Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: Novel Therapies to Treat and Potentially Cure Haemophilia		
Period when the underpinning research was undertaken: 2010 - 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:**
1) John Pasi	1) Professor of Haemostasis and Thrombosis	1) 08/2003 - present
2) Dan Hart	2) Senior Clinical Lecturer in Haematology	2) 09/2009 - present
3) Louise Bowles	3) Consultant Haematologist	3) 09/2008 - present
4) Vickie McDonald	4) Consultant Haematologist	4) 09/2017 - present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Research by Queen Mary's Prof. Pasi has revolutionised treatment for haemophilia and also made it more accessible, while offering a potential cure for the condition. Pasi's group has led clinical development programmes for new treatments that reduce the number of clotting factor infusions required to manage the disease. Typically, infusions are frequent and burdensome for both patients and healthcare systems, while also being either impractical or inaccessible for 75% of the global population of haemophiliacs. Pasi's novel therapies reduce the need for infusions by up to one-third in haemophilia A and half in haemophilia B. These therapies have been approved and licensed globally since 2014, and have been recommended in UK guidelines since 2016. Pasi has also developed a clinical programme for a gene therapy for severe haemophilia A, which received European Medical Agency approval in 2016. Pasi's developments overcome the problem of accessibility of treatment at a global level, and help directly alleviate the suffering and burden experienced by patients with severe forms of the disease.

2. Underpinning research (indicative maximum 500 words)

Haemophilia is a rare blood disease that affects about 7 in 100,000 people (around 36,000 people in Europe, mostly men). The condition is caused by defects in genes associated with coagulation and exists in two types: Haemophilia A (caused by a defect in the production of coagulation factor VIII) and Haemophilia B (caused by a far less common defect in the production of factor IX).

Treating severe haemophilia currently involves regular infusions of clotting factor concentrate, given every alternate day for haemophilia A and at least twice a week for haemophilia B. Although this treatment is regarded as state-of-the-art, it does not completely eliminate bleeding risk and is a significant treatment burden for men with severe haemophilia. Moreover, most (75%) of the world's haemophiliac population cannot access treatment— and, even if they did, in many places, the therapies would be entirely impracticable due to the demanding nature of the treatment regime. Therefore, there is a need for therapies that are less invasive — such as less frequent infusions, or one-off approaches such as gene therapy — to enable simpler, less burdensome treatment options for patients globally.

Development of bioengineered coagulation factor proteins VIII and IX

Coagulation factor proteins can now be bioengineered with a potentially prolonged half-life, which would mean less frequent treatments for patients. Pasi worked on previous clinical trials to develop the first factor IX proteins in the 1990s. Thus, due to this expertise and experience, Pasi co-led a more recent multi-centre global programme to develop Fc fusion proteins for coagulation factors VIII and IX. The new clinical trials — conducted in collaboration with Jerry Powell at the University of California, Davis and sponsored by Biogen Inc. — began in 2010 and became the world's largest phase 3 programmes in haemophilia [3.1, 3.2]. The trials led to a change in treatment regime for patients with the disease, reducing the numbers of infusions required by

one-third in haemophilia A patients and half in haemophilia B patients, thereby helping alleviate the issues of treatment burden and accessibility.

Development of gene addition therapy using AAV5-FVIII

Gene therapies hold great potential in treating various conditions. Pasi worked with BioMarin Pharmaceutical Inc. to develop a clinical research programme for severe haemophilia A, a gene addition technology using the vector AAV5-FVIII (adeno-associated virus serotype 5 (AAV5) encoding a B-domain-deleted human factor VIII). After being given once to the patient via an injection into a vein, the virus carries the factor VIII gene into the liver cells, enabling them to produce the missing factor VIII. The adeno-associated virus does not cause disease in humans. The programme had outstanding results [3.3, 3.4]: factor VIII levels normalised in 11 of 13 patients treated at therapeutic dose, with all patients coming off factor replacement therapy. This work offers the real prospect of a 'cure' for severe haemophilia, especially given that further follow-up data has shown continued effectiveness after three years [3.5].

