Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA1 (Clinical Medicine)		
Title of case study: A new first-in-class drug transforms treatment for heart failure, improves patient outcomes, and reduces hospitalisation		
Period when the underpinning research was undertaken: 2009-2020		
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:**
Prof. John McMurray	Professor of Medical Cardiology	1999–present
Dr Pardeep Jhund	Lecturer; Senior Clinical Lecturer	2008–2015; 2015–present
Period when the claimed impact occurred: 2015–present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Heart failure (HF) is a major cause of premature death globally, however treatment has been sub-optimal. Identifying new and efficacious treatments for HF remains a public health priority. UofG researchers have contributed significantly by leading landmark clinical trials assessing new HF therapies. The 2016 UofG-led PARADIGM-HF study transformed HF treatment by underpinning the worldwide approval of a new first-in-class drug, sacubitril/valsartan—a major breakthrough in HF management since betablockers and other disease-modifying drugs. Approved in 112 countries, sacubitril/valsartan is used to treat over 1.4 million HF patients worldwide, reducing premature death and hospitalisation rates and is incorporated in international clinical guidelines. Over USD4 billion has been generated in sales since 2015.

2. Underpinning research

UofG is internationally renowned for its HF research and has led seminal studies that have established the current standard of HF care globally. Prof. John McMurray, a world-leading clinical triallist, has for over 25 years been studying natriuretic peptides for diagnosing and treating HF with reduced ejection fraction (HFrEF)—a condition where insufficient blood is pumped from the heart's left side. In 2000, Prof McMurray joined Prof. Milton Packer (then at Columbia University) on the executive committee of a major randomised trial (OVERTURE 2002). This trial demonstrated the potential benefit of inhibiting an enzyme that breaks down natriuretic peptides (called neprilysin), in combination with angiotensin-converting enzyme (ACE) inhibitors (the gold standard HF treatment), using the combined ACE inhibitor/neprilysin inhibitor, omapatrilat [3.1]. Although omapatrilat was not developed further, the trial highlighted the potential of this treatment strategy for reducing HFrEF patient morbidity and mortality.

In August 2008, building on a 20-year history of collaboration, Novartis identified Prof. McMurray to lead studies on a novel angiotensin receptor-neprilysin inhibitor (ARNi), LCZ696 (sacubitril/valsartan). McMurray was ideally placed to direct studies of LCZ696 in HFrEF given his previous involvement in numerous major HF-related clinical trials, such as endothelin receptor antagonism (VERITAS 2007), of angiotensin receptor blockers for HFrEF (CHARM 2003), and of therapies blocking the renin-angiotensin-aldosterone system in HFrEF (EMPHASIS-HF 2011). McMurray directed Novartis to undertake a pharmacokinetic study to demonstrate bioequivalence of the valsartan component of the proposed dose of sacubitril/valsartan with the dose of valsartan shown in previous trials to be effective, to support a subsequent, randomized study. McMurray also proposed and supported the decision to bypass a phase 2 study, citing previous experience with omapatrilat, thereby accelerating the drug development process. McMurray was also instrumental in discussions with Novartis and regulatory authorities, such as the US Food and Drug Administration (FDA), that enabled the

PARADIGM-HF phase 3 trial, which was designed to test whether sacubitril/valsartan (at 200 mg twice daily) was superior to the ACE inhibitor, enalapril (10 mg twice daily), in reducing the risk of cardiovascular (CV) death or of HF hospitalisation [3.2]. This study was the largest ever drug therapy trial in patients with HFrEF (8,399 participants), designed and led by McMurray and Packer (University of Texas) as co-chairs of the steering committee, with Dr Pardeep Jhund as a clinical events adjudication committee member. In 2014, the trial was stopped early by the data monitoring committee due to unequivocal evidence of sacubitril/valsartan's superiority to enalapril; patients treated with sacubitril/valsartan achieved a sustained and highly significant 20% reduction in the risk of the primary composite end point (CV death or HF hospitalisation) and a 16% reduction in all-cause mortality [3.2].

