Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Secukinumab becomes the first interleukin-17A inhibitor approved for psoriatic arthritis		
Period when the underpinning research was undertaken: 2000–present		
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 Iain B McInnes	Muirhead Chair of Medicine and Director of the Institute of Infection, Immunity and Inflammation.	1993–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

Translational research by McInnes identified interleukin-17A (IL-17A) as a novel therapeutic target for psoriatic arthritis (PsA), which affects approximately 1% of the population. His subsequent clinical research delivered proof-of-concept and phase 3 trials for Novartis' IL-17A inhibitor secukinumab. This work supported regulatory approval of secukinumab for PsA (>80 countries) and informed UK, European and US clinical guideline recommendations. Global net sales for all approved indications (PsA, psoriasis and ankylosing spondylitis) were USD13.6 billion during January 2016–December 2020. Secukinumab offers healthcare systems a cost-effective option for treating PsA. Patients worldwide have benefitted from clinical improvements (e.g. skin and joint) and slowing of disease progression, directly improving quality of life.

2. Underpinning research

IL-17A identified as a potential therapeutic target for PsA

In 2000, UofG rheumatologist **Prof Iain McInnes** described the cytokine milieu in PsA synovial membranes and showed that the cytokine expression profile in PsA and rheumatoid arthritis synovial membranes differed [3.1]. The McInnes laboratory subsequently observed that patients with PsA express high levels of IL-17A and deduced that this cytokine might offer a therapeutic target for PsA (Dr Hilary Wilson, Clinical Research Fellow; UofG MD thesis, 2003).

In parallel, McInnes' team investigated the IL-12/IL-23/IL-17 cytokine regulatory axis in PsA pathogenesis. This work supported regulatory approval of an IL-12/IL-23 inhibitor (ustekinumab) for treating PsA (outlined in our REF2014 impact case study), establishing UofG researchers as global leaders in translational PsA therapeutics.

Proof of concept

McInnes proposed PsA as an indication of interest for IL-17A inhibition through ongoing interactions with the Novartis Scientific Advisory Committee around cytokine biology [5.A]. As a result, Novartis invited McInnes to lead a 24-week phase 2a proof-of-concept trial of its IL-17A inhibitor secukinumab (then known as AIN457) among 42 adults with active PsA recruited from across Europe (NCT00809614; 2009–2010) [3.2]. This trial did not meet its primary endpoint of a 20% change from baseline in American College of Rheumatology response criteria (ACR20) at 6 weeks, reflecting a composite of articular, inflammatory and quality-of-life measures. Nonetheless, secukinumab did demonstrate rapid and sustained improvements in clinical response such as disability and quality of life [3.2]. These findings were sufficient in an otherwise discouraging clinical therapeutic landscape to encourage further development of secukinumab with an optimised dose regimen for PsA.

The FUTURE clinical trials

Moving on from the proof-of-concept study [3.2], McInnes was instrumental in providing advice to generate support within Novartis to advance clinical trials of secukinumab as a treatment for PsA [5.A]. He continued to be critically involved in the design of the phase 3 programme for this indication. In 2012, Novartis invited McInnes to co-lead the Steering Committee for phase 3 clinical trials among adult patients with active PsA, which initially comprised the parallel FUTURE 1 and 2 studies but later broadened to include FUTURE 3–5. McInnes played a prominent role in the leadership of FUTURE 1 (i.e. he was instrumental in the design and

general guidance/shaping of this trial and its outcome measures); was Chief Investigator for FUTURE 2; and served on the Steering Committee for the extended phase 3/4 programme, particularly post hoc analyses of FUTURE 2.

FUTURE 2 (NCT01752634; 2013–2019) was the first study to investigate secukinumab administered solely by subcutaneous injection—representing its final approved, indicated dose and route of administration. FUTURE 2 recruited 397 patients worldwide who received either placebo or secukinumab once per week for 4 weeks and every 4 weeks thereafter. High doses of secukinumab (150 mg or 300 mg) improved signs and symptoms of PsA: 64% of patients had achieved ACR20 at 52 weeks [3.3]. **FUTURE 1** (NCT01392326; 2011–2014) recruited 606 patients worldwide [3.4]. The participants received either placebo or secukinumab, initially intravenously every 2 weeks and then by subcutaneous injection every 4 weeks. By 24 weeks, secukinumab showed superiority in primary and secondary endpoints, with approximately 50.0% of patients in the secukinumab group achieving ACR20 versus 17.3% in the placebo group [3.4]. These improvements were sustained in long-term extension studies of up to 2 years [3.5, 3.6].