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

[3.1] Powell, J. S., Pasi, K. J., Ragni, M. V., Ozelo, M. C., Valentino, L. A., Mahlangu, J. N., Josephson, N. C., Perry, D., Manco-Johnson, M. J., Apte, S., Baker, R. I., Chan, G. C., Novitzky, N., Wong, R. S., Krassova, S., Allen, G., Jiang, H., Innes, A., Li, S., Cristiano, L. M., Goyal, J., Sommer, J. M., Dumont, J. A., Nugent, K., Vigliani, G., Brennan, A., Luk, A. & Pierce, G. F. (2013). Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *The New England Journal of Medicine, 369*, 2313-2323. https://doi.org/10.1056/NEJMoa1305074

[3.2] Mahlangu, J., Powell, J. S., Ragni, M. V., Chowdary, P., Josephson, N. C., Pabinger, I., Hanabusa, H., Gupta, N., Kulkarni, R., Fogarty, P., Perry, D., Shapiro, A., Pasi, K. J., Apte, S., Nestorov, I., Jiang, H., Li, S., Neelakantan, S., Cristiano, L. M., Goyal, J., Sommer, J. M., Dumont, J. A., Dodd, N., Nugent, K., Vigliani, G., Luk, A., Brennan, A. & Pierce, G. F. (2014). Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood, 123* (3), 317-325. https://doi.org/10.1182/blood-2013-10-529974

[3.3] Rangarajan, S., Walsh, L., Lester, W., Perry, D., Madan, B., Laffan, M., Yu, H., Vettermann, C., Pierce, G. F., Wong, W. Y. & Pasi, K. J. (2017). AAV5-Factor VIII Gene Transfer in Severe Hemophilia A. *The New England Journal of Medicine, 377* (26), 2519-2530. https://doi.org/10.1056/NEJMoa1708483

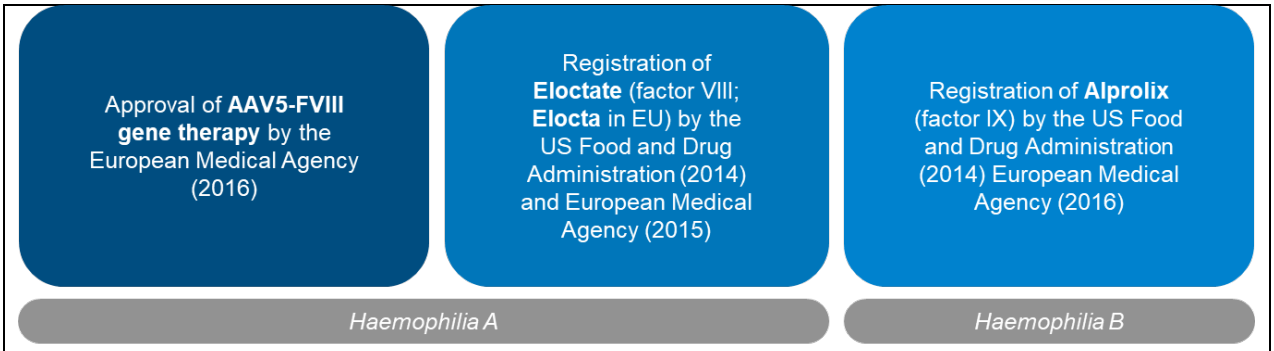
[3.4] Pasi, K. J., Rangarajan, S., Mitchell, N., Lester, W., Symington, E., Madan, B., Laffan, M., Russell, C. B., Li, M., Pierce, G. F. & Wong, W. Y. (2020). Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. *New England Journal of Medicine*, 382, 29-40. https://doi.org/10.1056/NEJMoa1908490

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

Research by Queen Mary's Prof. Pasi has provided evidence of the clinical efficacy and safety of novel, cutting-edge therapies for treating haemophilia. This has resulted in life-changing new treatments being brought to market. Based on Pasi's findings, UK guidelines for treatment of haemophilia have been updated to recommend the use of these therapies in routine clinical practice, in turn providing better care, prognosis, and quality of life to patients (and families) who would typically be debilitated by the condition.