Novartis said, '*Professor McMurray has been instrumental in developing the PARADIGM-HF study design including discussions with Novartis Senior Management and Health Authorities and his involvement has largely helped to defend the design of the study. His leadership as co-chair of the study executive committee throughout the study was key for the study planning, execution, and reporting and was highly appreciated by the study investigators and the Novartis study team*.' [5.A]

Subsequently, UofG researchers have led PARADIGM-HF data analyses that have supported submissions to regulatory authorities, demonstrating the efficacy of sacubitril/valsartan in patients of all ages [3.3]. Other UofG researcher-led analyses demonstrate the benefits of this drug in specific populations, such as patients with diabetes [3.4], and its efficacy at reducing the risk of recurrent hospitalisations [3.5], for treating HFrEF in outpatient settings, and its cost effectiveness [3.6].

3. References to the research

1. Packer M, Califf RM, Konstam MA, Krum H, **McMurray JJ**, Rouleau JL, Swedberg K. (2002) Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*.106(8):920-6. (doi: 10.1161/01.cir.0000029801.86489.50)
2. **McMurray JJV**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 371:993–1004. (doi: 10.1056/NEJMoa1409077)
3. **Jhund PS**, Fu M, Bayram E, Chen C-H, Negrusz-Kawecka M, Rosenthal A, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, **McMurray JJV**, Packer M, PARADIGM-HF Investigators and Committees. (2015) Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *Eur Heart J*. 36:2576–2584. (doi: 10.1093/eurheartj/ehv330)
4. Kristensen SL, Preiss D, **Jhund PS**, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, **McMurray JJ**, Packer M; (2016) PARADIGM-HF Investigators and Committees. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. Circ Heart Fail. 9(1). pii: e002560. (doi: 10.1161/CIRCHEARTFAILURE.115.002560)
5. Mogensen UM, Gong J, **Jhund PS**, Shen L, Køber L, Desai AS, Lefkowitz MP, Packer M, Rouleau JL, Solomon SD, Claggett BL, Swedberg K, Zile MR, Mueller-Velten G, **McMurray JJV**. (2018) Effect of sacubitril/valsartan on recurrent events in the Prospective comparison

of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*.17:49–50. (doi: 10.1002/ejhf.1139)
6. **McMurray JJV** et al. (2018) Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart, 104(12):1006–1013. (doi:10.1136/heartjnl-2016-310661)

4. Details of the impact

Heart failure (HF) is a condition when the heart cannot meet the body's demands, with devastating consequences. HF patients have a survival rate of five years post-diagnosis, reduced quality of life and die prematurely. HF is also a substantial burden on health services; it is the leading cause of hospitalisations for adults over 65 years, costing the NHS over GBP2 billion (2010) and the US Medicare system, USD17 billion.

Around 50% of HF patients suffer from HF with reduced ejection fraction (HFrEF). Prior to the PARADIGM study, HFrEF was treated by ACE inhibitors, the gold standard of treatment for over 25 years. However, ACE inhibitors only partially improve HF, highlighting the need for new and improved drugs to treat HFrEF. PARADIGM-HF showed that sacubitril/valsartan considerably outperforms ACE inhibitors for treating HFrEF, making it the new gold standard of treatment. With approximately 20 million HF patients in Europe and the US alone, this discovery addresses a substantial, international public health burden.

PARADIGM-HF supports sacubitril/valsartan as a new HFrEF treatment

In 2014, based on preliminary results from the PARADIGM-HF trial, sacubitril/valsartan underwent a fast-track review by the FDA and European Medical Agency (EMA); indeed, it was the first CV drug to receive an EMA-accelerated review. Prof McMurray attended meetings with, and led responses to, questions posed by Health Authorities [5.A]. In 2015, Novartis gained regulatory approval for sacubitril/valsartan (trade name, Entresto) in the USA (FDA, July 2015) under the Accelerated Approval Programme; it was the first non-cancer drug ever to do so, reflecting the importance of this first-in-class (ARNi) drug. Approvals followed in Europe (EMA, Nov 2015), and, as of 2018, the drug has been approved in 112 countries and launched in over 90, each underpinned by the PARADIGM-HF findings [5.A, 5.B].

