Institution: King's College London		
Unit of Assessment: 4		
Title of case study: Developing innovative new drugs to prevent migraine		
Period when the underpinning research was undertaken: 2014 – 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:**
Professor Peter Goadsby Dr Phillip Holland	Professor of Neurology Senior Lecturer Neuroscience	2014 - Present 2013 - Present
Period when the claimed impact occurred:		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Migraine affects over one billion people globally and is debilitating, impeding the ability of sufferers to work or perform daily tasks. Previously used generic medications cause side effects so severe that ~43% of patients discontinue their treatment. King's College London research underpinned the development and regulatory approval of the first class of medications that prevent migraine in previously untreatable patients; specifically, Amgen's Erenumab, TEVA pharmaceuticals' Fremanezumab and Eli-Lily's Galcanezumab. King's had a substantial role in clinical trials of the new antibody therapies, with fewer side effects, and reducing the number of monthly migraine days by as much as 50% for typically 50% of those experiencing episodic or chronic migraine, or cluster headache. In 2018 this led to FDA and EMA approvals for use of the migraine therapies in the US and Europe. The new therapies are already being used to treat 500,000 patients in the US, and in 2020, NICE approved Fremanezumab and Galcanezumab for use by the NHS, initially available to an estimated 5,300 previously untreatable migraine sufferers, resulting in dramatic improvements in quality of life. The development of a second novel class of small molecule drugs has, in 2020, led to two further drugs gaining FDA approval (Rimegepant, Ubrogepant) and demonstration that this class is unlikely to produce medication overuse headache.

2. Underpinning research

Migraine is the most common disabling neurological disorder. Globally over one billion people suffer from migraine, and it is three times more prevalent in women than men. Migraine attacks involve severe headaches often accompanied by nausea and vomiting, and cause disruption to a sufferer's daily life. Migraine-related absenteeism and lost productivity is responsible for 86 million equivalent lost workdays per year in the UK alone at a cost of approximately £8.8 billion per annum. The cost of headache in Europe is estimated at €173 billion per annum, €111 billion of which is attributed to migraine.

There was a severe unmet need for new therapies tailored specifically to migraine. There are two broad categories of migraine, in which sufferers experience either severe attacks frequently (chronic), or less frequent attacks (episodic). Another headache type, cluster headache, involves excruciating attacks of head pain daily over a period of weeks or months. Previously, there had never been a medicine developed specifically to prevent migraine: all were repurposed drugs originally developed for conditions such as epilepsy or high blood pressure. Typically, the older drugs work slowly; are not effective in all migraine sufferers; and when effective, ~43% of people have such severe side effects that they stop taking the treatment.

Professor Goadsby has, for more than 30 years, led a programme of translational migraine research from identifying a new target for migraine drugs to developing two entirely new drug classes. In early work in Australia, the team identified a small protein, calcitonin gene-related peptide (CGRP), which is released by the nervous system of sufferers during migraine attacks; this discovery has proved transformational for migraine research globally. The work suggested that reducing the amount of CGRP released may reduce the likelihood of a migraine attack. Subsequent research by this group, first at the University of California and since 2014 at King's,

has focused on creating novel drugs which do exactly this. Specifically, King's research has unlocked the potential of two novel migraine drug classes: the first using antibodies that target CGRP or its receptor; the second based on small molecules, CGRP receptor antagonists ('gepants'). This work led to the first drugs specifically designed to prevent migraine.

Demonstrating that antibody therapies can safely and effectively target CGRP to prevent episodic migraine. Following the commercial development of two specific antibodies that bind to CGRP or its receptor (AMG334, ALD304), studies by King's and US collaborators, with Alder Biopharmaceuticals and Eli Lilly, showed that CGRP could be targeted safely and effectively using antibody therapies. In two Phase II randomised placebo controlled clinical trials run by the collaborating group, there were no safety concerns for the 163 and 483 participants who experienced severe migraine **(1, 2)**. Preliminary indication showed that the number of migraine days per month was reduced when treated with either antibody therapy **(1, 2)**.

King's played a critical role in clinical trials for the novel migraine drug Erenumab, showing effective treatment of episodic migraine. Following an initial trial establishing the safety and efficacy of the antibody drug Erenumab (Amgen), King's led a phase 3 clinical trial which demonstrated a 50% or greater reduction in the mean number of migraine days per month for 43.3% - 50% of patients (dose-dependent) **(3)**. King's researchers then collaborated on the design and execution of large phase 2 multi-centre trials that established the long-term safety of the drug over 3 years in 253 patients (79% of whom were women) **(4)**. In both trials Erenumab reduced the effects of migraine on daily activities and also reduced some of the side effects from previous medications, such as nausea and vomiting.

