Institution: University College London

Unit of Assessment: 8 - Chemistry

Title of case study: Pitolisant: a novel therapy for narcolepsy and other rare neurological disorders

Period when the underpinning research was undertaken: 2000 - 2007

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:
Robin Ganellin	Emeritus Professor of Medicinal Chemistry	1986 - Present

Period when the claimed impact occurred: 2016-present

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

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

The large body of research initiated and conducted at UCL by Professor Ganellin into non-imidazole candidate compounds acting at H3 histamine receptors, in collaboration with Bioprojet Phama/INSERM (France) and the Free University of Berlin, has directly resulted in the development of novel orphan drug pitolisant (Wakix™) for treating narcolepsy, excessive daytime sleepiness (EDS) and Prada Willi Syndrome, significantly improving the quality of life for people with these rare diseases around the globe. The drug has been added to the formulary of multiple clinical commissioning groups in the UK. It has been licenced and sold across the UK, EU and in North America since 2016, generating approximately [TEXT REDACTED OR PUBLICATION] from sales revenue for Bioprojet and Harmony Biosciences. In the UK, Wakix has resulted in a saving of 42% of the treatment cost for narcolepsy for the NHS when compared to other therapies.

2. Underpinning research (indicative maximum 500 words)

The discovery of pitolisant (Wakix™) embodies a truly European scientific research collaboration, one led by and initiated by the fundamental research of Professor Robin Ganellin FRS at UCL and Professor Jean-Charles Schwartz at INSERM laboratory in Paris, France. The collaboration led to several joint publications (**R1-R4**) and additional funding by an EU Biomed 2 grant. From the work between Professor Ganellin's group and collaborators, a number of key breakthroughs have led to the eventual development of the drug.

Initially, UCL made several compounds that were selected for drug development but not chosen for a human study due to side effects. However, a subsequent change in approach derived from first principles, resulted in Professor Ganellin's discovery of a potent non-imidazole histamine H3-receptor antagonist, which was able to cross the blood-brain barrier and reduce interaction with the cytochrome P450 system and other metabolic enzymes (**R2, R4**).

Professor Ganellin's group went on to investigate the general structure Ph-X-(CH_2)m-NR_1R_2, where X = O or S, m = 3–6, R_1 = R_2 =Me, Et, ^{n}Pr, ^{n}Bu. A UCL PhD student took the structure Ph-O-(CH2)5-NR1R2 and explored the effect of changing the R_1R_2 groups (**R2, R3**). Importantly, the team showed that simple non-imidazole histamine H3-receptor antagonists had pronounced biological activity with the most active compounds *in vivo* containing p-cyanophenoxy and p-acetyl-phenoxy groups. The removal of the imidazole ring from Nα-(4-phenylbutyl)histamine, led to the synthesis of N-ethyl-N-(4-phenylbutyl)amine and resulted in only a twofold drop in affinity. This UCL-led research led the way in developing a non-imidazole H3-receptor histamine antagonist (**R2, R3**). Further UCL work that explored the structure-activity optimisation involved

synthesising simple chemical structures that were sent to Panlabs for screening against approximately 90 targets to elucidate receptor specificity for the histamine H3 receptor. The results identified that at least one compound (number UCL2283) that was potent and very selective for histamine H3 receptors (**R2**). Detailed investigation showed that such structures resembled the imidazole-containing structures, which had previously been investigated, having simply replaced the imidazole moiety with a piperidine ring (**R4, R5**). The structural analogy between cyclopropylcarbonyl compound (number UCL2190) (**R4**) and ciproxifan (a potent H3 receptor antagonist and previous clinical candidate), directed collaborating chemists at the Free University of Berlin to replace the imidazole moiety within compound UCL2190 in many other different structural types of histamine H3-receptor antagonists (**R1**). Replacing imidazole with piperidine in [3-(4-chlorophenyl)propyl-3-(1H-imidazol-4-yl)propylether, gave rise to pitolisant, 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine hydrochloride (trade name Wakix™). UCL then carried out further work towards understanding the pre-clinical pharmacology of pitolisant by synthesising chemical compounds, such as imetit, to assess the competitive antagonism of pitolisant (**R6**).

Bioprojet, a pharmaceutical company, founded by Jeanne-Marie Lecomte (who is on relevant patents with Professor Ganellin) and Jean-Charles Schwartz at INSERM (who discovered the H_3 receptor), continued to the clinical development and commercialisation of pitolisant. Several patents related to the discovery, development and therapeutic applications of non-imidazole H3-receptor ligands and pitolisant, have been assigned to Bioprojet Pharma. Professor Ganellin is named as an inventor on 4 US and 2 European patents granted since 2000 that underpin the work.

