment of Type 1 and Type 2 diabetes in the European Union, in adults and children aged 1-18 years **[5.4]**. The basis of this authorisation included evidence published by Prof Russell-Jones **[3.3]**, such as clinical study NCT01079234. Furthermore, degludec was approved in the USA by the Food & Drug Administration (FDA) in 2015 **[5.5]**, who also cite NCT01079234 by its other study identification number NN1250-3770.

**Fiasp®**
Underpinned by the clinical trials led by Prof Russell-Jones **[3.2, 3.4, 3.5, 3.6]**, Fiasp® was approved throughout the European Union in January 2017 by the EMA **[5.6]**, citing clinical trial NCT01831765 to which Prof Russell-Jones' studies contributed **[3.4, 3.5]**, in Canada by Health Canada, also in January 2017 **[5.7]**, and in the USA in September 2017 by the FDA **[5.8]** who cite clinical trial NCT01831765 by its other study identification number NN1218-3852.

**2. Impact on patient quality of life and cost-effectiveness of healthcare delivery**

The long-acting liver-selective nature of degludec enables more consistent day-to-day blood glucose profiles. Also, it reduces glucose variability during the day compared with conventional neutral protamine Hagedorn (NPH) insulin preparations **[5.9]**. This mitigates extreme fluctuations in blood glucose, which in turn defers the onset and reduces the severity of the widely experienced long-term complications of glycaemic dysregulation which affects the eyes, kidneys, nerves and blood vessels of diabetes patients. Furthermore, it helps to prevent blood glucose levels falling too low (hypoglycaemia) when patients can feel hungry and eat more, contributing to weight gain with concomitant poorer health outcomes. Despite the advantages of the long-acting insulin analogues, many diabetes patients receiving them still struggle to achieve control of their blood glucose levels around mealtimes. Prof Russell-Jones' research demonstrated that the fast-acting insulin analogue Fiasp® improves glycaemic control after mealtimes and that combining the long-acting (degludec) and fast-acting (Fiasp®) insulin analogues significantly reduced night-time episodes of dysregulated glycaemic control **[3.2, 3.6]**. This work has significantly benefitted diabetic patients globally and contributed to improved cost-effectiveness of healthcare delivery for diabetic patients. The cost-effectiveness of degludec has been

analysed using the IMS CORE diabetes model. The model showed that over a lifetime, treatment for Type 1 with degludec is cheaper and more effective than treatment with either glargine or detemir, with a cost per quality-adjusted life-year (QALY) of £13,220 (below the commonly used cost-effectiveness threshold of £20,000/QALY) **[5.10]**.

**3. Commercial impact**

Degludec (Tresiba®) and insulin aspart (Fiasp®) are truly ground-breaking products providing not only significant patient benefit but also impressive revenue generation. They are currently marketed globally by Novo Nordisk both as discrete products and in insulin combinations (Ryzodeg® & Xultophy®) with a combined sales revenue in 2019 in excess of £1.6bn **[5.11]**.
- Tresiba®, insulin degludec (DKK9259m=£1.1bn)
- Fiasp®, fast-acting insulin aspart (DKK1243m=£151m)
- Ryzodeg® 70/30, insulin degludec/insulin aspart (DKK993m=£120m)
- Xultophy®, insulin degludec/liraglutide (DKK2210m=£269m).

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

**[5.1]** Testimonial Letter from Prof Mads Krosberg, Head of R & D, Novo Nordisk. (PDF)

**[5.2]** Guidelines for degludec treatment of Type 1 diabetes in the UK. National Institute for Health and Care Excellence. Type 1 diabetes: insulin degludec. NICE guideline ESNM24. September 2013. https://www.nice.org.uk/advice/esnm24/resources/type-1-diabetes-insulin-degludec-1502680863357637

**[5.3]** NICE 2019 surveillance of diabetes (NICE guidelines NG17, NG18, NG19 and NG28). https://www.nice.org.uk/guidance/ng17/resources/2019-surveillance-of-diabetes-nice-guidelines-ng17-ng18-ng19-and-ng28-6837997933/chapter/Surveillance-decision?tab=evidence

**[5.4]** European Medicines Agency approval of degludec. Updated 26/2/2019. https://www.ema.europa.eu/en/medicines/human/EPAR/tresiba

**[5.5]** US Food and Drug Administration approval of degludec. September 2015 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313and203314Orig1s000TOC.cfm

**[5.6]** European Medicines Agency (EMA) approval of Fiasp throughout the European Union, January 2017. https://www.ema.europa.eu/en/medicines/human/EPAR/fiasp

**[5.7]** Health Canada approval to market Fiasp in Canada, January 2017. See: https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00206

**[5.8]** US Food and Drug Administration approval of Fiasp. September 2017 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208751Orig1s000TOC.cfm

**[5.9]** Mathieu C, Gillard P, Benhalima K. Insulin analogues in type1 diabetes mellitus: getting better all the time. Nature Rev Endocrinol 2017; 13: 385-399. doi: 10.1038/nrendo.2017.39

**[5.10]** Evans M, McEwan P. Clinical and cost–effectiveness of insulin degludec: from clinical trials to clinical practice. J Comparative Effectiveness Research 2015; 4: 279-286. doi: 10.2217/cer.15.10

**[5.11]** Novo Nordisk annual report 2019 (cf. Page 51). Available at: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/irmaterial/annual_report/2020/Novo-Nordisk-Annual-Report-2019.pdf