King's collaborated on clinical trials establishing that the novel drug Fremanezumab, can preventively treat chronic migraine, safely and long term. King's collaborated on a multi-centre trial of over 1000 patients who were experiencing an average of 13 days of migraine each month. They were given either placebo or a monthly or quarterly dose of Fremanezumab (TEVA pharmaceuticals). Fremanezumab reduced the number of migraine days by 4.3 - 4.6 mean days per month (administered quarterly or monthly, respectively) **(5)**. For 38% of patients treated quarterly and 41% of patients treated monthly, the number of days on which they experienced migraine was at least halved. King's then led a trial demonstrating that reduction in both migraine days and side effects was maintained over 12 months **(6)**.

King's contributed to clinical trials of the novel drug Galcanezumab for the preventive treatment of chronic migraine, and demonstrated effective treatment of cluster headache. King's collaborated on a trial of over 1000 patients experiencing an average of 19 days of migraine each month; 85% of patients in the trial were female and over 60% had experienced headache side effects of previous migraine treatments. Patients were given either placebo, or a low or high dose of Galcanezumab (Eli-Lilly). Treatment with Galcanezumab reduced the number of migraine days that sufferers experienced by 4.6 days (low dose) or 4.8 days (high dose) per month, respectively **(7)**. King's subsequently led clinical trials which showed that Galcanezumab was also effective in the treatment of cluster headache. In a group of sufferers who experienced on average 17-18 headache attacks during a week of cluster headache, 3 weeks of treatment with Galcanezumab reduced the number of headache attacks by half in 71% of patients **(8)**.

Further trials found that new CGRP drugs were effective in previously untreatable migraine patients. King's researchers collaborated on an RCT carried out across 59 sites in 16 countries, of ~250 migraine patients who previously failed to respond to 2-4 preventive migraine therapies. The study found that Erenumab reduced the number of monthly migraine days by over 50% in 38% of these patients with difficult-to-treat migraine and few treatment options **(9)**.

King's researchers demonstrated efficacy of the first small molecule-based drugs to treat migraine symptoms. Early trials by King's and collaborators have shown that a second novel class of drugs, gepants, are able to relieve the symptoms of a migraine attack. For example, a study on the drug Rimegepant found that ~20% of participants were pain free at 2 hours after treatment, and almost 40% were free of their next most debilitating symptom **(10)**.

3. References to the research

1. Dodick, DW, et al., 2014.*Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial*. Lancet Neurol. 13(11): 1100-1107.
2. Sun, H, et al., 2016. *Safety and efficacy of AMG334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial*. Lancet Neurol. 15(4): 382-90.
3. Goadsby, et al. 2017. *A Controlled Trial of Erenumab for Episodic Migraine*. N Engl J Med. 377(22), 2123-2132. https://doi.org/10.1056/NEJMoa1705848
4. Ashina, M., et al., 2019. *Long-term safety and tolerability of erenumab: Three-plus year results from a five-year open-label extension study in episodic migraine*. Cephalalgia, 39(11): 1455-1464.
5. Silberstein, SD, et al. 2017. *Fremanezumab for the Preventive Treatment of Chronic Migraine*. N Engl J Med. 377(22): p. 2113-2122.
6. Goadsby, PJ et al. (2020). *Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study*. Neurology. DOI: 10.1212/WNL.0000000000010600
7. Detke HC, et al., 2018. *Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study.* Neurology. 11;91(24):e2211-e2221.
8. Goadsby, P, et al., 2019. *Trial of Galcanezumab in Prevention of Episodic Cluster Headache.* N Engl J Med, 381:132-141
9. Reuter, U., et al., 2018. *Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study*. Lancet, 392(10161): 2280-2287.
10. Lipton RB,…Goadsby PJ. 2019. *Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine.* N Engl J Med. 381:142-9.

4. Details of the impact

King's research was central to the development of two new classes of drugs which can prevent migraine, addressing a huge unmet clinical need. These drugs are highly effective, well-tolerated (a significant issue for previous therapies), and effective in patients who failed to respond to generic therapies. As a direct result of our research, five new therapies have been licensed in the US and EU, and made available to 500,000 patients in the US (5,300 in the UK). The significance of this work in transforming the treatment of migraine and the lives of migraine sufferers, has been recognised with the 2021 Brain Prize – the world's largest neuroscience prize – and the 2021 ABF Scientific Breakthrough Award, to Professor Goadsby.

