Institution: Newcastle University		
Unit of Assessment: UoA1		
Title of case study: Ataluren: the first approved oral treatment for Duchenne muscular dystrophy		
Period when the underpinning research was undertaken: 2006-2010		
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:**
Emerita Prof Katie Bushby	Acting Research Chair of Neuromuscular Genetics	25/9/19 to 31/5/18
Dr Michela Guglieri	Clinical Senior Lecturer/Honorary Consultant	1/12/06 to present
Prof Volker Straub	Harold Macmillan Professor of Medicine	1/11/03 to present
Dr Michelle Eagle	Consultant Physiotherapist	1/6/09 to 23/8/16
Prof Hanns Lochmüller	Professor of Experimental Myology	1/7/07 to 31/12/17
Dr Catherine Bladen	Research Associate	1/3/13 to 11/5/15
Dr Karen Rafferty	TREAT NMD Co-ordinator and Project Manager	5/10/09 to 31/12/14
Dr Brigitta von Rekowski	Project Manager	1/3/08 to 30/11/13
Dr Stephen Lynn	Project Manager	5/3/07 to 29/1/17
Mrs Emma Heslop	DMD Clinical Research Hub Manager	14/12/06 to present
Mr Sunil Rodger	Communications Officer	May 2010 to 30/9/14
Prof Annemieke Aartsma-Rus	Visiting Professor	1/1/13 to 30/4/18
Period when the claimed impact occurred: 2014-present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Duchenne muscular dystrophy (DMD) has no cure. 10% of patients carry a stop codon mutation in the dystrophin gene that is potentially treatable. Newcastle University was instrumental in the development of the first large international multicentre study in DMD (double blind placebo control study with ataluren in 174 patients at 37 sites across 11 countries) which found a positive change in the 6-minute walking distance (6MWD) of patients taking 40 mg/kg/day doses versus placebo. This data was the basis for the EMA granting ataluren conditional marketing authorisation in 2014, which was then followed by NICE approval through a Management Access Agreement (MAA) in the UK in 2016. Additionally, 279 patients are now receiving ataluren as part of regular clinical practice.

2. Underpinning research

Duchenne muscular dystrophy (DMD) and current management

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy, though is still a relatively rare disease. It is a severe, progressive X-linked recessive disorder that mainly affects males. In the UK, about 100 boys are born with DMD each year, with approximately 2,500 boys currently living with the condition.[1] Approximately 10% of patients carry a nonsense mutation in the dystrophin gene, resulting in a premature stop codon and ultimately leading to a truncated, non-functional dystrophin protein which affects the skeletal and cardiac muscle fibres (R6). The main symptoms of DMD are a gradual decline in motor function, cardiac and respiratory impairment ultimately leading to death, usually before the age of 30. There is no cure for DMD and the few treatment options available, such as corticosteroid treatment, are associated with significant adverse effects.

[1] http://www.nhs.uk/conditions/Muscular-dystrophy/Pages/Introduction.aspx

Development of Translarna

PTC Therapeutics developed ataluren in 2003, the "first-in-class" orally bioavailable drug enabling ribosomal readthrough of premature stop codons.[2] That is, production of functional dystrophin protein by "skipping" the premature stop codon caused by the nonsense mutation. Following a successful proof-of-concept Phase 2a clinical trial demonstrating dystrophin expression in skeletal muscle of patients with a nonsense mutation in the dystrophin gene[3], PTC Therapeutics approached Newcastle University to be one of the leading sites for the delivery of an international randomised, double-blind, placebo-controlled Phase 2b registration-directed study (R1, ClinicalTrials.gov ID: NCT00592553). This was the first ever large, international registration study for a drug targeting DMD, and Newcastle PIs were integral to the study design and patient evaluation.