Uptake of the new therapies into clinical guidelines and practice

The clinical trials and multi-centre global studies led by Pasi demonstrate that the newly developed coagulation factor proteins for factor VIII and factor IX are safe and effective, and also offered evidence of the efficacy of AAV5-FVIII gene therapy (across phase 1/2 programmes and first part of phase 3 studies). This work directly enabled [5.1-5.5]:



Prof. David Lillicrap from the Department of Pathology and Molecular Medicine at Queen's University, Canada said "to prevent spontaneous episodes of bleeding, patients with severe haemophilia have had to inject their substitution clotting factor 2-3 times each week to maintain protective levels of the missing protein. Thus, although this treatment is safe and effective the quality of life of these patients left a lot to be desired" [5.6]. However, Eloctate and Alprolix make it possible to "reduce the number of infusions while the bleeding rate remains comparable with that of more frequent infusions with classic FVIII and FIX products. This improves the adherence and quality of life for patients, and for children who have difficult venous access it might reduce the need for intravenous catheters during the first years of life," according to the Director of the PedNet Haemophilia Research Foundation, Dr. H. Marijke van den Berg [5.7].

In 2016, Pasi also helped shape the UK's Haemophilia Centres' Doctors' Organisation national guidelines, which now recommend the use of these therapies in routine clinical practice [5.8].

Improving patients' lives

By making extended half-life therapies available on a wider scale, Pasi has helped reduce the numbers of infusions required by patients to manage their condition by one-third in haemophilia A and half in haemophilia B.

For patient Jack [5.9], bleeding centred around his ankles would usually mean two or three days of rest, treatment and recuperation. His health was particularly worrisome for his family and girlfriend, and he was already being treated for arthritis as a result of repeated ankle bleeds. However, since starting on AAV5-FVIII treatment Jack has not needed any treatment for bleeding, saying "The treatment has given my family, friends and girlfriend the freedom not to worry. It's a massive change for them because they know I'm protected now."

Another patient, Darren, was also suffering from co-morbidities related to haemophilia bleeds — namely arthritis and damage in some joints. "It was such a relief to know [these] wouldn't continue to get worse," says Darren, going on to state that "the treatment has changed my life considerably." Within a few days of starting the AAV5-FVIII treatment, Darren's coagulation factor levels had already increased. "I started noticing that minor knocks weren't bruising like they used to," he said. Darren gives an example of the improvement of his quality of life: "Just a week after treatment, I was at work when a child accidently rammed me with a shopping trolley. I thought 'oh no, that's really going to be bad', and I was prepared for a bad ankle bleed. But instead of needing four days of bed rest it healed within 24 hours. I couldn't believe it. It's brilliant not having to worry all the time whether I might bump or scratch myself. There's no more need to panic." Darren's factor VIII levels continued to rise and a month later, his readings were up to 90% of normal levels [5.10].

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

[5.1] U.S. Food and Drug Administration. (2014). *June 6, 2014 Approval Letter- Eloctate*.

[5.2] European Medicines Agency. (2015). *Assessment report: ELOCTA*.

[5.3] U.S. Food and Drug Administration. (2014). *March 28, 2014 Approval Letter – ALPROLIX.*

[5.4] European Medicines Agency. (2016). *Assessment report: Alprolix*.

[5.5] European Medicines Agency. (2016). *Public summary of opinion on orphan designation: Adeno-associated viral vector serotype 5 containing a B-domain deleted variant of human coagulation factor VIII gene for the treatment of haemophilia A*.

[5.6] D. Lillicrap. Professor in Molecular Haemostasis. *Queen's University, Canada* (testimonial letter, 8 January 2019). [Corroborator 1]

[5.7] H. M. van den Berg. Director. *PedNet Haemophilia Research foundation* (testimonial letter, 19 January 2019). [Corroborator 2]

[5.8] Collins, P., Chalmers, E., Chowdary, P., Keeling, D., Mathias, M., O'Donnell, J., Pasi, K. J., Rangarajan, S. & Thomas, A. (2016). The use of enhanced half-life coagulation factor concentrates in routine clinical practice: guidance from UKHCDO. *Haemophilia, 22*, 1-12. https://doi.org/10.1111/hae.13013

[5.9] NIHR. (2020, 31 January). Case study: Jack living life to the full after Haemophilia A 'cure' following study. https://local.nihr.ac.uk/case-studies/jack-living-life-to-the-full-after-haemophilia-a-cure-following-study/23909. Accessed 10 December 2020.

[5.10] Berrill, L. (2020, 26 February). Man effectively 'cured' of life-threatening haemophilia following clinical trial. Epping Forest Guardian. https://www.eppingforestguardian.co.uk/news/18262501.man-effectively-cured-life-threatening-haemophilia-following-clinical-trial/. Accessed 10 December 2020.