Institution: The University of Manchester

Unit of Assessment: 1 (Clinical Medicine)

Title of case study: Clinical trials in chronic obstructive pulmonary disease (COPD) advancing effective combination treatments

Period when the underpinning research was undertaken: June 2003 – July 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:
Dave Singh	Clinical Professor of Respiratory Medicine	2003 – present
Jørgen Vestbo	Clinical Professor of Respiratory Medicine	2003 – present

Period when the claimed impact occurred: 1 August 2013 – 31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

University of Manchester (UoM) research has led to a step change in care, from simple inhaled therapies to more effective, simpler to use, combination dual and triple therapies. UoM's industrial collaborations delivered a new dual therapy, and three new triple therapies. Most recently, the first triple combination therapy to be approved in Europe for COPD. These treatments have reduced known risks of multiple single inhaler use and brought more effective treatment options to patients globally. Notably, AstraZeneca's dual inhaler, approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), is available in 25 countries. UoM research has been included in the National Institute for Health and Care Excellence (NICE) guidance evidence reviews, cited in Australian and New Zealand Clinical Guidelines and in internationally renowned Global Initiative for Chronic Obstructive Lung Disease (GOLD) Strategy documents.

2. Underpinning research

UoM has driven practice-changing research in airway inflammation and biomarkers since 2001. UoM researchers have applied and developed clinical trial design in COPD and have been at the forefront of trials for both dual and triple inhaled combination therapy. Inhaled combination therapy refers to combinations of long-acting muscarinic antagonists (LAMA), long-acting beta2 agonists (LABA), and inhaled corticosteroids (ICS).

From 2011 to 2013, Singh collaborated with AstraZeneca in leading the ACLIFORM trial [1] to test the efficacy and safety of a new twice-daily fixed dose combination inhaler using aclidium/formoterol (marketed as Duaklir Genuair in Europe and Duaklir Pressair in US) versus monotherapy and placebo in COPD patients. The trial demonstrated significant improvements in bronchodilation compared with monotherapy and indicated that twice-daily combination therapy would be an effective new treatment option for patients with moderate-to-severe COPD.

Singh was the first to test triple inhaled therapy in COPD [2] and showed the advantages of triple therapy in improved bronchodilation and across a range of physiological parameters, including airway conductance and lung volumes.

Between 2014 and 2017, in collaboration with Chiesi Pharmaceuticals (Parma, Italy), Singh and Vestbo combined three drugs in one inhaler – an inhaled corticosteroid, a long-acting beta-agonist, and a long-acting anticholinergic, now marketed as Trimbow. UoM researchers helped design the registration trials (as EMA had no experience with triple combinations) and carried out the key efficacy trials leading to the first registration of a triple inhaler, 6 months prior to that of the closest competitor. UoM work was built on previous collaborations with the company on

inhalation devices. The TRILOGY trial [3] was a randomised, parallel group, double blind, active-controlled study carried out in 159 sites across 14 countries, showing superiority of the triple combination over a fixed ICS/LABA combination. The TRINITY trial [4] showed superiority of the triple combination over the most sold LAMA, tiotropium, and the related TRIBUTE trial [5] showed superiority over a LAMA/LABA combination. Singh and Vestbo were either first or last author on all 3 pivotal papers.

Singh's expertise in the design, operations and interpretation of triple therapy clinical trials led to UoM involvement in two other pivotal international phase III triple therapy studies: the IMPACT study for Trelegy Ellipta [6] (GlaxoSmithKline (GSK); n=10,355) and the ETHOS study for Breztri Aerosphere (Breztri; n=8,509). Both studies showed a reduction in exacerbations and hospitalisations with triple therapy over ICS/LABA and LAMA/LABA. Importantly, both studies also demonstrated a benefit of the ICS component of triple therapy on reducing mortality.

3. References to the research

1. **Singh, D**, Jones, PW, Bateman, ED, Korn, S, Sera C, Molins, E, Caracta, C, Gil, EG, Leselbaum, A. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulmonary Medicine* 2014 Nov 18;14:178. DOI:10.1186/1471-2466-14-178
2. **Singh D**, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008; 63; 592-8. DOI:10.1136/thx.2007.087213
3. **Singh D**, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, **Vestbo J**. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963-73. DOI:10.1016/S0140-6736(16)31354-X
4. **Vestbo J**, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, **Singh D**. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomized controlled trial. *Lancet* 2017; 389: 1919-29. DOI:10.1016/S0140-6736(17)30188-5
5. Papi A, **Vestbo J**, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, and **Singh D** (2018) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-84. DOI:10.1016/S0140-6736(18)30206-X
6. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, **Singh D**, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *New England Journal of Medicine*. 2018 May 3;378(18):1671-1680. DOI:10.1056/NEJMoa1713901

4. Details of the impact

Context

COPD is the third leading cause of death worldwide with almost 4,000,000 patients dying each year globally. In the UK, approximately 1,200,000 patients are living with COPD, with >100,000 emergency NHS admissions and >100,000 patients diagnosed each year, the burden is substantial. More effective, simpler to use treatments are needed to improve patient adherence to treatment routines and reduce the risk of exacerbations that can impair quality of life, lead to hospitalisation or death.