PTC Therapeutics approached Newcastle because of the long-standing clinical expertise of the PIs, internationally recognised in the DMD field (R2, R3). Additionally Newcastle has a leading role in TREAT NMD, a well-established global academic network focused on advancing research in rare neuromuscular diseases. TREAT NMD was established in 2007 with its coordinating centre at Newcastle University, led by Professor Bushby and Professor Straub. The network comprises over a hundred research centres and patient organisations as well as independent academics and patient representatives, creating the robust collaborative infrastructure necessary to deliver an international clinical trial (R4, R5, R6).

Newcastle-led ataluren clinical trial

The international ataluren study (R1) ran across 37 sites in 11 countries and tested the efficacy and safety of 2 doses of ataluren (40 and 80mg/kg/day) compared against placebo. Ataluren or placebo were given to 174 male patients aged ≥5 years with a dystrophin nonsense mutation and the ability to walk ≥75m unassisted during the 6-minute walk test (6MWT). The 6MWT records the distance patients can walk in 6 minutes and was the primary outcome measure of the study. As ambulation is lost over time in DMD patients, increasing the time until loss of ambulation is the major goal of intervention measures. Worsening of the 6MWT was defined as a consistent 10% reduction in ability from baseline. After 48 weeks of treatment, patients taking 40mg/kg/day of ataluren showed increased retention of their motor function compared to the placebo group, measured as decline in the distance covered during the 6MWT (R1). Patients on the same dose regimen also showed meaningful differences across secondary outcome measures (including time to climb/descend stairs, run/walk 10m, wheelchair use and muscle strength) compared to placebo. Notably, the risk of falling (a significant contributor to the loss of ambulation) was also reduced in patients receiving ataluren compared with placebo.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. **Bushby K,** … **Eagle M**, … FOR THE PTC124-GD-007-DMD STUDY GROUP (2014) Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle & Nerve*. 50(4):477-487. DOI**:** 10.1002/mus.24332. FWCI: 11.01.

R2. **Eagle M**, **Baudouin SV**, Chandler C, Giddings DR, Bullock R, **Bushby K**, (2002) Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders.* 12:926–929. DOI: 10.1016/S0960-8966(02)00140-2. FWCI: 6.19.

R3. **Bushby K**, … for the DMD Care Considerations Working Group (2010) Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *The Lancet Neurology*. 9(2):177-189. DOI: https://doi.org/10.1016/S1474-4422(09)70272-8. FWCI: 12.56.

R4. **Bladen CL**, **Rafferty K**, **Straub V**, … **von Rekowski B**, **Lynn S, Heslop E**, Gainotti S, Taruscio D, Kirschner J, Verschuuren J, **Bushby K**, Béroud C, **Lochmüller H**. (2013) The

[2] http://www.ptcbio.com/en/pipeline/ataluren-translarna/

[3] Finkel RS, et al. (2013) Phase 2a study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. *PLoS ONEOpen Access*. 8(12). DOI: 10.1371/journal.pone.0081302.

TREAT-NMD Duchenne muscular dystrophy registries: conception, design, and utilization by industry and academia. *Human Mutation*. 34(11):1449-57. DOI: 10.1002/humu.22390. FWCI: 3.35.

R5. **Rodger S**, **Lochmüller H**, Tassoni A, Gramsch K, König K, **Bushby K**, **Straub V**, Korinthenberg R, Kirschner J. (2013) The TREAT-NMD care and trial site registry: an online registry to facilitate clinical research for neuromuscular diseases. *Orphanet Journal of Rare Diseases*. 8(171). DOI: 10.1186/1750-1172-8-171. FWCI: 1.41.

R6. **Bladen CL**, … **Straub V**, **Bushby K**, Verschuuren J, Aartsma-Rus A, Béroud C, **Lochmüller H**. (2015) The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Human Mutation*. 36(4):395-402. DOI: 10.1002/humu.22758. FWCI: 10.36.

4. Details of the impact

PTC Therapeutics recognise the key role Newcastle University played in the ataluren clinical trial confirming that "*The role of the research led by Newcastle University and the participation in the PTC clinical trials was integral to the success of Translarna [ataluren] and PTC Therapeutics are proud of this close collaboration.*" (EV1).