FUTURE 3–5 provided understanding of the clinical use of secukinumab across the PsA spectrum. **FUTURE 3** (NCT01989468; 2014–2018) assessed 24-week efficacy, as well as 3-year safety and efficacy, of subcutaneous self-administration of secukinumab using an autoinjector [3.7]. McInnes served on the steering committee for this trial. **FUTURE 4** (NCT02294227; 2015–2017) was a 16-week efficacy and 2-year safety, tolerability and efficacy trial of secukinumab. **FUTURE 5** (NCT02404350; 2015–2019) investigated the efficacy (e.g. inhibition of structural damage), safety and tolerability of up to 2 years' secukinumab treatment and showed overall slowing of disease progression.

Placing secukinumab in the therapeutic armamentarium: the EXCEED clinical trial
McInnes was the Chief Investigator of EXCEED (NCT02745080; 2017–2019), the first head-to-head monotherapy comparison of secukinumab versus a tumour necrosis factor (TNF) inhibitor for PsA [3.8]. EXCEED showed that secukinumab was at least equivalent to TNF inhibition for treating PsA articular disease and superior for managing cutaneous disease.

3. References to the research

1. Danning CL, […], **McInnes IB** (2000) Macrophage-derived cytokine and nuclear factor kappaB p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheum* 43(6):1244–1256 (doi:10.1002/1529-0131(200006)43:6<1244::AID-ANR7>3.0.CO;2-2).
2. **McInnes IB** *et al*. (2014) Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 73(2):349–356 (doi:10.1136/annrheumdis-2012-202646).
3. **McInnes IB** *et al*. (2015) Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 386(9999):1137–1146 (doi:10.1016/S0140-6736(15)61134-5).
4. Mease PJ, **McInnes IB** *et al*. (2015) Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med* 373(14):1329–1339 (doi:10.1056/NEJMoa1412679).
5. **McInnes IB** *et al*. (2017) Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. *Rheumatology (Oxford)* 56(11):1993–2003 (doi:10.1093/rheumatology/kex301).
6. **McInnes IB** *et al*. (2018) Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study. *Arthritis Res Ther* 20(1):113 (doi:10.1186/s13075-018-1610-3).
7. Nash P, Mease PJ, **McInnes IB** *et al*. (2018) Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). *Arthritis Res Ther* 20(1):47 (doi:10.1186/s13075-018-1551-x).

8. **McInnes IB** *et al*. (2020) Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *Lancet* 395(10235):1496–1505 (doi:10.1016/S0140-6736(20)30564-X).

4. Details of the impact

The need for a new approach to treat PsA

PsA is a lifelong condition that affects up to 42% of all patients with psoriasis, representing a prevalence of approximately 1% in the general population. The clinical manifestations of PsA are heterogeneous and comprise disease of the skin, nails, joints, entheses, eyes, gut and axial skeleton. Quality of life is impaired by pain, fatigue and physical disability; furthermore, cardiovascular, metabolic, psychologic and bone conditions confer substantial comorbidity.

Clinical management of PsA aims to target the underlying mechanisms of disease manifestation in each tissue type, with the goal to improve symptoms, abrogate damage and ultimately achieve clinical remission (or at least minimal disease activity). Treatment options for PsA have traditionally included non-steroidal anti-inflammatory drugs; corticosteroids; disease-modifying anti-rheumatic drugs (DMARDs), with methotrexate as the first-line choice; and TNF inhibitors. Nonetheless, over half of all patients who receive these interventions remain with active PsA and poor quality of life.

Identification of IL-17A as a therapeutic target for PsA and the advent of a specific IL-17A inhibitor (secukinumab) delivered a novel solution to this problem. Supported by McInnes' translational science, clinical research and clinical trials leadership, secukinumab has rapidly become widely used as a first-choice biologic agent, thereby providing benefits for Novartis, clinical practice and patients.

Benefits for Novartis

Secukinumab (trade name, Cosentyx) was developed by Novartis, one of the world's largest pharmaceutical companies in terms of total revenue. Since 2010, McInnes has been a key consultant for Novartis in the disease area of rheumatology [5.A]. He co-led the company's Global Steering Committee (approximately six members); served on the Global Scientific Oversight Committee; and joined the Global Scientific Discovery Advisory Board in March 2020. The strength of this relationship for the PsA development programme is highlighted by the Novartis Global Brand Medical Director: "*Together through the academic/Novartis partnership with Prof McInnes we have been able to see that secukinumab is becoming a leading medication within Novartis and the preferred treatment option for individuals suffering from PsA in the US*" [5.A].