Pitolisant was the first histamine H3-receptor inverse agonist taken through all pre-clinical and clinical phases and it has been demonstrated to be effective in treating all major symptoms of narcolepsy. Pitolisant's mode of action leads to increased histamine transmission in the brain by blocking histamine auto-receptors, thereby enhancing the activity of histaminergic neurons, in addition to increasing the signalling of other neurotransmitters (e.g. norepinephrine, dopamine) in the brain. This enhances wakefulness and alertness and decreases cataplexies and hallucinations in patients with narcolepsy.

Key UCL researchers: PhD students (Antonia Piripitsi 1992-96, Fabien Leurquin 1995-99) and MSc student (Titi Akinleminu 1998-99).

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

R1. **Ganellin CR**, Leurquin, F, Piripitsi A, Arrang J-M, Garbarg M, Ligneau X, Stark, H, Schunack W, Schwartz J-C. (2001) The Discovery of Potent Non Imidazole H3-receptor Histamine Antagonists. Histamine Research in *the New Millennium. Eds. T. Watanabe, H. Timmerman and K. Kanai,* pp 25-31, Elsevier. Available on request.
R2. **Ganellin CR**, Schwartz J-C, Stark H. (2018) Discovery of Pitolisant, the first marketed histamine H3-Receptor Inverse Agonist/Antagonist for Treating Narcolepsy. *Successful Drug Discovery, V3,* Wiley-VCH.
R3. Meier G, Apelt J, Reichert U, Grassman S, Ligneau X, Elz S, Leurquin F, **Ganellin CR**, Schwartz J-C, Schunack W , Stark H. (2001) Influence of Imidazole Replacement in Different Structural Classes of Histamine H3- receptor Antagonists. *Eur. J. Pharmaceut*. Sci.,13, 249-259. DOI:10.1016/s0928-0987(01)00106-3
R4. Mikó T, Ligneau X, Pertz HH, **Ganellin CR**, Arrang J-M, Schwartz J-C, Schunack W, Stark H. (2003) Novel Nonimidazole Histamine H3 Receptor Antagonists: 1-(4-(Phenoxymethyl)benzyl)piperidines and Related Compounds. *J. Med. Chem.* 46, 1523-1530 DOI:10.1021/jm021084k
R5. Meier G, Ligneau X, Pertz HH, **Ganellin CR**, Schwartz J-C, Schunack W, Stark H. (2002) Piperidino-Hydrocarbon compounds as novel non-imidazole histamine H3-Receptor antagonists. *Bioorganic & Medicinal Chemistry, 10*(8):2535-2542. DOI:10.1016/s0968-0896(02)00115-3

R6. Ligneau X Perrin D, Landais L, Camelin J-C, Calmels TPG, Berrebi- Bertrand I, Levoin N, Capet M, Lecomte J-M, Parmentier R, Anaclet C, Lin J-S, Bertaina-Anglade V, Drieu la Rochelle C, d'Aniello F, Rouleau A, Gbahou F, Arrang J-M, **Ganellin CR**, Stark H, Schunack, W, Schwartz J-C. (2007) BF2.649 [1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine, Hydrochloride], a Non-imidazole Inverse Agonist/Antagonist at the Human Histamine H_3 Receptor: Preclinical Pharmacology. *J. Pharmacol. Exper. Therap*., 320, 365-375 DOI:10.1124/jpet.106.111039

Patents

Arrang JM, **Ganellin CR**, Garbarg M, Lecomte JM, Leurquin F, Ligneau X, Schunack WG, Schwartz J-C, Sigurd E, Stark H. (2004) Non-imidazole alkylamines as histamine H-3-receptor ligands and their therapeutic applications. Patent **EP1428820A1**

Schwartz J-C, Garbarg,M, Lecote JM, Ligneau X, Schunack WG, Stark H, **Ganellin CR**, Leurquin F, Elz S, Arrang JM. (2006) Non-imidazole alkylamines as histamine H3-receptor ligands and their therapeutic applications. Patent **US7138413, EP1428820B1**.

Schwartz J-C., Arrang JM, Garbarg M, Lecomte JM, Ligneau X, Schunack WG, Stark H, **Ganellin CR**, Leurquin ., Elz S. (2007) Non-imidazole alkylamines as histamine H3-receptor ligands and their therapeutic applications. Patent **US7169928**.