The FDA and EMA approve novel, effective migraine therapies for use in the US and Europe based on King's clinical trials. Large phase 2 and 3 clinical trials, in which King's researchers played a major role, of the drugs Aimiovig (Erenumab; Amgen), Ajovy (Fremanezumab; TEVA Pharmaceuticals) and Emgality (Galcanezumab; Eli-Lilly), showed that these novel drugs are safe to use in humans and effectively treat and prevent migraine. These trials provided primary evidence upon which, in 2018, regulatory approval for use of these drugs was granted by two of the largest regulatory bodies globally, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Securing regulatory approval from the FDA is a legal requirement for the sale and use of drugs in the US, and from the EMA for the sale and use of drugs in Europe **[A-C]**. To date, these novel medicines have been approved in more than 40 countries **[C]**. In 2020, King's clinical trials also provided the critical evidence for the further approval of Emgality as the first in class treatment for cluster headache by the FDA and EMA **[C]**.

First tailored migraine therapies are recommended for use in UK clinical guidelines based on King's research. The National Institute for Health and Care Excellence (NICE) in England and Wales, and the Scottish Medical Council (SMC) in Scotland, are the UK bodies providing evidence-based guidance on the best and most cost-effective drugs and treatments available. Any new drug must be recommended by NICE or the SMC for use in the NHS. In 2019 NICE recommended Fremanezumab for the treatment of chronic migraine in patients who have not responded to 2-4 other treatments; King's research was central to appraisal of the drug **[D]**. Further to this, in 2020 NICE recommended another of the novel treatments, Galcanezumab, for the treatment of both chronic and episode migraine, also drawing on King's research **[D]**. In 2019 the SMC advised the

use of Erenumab and Fremanezumab for chronic migraine sufferers, citing the trials led and co-ordinated by King's **[E]**. Anyone who has suffered at least 8 migraine days per month and has not responded to three different treatments can now benefit from these drugs, which NICE initially estimates as 5,300 people. These are the first drugs of their kind available to patients in the UK.

Enabling effective, evidence-based campaigning by the Migraine Trust. King's research has informed the work of the Migraine Trust charity which provides information and support to migraine sufferers, and campaigns on their behalf. The work directly influenced the Migraine Trust's response to NICE consultations on the novel antibody therapies, as the MT Chief Executive explains: *"Our collaboration with King's researchers facilitated our comprehensive understanding of the importance of the treatment. This knowledge fed into our design of a patient survey, for our submission as part of the NICE technology appraisal process, allowing us to successfully contribute to the March 2020 decision by NICE to bring this drug [Fremanezumab] to the NHS"* **[F]**. The charity welcomed the NICE decision influenced by King's work: *"We are delighted that for the first time chronic migraine patients in England and Wales will be able to access an effective drug on the NHS that has been specifically designed to prevent migraine attacks. Migraine is a painful, debilitating, and exhausting brain disease and it is vital that people living with this awful condition have access to the best treatments available"* **[F]**.

King's research has led to financial benefit for pharmaceutical companies Amgen, Eli-Lilly, TEVA. Following the 2018 approvals, the three novel antibody drugs have been marketed by these companies, creating millions of dollars in revenue: In the last quarter of 2019 alone, company accounts report revenues between 25 and 90 million USD, with an estimated 1 billion USD per annum market **[G]**.

First FDA approvals for new small molecule class of migraine drugs, crucially shown to be free of medication overuse headache [H]. While earlier in development than CGRP antibody therapies, the first drugs from the second novel class – the small molecule-based gepants – are now available. In December 2019 the FDA approved the first-in-class drug Ubrogepant for the treatment of migraine, followed in February 2020 by approval for the drug Rimegepant; King's research provided evidence supporting the latter decision. Importantly, a 2020 King's study showed that this class of drugs does not have the side-effect of medicine-overuse headache common to other treatments; for migraine sufferers, this is in itself a game-changer. The significance of these approvals – with others in the pipeline – is that when this class of drugs comes off-patent, they will be incredibly inexpensive to produce – unlike the antibody drugs, which are complicated and expensive to make. This means that these early steps pave the way for phenomenal impact through migraine treatments which will have far greater reach, and can be made available to everyone, around the world.