Worldwide approval of secukinumab as a treatment for PsA

The phase 2a, FUTURE 1 and FUTURE 2 studies [3.2–3.4] provided key evidence that enabled Novartis to apply to regulatory authorities worldwide regarding an extension of indication for secukinumab to include PsA, making this drug the first IL-17A inhibitor available for treating active disease:

- The European Medicines Agency (EMA) approved this indication in October 2015, stating secukinumab should be used "*alone or in combination with methotrexate … when the response to previous DMARD therapy has been inadequate*" [5.B].
- The US Food and Drug Administration (FDA) approved the use of secukinumab among adults with active PsA in January 2016 [5.C].
- Secukinumab has now been approved for PsA in more than 80 countries worldwide (see Novartis 2018 Annual Report; p.40).
- In 2018, FUTURE 5 formed the basis for EMA approval of a label update to include secukinumab dosing flexibility up to 300 mg [5.D].

Supporting uptake of secukinumab in the clinical management of PsA

McInnes participated in the design and development of detailed post hoc evaluations to help Novartis maximise uptake of secukinumab for PsA. This suite of analyses (published November 2013–June 2019) used a variety of clinical outcome tools and statistical methods, including matching adjusted indirect comparisons, to investigate patient-reported outcomes;

quality-of-life measures; and the relative value of secukinumab versus other biologic agents [5.E]. These studies also introduced an autoinjector for ease of use (well tolerated by 93% of patients) and demonstrated very low immunogenic risk (<1%), enabling monotherapeutic use in clinical practice. The post hoc evaluations therefore supported the introduction of secukinumab in PsA, and provided evidence for ease of use, longevity of response and clinical utility. In addition, the EXCEED trial [3.8] demonstrated unequivocally that secukinumab offers at least equivalent efficacy to a TNF inhibitor for articular PsA and superior benefits in cutaneous PsA.

Global sales position secukinumab as a blockbuster drug
The foregoing paved the way for a second IL-17A inhibitor (ixekizumab; Eli Lilly), which is now approved by the FDA (December 2017) and the EMA (January 2018); however, there is currently no generic competition to secukinumab. Consequently, marketing extensions for PsA have provided considerable economic value to Novartis in terms of worldwide sales of secukinumab for all approved indications (PsA, psoriasis and ankylosing spondylitis) [5.F]. The Novartis 2020 Annual Report ranked secukinumab first in global net sales for the Innovative Medicines Division (USD4 billion), with USD2.5 billion recorded in the USA and USD1.5 billion in the rest of the world. By contrast, secukinumab was ranked eighth in 2016, with global net sales of USD1.1 billion (USA: USD765 million; rest of world: USD363 million). From January 2016 to December 2020, Novartis accrued a total of USD13.6 billion in net sales of secukinumab worldwide [5.F].

Benefits for clinical practice
Clinical guidelines recommend secukinumab for the treatment of PsA
The European League Against Rheumatism (EULAR) and US-based Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) develop the dominant clinical guidelines used by the rheumatology community worldwide. In 2015, both EULAR and GRAPPA included secukinumab in their PsA treatment charts for the first time, recommending its use alone or in combination among patients with poor or no response to conventional therapy with DMARDs and TNF inhibition [5.G]. The 2019 update to the EULAR recommendations for the management of PsA with pharmacological therapies (McInnes, Steering Group member) placed secukinumab as (1) an optional first-choice biologic after methotrexate failure (equal weighting to TNF inhibitors) and (2) the preferred IL-17 inhibitor above TNF inhibition for patients with a particular cutaneous disease burden [5.G]. In 2017, the UK National Institute for Health and Care Excellence (NICE) published a technology appraisal guideline for the treatment of PsA after inadequate response to DMARDs (TA445) [5.G] that cites FUTURE 2 [3.3]. NICE guideline recommendations inform clinical practice in the NHS.

Secukinumab confirmed as a cost-effective treatment for PsA
Health economic analyses conducted in the UK, Canada and Finland (2018) demonstrated that secukinumab is a cost-effective option for health systems caring for patients with active PsA not previously treated with any conventional therapy [5.H].