Pathways to impact

Establishing excellent trial facilities - Singh is the Medical Director of the charity-owned dedicated respiratory clinical trial unit, Medicines Evaluation Unit (MEU, located on the grounds of Wythenshawe Hospital in Manchester) (36 beds, employs >100 people).

Committee membership - Vestbo and Singh sit on the GOLD Science Committee. GOLD works with healthcare professionals and public health officials worldwide to improve treatments of COPD.

Reach and significance of the impact

More effective and simpler treatments available for COPD patients

Aclidinium bromide /formoterol fumarate (Duaklir Genuair) received European EMA approval to treat COPD in December 2014 [Ai,1]. It was approved by US FDA in April 2019 (Duaklir Pressair) [Aii,1]. At the time, it was the only twice daily LAMA/LABA in the US, which included COPD exacerbation data in its prescribing information [Aii].

In July 2017, Chiesi's Trimbow was the first fixed-dose triple combination inhaler for COPD treatment approved in Europe [Bi,3,4]. In March 2019, EMA expanded the label as a treatment for patients with moderate to severe COPD not adequately treated with long acting dual bronchodilation [Bii,5].

Both products are simpler to use than traditional separate inhalers. Chiesi confirmed, COPD "*requires patients to be treated with many drugs that, to date, have to be taken through two or even three inhalers. The possibility of taking all drugs needed by using only one inhaler considerably simplifies the treatment of patients, decreasing the burden on patients and may improve adherence*" [Biii]. Improved adherence improves clinical outcomes, including exacerbations, which impair quality of life, lead to hospitalisation or death.

Commercial and industrial Impacts

AstraZeneca reported European sales of USD26,000,000 in 2015 following EMA authorisation of Duaklir Genuair. From 2016, it was available in 25 countries across Europe, Asia and Latin America [Ci]. By 2018, European sales had risen to USD91,000,000 [Cii].

Chiesi said of its Trimbow collaboration, UoM "*has been and remains fundamental to the success of these product developments in providing world-leading expertise in shaping the clinical studies, leading their execution and in the intelligent interpretation of their findings*." [D]. In 2018 Trimbow generated sales of EUR40,000,000 and was commercially available in 19 European countries, as at 31 December 2018 [Ei]. Following the label expansion based on TRIBUTE [5], Trimbow sales in 2019 totalled EUR127,000,000 [Eii].

Impact on UK guidelines

In December 2018, NICE updated guidelines for COPD diagnosis and management. NICE stated "*The evidence showed that, compared with other dual therapy combinations and with monotherapy, LAMA+LABA provides the greatest benefit to overall quality of life, is better than other inhaled treatments for many individual outcomes… is the most cost-effective option*" and "*minimising the number and types of inhalers prescribed will make it easier for people to use their inhalers correctly"* [Fi]. ACLIFORM was part of the evidence reviewed [Fii,1].

In July 2019, NICE recommended triple therapy as an option for some patients, noting, "*from the economic evidence, using a single inhaler device was more cost effective*" [Fi,3,5]. TRILOGY and TRIBUTE provided clinical evidence [Fiii].

Impact on global guidelines

GOLD's 2020 strategy report confirmed "*Combination treatment… reduces symptoms compared to monotherapy*" and "*reduces exacerbations compared to monotherapy*". GOLD cited ACLIFORM [Gi, 1]. GOLD stated triple therapy "*may improve lung function, patient reported outcomes and prevent exacerbations*." [Gi,2,3].

GOLD's Executive Director confirmed, "*In a 9-month period in 2019, the GOLD website recorded 337,711 hits from 211 countries (28,902 from the UK…), the most recent GOLD strategy document was downloaded 238,536 times demonstrating the reach of our documents and the research cited within them. University of Manchester research on dual and triple inhalers has been critical in progressing the treatment of COPD to more effective and simpler to use inhalers, marking an important change and benefit for COPD patients… The work of Singh and Vestbo on inhaled treatments were important factors in our 2017 and 2019 major revisions, and the updated 2020 guidance"* [H].

Australian and New Zealand Guidelines for COPD 2020 (COPD-X Plan), noted that Genuair was one of four LAMA/LABA devices available in Australia, citing ACLIFORM as one of two trials for this treatment [Gii,1]. Regarding triple therapy, it stated "*triple therapy results in a lower rate of moderate or severe COPD exacerbations, and better lung function*" and "*Triple therapy delivered in a single inhaler is convenient for patients and may improve adherence*" [Gii,3,4,5].