New drugs are already being used to treat thousands of migraine patients in the US, and allowing clinicians to treat patients more effectively. In the US more than 500,000 patients are already being treated with the new drugs **[I]**. A consultant neurologist of the Mayo Clinic in Arizona – which sees 2500 patients a year of whom 80% suffer with chronic migraine – explained that over 60% of patients have responded to the drugs. He notes other benefits, most notably, that these therapies do not restrict blood vessels, or cause severe headaches when overused, unlike previous treatments, saying*: "as a result of this ground-breaking research, we have witnessed a wholly unprecedented breakthrough in this field with the FDA-approval of 6 new CGRP targeted biologics and drugs for the acute and preventive treatment of migraine. These new therapies have completely transformed our practice as clinicians"* **[I1]**. The President of the American Brain Foundation (ABF) also explained that it is the impact of King's research for treatment and patient benefit which is recognised by the ABF's Scientific Breakthrough Award 2021: *"within the past three years only… approximately 1 million patients in over 40 countries around the world have been treated with these therapeutics"* **[I2]**.

New drugs improve the quality of life of migraine sufferers in the UK: "I have been given my life back". According to NICE estimates, of the 58,900 people who experience chronic migraine in the UK, only 9% currently receive the best existing generic treatment (Botulinum Toxin A), with 53,500 people receiving only 'best supportive care' – not treating the migraine itself, but supporting patients to cope with its effects as far as possible. NICE predict that 11,700 people in the UK can now receive Fremanezumab **[J]** and, based on trials showing the drug to be effective

in 45% of patients, predict that 5,300 migraine sufferers will therefore benefit. With the recent further recommendation by NICE for the use of Galcanezumab for not just chronic, but also episodic migraine, many more migraine sufferers in the UK will benefit.

Those migraine sufferers who have already received the treatment say that they have been given their life back: *"My family no longer have to see me in the depths of depression and with no hope that life will ever get better again"* **[F]**. These novel therapies improve quality of life, particularly for migraine sufferers who have previously tried 2–4 unsuccessful treatments. Migraine is debilitating, leaving many sufferers unable to work, as one patient reports to the NICE consultation on Fremanezumab: *"It [chronic migraine] defines what I am able to do, how I am able to function, how I'm perceived by the world and disables me beyond belief"* **[K]**. Patients who received one of the new therapies trialled by King's, report being able to return to employment, reduced side effect and improved mental health: *"(I) have been taking Aimovig [Fremanezumab] for 6 months and it has helped so much I can't even put it into words"* **[K]**.

"I've now been on Aimovig [Fremanezumab] for the last 6 months and all I can say is that it's been life changing. I no longer live in fear of the next migraine and I no longer have a permanent headache. Gone is the gastroparesis and the nausea. Gone is my hyperosmia. I no longer have debilitating fatigue. Bright lights no longer bother me, and I can drive at night. I've started to volunteer with a view to returning to work. It's amazing" **[K]**.

"I received 3 months Fremanezumab… as part of the FOCUS trial at King's and have been taking Erenumab for the last 12 months as part of the free-access scheme. These medications have been more effective than any others for me and have allowed me a significant reduction in pain and an increase in functional ability. I no longer want to die." **[K]**.

5. Sources to corroborate the impact

[A] Evidence King's research underpins clinical trials, FDA & EMA approvals for Erenumab.

[B] Evidence King's research underpins clinical trials, FDA & EMA approvals, Fremanezumab

[C] C1. Evidence King's research underpins clinical trials, FDA & EMA approvals, Galcanezumab; C2. CGRP Forum overview of regulatory status for anti-CGRP therapies worldwide.

[D] Evidence King's research informed NICE recommendations: D1. NICE recommendation for Fremanezumab for the treatment of chronic migraine; D2. NICE recommendation for Galcanezumab for the treatment of chronic and episodic migraine in the NHSE.

[E] Evidence that King's research informed the SMC recommendations for use in NHS Scotland: E1. Erenumab; E2. Fremanezumab.

[F] Evidence of the impact of King's research for the Migraine Trust. F1. Testimonial, Migraine Trust; F2. Article "Life-changing migraine medication approved for use within NHS Scotland"; F3. Article: "NICE gives chronic migraine patients access to 'life changing' new drug"

[G] Publicly available accounts evidencing financial benefit to Amgen, Eli-Lilly, TEVA.

[H] Evidence on the impact of gepants: J1, FDA approvals for Ubrogepant, Rimegepant; J2, Saengjaroentham, C et al. (2020). *Differential medication overuse risk of novel anti-migraine therapeutics.* Brain, 143:9, 2681–2688.

[I] Testimonials on the impact of novel migraine drugs: I1, on clinical practice in the US (the MAYO clinic); I2, in transforming the treatment of migraine (American Brain Foundation).

[J] NICE impact report, Fremanezumab, evidencing the number of people eligible for novel therapies on the NHS.

[K] NICE consultation, evidencing impact of new therapies on migraine sufferers.