Impact on international and national guidelines

Based on key evidence from the PARADIGM-HF trial and UofG studies, the world's most influential cardiovascular societies have given sacubitril/valsartan their highest-level recommendation, including the European Society of Cardiology (ESC), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and Heart Failure Society of America (HFSA) ['international guidelines', 5.C]. For example:

- ESC (2016) guidelines on heart failure recommend that ambulatory HFrEF patients with left ventricular ejection fraction (LVEF) of <35%, who remain symptomatic (class I,B recommendation), are treated with sacubitril/valsartan in place of an ACE inhibitor [5.C]
- ACC, AHA, and HFSA issued a Class 1 recommendation to switch HFrEF patients with LVEF <45%, from ACEi or an ARB to sacubitril/valsartan, as did the Canadian Cardiovascular Society (CCS) and the National Heart Foundation of Australia and Cardiac Society of Australia & New Zealand (NHFA/CSANZ) guidelines [5.C]
- The ESC (2019) Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases, developed in collaboration with the EASD (European Associations for the Study of Diabetes) recommend sacubitril/valsartan instead of ACEIs to reduce the risk of HF

hospitalization and death in patients with HFrEF and type-2 diabetes who remain symptomatic, despite treatment with ACEIs (class 1,B) [5.C]

Furthermore, in March 2016, the UK guidelines—National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN)—on HF management, recommended the use of sacubitril/valsartan in adult patients [5.D]. The NICE Technology Assessment and Scottish Medicines Consortium review [5.E], which both approved the drug for reimbursement, are framed entirely around the PARADIGM-HF study, with further support drawn from a UofG cost-effectiveness study [3.6]. The NICE expert review panel also highlighted [5.E] as particularly relevant to the UK the UofG findings that showed sacubitril/valsartan prevented hospitalisation across all ages, including older patients [3.3].

Changes in prescribing trends for HFrEF

Since the PARADIGM-HF study, McMurray and Jhund have continued advising Novartis, to support the clinical marketing of sacubitril/valsartan, sitting on advisory boards and delivering lectures, both promotional and non-promotional. Novartis said, '*Professor McMurray has been a critical medical expert for our global medical education activities to cardiologists during international scientific conferences…*[His] *advice as a participant in several advisory board meetings was crucial to inform our understanding of heart failure and best course of action to bring and innovative treatment to patients* [5.A].

The ACC/AHA/HFSA and ESC's class I recommendations—to prescribe sacubitril/valsartan to HFrEF patients—widely supported the subsequent upturn in this drug's prescription, and commercial returns from the drug in the US and EU [5.F]. Currently, 25–30% of HFrEF patients in Europe are treated with sacubitril/valsartan, constituting over 1 million people in 2018. In the USA, 5.7 million people have heart failure, of whom 48% have a LVEF of <40%. Allowing for exclusions and other contraindications, around 2.6 million patients stand to benefit from sacubitril/ valsartan. By 2018, in the USA, a significant contributor to increase in prescriptions has been through inclusion in Medicare plans—currently 100% of these plans cover sacubitril/valsartan with an eligible Medicare population of ~1.86 million [5.G]. In November 2019, China added the drug to their National Drug Reimbursement Plan, which also increases the volume of patients benefitting.

Improved patient health and quality of life

The treatment of HF patients with sacubitril/valsartan reduced the risk of dying from a cardiovascular cause by 20%, HF hospitalizations by 21%, and the risk of dying from any cause by 16%, relative to enalapril, the previous gold standard treatment. The magnitude of benefit has been observed subsequently in real world studies across international settings [5.H]. The optimal implementation of sacubitril/valsartan therapy has been empirically estimated to prevent 28,484 deaths per year in the USA [5.I] and, based on a 20% reduction in deaths, equates to 5,700 deaths prevented in the UK. A UofG-led cost-effectiveness study suggested an additional 0.91 years of life with treatment on average per patient [3.6], which in this patient group for some means a 50–100% increase in life span, and 1.27 million life years saved in the 1.4 million people prescribed to date.