Increasing triple therapy options for patients

As a result of the IMPACT trial, both FDA (April 18) and EMA (November 18) expanded their authorisations for the triple inhaler Trelegy Ellipta, to include a broader population of COPD patients [Ii, Iii, 6]. In EU, it was the first single inhaler triple therapy to be specifically indicated for COPD patients, not adequately treated with dual bronchodilation [Iii]. Trelegy was the first triple inhaler administered by dry powder inhaler, benefiting patients who use this type of inhaler more effectively. In 2018, the product was launched in 26 countries [Ji], increasing to 40 in 2019 [Jii]. GSK reported sales of GBP156,000,000 in 2018 [Ji], rising to GBP518,000,000 in 2019 [Jii]. In July 2020, AstraZeneca's Breztri Aerosphere was approved by FDA based on the results of ETHOS, thereby bringing a new product to US patients, offering them broader treatment options [Iiii].

5. Sources to corroborate the impact

A. Duaklir Genuair/Duaklir Pressair - ***regulatory approvals based UoM reference 1 (ACLIFORM).***

   i. AstraZeneca press release 'Duaklir Genuair approved in the European Union for chronic obstructive pulmonary disease' 24 November 2014 – ***confirms European (EMA) approval.***

   ii. Drugs.com article 'FDA Approves Duaklir Pressair' 1 April 2019 – ***confirms US (FDA) approval.***

B. Trimbow - ***EC regulatory approvals based on UoM references 3,4,5 (TRILOGY, TRINITY, TRIBUTE).***

   i. Chiesi press release 'Chiesi Group receives the European Marketing Authorisation for Trimbow' 24 July 2017 – ***confirms European (EMA) approval.***

   ii. Chiesi press release 'Chiesi extrafine formulation triple therapy combination Trimbow… gains expanded Chronic Obstructive Pulmonary Disease (COPD) indication in Europe' 6 March 2019 - ***confirms expanded European (EMA) authorisation.***

   iii. Chiesi press release 'Trimbow is the first triple combination in a single inhaler for the treatment of COPD to receive positive opinion from the CHMP in Europe' 22 May 2017 - ***confirms EMA's Committee for Medicinal Products for Human Use (CHMP)'s positive opinion.***

C. AstraZeneca Annual Reports - ***showing sales figures for Duaklir Genuair.***

   i. AstraZeneca Annual Report 2016 - ***showing sales figures and confirming Duaklir Genuair was commercially available in 26 countries.***

   ii. AstraZeneca Annual Report 2018 - ***showing growth of Duaklir Genuair sales figures.***

D. Testimonial from Head Corp Drugs Development and Vice President and Director R & D, Chiesi, 16 January 2020 - ***confirming importance of UoM role and expertise in Trimbow product development.***

E. Chiesi Annual Reports - ***showing details for Trimbow.***

   i. Annual report 2018 - ***showing sales figures and confirming Trimbow was commercially available in 19 European countries.***

   ii. Annual report 2019 - ***showing growth of Trimbow sales figures.***

F. UK NICE guideline NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management.

   i. NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 5 December 2018 - ***stating benefits of dual therapy and recommending triple therapy for some patients.***

   ii. NICE guideline NG115 Evidence Review F- Inhaled Therapies, December 2018 - ***cites UoM reference 1.***

   iii. NICE guideline NG115 Evidence Review I- Inhaled Triple Therapy July 2019 – ***cites UoM references 3 & 5.***

G. Global guidelines – ***confirming benefits of dual and triple therapies.***

   i. GOLD Report 2020. Global Strategy for the Diagnosis, Management, and Prevention of COPD - ***cites UoM references 1,2,3.***

   ii. Australian and New Zealand Guidelines for the Management of COPD, February 2020 - ***cites UoM references 1,3,4,5.***

H. Testimonial from Executive Director, GOLD and Chairman of the GOLD Board of Directors, 8 September 2020 - ***stating importance of UoM research to GOLD guidance.***

I. **Approvals for other triple therapies** (Trelegy, Ellipta and Breztri Aerosphere)

   i. Drugs.com article 'Once Daily Trelegy Ellipta Gaines Expanded Indication in the US for the Treatment of Patients with COPD' 24 April 2018 - ***confirming Trelegy Ellipta's US (FDA) approval, based of UoM reference 6 (IMPACT).***

   ii. GSK press release 'Once-daily Trelegy Ellipta gains expanded COPD indication in Europe' 9 November 2018 - ***confirming Trelegy Ellipta's European (EMA) Approval, based of UoM reference 6 (IMPACT).***

   iii. Drugs.com article 'FDA Approves Breztri Aerosphere' 24 July 2020 - ***confirming Breztri Aerosphere's US (FDA) Approval, based on ETHOS study*** (Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *New England Journal of Medicine*. 2020 Jul 2;383(1):35-48) ***co-authored by UoM's Singh.***

J. GSK Annual Reports - ***including details on Trelegy Ellipta.***

   i. GSK Annual Report 2018 - ***confirming number of countries Trelegy Ellipta was launched in and sales figures for 2018.***

   ii. GSK Annual Report 2019 - ***confirming number of countries Trelegy Ellipta was launched in and sales figures for 2019.***