Schwartz J-C, Arrang JM, Garbarg M, Lecomte JM, Ligneau X, Schunack WG, Stark H, **Ganellin, CR**, Leurquin F, Elz S. (2011) Non-imidazole alkylamines as histamine H3-receptor ligands and their therapeutic applications. Patent **US7910605.**

Manuel R, Sallares J, Guerrero M, Guglietta A, Arrang J-M, Schwartz J-C, Stark, H, Schunack, W, Ligneau X, Lecomte J-M, **Ganellin CR** (2012). Monohydrochloride salt of 1-[3-[3-(4-chlorophenyl) propoxy] propyl] –piperidine. Patent **US8207197.**

Manuel R, Sallares J, Guerrero M, Guglietta A, Arrang J-M, Schwartz J-C, Stark, H, Schunack W, Ligneau X, Lecomte J-M, **Ganellin CR** (2013). Monohydrochloride salt of 1-[3-[3-(4-chlorophenyl) propoxy]propyl]-piperidine. Patent **US8354430B1.**

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

Prior to the commercial release of pitolisant, there was an unmet need for an effective, safe and tolerable treatment regime in the management of narcolepsy. The collaboration between UCL and universities in Germany and France, culminated in the development and commercialisation of pitolisant (Wakix™) by Bioprojet and Harmony Biosciences in Europe and the USA, respectively. Pitolisant, the first in its class, has changed the guidelines on how narcolepsy (with/without cataplexy) is managed and dramatically improved the quality of life for those suffering from the condition. Pitolisant has led to commercial profitability and growth of Harmony Biosciences and Bioprojet resulting in [TEXT REDACTED OR PUBLICATION] sales revenue and employment [TEXT REDACTED OR PUBLICATION]

Narcolepsy is a disabling, long-term neurological disease that affects 1 in 2,000 individuals (approximately 30,000 people in the UK and 165,000 people in the USA). The two major symptoms of narcolepsy are excessive daytime sleepiness (EDS), and, in 60-70% of patients, cataplexy. Cataplexy consists of a sudden loss of muscle tone, which can range from mild muscle weakness to full body collapse. Narcolepsy significantly decreases the quality of life of the affected individuals, with two-thirds of patients being unable to work.

Adoption and changes to prescribing practices for narcolepsy at the national level

As a first in class medicine that acts on histamine H3 auto-receptor in the brain, pitolisant represented the first new therapy in over a decade for the treatment of narcolepsy. After being granted marketing authorisation by the European Medicines Agency's Committee for Medicinal Products in 2016, pitolisant received NHS appraisal by the National Institute for Clinical Excellence (NICE) and is deemed to be **42% more cost-effective** for the NHS. Compared to the alternative treatment of sodium oxybate, which is priced between GBP540 to GBP1,080, pitolisant costs between GBP310 to GBP620 per month per patient in the UK (**S1**). Additionally, in the UK pitolisant has received the approval of multiple clinical commissioning groups including the Northern Treatment Advisory group (2018), Pan Mersey

Area (2019), South East London Area Prescribing Committee (2019), Derbyshire Joint Area Prescribing Committee (2016), Surrey & North West Sussex Area Prescribing Committee (2019), Devon Clinical Commissioning Group (2020) for use as the last line, single-agent therapy, for the treatment of narcolepsy (**S2**). Pitolisant is currently used by 60 patients at the Sleep Centre at Guy's and St. Thomas's Hospital. These patients have reported increased quality of life scores as well as "**significant improvement in sleep quality, and a reduction of concomitant stimulant therapy usage**" (**S3**). The development of pitolisant has enabled clinicians to offer an alternative treatment option with reduced side effects. At the Sleep Centre at the National Hospital for Neurology and Neurosurgery pitolisant is used by two patients with "excellent effect" as noted by the consulting physician. The centre views pitolisant as a "**significant step forward**, as our mainstay of treatment have been stimulants or sodium oxybate (often with side-effects)" (**S4**).

Adoption and changes to prescribing practices internationally

In August 2019, the Food and Drug Administration (FDA) approved pitolisant (trade name Wakix™, Harmony Biosciences) for use in the USA to treat EDS in adult patients with narcolepsy. As of June 30, 2020, "**over 1,750 unique health care providers have prescribed Wakix**™ since it became available in November 2019, which represents 2,700 unique patients […..] Harmony Biosciences has also been able to secure formulary access for over 166 million lives, which represents 70% of their target covered lives" (**S5**).

Impact of pitolisant on the treatment and quality of life of patients with narcolepsy

Patients receiving treatment have described pitolisant as having a marked impression on their lives, "I can definitely feel the difference in the afternoon. The mental anguish I felt every day has lifted. I'm so much less tired in the afternoon and don't feel so miserable every day" (**S6**). Another patient reported, "Wakix™ is the **most wonderful drug I've known over my 50 years suffering narcolepsy**. If I'd been able to have it 30 years ago my life would have been so much easier" (**S6**). Other patients have also indicated that "the only reason I can work full time is that I started a drug called Wakix™, which is doing wonders" and that pitolisant has "**changed my life**, I can function as a normal human in mornings along with my other narcolepsy meds" (**S6**).