Economic benefits to health services and industry

In the five years following its launch in July 2015, sacubitril/valsartan (Entresto) has made USD 4.2 billion in sales for Novartis to July 2020 [5.A]. Sacubitril/valsartan has been found to be cost-effective in the USA, UK and in other developed health care systems. A US cost-effectiveness study (co-authored by McMurray [5.J]) estimated that 220 fewer hospital

admissions will occur per 1000 HF patients treated with sacubitril/valsartan, compared to enalapril-treated patients, over 30 years; this equates to ~19,000 fewer hospitalisations per year among the 2.6 million US individuals eligible for sacubitril/valsartan treatment. Based on real data, it also reduces hospital re-admissions by 38% after first admission [5.K]. A report using real-world data showed a reduction in all-cause healthcare costs averaging 28% in the US (~USD1,275 per month per patient) compared with the previous gold standard ACE inhibitors [5.L].

5. Sources to corroborate the impact [PDFs provided unless otherwise indicated]

A. Testimony from Medical Affairs Director, Novartis
B. Regulatory approvals: FDA approval; EMA approval
C. International guidelines: **Europe**: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (cites [3.2], ref.162, on p.2151); **USA**: 2017 ACC/AHA/HFSA Focused Update for the Management of Heart Failure (cites [3.2], ref. 138, on p.e144); **Canada**: CCS Guidelines for the Management of Heart Failure (Nov 2017) (cites [3.2], ref.125, on p.1360-1); **Australia/NZ**: NHFA/CSANZ Guidelines for the Prevention, Detection, and Management of Heart Failure (Oct. 2018) (cites [3.2], ref.193, on p.1159); **Europe**: 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD (cites [3.2], ref. 421; and [3.4], ref. 471. on p.293)
D. UK guidelines**: England/Wales**: NICE [NG106] chronic heart failure: diagnosis and management (Sept 2018) (recommendation 54, p.205); **Scotland:** SIGN 147 guideline: management of chronic heart failure (cites [3.2], ref.79, p.21)
E. NICE Technology appraisal guidance [TA388] (April 2016) (Cites 'PARADIGM-HF' trial, p.6; cites [3.3], p.19, last para); Scottish Medicines Consortium [1132/6] (February 2016) sacubitril/valsartan (p.2, para 2)
F. Novartis gets a much needed boost for Entresto in new heart failure guidelines, FierceBiotech article; Novartis Annual Report (2016) [p.33 discussion on Entresto under 'Cardio-Metabolic']
G. Sumarsono *et al*. (2019) *JAMA Cardiol*. 5: 336–339 (doi: 10.1001/jamacardio.2019.4982) (see, p.E3)
H. Real world studies with sacubitril/valsartan: Albert *et al*. (2019) *JAHA* 8(9): e011089. (doi:10.1161/JAHA.118.011089); Polito *et al*. (2020) *Scientific Reports* 10: 6665 (doi: 10.1038/s41598-020-63801-2); Faile *et al*. (2018) *ESC Heart Failure* 5: 957–960 (doi: 10.1002/ehf2.12338)
I. Fonarow *et al*. (2016) *JAMA Cardiol*. 1(6): 714–717 (doi: 10.1001/jamacardio.2016.1724)
J. Gaziano *et al*. (2016) *JAMA Cardiol*. 1(6): 666–672. (doi: 10.1001/jamacardio.2016.1747)
K. Desai *et al*. (2016) *J Am Coll Cardiol*. 68(3): 241–248. (doi: 10.1016/j.jacc.2016.04.047)
L. Real-world data shows that Entresto® lowered healthcare costs in patients with HFrEF, Novartis press-release of study: Albert *et al*. (2019) *JAHA* 8(9): e011089. (doi:10.1161/JAHA.118.011089)