Impact on policy

In August 2014 ataluren (marketed as Translarna) was granted conditional marketing authorisation throughout the European Union by the EMA for the treatment of ambulatory DMD patients older than 5 years with nonsense mutations (EV2). As stated by PTC Therapeutics "*The Newcastle University-led trial, indicated above* (R1)*, was essential for the conditional marketing authorisation granted to Translarna by the European Medicines Agency in 2014.*" (EV2). The summary of the EMA approval states "*On 22 May 2014, following a re-examination procedure, the Committee for Medicinal Products for Human Use (CHMP), adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Translarna intended for the treatment of Duchenne muscular dystrophy (DMD).*" It went on to detail that the Newcastle-authored clinical trial (R1) was a key part of supporting the authorisation "*Translarna was investigated in a pivotal study involving 174 patients with DMD. The results showed some evidence of efficacy of Translarna in slowing down the loss of walking ability in DMD patients.*" (EV2). Successful EMA authorisation prompted other countries including Israel, South Korea (both 2015), Chile (2018) and Brazil (2019) to grant Translarna marketing authorisation (EV3).

In September 2015 NICE, published Highly Specialised Technology Committee Papers (ID 428) (EV4), again citing R1 several times as the evidence base for its assessment of Translarna, highlighting the importance of the clinical trial in its assessment of the drug.

- Page 18 "*The safety and efficacy of ataluren have been demonstrated in a Phase 2b placebo-controlled, randomised, double-blinded, international study, which forms the primary evidence base for this submission (Study 007, Bushby, 2014 [R1]).*"
- Page 44-45: "*Ataluren is the first therapy addressing the underlying cause of nmDMD [nm = nonsense mutation] that has been shown to offer clinically meaningful and statistically significant changes in parameters that assess ambulation and activities of daily living (Bushby, 2014, [R1]), thereby changing the course of this devastating condition.*"
- Page 66: "*Out of these 281 studies, only one RCT evaluating ataluren met the eligibility criteria for the clinical systematic review: PTC124-GD-007-DMD (Study 007; PTC Therapeutics, 2012, [Study 007 is R1]).*"

Following a successfully negotiated Managed Access Agreement (MAA) with PTC Therapeutics by NHS England, Translarna was approved by NICE in July 2016 (EV5). The final NICE evaluation determination approved the use of Translarna for ambulatory DMD patients with nonsense mutations who are older than 5 years. In particular the evaluation noted on page 38: "*The committee acknowledged the potential wider societal benefits of ataluren treatment proposed by the company and patient experts, including the ability to contribute to society, continue education and spend more time with friends and family. It heard from the patient experts that, because*

ataluren is expected to delay the loss of walking, it will enable people with DMD to maintain their independence for longer and this will lead to cost savings."