Improvement to the quality of life of children with Prader- Willi Syndrome and EDS

A new patient group benefiting from pitolisant are children with Prader-Willi syndrome (PWS) who often experience EDS. Both PWS and EDS can affect the cognitive development of children, leading to mild to moderate intellectual impairment. In the USA, a group of children with PWS and EDS have trialled pitolisant with positive outcomes. One child taking pitolisant reported: "**I was more awake, I was more energetic**… my brain was moving really quickly so I could catch up with all the learning that I had missed in my early childhood which was really, really amazing" (**S7**). Another patient reported that taking pitolisant has had a positive effect on his education: "**it was much easier for me to answer questions** for my readings, now I get 'A's" (**S7**). EDS has a dramatic effect on a sufferer's quality of life. One patient with EDS testified that since taking pitolisant she has been able to do normal everyday social activities: "I don't have to go to bed at the same schedule, so I can go to dances and stuff and stay up later at watch movies at night. **[Before pitolisant] I would actually fall asleep watching a movie, but now I can actually watch a movie**" (**S7**). Furthermore, a parent of a child with PWS and EDS attested to pitolisant making a significant difference to his child's life as he could now envisage a positive future for him: "Personally am looking at him and going, you know what, you are going to college and you are going to graduate and you are going to live independently, you are going to find a partner. I think there's a tangible, defined, independent future" (**S7**).

The growth of Bioprojet and Harmony Biosciences attributed to pitolisant

Bioprojet has benefited from a close working relationship with Professor Ganellin [TEXT REDACTED FOR PUBLICATION]. Pitolisant was launched in western Europe (UK, Netherlands, Belgium, Germany, France, Italy, and Spain) in 2016, followed by distribution in Northern and Central Eastern Europe in 2018. In the USA, pitolisant was licenced to Harmony Biosciences who made a milestone payment of USD50,000,000 to Bioprojet as per the License Agreement

upon FDA's acceptance of pitolisant in February 2019 (**S5**). As one of three product lines at Bioprojet Pharma, a subsidiary of Bioprojet, pitolisant has [TEXT REDACTED OR PUBLICATION].

Pitolisant is currently Harmony Biosciences only commercial product and therefore growth of the company is directly attributed to pitolisant and the work at UCL, which underpinned its discovery. Harmony Biosciences affirmed that the company has experienced "**growth associated with the commercial launch of Wakix™**" (**S5**). As direct consequence of the licensing agreement between Bioprojet and Harmony Biosciences, Harmony Biosciences raised USD270,000,000 in equity funding from 29 investors (**S9**) and secured a USD 200,000,000 debt facility to provide additional working capital to fuel the company's continued growth (**S5**). Harmony Biosciences reported revenue of USD38,000,000 from pitolisant for the three months ended June 30, 2020, representing an increase of USD18,200,000 from the previous three months ended March 31, 2020. This increase was "driven by increased adoption of Wakix™ following commercial launch". Since its launch in November 2019, the drug has accounted for net sales of USD57,800,000 (**S5**).

Due to the commercial success of pitolisant, Harmony Biosciences was able to **start publicly trading** on the Nasdaq Global Market in August 2020. Public trading is favourably regarded as it is indicative of a high level of operational and financial success. Another important indicator of the drug's commercial success has been the employment of "150 professionals that possess comprehensive life sciences experience" (**S5**). This team is in touch with "the approximately 8,000 HCPs [health care providers] who treat approximately 90% of narcolepsy patients in the US" (**S5**).

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

S1. NICE evidence summary (accessed 18/02/2021) - corroborates cost-effectiveness of pitolisant.
S2. CCGs approval of pitolisant (accessed 18/02/2021) - corroborates formulary approval of pitolisant by regional clinical commissioning groups.
S3. Evidence of pitolisant trial at Sleep Disorders Centre, Guy's & St Thomas' Hospitals - corroborates use of pitolisant as treatment.
S4. Testimonial from pharmacist and consulting physician – corroborate the use of pitolisant as treatment at the National Hospital for Neurology and Neurosurgery Sleep Centre, respectively.
S5. Harmony Biosciences Registration Statement (accessed 18/02/2021) - corroborates Harmony Biosciences company and financial details.
S6. Patient testimony on pitolisant (accessed 18/02/21) - corroborates the impact of pitolisant on patients with narcolepsy.
S7. Video produced by the Chion Foundation on the treatment of PWS patients with pitolisant – (accessed 19/02/2021) - corroborates impact of pitolisant on the lives of PWS experiencing EDS and narcolepsy.
S8. Supporting statement from Bioprojet Chairman - corroborates contribution of UCL research, financial data and number of employees.
S9. Executive summary "Rare disease start-up Harmony raises $270mm in early equity funding" published on 20/08/2020 by In vivo Informa Pharma Intellingence - corroborates funding raised.