Benefits for patients
Regulatory approvals and clinical guideline recommendations have provided access to secukinumab for patients worldwide who are living with active PsA. For example, community prescribing data from 13 of the 14 Scottish health boards demonstrates an increase in the cumulative number of PsA patients treated with secukinumab from [text removed for publication] in September 2015 to [text removed for publication] in November 2019 [5.I]. However, the total number of patients treated during this timeframe is likely to be higher given that community prescribing data do not capture individuals receiving secukinumab in clinical trials.

Treatment with secukinumab offers affected individuals symptom relief; slowing of disease progression (e.g. joint damage at 1 year abrogated among >80% of patients, leading to improved mobility); and protection from comorbidity, all of which can translate into improved quality of daily living. Joint pain is one of the main factors affecting quality of life among patients with PsA, causing fatigue, poor physical functioning, and societal and economic

burdens such as absences from work. FUTURE 2 showed that secukinumab rapidly reduced pain (week 4 versus pre-treatment levels), with the benefits sustained at 2 years [3.6]. In addition, over 80% of patients have improvements in self-reported bodily pain scores and 27% achieve pain-free life at 2 years. Concerning patient convenience and treatment adherence, secukinumab was originally administered intravenously every 2 weeks. Changing the mode of delivery to a self-administered subcutaneous autoinjector devised by Novartis—used every 4 weeks and tested successfully in FUTURE 3 [3.7]—has enabled people to take more control in managing their disease. Patients have reported high levels of satisfaction with the autoinjector, considering it both easy and painless to use.

As secukinumab shows high efficacy for alleviation of the skin and joint symptoms of PsA, it is now considered a pivotal component of emerging treat-to-target (T2T) recommendations. T2T is a clinical strategy whereby treatment is escalated to achieve a prespecified target state (e.g. minimal disease activity). The T2T approach is supported by both EULAR and GRAPPA. McInnes serves on a taskforce that comprises rheumatologists from Europe and North America with experience in clinical research, as well as patient and healthcare professional representatives. This taskforce published a set of updated evidence-based recommendations for T2T in 2018 [5.J].

5. Sources to corroborate the impact

PDFs uploaded for all listed items.

A. Statement from Novartis Global Brand Medical Director to substantiate McInnes' leadership and contribution to progressing secukinumab for PsA.
B. Approval in Europe: (1) EMA assessment report regarding an extension of indication for secukinumab in PsA (EMA/CHMP/665427/2015; October 2015). The phase 2a [3.2], FUTURE 1 [3.4] and FUTURE 2 [3.3] clinical trials are cited throughout this document as 'A2206', 'F2306' and 'F2312', respectively; (2) EMA summary of opinion for the change to marketing authorisation (EMA/CHMP/670627/2015; October 2015); (3) Novartis press release (November 2015).
C. Approval in the USA: (1) FDA extension of indication report for secukinumab in PsA (January 2016). See section 14.2 for FUTURE 1 [3.4; cited as 'PsA2'] and FUTURE 2 [3.3; cited as 'PsA1']. See sections 1.2 (indications and usage) and 2.2 (dosage and administration); (2) Novartis press release (January 2016).
D. European label update: (1) EMA summary of product characteristics (October 2018). FUTURE 1 [3.4], FUTURE 2 [3.3] and FUTURE 5 are cited as 'PsA study 1', 'PsA study 2' and 'PsA study 3', respectively. See section 4.2 (posology and method of administration); (2) Novartis press release (October 2018).
E. PubMed record of post hoc evaluations (November 2013–June 2019).
F. Novartis financial reports: See F-25–F-27 of the 2018 Annual Report for the 2016–2018 sales data; see F-25 and F-26 of the 2020 Annual Report for the 2019 and 2020 sales data.
G. Clinical guidelines: (1) EULAR 2015. The phase 2a [3.2] and FUTURE 2 [3.3] trials are cited as refs. 87 and 88, respectively. See Abstract, Table 1, Figure 1, p.504, p.505; (2) EULAR 2019 update. See Table 1, Table 2, Figure 1; (3) GRAPPA 2015. FUTURE 2 [3.3] cited as ref. 28. See Table 2, Figure 1, p.1068; (4) NICE TA445 (May 2017; reviewed July 2020). Recommendation 1.2, p.4. See p.11, p.12, p.14, p.17, p.26 for evidence citing FUTURE 2 [3.3].
H. Cost-effectiveness: health economic analyses from UK, Canada and Finland (2018).
I. Access to secukinumab for PsA: Scottish community prescribing data (2015–2019).
J. T2T: The 2017 update of international task force recommendations for '*Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target*'. FUTURE 2 [3.3] cited as ref. 73.