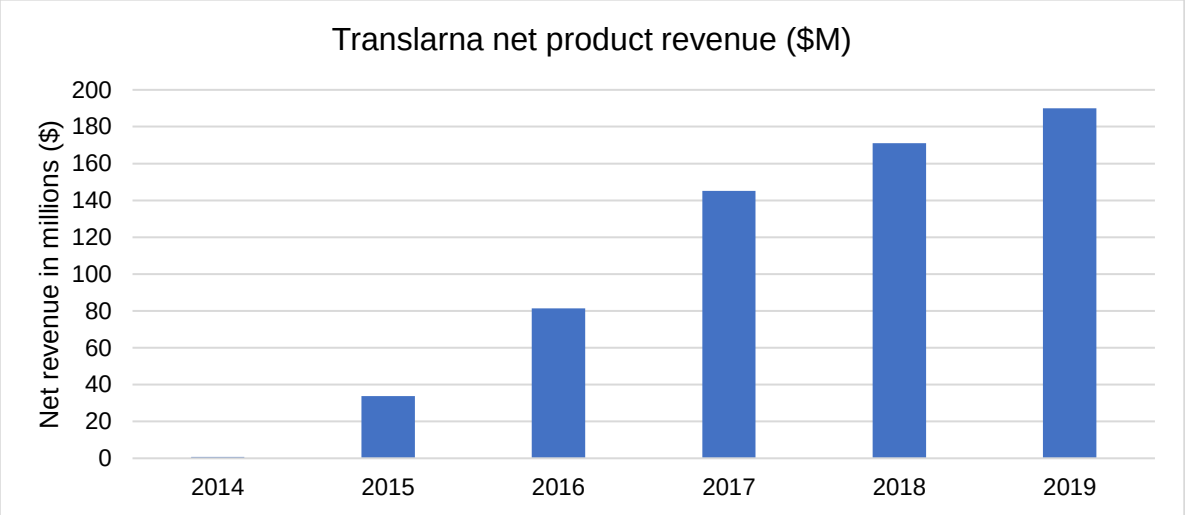
Impact on patients

In a statement, a clinical member of the ataluren MAA oversight committee confirms that "*Under the MAA, 97 patients are currently receiving Translarna in England outside of the clinical trial setting, representing practically all of those eligible in England.*" (EV6). A full report of outcomes will be submitted to NICE in 2021, but they confirm that "*currently all patients are expected to show a slower decline in motor function and possible delay in respiratory function decline*" (EV6).

Internationally PTC Therapeutics confirm that "*Post-marketing surveillance of patients taking Translarna is underway through the STRIDE Registry (Strategic Targeting of Registries and International Database of Excellence)*" (EV1). Established as a requirement of Translarna's EMA conditional approval, the STRIDE registry tracks real-world clinical practice of Translarna (EV1, EV7). It is a multi-centre collaborative partnership between PTC Therapeutics and TREAT-NMD, itself coordinated through Newcastle University (EV1). Interim results from the STRIDE registry show that patients remained ambulatory for longer (on average until 14.5 years of age) and were older than patients not treated with Translarna when functional decline began (EV7). As of July 2020 there are 279 patients from 13 countries receiving Translarna and being monitored through the STRIDE registry (EV1), including the 97 UK patients monitored under the MAA.

Impact on PTC Therapeutics (manufacturers of Translarna)

PTC Therapeutics reported a net Translarna revenue of $190 million at the end of 2019 (EV7), the highest reported since its approval in 2014 (see graph). A further combined $79.1 million for Q1 and Q2 has also been reported for 2020, though unfortunately a significant roll-out into Brazil in Q3 has been impacted by COVID-19 (EV9).



5. Sources to corroborate the impact

EV1. Letter of support from PTC Therapeutics Country Manager, UK & Ireland, speaking to the close link between Newcastle University and the development of Translarna. PDF.

EV2. EMA marketing authorisation – "Summary of Approval". PDF. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-translarna_en.pdf

EV3. PTC Therapeutics 2019 Annual Report. PDF. https://ir.ptcbio.com/static-files/cc04e540-756a-4e3e-9164-bd8dadcc6196

EV4. Highly Specialised Technologies Evaluation, 'Ataluren for treating Duchenne muscular dystrophy caused by a nonsense mutation in the dystrophin gene [ID 428]' Committee Papers. PDF.

EV5. NICE Final evaluation determination for ataluren. PDF. https://www.nice.org.uk/guidance/hst3

EV6. Letter of support from the Consultant neuromuscular speciality lead (Great Ormond Street Hospital) and clinical member of the ataluren MAA oversight committee. PDF available on request.
EV7. Muntoni et al. (2019) Ataluren use in patients with nonsense mutation Duchenne muscular dystrophy: patient demographics and characteristics from the STRIDE Registry. *Journal of Comparative Effectiveness Research.* 8(14):1187–1200. DOI: 10.2217/cer-2019-0086.
EV8. PTC Therapeutics 2019 annual report. PDF. https://ir.ptcbio.com/node/12651/pdf
EV9. PTC Therapeutics 2020 Q2 report. PDF. https://ir.ptcbio.com/node/13071/pdf